Reservoirs of Antimicrobial Resistance in Pet Animals

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Increasing amounts of antimicrobials are used in pets, including substances used in human medicine (in particular, broad-spectrum agents such as clavulante-potentiated aminopenicillins, cephalosporins, and fluoroquinolones). There is evidence that resistance to antimicrobials is growing among bacteria causing infection in pets. These bacteria include *Staphylococcus intermedius* and *Escherichia coli*, as well as other organisms of clinical importance in humans, including methicillin-resistant *Staphylococcus aureus*. Transmission of such organisms, particularly pathogenic staphylococci, occurs between pets, owners, and veterinary staff, and pets can act as reservoirs of such bacteria; this may have an impact on the use of antimicrobials in human medicine. There is a need to generate data regarding both the levels of carriage of such bacteria in pets and the risk factors associated with the transfer of the bacteria to humans who have contact with infected pets, as well as to improve hygiene measures in veterinary practice.

For some time, it has been clear that the use of antimicrobial agents in farming, either as growth promoters or for the treatment of bacterial infections, can result in the emergence of antimicrobial-resistant microbes and that this emergence can cause difficulties in the selection of therapeutic agents when these organisms cause disease in humans. However, antimicrobial-resistant human pathogens are unrelated to animal sources in the great majority of cases. A recent review suggested that <4% of antimicrobial-resistance problems in humans could be associated with animal sources and that this resistance is largely related to zoonotic organisms [1, 2]. The possible effects of antimicrobial use on the emergence of antimicrobial-resistant bacteria in pets have been much less studied. In agriculture, systems for recording levels of antimicrobial resistance and studies of indicator bacteria are quite well developed and are becoming increasingly sophisticated; however, the emergence of antimicrobial resistance in pets is poorly understood, and methods for surveillance are only beginning to be established in a few countries [3, 4]. Until recently, the risks posed by the use of antimicrobials in the treatment of infections in pets have been assumed to be quite low. However, recent publications indicate that much closer attention needs to be given to this subject [5, 6]. The present article will examine the amounts of antimicrobials used in veterinary practice, summarize the current status of antimicrobial resistance among zoonotic pathogens of pets, and examine the ability of pet animals to act as reservoirs of such organisms, focusing particularly on the development of resistance among pathogenic staphylococci in Europe.

**VETERINARY ANTIMICROBIAL USE IN EUROPE**

Data on sales of veterinary antimicrobials in the different European countries are published annually and enable assessment of the total volumes of the different types of antimicrobial agents. However, the quantities of antimicrobial agents used in the different species of animals are seldom available. The Scandinavian countries, Denmark, Norway, and Sweden, are exceptional in that they are now supplying more accurate data in their annual reports [7–9]. In Denmark, antimicrobial use in pets is being inferred from pharmacy sales of veterinary drugs. This information provides a good indicator of antimicrobial use but may still omit drugs administered directly by veterinary surgeons in their practice.
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practices, as well as the use in pets of drugs licensed for use in humans or farm animals. In other countries, attempts are also being made to record drug use in pets more accurately, but data are still fragmentary; the situation in the United States and plans for improved data collection are recorded by McEwan and Fedorka-Cray [4].

An additional difficulty in assessing veterinary antimicrobial use is that most usage data are expressed as kilograms of the active antimicrobial used in each category of animals, and this type of data expression does not allow for evaluation of the usage trends within categories of animals and the resistance selection pressure for different antimicrobial classes. Furthermore, differences in the potency of the drug, the rate of drug absorption, the weight of the animal, and the population size for each animal species are not taken into consideration.

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) now publishes data on antimicrobial use expressed as “animal daily doses” (ADDs; the daily dose given to animals of a defined weight in each age group), which enable valid comparisons of the selection pressure among species to be made. Figure 1, which is derived from data presented by Guardabassi et al. [6], illustrates this situation by use of data from DANMAP 2002 [10] that combine information on therapeutic use and feed additive use. Figure 1 shows that, although poultry represent the largest animal population, the greatest weight of antimicrobials and the highest number of ADDs, by far, are consumed by pigs. Although the pet dog and cat population is only two-thirds the size of the cattle population, it consumes 6 times as many ADDs; however, this represents only approximately one-fifth of the weight of drugs used in cattle.

Use of antimicrobials in pets is increasing in Europe. In 2001, Odensvik et al. [11] presented data showing that use in companion animals, expressed as a percentage of antimicrobials used by animals, had increased in Sweden and Norway from 3% in 1980 to 7% and 8%, respectively, in 1998. The equivalent percentage in the United Kingdom in 2003 was 7% [12]. Antimicrobial use in Denmark in 2003 was reviewed by Heuer et al. [13], who concluded that, for some antimicrobials, consumption by companion animals was substantial, compared with consumption by food animals; 1.2 million dogs and cats consumed 45% and 55%, respectively, of the total weights of fluoroquinolones and cephalosporins used in 2003 (table 1). Use of cephalosporins in Denmark between 2001 and 2004 increased by 70%, from 302 to 513 kg, and this increase was mainly due to increased cephalosporin use in pet animals [7]. Heuer et al. [13] suggested that a similar situation exists in other industrialized countries, and they warned that such use may create undesirable antimicrobial resistance that could spread to humans who are in close contact with their pets.

RESISTANCE TO ANTIMICROBIALS AMONG BACTERIA INFECTING PETS

In 2004, the issues associated with increasing resistance among bacteria infecting pets were raised by Guardabassi et al. [6], who highlighted increases in resistance reported in North America and Europe during the 1990s. The authors pointed out that nosocomial infections in hospitalized dogs, including the appearance of multidrug-resistant isolates of Acinetobacter baumannii, Escherichia coli, and Salmonella enterica serovars, were becoming more widely recognized. This was a problem especially in intensive care units, and the authors suggested that this might reflect abundant use of broad-spectrum antimicrobials in such units.

Increasing resistance among staphylococci is also being rec-
of antimicrobial use in and population size of pet animals and food animals in Denmark in 2003.

<table>
<thead>
<tr>
<th>Animal category</th>
<th>Populationa</th>
<th>Cephalosporins, kg</th>
<th>Fluoroquinolones, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>0.55</td>
<td>254</td>
<td>24</td>
</tr>
<tr>
<td>Cats</td>
<td>0.65</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pigs</td>
<td>24.00</td>
<td>207</td>
<td>29</td>
</tr>
<tr>
<td>Chickens</td>
<td>130.00</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cattle</td>
<td>1,200</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** Data derived from Heuer et al. [13].

In millions.

Table 1. Quantity of antimicrobial use in and population size of pet animals and food animals in Denmark in 2003.

ognized in pets. In 2002, Holm et al. [14] compared resistance among staphyloccal isolates associated with cases of canine pyoderma in Sweden. They compared the isolates recovered from first infections with those recovered from recurrent infections and demonstrated co-resistance to macrolides and lincomycins as well as to tetracyclines and streptomycin. No resistance to penicillinase-stable β-lactam antimicrobials was detected, but comparison with earlier studies showed a marked increase in resistance among canine staphylococci over the past 5 years.

Further evidence of increasing resistance—more specifically, among *Staphylococcus intermedius*, which is the principal cause of canine pyoderma—is available from different countries in Europe. Pellerin et al. [15] demonstrated that the prevalence of multidrug-resistant strains increased from 11% to 28% between 1986–1987 and 1995–1996 in France. Wissing et al. [16] showed in *S. intermedius* significant increases in the occurrence of resistance to penicillin, neomycin, sulfonamides, potentiated sulfonamides, and erythromycin between 1980 and 1999–2000 in Switzerland. In Norway, a comparison of resistance to fusidic acid and tetracycline demonstrated levels of resistance of 59% and 53% in 2002 [17], compared with levels of 1% and 20% in 1986–1987 [18], respectively. Resistance to fluoroquinolones, which were licensed for veterinary use in Europe during the mid-1990s, is also appearing. Lloyd et al. [19] reported resistance in 8 (0.9%) of 858 *S. intermedius* isolates examined between 1996 and 1998; however, in Sweden, much higher levels of resistance, ranging from 8% to 12%, were reported between 1992 and 2002 [20]. Until recently, resistance to β-lactam-resistant antimicrobials has been very rare in *S. intermedius*. Lloyd et al. [21] examined 2296 isolates of presumptive *S. intermedius* recovered from cases of canine pyoderma occurring in the United Kingdom during 1987 to 1998. They found no resistance to co-amoxiclav, methicillin, and oxacillin and found only a single isolate resistant to cefalexin. However, *S. intermedius* lacking susceptibility to β-lactamase-resistant antimicrobials is now being recognized in both infected dogs and cats in Europe (A. Loeffler, M. Linek, J. M. L. Sung, R. Weiss, M. Winkler, and D.H.L., unpublished data) and the United States [22]. Methicillin-resistant *S. intermedius* has also been reported among isolates recovered from normal cats in Brazil; it was detected in 31% of isolates recovered from skin and in 20% of isolates recovered from the oral cavity [23, 24].

Methicillin resistance has not been demonstrated among pathogenic staphyloccoci isolated from the skin or mucosae of normal cats in Europe. Indeed, *S. intermedius* isolated from pets with no history of skin disease commonly demonstrates resistance to few or no antimicrobials. However, there is evidence that staphyloccoci in cats are able to acquire resistance from environmental sources. Patel et al. [25] recovered isolates from normal feral cats and both normal pet cats and pet cats with lesions in London, England. They recovered 123 staphyloccal isolates from 19 pet cats (10 normal cats and 9 cats with lesions) and 64 such isolates from 10 feral cats. There were significantly more resistant isolates recovered from the feral cats than from the pet cats (figure 2) (P < .01). The authors suggested that the higher frequency of resistance among the isolates recovered from feral cats was associated with environmental exposure to antimicrobial contamination within their city environment, possibly originating from hospitals and nursing homes.

Figure 2. Percentages of resistant and moderately resistant staphylococcal isolates recovered from pet and feral cats in London. The diameters of the pie charts denote the numbers of isolates. More resistant isolates were obtained from 10 feral cats than from 19 pet cats (P < .01). Adapted from Patel et al. [25].
RISKS ASSOCIATED WITH THE TRANSFER OF RESISTANT ORGANISMS BETWEEN PETS AND THEIR OWNERS OR VETERINARY STAFF

In 1994, Harvey et al. [26] showed that 5 of 29 owners of dogs with atopy (a common predisposing cause of canine pyoderma) and attending veterinary staff who were treating the dogs became colonized by S. intermedia; the investigators suggested that transfer of S. intermedia from dog to human is probably not uncommon. In 2004, Guardabassi et al. [27] demonstrated that carriage of S. intermedia is a frequent occurrence among owners of dogs with severe (deep) pyoderma; 7 of 13 owners of dogs with deep pyoderma were shown to be carriers, whereas only 1 of 13 individuals who did not own a dog carried this organism. Strains isolated from 6 of the dog owners were shown by PFGE to be identical to the strains associated with the infections in their dogs. Dogs with deep pyoderma require prolonged and often repeated therapy with antimicrobials and commonly carry multidrug-resistant S. intermedia. In this study, multidrug-resistant strains that were resistant to up to 5 antimicrobial drugs were present in both the dogs and their owners.

S. intermedia is seldom responsible for infection in humans, who are more susceptible to infection with S. aureus. However, since 1999, in both Europe and the United States, the occurrence in dogs of staphylococcal infection caused by methicillin-resistant S. aureus (MRSA) has been recognized [28], and this type of infection can pose a much greater risk to owners. In 2003, Manian [29] described recurrent infection with mupirocin-resistant MRSA in a human patient with diabetes and in his wife. These infections only resolved when carriage of this strain in the dog was identified and eliminated. Although still uncommon, MRSA infection in both dogs and cats is now becoming a problem, particularly in North America and the United Kingdom [22, 30, 31], and there is increasing evidence that transfer between owners or veterinary staff and the pets with which they come in contact can readily occur. In a study performed in 2004, Loeffler et al. [32] demonstrated that 18% of 78 staff members in a small-animal veterinary referral hospital were carriers of MRSA; 82% of the isolates recovered were identical or closely related to EMRSA-15, the strain responsible for the great majority of human nosocomial infections in the United Kingdom, when compared by PFGE. In studies in Ireland reported in 2005, O’Mahoney et al. [33] have also shown that isolates recovered from small animals and from the attending veterinary personnel were indistinguishable from one another when compared by PFGE analysis. However, they demonstrated that, although isolates of MRSA recovered from horses and attending veterinary personnel in Ireland were also indistinguishable by PFGE, they differed from all of the non-equine isolates. These studies indicate that, in both Ireland and the United Kingdom, pets have acquired MRSA infections from human sources. The source of the Irish equine MRSA remains obscure.

It is apparent that both pets and horses can pose a risk of infection to their owners and to attending veterinary personnel. Human carriers of MRSA can also pose a risk of infection to susceptible animals in their care, particularly if they are being treated with antimicrobials to which the MRSA is resistant. Studies of the risk factors involved in the transfer of MRSA between humans and pets are in progress, and preliminary results were presented by Loeffler [34] at the 1st International Conference on MRSA in Animals in June 2006; Loeffler showed that 19 (17%) of 114 veterinary staff and 11% of pet owners who were in contact with MRSA-infected pets, drawn from practices in many parts of the United Kingdom, were MRSA carriers. Analysis showed a significant association between MRSA-infected dogs and the carrier status of attending veterinary staff (P<.002) and of owners (P<.05) and the presence in the dog owner’s home of someone working in the UK National Health Service (P<.01).

The problem of MRSA in pets and horses (i.e., companion animals) is becoming recognized, and measures are already being taken to reduce the risks of transfer of MRSA in veterinary practices in the United Kingdom, as well as to investigate the factors responsible for transfer. Advice on preventative measures is now becoming available from various sources, notably the British Small Animal Veterinary Association in the United Kingdom [35].

CONCLUSIONS

Antimicrobial resistance is increasing among organisms causing infections in pets. This is because of selection pressure associated with the use of antimicrobial agents both in veterinary medicine and in human medicine. Pets are able to acquire and exchange multidrug-resistant pathogens with humans, and this problem has been particularly recognized with respect to MRSA. Currently, infections with MRSA and multidrug-resistant S. intermedius are relatively uncommon in pets, but veterinary personnel urgently need to address the factors responsible for transfer of and colonization with such organisms among pets, as well as the risks posed to the pet owners and attending veterinary staff. This situation should act as a wake-up call to veterinary surgeons and others individuals involved in animal health. New and effective strategies need to be developed to combat this problem and prevent it from becoming endemic among companion animals.

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References


