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Schoster, Angelika

MULTIDRUG RESISTANT BACTERIA IN EQUINE MEDICINE

Angelika Schoster, DVM, DVSc, PhD, DACVIM (Large Animals), DECEIM
Zurich, Switzerland

INTRODUCTION

Antimicrobial-resistant bacteria are an emerging threat in human and veterinary medicine. Often, bacteria with resistance to three or more antimicrobial categories are called multidrug-resistant (MDR), however, naturally occurring intrinsic resistances present in an entire bacterial species should be excluded from this definition. Pathogen specific guidelines are available for human medicine, however, lacking for veterinary pathogens, complicating comparison between studies.

Few studies on infections caused by MDR bacteria have been published in horses and most often they focused on methicillin-resistant Staphylococcus spp. (MRS) and extended spectrum beta-lactamases (ESBL)-producing *Escherichia coli*. *Staphylococcus* spp. and *E. coli* are commensals on the equine mucosal membrane and gut, respectively; however, they are also important pathogens causing a wide range of infections. Both species have developed resistance towards beta-lactam antibiotics, one of the most important antimicrobial classes in veterinary medicine. The majority of these isolates have also acquired resistance to other important antimicrobial categories further complicating therapy of infections caused by these bacteria. Less is known about the role of other MDR isolates such as *Acinetobacter baumannii*, *Enterococcus* spp. and *Pseudomonas aeruginosa* in equine infections but a high rate of multidrug resistance was recently shown in these pathogens isolated from infections in horses.[1]

Studies in human subjects have repeatedly demonstrated an increased length of hospitalization, higher costs and a higher mortality of infections caused by MDR isolates compared with similar conditions caused by susceptible organisms. A delay in appropriate therapy is suggested to be the main reason for this association. Information about the outcome of infections caused by MDR isolates in horses is scant.

EXTENDED SEPCTRUM BETA-LACTAMASE PRODUCING ENTEROBACTERIACEAE

Enterobacteriaceae are comprises of a variety of bacterial species, including important human and veterinary pathogen such as *E. coli, Klebsiella, Enterobacter and Proteus*. The gastrointestinal tract, which harbors these species in large numbers, represents an ideal 'market place' for transfer and exchange of resistance genes. Genes encoding for extended spectrum beta lactamase (ESBL), AMP C beta lactamase and carbapenemase are of particular concern as their production renders the bacterium resistant to almost all beta lactam antimicrobials.

Of the three, ESBLs have most commonly been isolated from horses and some epidemiologic data are available. The resistance genes encoding for ESBLs are often located on plasmids allowing for easy horizontal spread between bacteria. The distribution of ESBL-types varies between human and animal isolates as well as geographically. In recent years, the ESBL enzyme CTX-M has largely replaced other types such as TEM and SHV in human and animal populations.[2,3] While ESBL-producing Enterobacteriaceae are monitored closely in food-producing animals, little is known about these bacteria in horses. ESBL-producing commensal Enterobacteriaceae in healthy horses occur with a prevalence of 6.5%-60% in Europe.[4-6] Similar prevalence (0.5%-60%) have been described for equine clinical isolates from Europe and North America.[1,6-9] ESBL-producing Enterobacteriaceae are emerging as important etiological agents of extra-intestinal nosocomial infections in equine clinics.[8,10,11] AMP C beta lactamase, causing the bacterium to be resistant to cephamycins in addition to penicillin and cephalosporins, has rarely been detected in horses. Carbapenemase producing Enterobacteriaceae, a significant threat in human medicine, have not been described in horses. Carbapenemase producing Enterobacteriacea have often acquired additional resistance genes, making them resistant to most antimicrobials. New Delhi metallo-beta-lactamase-1 (NDM-1), an enzyme first detected in 2008 is of great concern in human medicine due to resistance against almost all available antimicrobials. This enzyme has been detected in companion animals but not horses.

Use of antimicrobials, particularly cephalosporins, is a well-known risk factor associated with the occurrence of ESBLs in human medicine. It has been suggested that this is similar in horses, for example in one study where broad-spectrum antimicrobial prophylaxis, including cefquinome (a 4th generation cephalosporin), was shown to select for ESBL-producing bacteria in horses.[4] Cephalosporins are widely used in equine medicine for prevention or treatment of infections. Hospitalization is known to be associated with increased prevalence of antibiotic resistant bacteria[12,13], and the selective pressure in a hospital environment may select for particularly resistant strains.[14] Similar knowledge for equine hospitals is sparse, although direct horse-to-horse transmission and indirect transmission via caretakers and the hospital environment have been suggested.[13] Furthermore, the duration of carriage of ESBL-producing bacteria after hospitalization and antimicrobial administration is incompletely studied. One study showed persistent carriage upon antimicrobial selection in horses for two weeks after hospital discharge. However, the probability of carriage significantly decreased eight weeks after discharge, suggesting that carriage of ESBL-producing bacteria is gradually reduced in the absence of antimicrobial exposure.[15]

METHICILLIN RESISTANT STAPHYLOCOCCI

Staphylococcus aureus is a common commensal of the mucosal membranes, approx. 8-10% of horses are carriers,[16] however not all are multi drug resistant (MRSA carriage rate in horses is approx. 0-5%).[17] Staphylococci can easily acquire resistance to a variety of antimicrobials, the most notable being methicillin resistance. Methicillin resistance in staphylococci is due to a modification of the penicillin-binding protein (PBP), making them resistant to all beta-lactam antimicrobials, including carbapenem.

MRSA should therefore be considered resistant to all beta-lactam antimicrobials, irrespective of in-vitro susceptibility results. Antimicrobial treatment is often complicated by acquisition of additional resistance genes. MRSA are mainly responsible for incisional infections, skin, soft tissue and synovial infections. [8,18,19] Remaining antimicrobial treatment options often include amikacin, chloramphenicol or fluorquinolones, however should be based on susceptibility results. Gentamicin and trimethoprim-sulfonamide resistance are common. Topical and local therapy should be considered if feasible, particularly in synovial and skin infections. Eradication of MRSA colonization in horses cannot be recommended at this point due to a lack of information on efficacy.

Methicillin-resistant coagulase-negative staphylococci have so far not been recognized as important pathogens in horses due to their inferior pathogenicity compared with *S. aureus*. A considerable number of infections caused by these isolates were seen in one study[8] and case reports of MR-CNS causing osteitis and implant infection also reported these isolates to be relevant pathogens. [20,21]

OTHER MDR BACTERIA

Other common MDR isolates implicated as etiologic agents in equine infections are *Acinetobacter baumannii*, *Enterococcus spp*. and *Pseudomonas aeruginosa*. In addition to their high rates of intrinsic resistance, these species are known for their ability to rapidly acquire resistance to further antimicrobials. [1,22-24]

Acinetobacter are gram-negative members of the gastrointestinal microflora of horses. They are opportunistic pathogens which can cause a variety of infections. Pan-resistant *A. baumannii* strains are a serious problem in human medicine as they possess large numbers of mobile resistance elements which are readily transferable and have a high mutation rate making them susceptible to de novo acquisition of resistance. MDR *A. baumannii* have also been isolated from horses, particularly from incisional infections, intravenous catheters and soft tissue infections such as abscesses, wounds and hematomas. [8,22] Antimicrobial choice should be based on susceptibility results, however relating in vitro information to in vivo efficacy is often difficult for Acinetobacter species. Enrofloxacin, imipenem and amikacin are often reported susceptible. Local and topical therapy should be implemented in addition to systemic antimicrobial therapy.

Enterococci are comprised of a variety of gram-positive bacteria that are part of the gastrointestinal microflora. The most notable pathogens in equine medicine being *Enterococcus faecium* and *Enterococcus faec*alis. Enterococci are inherently resistant to a variety of antimicrobial classes and acquire resistance genes rapidly. As their virulence is limited, they mainly cause infection in immunocompromised hosts and are considered opportunistic pathogens. The isolation of the bacterium from an infection is of questionable significance and its isolation often questioned as a contaminant, which complicates therapeutic choices. Enterococcus spp. Have been recognized as a pathogen in septic synovial diseases, respiratory diseases, and sepsis in foals in rare clinical reports.[23,24] Antimicrobial treatment options are often limited, therefore therapy needs to be based on susceptibility results. Particularly vancomycin resistance (VRE) mediated by vanA and vanB strains is becoming a great concern. There are rare reports of VRE colonization in horses.[25] Enterococci should be considered resistant to all cephalosporins and TMPS irrespective of susceptibility results. Ampicillin often remains effective, and can be combined with aminoglycosides (even if low level resistance is reported) due to the synergistic activity and cell wall destruction by ampicillin, which allows entry of the aminoglycoside into the cell. The use of vancomycin should be avoided in horses, due to this antimicrobial being a critically important antimicrobial in human medicine.

Pseudomonas spp. are ubiquitous gram-negative bacteria that show high resistance to antiseptics, making them a common nuisance in health care setting. Various resistance determinants can be found in this species and they are able to survive in biofilms further complicating their treatment. Wound infection, reproductive tract infections, respiratory tract infections and skin infections have been reported in horses. [8,26-28] Treatment should be based on susceptibility results, often fluorquinolones and aminoglycosides remain effective.

CLINICAL INFECTIONS DUE TO MDR BACTERIA

Resistant bacteria cause the infections as their susceptible counterparts. Therefore, MDR bacteria can cause a variety of infections, however post-procedural infections represented almost half of the presented cases, followed by soft tissue infections and musculoskeletal infections.[8] In contrast, respiratory infections, septicemia, dental and skin infections caused by MDR isolates are rare. Nosocomial infections caused by MDR E. coli and MRSA have been reported in horses.[11,29] The mortality rate in MDR infection in horses is generally low.[8,29]

Factors which have been shown to be significantly associated with the presence of MDR isolates in infections in humans are prior use of antimicrobials, length of hospital stay, stay in the intensive care unit, the presence of co-morbidities, placement of various types of catheters, intubation and mechanical ventilation and therapeutic interventions. Many of these factors are typically also present in equine cases with nosocomial-acquired postprocedural infections. The previous use of antimicrobial drugs is the most common and consistent factor in all studies evaluating risk factors for the presence of MDR isolates. 89% of the horses included in one study were treated with antimicrobials prior to the diagnosis of MDR infection. [8]

SUMMARY

Treatment should be strictly based on susceptibility results to reduce the absolute amount of antimicrobials used and their adverse effects. Local therapy (i.e. drainage and disinfection) should be considered whenever possible to eliminate the infectious agent and to overcome infections caused by MDR isolates.[30] Fluoroquinolones, macrolides, imipenem and vancomycin usually remain

effective against many MDR isolates, but their usage should be strictly limited in horses due to their critical importance in human medicine. Chloramphenicol, a drug that is sometimes avoided because of its adverse effects in human patients, is regaining importance because of its frequent efficacy against MDR isolates.

Aside from infections in individual horses, multidrug resistant bacteria also have significant implications on an epidemiologic level due transfer of antimicrobial resistance genes. Antimicrobial resistance is mainly acquired by horizontal gene transfer, allowing its rapid spread within a susceptible bacterial population. At an individual horse level or short-term population level, such as in a hospital population, clonal spread is also an important means of spread of resistance.

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