

Recognising and controlling risk factors for antimicrobial resistance

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Summary

Antimicrobial resistance amongst organisms such as *Escherichia coli*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. pseudintermedius* has become a serious threat to veterinary small animal practice. There is an urgent need to adopt measures which will control and reduce this problem. Risk factors for infection by resistant organisms in small animals are now becoming recognised and appear to mirror those in human medicine. They include contact with carriers or infected animals, hospital admission, invasive procedures and antimicrobial therapy. Key recommendations which enable such risk factors to be avoided are: development of protocols which ensure that antimicrobials are used only when necessary, selection of appropriate antimicrobials and compliance with correct dosage and administration, limitation of prophylactic and perioperative use, and recording of treatment outcomes so that therapeutic regimens can be evaluated and modified if necessary. In addition, there is a need for rigorous hygiene protocols to prevent survival and transfer of resistant bacteria in clinics and hospitals.

Keywords: Risk factors, antimicrobials, therapy, resistance, hygiene

Erkennung und Kontrolle von Risikofaktoren für Antibiotika Resistenz

Die Antibiotikaresistenz bei Organismen wie *Escherichia coli*, *Pseudomonas aeruginosa*, Methicillin resistenten *Staphylococcus aureus* (MRSA) und *S. pseudintermedius* ist zu einer ernsthaften Bedrohung in der Kleintiermedizin geworden. Es besteht deshalb zur Kontrolle und Verminderung dieses Problems ein dringender Bedarf für Massnahmen. Risikofaktoren für resistente Organismen bei Kleintieren widerspiegeln anscheinend jene in der Humanmedizin. Dazu gehören Kontakt mit Trägern oder infizierten Tieren, Spitalaufenthalt, invasive Eingriffe und Antibiotikatherapie. Zur Vermeidung solcher Risikofaktoren wird die Ausarbeitung von Richtlinien zum Antibiotikaeinsatz dringend empfohlen. Solche Richtlinien sollen den Einsatz von Antibiotika nur bei tatsächlichem Bedarf sowie die sinngemässe Antibiotikawahl in korrekter Dosis und Applikationsart und die Einschränkung prophylaktischer und perioperativer Anwendung regeln und sicherstellen. Dazu gehört auch die schriftliche Dokumentation des Behandlungserfolges, damit die Behandlungsprotokolle evaluiert und bei Bedarf modifiziert werden können. Schliesslich besteht zur Verhinderung des Überlebens und der Übertragung resistenter Bakterien in Kliniken und Spitälern auch ein Bedarf für rigorose Hygieneprotokolle.

Schlüsselwörter: Risikofaktoren, Antibiotika, Therapie, Resistenz, Hygiene

Introduction

The problem of increasing antimicrobial resistance is now clearly recognised throughout the world not only in human and veterinary medicine but also in related industries such as agriculture and aquaculture (Gould, 2009). This is a consequence of misuse of antimicrobial agents

leading to the selection of multiresistant bacteria. Although the issue of multiresistance was first highlighted and publicised in the human field and agricultural use of antimicrobial agents as growth promoters was incriminated as a contributor, the role of small animal practice is becoming more apparent (Guardabassi et al., 2004). Infections with strains of multi-resistant bacteria that are

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difficult to treat, such as *Escherichia coli* and *Pseudomonas aeruginosa* are now commonly encountered in dogs and cats, and methicillin-resistant *Staphylococcus aureus* (MRSA) infections are increasingly recognised. Outbreaks of infection with highly resistant strains of *Acinetobacter baumannii* are also being reported (Boerlin et al., 2001). Worryingly, the common staphylococcal species associated with infections in dogs and cats, *S. pseudintermedius* (formerly *S. intermedius*; Sasaki et al., 2007) has now developed increased capacity for multiresistance, including acquisition of the *mecA* gene, giving resistance to all beta-lactam antibiotics. This methicillin-resistant *S. pseudintermedius* (MRSP) now has a worldwide distribution with high prevalence in certain countries and rapid spread in Europe since first described in Germany (Loeffler et al., 2007).

The consequences of the rise in frequency of these multi-resistant bacteria in veterinary practice go beyond clinical difficulties experienced in treating cases successfully. These bacteria can cause zoonotic infections and act as a source of resistance genes for organisms associated with human infection. Alarm has been raised in the human field with the suggestion that certain agents should be withdrawn from veterinary use. Indeed, the English Chief Medical Officer has suggested that quinolones and cephalosporins should be banned from animal use (Donaldson, 2008). Veterinary clinicians need to respond to these threats by more careful use of antimicrobials. This review summarises risk factors which can lead to the development of antimicrobial resistance and identifies measures which can be taken to reduce their significance in small animal practice.

Antimicrobial resistance risk factors

Risk factor analysis in relation to antimicrobial resistance requires systematic identification and assessment of factors that influence the probability and consequences of its development. Although there is a lack of such systematic studies both in human medicine and small animal medicine (Lloyd, 2007; Carmeli, 2008), there is agreement on the principal bacterial pathogens causing concern. These include the pathogenic staphylococci and particularly *S. aureus*, *Enterococcus* spp., members of the Enterobacteriaceae, especially *E. coli*, and *Ps. aeruginosa*, organisms which share risk factors promoting nosocomial colonisation and infection (Sadfar and Maki, 2002). These bacteria can be carried by diseased and healthy individuals and may persist for long periods in hospitals and other healthcare institutions, and in domestic environments. The hospital or clinic environment is particularly suited to their survival and transmission; there is a continual supply of susceptible patients receiving antimicrobials to which the bacteria may be resistant and patients can thus be colonized or infected and cause further contamination.

Sadfar and Maki (2002) reviewed evidence of risk factors for such organisms in a total of 74 studies in human medicine and demonstrated that advanced age; underlying diseases and severity of illness; inter-institutional transfer of the patient; prolonged hospitalization; gastrointestinal surgery or transplantation; exposure to invasive devices, especially central venous catheters; and exposure both individually and to combinations of narrow and broad spectrum antimicrobials were involved. Such studies are lacking in the veterinary field but there is evidence from publications on MRSA infection which indicates that risk factors for dogs and cats mirror those in the human field and include carriage of MRSA, contact with carriers, duration of hospital admission and invasive procedures (Lloyd et al., 2007; Loeffler and Lloyd, 2010). In the USA, Black et al. (2009) showed that amongst 74 dogs in an intensive care unit, multidrug-resistant patterns occurred in 27% of all isolates and were more likely to occur in organisms cultured after 48 hours of hospitalisation. Veterinary staff members and owners are at increased risk of becoming carriers of such nosocomial organisms when they are in contact with infected animals (Loeffler and Lloyd, 2010). Indeed studies in animal hospitals have shown that staff MRSA carrier rates as high as 27% can occur (Baptiste et al., 2005).

Strategies for avoidance of risk factors

There is now an impetus in many countries to define measures which can be taken to use antimicrobial agents in animals in responsible ways and reduce levels of resistance (Prescott, 2008). Guidelines are being created at different levels of complexity varying from general concepts to specific recommendations for individual disease conditions and specific infective organisms. An example of the latter is the article on dealing with MRSA in small animal practice (Lloyd et al., 2007) commissioned by FECAVA (The Federation of European Companion Animal Veterinary Associations) which has established a Working Group on Hygiene and the Use of Antimicrobials in Veterinary Practice to bring together and co-ordinate recommendations within small animal practice in Europe (Lloyd et al., 2009).

In the UK, both the British Veterinary Association and the British Small Animal Veterinary Association have published recommendations on prudent use of antimicrobials on their websites (see BVA, 2009; BSAVA 2009). The BVA has produced a downloadable poster suitable for display which lists an 8 point plan (Tab. 1) providing actions and advice suitable for veterinary practice. The key points are a) development of protocols which ensure that antimicrobials are used only when necessary, b) selection of appropriate antimicrobials following sensitivity tests if possible, and compliance with correct dosage and administration, c) limitation of prophylactic and periop-

Table 1: Summary of the British Veterinary Association 8-Point Plan for Responsible Use of Antimicrobials (BVA, 2009).

The 8 Points	Details and Comments
1. Work with clients to avoid need for antimicrobials	Adopt integrated disease control programs. Isolate infected animals wherever possible.
2. Avoid inappropriate use	Restrict to ill or at risk animals. Advise clients on correct administration and the need for completion. Avoid underdosing.
3. Choose the right drug for the right bug	Identify likely target organisms and their susceptibility. Create practice-based protocols for common infections based on clinical judgement and up-to-date knowledge. Know how antimicrobials work and their pharmacodynamic properties. Use antimicrobials with a spectrum as narrow as possible.
4. Monitor antimicrobial sensitivity	While clinical diagnosis is often the initial basis of treatment, microbial sensitivity must be determined whenever possible so that modified treatment can be implemented if necessary.
5. Minimise prophylactics use	Only when animals are at risk and usage indicates reduced morbidity and or mortality. Regularly assess prophylactic use. Develop written protocols for when prophylactic medication is considered appropriate. Monitor antimicrobial sensitivity trends.
6. Minimise use perioperatively	Use only when necessary and supported by strict aseptic techniques is alongside written practice guidelines.
7. Record and justify deviations from protocols	Be able to justify your choice of antimicrobial and dose. Record treatment and outcome to help evaluate therapeutic regimens.
8. Report suspected failure to VMD*	This may be the first indication of resistance. Report through the Suspected Adverse Reaction Surveillance Scheme of the VMD.

*UK Veterinary Medicines Directorate

Table 2: Strategic use of antibacterials in animals (after Weese, 2006).

Drug Class	When Used	Drug Examples
First-line	Initial treatment of known or suspected bacterial infection in absence of susceptibility results. These drugs may commonly be used in human medicine but are usually considered less important for treating serious human (and animal) infections or raise less concern about development of resistance.	Penicillin, most cephalosporins, trimethoprim-sulphonamides, tetracyclines
Second-line	Used when culture and susceptibility testing, plus patient or infection factors, indicate that no first-line drugs are reasonable choices. Drugs in this class may be more important for treatment of serious human (and animal) infections or there may be particular concern about development of infection.	Fluoroquinolones, 3rd and later generation cephalosporins
Third-line	Used in serious, life-threatening infections, with support of culture and susceptibility results, when no first-line or second-line drugs are indicated.	Carbapenems
Restricted	Used only in life-threatening infections when culture and susceptibility testing indicates no other options.	Vancomycin

erative use, and d) maintenance of records of treatment outcomes so that therapeutic regimens can be evaluated and modified if necessary.

Selection of appropriate drugs and their correct use is, of course, of vital importance. When treatment must be instituted rapidly or there is a high level of confidence that the causative organism and its sensitivity can be predicted, appropriate “first line” drugs can be selected (Tab. 2). Otherwise, sensitivity tests should be carried out and “second line” drugs may be required. An important component of this process is client education conveying the dual message that both avoidance of non-essential antimicrobial administration and full compliance with dos-

age regimens of prescribed courses of antimicrobial drugs reduce the risk of increasing bacterial resistance. To this list must be added the need for rigorous hygiene so that as resistant organisms are encountered, in infected animals or in healthy carriers, transmission to other patients or humans is prevented. This applies not only to hospital facilities, where barrier nursing or isolation needs to be applied if there is a risk of carriage, but also in the clinic where protective clothing should be worn and replaced after handling animals known or suspected to carry resistant bacteria and where surfaces touched by patients should be disinfected before admission to the consulting room of the next animal.

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