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Multidrug-resistant opportunistic pathogens challenging veterinary infection control

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ABSTRACT

Although the problems associated with healthcare-associated infections (HAI) and the emergence of zoonotic and multidrug-resistant pathogens in companion animal (dogs, cats and horses) medicine have been well-known for decades, current progress with respect to practical implementation of infection control programs in veterinary clinics has been limited. Clinical outbreak events reported for methicillin-resistant *Staphylooccus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP), extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and multidrug-resistant (MDR) *Salmonella* Serovars indicate the necessity of infection control strategies for protecting animal patients at risk as well as veterinary personnel. The close bond between humans and their companion animals provides opportunities for exchange of microorganisms, including MDR pathogens. This particular aspect of the "One Health" idea requires more representative surveillance efforts and infection control strategies with respect to animal-species specific characters.

1. Introduction

Drug-resistant opportunistic pathogens are a major challenge in human and veterinary medicine and beyond (e.g. in food production) worldwide. The European Centre for Disease Prevention and Control (ECDC) estimates that approximately 4100,000 patients acquire a healthcare-associated infection (HAI) in the EU each year. The number of deaths occurring as a direct consequence of these infections is estimated to be at least 37,000 each year (http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/). In modern veterinary medicine HAI represent an urgent but largely unresolved issue, and infection control remains in its infancy (Weese, 2011). Multidrug-resistant (MDR) pathogens were long regarded as epidemic to the veterinary hospital environment (Sanchez et al., 2002), and pose a significant challenge due to the apparent spread of these pathogens within veterinary environments (Morley, 2013). Data about HAI in veterinary medicine remains limited, but the problem has gained increasing awareness (Ruple-Czerniak et al., 2013; Stull and Weese, 2015). Medical and technical progress has enhanced the length and quality of animal patients' lives, including animal patients receiving surgical implants, long-term hospitalization, as well as the geriatric, chronically ill or those with immune-deficiencies (Wieler et al., 2014). These patient groups are commonly regarded as "patients at risk" for HAI and likely among the first developing diseases. The most frequently reported HAI in companion animal medicine, in particular dogs, cats and horses, are surgical site infections (SSI), wound infections, central line-associated bloodstream infections and catheter-associated urinary tract infections (Stull and Weese, 2015; Weese, 2011; Wieler et al., 2011). One the other hand, ventilator-associated infections are comparably rare since long-term artificial respiration is not common in companion animal patients (Boerlin et al., 2001).

Opportunistic bacteria frequently associated with HAI in veterinary medicine are methicillin-resistant staphylococci (MRS), including *Staphylococcus aureus* (MRSA) and *Staphylococcus pseudintermedius* (MRSP) as well as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and *Acinetobacter baumannii* (Müller et al., 2014; Stull and Weese, 2015; Wieler et al., 2014).

Pathogens associated with HAI have been found to accumulate factors conferring drug resistance, suggesting an adaptation to the (veterinary) hospital environment (Walther et al., 2014b). As these pathogens are considered to be transmissible between humans and animals (Wieler et al., 2014), they pose a genuine threat not only to hospitalized animal patients at risk but also to the work place safety of veterinary personnel and animal owners (Walther et al., 2014a). The intention of this review is not to summarize

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reports published on HAI in veterinary medicine, but rather to elucidate important epidemiological aspects with respect to the companion animal patients, veterinary personnel and –environment. We discuss representatives of Gram-positive (MRS) and Gram–negative (ESBL-producing *E. coli*) pathogens causing HAI. In addition, long-term consequences for public health associated with the current state of infection control in companion animal medicine are discussed.

2. Healthcare-associated infections (HAI), outbreak situations and multidrug resistance (MDR): definitions

As early as 1925 it was recognized that the causative agents of epidemic diseases in animals are not the exclusive source of infectious diseases, such a *causa externa* requires additional, intrinsic predisposition or factors supporting disease (*e.g.* susceptibility and disposition of the individual) to enable an infection (Klimmer, 1925). This early statement describes the nature of the relationship between bacterial pathogens predominantly causing HAI and the human or animal patient at risk: opportunistic pathogens often residing asymptomatically amongst the natural host microbiota at mucosal surfaces and/or the epidermis but which are competent to cause mild to fulminate, severe and often life-threatening diseases whenever other circumstances permit invasion of inner body sites or pre-damaged tissues. In human medicine, the Centers for Disease Control and Prevention (CDC) define an HAI as "a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s). There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting. HAI may be caused by infectious agents from endogenous or exogenous sources. Endogenous sources are body sites, such as the skin, nose, mouth, gastrointestinal (GI) tract or vagina that are normally inhabited by microorganisms. Exogenous sources are those external to the patient, such as patient care personnel, visitors, patient care equipment, medical devices, or the health care environment" (Horan et al., 2008). Nosocomial infections may also be considered either endemic or epidemic. Endemic infections are most common. Epidemic infections occur during outbreaks, defined as an unusual increase above the baseline of a specific infection or infecting organism (WHO/CDS/CSR/EPH, 2002). The general principles of occurrence and transmission concerning HAI in veterinary medicine do not differ from these universal definitions (Walther et al., 2014b). In medical literature, many different definitions of multidrug resistance have been used. With respect to different drug-resistant pathogens often causing HAI, specific definitions have been proposed for classifying these bacteria (e.g. *S. aureus*, *Enterobacteriaceae* and *A. baumannii*) either as multidrug-resistant (MDR), extensively drug-resistant (XDR) or pandrug-resistant (PDR) according to their phenotypical resistance profile. Here, the term MDR will be used for the pathogens addressed, since MRSA are considered as MDR by definition and extended-spectrum beta-lactamase producing *E. coli* frequently exhibit resistance towards (at least) ≥ 1 agent in ≥ 3 antimicrobial classes (Magiorakos et al., 2012).

3. Nosocomial spread of zoonotic and drug-resistant pathogens in veterinary medicine: a new phenomenon?

An early report on the spread of drug-resistant staphylococci in a veterinary university clinic described transmission of resistant staphylococci between students, veterinary staff and animal patients (Live and Nichols, 1961). In that study, a striking percentage of senior veterinary students had been suffering from troublesome skin infections at the University of Pennsylvania (Philadelphia) between 1956 and 57. A screening study of the entire student body was performed and revealed the presence of an *S. aureus* strain described as "phage type 52/42B/81" in 50% of the collected nasal swabs and students' skin lesions. This particular strain was also found in cultures of nasal specimens from hospitalized canine patients, whereby the length of hospital stay (>7 days) of the dogs was associated with a rise in the colonization rate (Live and Nichols, 1961). In that outbreak, antibiotic resistance towards penicillin, streptomycin and tetracycline was observed. Later, this *S aureus* strain was denominated as "phage type 80/81" and was found to represent a predominant lineage in human hospitals in the late 1950s (DeLeo et al., 2011). A similar cluster of skin infections in workers who had contact with a neonatal foal colonized and infected with MRSA was reported in 2004 (Weese et al., 2006a). Such exemplary studies indicate that veterinary personnel are constantly at risk of acquiring diseases from animal patients, and further, that this phenomenon is not a recent development. These studies also highlight open questions concerning work place safety and infection control in companion animal medicine.

4. Multidrug-resistant (MDR) bacteria as a cause of nosocomial infections in veterinary medicine

4.1. Methicillin-resistant staphylococci: MRSA and MRSP

Methicillin-resistant Staphylococci (MRS) harbour an additional penicillin binding protein (PBP2a, encoded by either *mec*A or *mec*C), which confers resistance to beta-lactam antibiotics by allowing continued essential cross-linking steps in the process of cell wall biosynthesis despite inactivation of other PBPs by beta-lactams (Pinho et al., 2001). Acquisition of *mec*A or *mec*C results in a broad resistance towards antibiotic agents based on the beta-lactam ring, at least to those beta-lactams which are permitted for use in veterinary medicine. In companion animal medicine, MRSA (Cuny et al., 2006; Walther et al., 2009b) and MRSP (Gronthal et al., 2014; Ishihara et al., 2010; Sasaki et al., 2007) are a common cause of HAI worldwide. In the late 1990s, the first reports on MRSA outbreaks in veterinary settings were published. A study in Japan reported on the occurrence of a distinct MRSA strain isolated from equine cases of infection (n = 15; mainly metritis) with a putative epidemiological relationship (Shimizu et al., 1997). In 1999, 11 equine patients visiting Michigan State University's Veterinary Teaching hospital (USA) for various diagnostic and surgical procedures developed post-procedural MRSA infections (Seguin et al., 1999). In following years, a number of reports have addressed the animal hospital environment (Singh et al., 2013; Walther et al., 2006; Weese et al., 2004), colonized animal patients (see chapter below), human-to-animal transmissions (Rutland et al., 2009; Steinman et al., 2015; van Duijkeren et al., 2004), the pathogen's molecular characteristics (Vincze et al., 2012; Walther et al., 2009a), contamination of multiple-dose vials (Sabino and Weese, 2006) and risk factors for MRSA colonization- and infection (addressed below).

Recently, the general importance of MRSA as a significant cause of wound infections in companion animals was demonstrated by a nationwide German study. Based on isolates from 3479 canine, 1146 feline and 604 equine wound swabs received from 1170 veterinary practices and which were acquired over a sampling period of 17 month, *S. aureus* was identified in 201 (5.8%) of the canine, in 140 (12.2%) feline and 138 (22.8%) equine wound swabs. When one looks at the total MRSA proportion among all these *S. aureus* isolated from wounds, the numbers were striking: 62.7% for canine, 46.6% for feline and 41.3% for those of equine origin (Vincze et al., 2014). The occurrence of MRSA in dogs and cats is often discussed as the result of a "spill-over" from human medicine, since the genetic background and –composition of

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