Surveillance Focus

Antimicrobial resistance in horses

Cajsa Isgren and colleagues from the University of Liverpool discuss issues around the problem of antimicrobial resistance in bacteria associated with horses and introduce a new surveillance initiative.

Antimicrobial resistance (AMR) is a global problem of growing concern due to increasing resistance to commonly used antimicrobials. The issue is further compounded by a lack of new classes of antimicrobials being developed and authorised, especially for the horse.

AMR is abundant across a wide range of equine pathogens, including Escherichia coli, staphylococci and Salmonella, Klebsiella and Pseudomonas species, as well as other opportunistic pathogens. The identification of resistance in high-profile pathogens from horses, especially potentially zoonotic bacteria such as E. coli that produce extended-spectrum lactamases (ESBL) (Fig 1), meticillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant (MDR) Salmonella has increased the attention on AMR in horses.

There is strong evidence from human and veterinary studies in other species that antimicrobial use is associated with the emergence and dissemination of resistance in ESBL-producing Enterobacteriaceae and MRSA. In horses there is also increasing evidence of a similar association.

How do antimicrobials work?

Antimicrobial agents act by disrupting specific metabolic and normal functions of bacterial cells. There are four predominant targets for antimicrobial action:

- disruption of cell wall synthesis;
- inhibition of DNA/RNA synthesis;
- inhibition of protein biosynthesis;
- interference with a vital metabolic pathway.

Resistance mechanisms

The mechanisms through which bacteria can achieve resistance to antimicrobials can be grouped into three major categories:

- protection or alteration of the antimicrobial target site;
- exclusion of the antimicrobial agent from the cell interior (via reduced cell permeability or efflux pump expulsion);
- production of antimicrobial inactivating enzymes.

Bacterial resistance mechanisms can either occur due to a certain trait common to all bacteria of that group (ie, intrinsic) or arise from acquired mechanisms found only in some members of a genus or species due to alteration of the bacterial genome (ie, extrinsic).

Acquired resistance can arise from endogenous mutations in chromosomal genes but it is more often achieved by exogenous horizontal acquisition of novel genetic elements. The transferable genetic material participating in exogenous resistance can involve plasmid-encoded resistance genes, gene cassettes linked to integrons, transposons, and other mobile genetic elements. These genetic elements can encode pumps for drug efflux, enzymes for antimicrobial inactivation, alternatives of the antimicrobial target site and mechanisms that provide protection for the molecular target.

Exogenous exchange of genetic material may occur between differing strains of the same species or even across genera, and can occur via bacterial transformation (incorporation of exogenous DNA from dead bacteria), conjugation (transfer of plasmids), or transduction (DNA transferred by viral bacteriophages that infect bacteria).

Acquired AMR mechanisms are of particular concern, irrespective of their specific origin, as they allow both the emergence and rapid dissemination of resistance in formerly susceptible populations of bacteria. This report will focus on AMR in E. coli.

AMR in E. coli

E. coli is considered part of the normal gastrointestinal tract flora in horses but despite a predominantly commensal nature, many strains of E. coli are capable of causing disease of both gastrointestinal and extraintestinal sites.

AMR is commonly encountered and β-lactam resistance is of particular concern. E. coli is intrinsically resistant to penicillin (which is unable to penetrate its outer membrane) but there is widespread acquired resistance to other β-lactams, mostly via the production of inactivating lactamase.
enzymes such as TEM-1, TEM-2 and SHV-1, or AmpC β-lactamases, all encoded by various bla resistance genes.17,14

The extended-spectrum β-lactam antimicrobials (including cefotaxime, cefotrub and cefquinome) were developed to counter resistance seen to the early β-lactams. Resistance to these agents is conferred by bacterial production of ESBL enzymes,17 many of which are simple mutations of the original TEM/SHV β-lactamases and only a small number of amino acid substitutions is required to extend their spectrum of resistance to include novel agents.20

A family of ESBL enzymes distinct from the SHV and TEM types has emerged in the past two decades and now predominate within E coli.21 These enzymes preferentially hydrolyse the extended-spectrum β-lactam cefotaxime and are consequently named cefotaximases (CTX-M). They have been found in isolates from both humans and animals.8

**Antimicrobial resistant E coli in horses**

E coli that are resistant to most antimicrobials currently authorised for use in horses in the UK have been identified in previous studies in both clinical and commensal isolates.12,21

An increased prevalence of faecal carriage of antimicrobial resistant E coli has been identified in hospitalised horses compared with those in the community and the same is true for MDR and ESBL-producing E coli.4,24,26

The prevalence of faecal carriage of MDR and ESBL-producing E coli has also been shown to increase significantly during hospitalisation.25,27 Some studies have reported a consistent association between antimicrobial exposure in hospitalised horses and increased risk of resistance in faecal E coli.1,24 One study reported an association between overall hospital use of antimicrobials and increased prevalence of resistance, even in horses not actually receiving antimicrobials.9 Other studies have identified that hospitalisation (even without antimicrobial treatment) is a further risk factor.27,28

Being stabled on the same yard as a recently hospitalised horse has also been associated with ESBL-producing E coli carriage in the equine community2 and the identification of continued faecal carriage of MDR bacteria by horses discharged from hospital suggests these horses may act as a reservoir.29 Commensal carriage of ESBL-producing and MDR E coli has been studied in detail1 but their role in clinical infections has not been quantified. Recent publications have reported an increase in clinical infections in horses caused by MDR E coli30 and E coli accounted for the majority of all surgical site infections (SSIs) following exploratory laparotomy in a recent hospital study,26 but the source of these infections is not yet clear.

Monitoring and surveillance of emerging resistance, both in commensals and pathogens, is essential in order to allow us to estimate the growing burden of AMR in the horse population. Apart from the data collated in the Defra/AHT/BEVA quarterly surveillance reports and the limited reporting in the UK-VARSS report31 there is little research or large-scale coordinated surveillance of clinical bacterial infections in horses within the UK.

**A new surveillance initiative**

Funded by the Horse Trust, we are currently undertaking a surveillance project of the AMR profiles of bacterial infections in horses using diagnostic laboratories submissions across a wide geographical range of equine practices. We will report on bacteria commonly associated with clinical infections and their patterns of AMR across most of the UK.

We have also undertaken a multicentre study investigating risk factors for carriage of ESBL-producing bacteria across five equine referral hospitals in the UK. In this study we obtained daily faecal samples from equine inpatients as well as weekly environmental samples at these hospitals to determine which bacteria reside in the patient faecal flora and hospital environment. We are sampling SSIs from patients at these hospitals in an attempt to determine any link between faecal carriage of MDR E coli and any role in SSI.

Comparison of AMR in commensal E coli versus those found in clinical infections and in the equine hospital environment will be key to our understanding of reservoirs of infection and transmission. Interventions can then be developed to help mitigate transmission, which will aid prevention of resistant infections in our equine population.

If any hospital has a suspected outbreak of MDR E coli from SSIs we would be happy to receive and process samples free of charge and feed back results. For more information contact Cajsa Isgren (cjsgren@liverpool.ac.uk) or Gina Pinchbeck (ginap@liverpool.ac.uk; telephone 0151 794 6195).

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