Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies

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This meeting focused on infections in humans and animals due to methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum β-lactamase (ESBL)-producing bacteria and Clostridium difficile, and their corresponding treatments. MRSA is predominantly a human pathogen, and molecular typing has revealed that certain clones have spread widely both between humans and from humans to animals. ESBL-producing bacteria, particularly those that express the CTX-M β-lactamases, have been disseminated worldwide. Whilst such strains are usually isolated from humans, some animal isolates also produce CTX-M enzymes. In humans, one clone of CTX-M-producing Escherichia coli, sequence type (ST)131, has been particularly successful. C. difficile, often ribotype 027, commonly colonizes the hospital environment and causes serious infections in humans. In animals, ribotype 078 is more often found, and is an important cause of diarrhoea in piglets. There is a concern that the numbers of MRSA or other antimicrobial-resistant bacteria might increase further when human isolates become established in animals, as this can amplify the numbers of such bacteria by dissemination within animal groups with subsequent spread back to humans. Certain antimicrobials have been implicated in the selection of MRSA, ESBL-producing bacteria and predisposition to infection by C. difficile. Guidelines for treatment and prevention of infections by MRSA, ESBL-producing bacteria and C. difficile were discussed and evidence-based policies were recommended for both humans and animals.

Methicillin-resistant Staphylococcus aureus

Methicillin-resistant Staphylococcus aureus in man

Peter M. Hawkey

Methicillin-resistant Staphylococcus aureus (MRSA) is carried by approximately one-third of the human population and another third are occasional carriers. Data from the European Antibiotic Resistance Surveillance System (EARSS) have shown that the incidence of bacteraemia caused by MRSA in hospitals in Europe has increased in many countries between 2001 and 2006 although the incidence in Scandinavia remains low when compared with the UK, France, Spain and Italy.1

Strains of MRSA arose from methicillin-susceptible S. aureus (MSSA) by the acquisition of the mecA gene which encodes an additional penicillin-binding protein (PBP2’). This PBP has a low affinity for isoxazolyl penicillins, such as methicillin, cloxacillin and oxacillin, and the cell is thus able to maintain peptidoglycan synthesis in the presence of what would otherwise be lethal β-lactam concentrations. The mecA gene is located on a genetically mobile chromosomal determinant termed staphylococcal cassette chromosome mec (SCCmec).

The earliest recorded MRSA was identified in England shortly after the introduction of methicillin.2 Hospital-acquired strains of MRSA (HA-MRSA) increased in prevalence over the next 45 years throughout the world, particularly in the last two decades. It was originally suggested that all the clones of MRSA had derived from a single introduction of SCCmec into S. aureus with subsequent evolution of the host strains of S. aureus.3 However, there is now irrefutable evidence that SCCmec has been introduced into a number of different lineages of S. aureus (multicline theory).4 The development of multilocus sequence typing (MLST) is the technique that has given this insight. Seven genes responsible for essential cellular processes...
are sequenced, and both synonymous and non-synonymous changes in DNA bases are scored. Because there is no direct selection of these genes, the accumulation of single nucleotide polymorphisms (SNPs) is directly correlated with the evolutionary pathway of the clone (defined as isolates with identical sequence type (ST) and SCCmec type). The original MRSA (‘Jevon strain’) was derived from a successful ST8 clone of MSSA, which caused disease worldwide, by acquisition of SCCmec from another bacterial species together with an SNP in the yqiL gene, which gave rise to ST250. Further acquisition of SNPs gave rise to ST247 MRSA (the Iberian clone). The Brazilian–Hungarian clone (ST239), which arose by the recombination of 537 kb of DNA from the successful ST30 MSSA into ST8 MRSA, is widely distributed across the world, particularly the Far East, and was recently shown to be the dominant clone in the Indian subcontinent. The evolutionary relationships of the major MRSA clones have been reviewed and the evolution of ST8 derivatives is summarized in Figure 1.

In UK hospitals, data from the former UK Public Health Laboratory Service [now the Health Protection Agency (HPA)] showed that the incidence of the epidemic MRSA (EMRSA) strain EMRSA-3 (ST5) consistently remained fairly low between 1993 and 1996. In contrast, the incidence of EMRSA-15 (ST22) and EMRSA-16 (ST36) increased dramatically over this period (Figure 2). We still have little understanding of the factors, intrinsic to both the MRSA strain and the environment (antibiotic selection pressures, routes of transmission, etc.), that allow some clones to be so successful.

Resistance to a number of antibacterial agents among EMRSA is widespread, with isolates of EMRSA-15 and EMRSA-16 in the UK being frequently resistant to ciprofloxacin and erythromycin. Similarly, in a survey of MRSA isolates from 112 Belgian hospitals, among 511 isolates comprising nine clones (including some that produced Panton–Valentine leucocidin (PVL)), 97% were resistant to ciprofloxacin, 60% to erythromycin, 45% to tobramycin and 5% to gentamicin. All were susceptible to tigecycline, daptomycin, ceftobiprole and linezolid, suggesting that, as yet, resistance to these novel agents is not common.

It was thought that when colonized patients are discharged, MRSA might transmit from the hospital setting to the community. However, data from several countries, particularly the USA, have shown the independent emergence of strains of MRSA in the community. There are differences between these community-associated (CA-MRSA) and HA-MRSA strains and the infections they tend to cause. In particular, the age group affected is different, with CA-MRSA commonly (but not exclusively) infecting children with no underlying classical risk factors. CA-MRSA predominantly cause skin and soft tissue infections, which are often clinically severe, although CA-MRSA are still susceptible to most classes of antibacterials other than β-lactams. CA-MRSA strains are genetically unrelated to HA-MRSA and have diverse lineages as they are frequently enriched with genes encoding SCCmec IV, PVL and other exotoxins. In Europe, the predominant strains are ST80, ST8 and ST30, while in the USA they are ST8, ST5 and ST59.

Although the vanA gene, which confers high-level transferable vancomycin resistance, has been acquired by S. aureus from Enterococcus spp., this is still a rare occurrence (<10 documented occasions) but is a worrying prospect, as infection with vancomycin-resistant strains has a poor outcome when treated with vancomycin.

There are a number of important strategies for controlling the spread of MRSA in hospitals. The early identification of carriers is essential, and has recently been shown to reduce transmission when combined with decolonization followed by the isolation or cohorting/labeling of patients. However, a major problem in many hospitals is a lack of available side-rooms to enable the isolation of patients. Transmission can also be interrupted by

![Figure 1. Molecular evolution pathway of S. aureus ST8 derivatives determined by MLST (adapted from Deurenberg et al. 2008). SNP, single nucleotide polymorphism in a specified gene.](http://jac.oxfordjournals.org)

![Figure 2. The occurrence of EMRSA-3, -15 and -16 among isolates submitted to the national Reference Laboratory by hospitals in England and Wales, 1993–1997.](http://jac.oxfordjournals.org)
hand washing and environmental cleaning. Appropriate treatment needs to be initiated promptly and vancomycin is often the drug of choice. The use of certain antibacterials to which MRSA are commonly resistant, such as third-generation cephalosporins and quinolones, should be restricted. Colonized patients can be decolonized by the use of triclosan baths and mupirocin nasal cream. Surveillance is essential, optimally with molecular typing, and recent data from the HPA have shown encouraging results, with a gradual decline in cases of bacteraemia due to MRSA in the UK (Figure 3).

Future challenges include whether the reduction of HA-MRSA can be maintained and whether the occurrence of CA-MRSA in the UK increases. Unknowns include how common and how important is low-level vancomycin resistance, will high-level vancomycin resistance occur and, if so, will it have the ability to spread?

MRSA in animals

Mireille W. Wulf

There are differences in the occurrence of MRSA between companion animals (pets and horses) and livestock (mostly pigs, poultry, cattle and sheep). Up to 2006, MRSA was rare in pets but is now increasing. Carriage in healthy dogs is still rare but it can be found in 2% of those with skin conditions. There are occasional outbreaks seen in some animal hospitals, including those treating horses, with the majority of these infections appearing to be caused by the same strains that are seen in humans.

MRSA infections are more common in livestock but the strains are often different from those found in humans. The occurrence in dairy cattle is still low in various countries and is usually associated with mastitis. There is a limited overlap with humans, and transmission to humans is rare. Dairy cows have been treated with penicillins for decades, predominantly for mastitis, but the incidence of resistance nonetheless remains low.

The situation with regard to MRSA carriage in veal calves is different from that in adult milking cows, with a far higher incidence of MRSA. A study carried out on 102 farms in the Netherlands found that 28% of calves carried MRSA and 88% of the farms sampled had calves with MRSA. The farmers and their family members were also sampled, and 33% of the farmers carried MRSA but only 8% of family members. The isolates from both animals and humans belonged to the clonal complex ST398.11,12

A high incidence of MRSA is found in pigs in the Netherlands, Denmark, Belgium and Canada (up to 40%) and in their handlers. In a slaughterhouse study in the Netherlands 80% of herds and 39% of the pigs carried strain ST398 MRSA.13 The isolates were resistant to oxacillin but were not PVL producers. Dust samples from 50% of the farms contained the same strain and 30% of the farm workers were carriers. There was an association with use of antibiotics. In contrast, the incidence of MRSA in chickens appears to be lower, with a study in Belgium finding only 5/39 chickens from broiler farms carrying MRSA and 10/98 S. aureus being MRSA ST398.14 ST398 has also been isolated from manure and broiler farms in the Netherlands.15

The most common MRSA isolates from animals are ST398, the main reservoirs being pigs and veal calves. This type, which is also isolated from chickens and horses, can be transferred to humans. Most isolates are multidrug resistant, and some PVL-positive isolates are found. MRSA is rarely found in meat and then only in low quantities; the source is thought to be the butcher/meat handler rather than animals.

The routine use of antibiotics, which disrupts the normal bowel flora in piglets, could be a selective pressure and thus a contributory factor in the occurrence of ST398 in this species. It is possible that a biovar acquired the mecA gene and this thrives in animals. There is some evidence that organisms can be disseminated from contaminated dust, as Gibbs et al.16 detected resistant S. aureus inside and downwind of partially open swine confinement facilities, at levels of $10^6$ cfu/m$^3$. This would be regarded as a potential human health hazard and the recommendation is that swine facilities should be placed at least 200 m from residential areas to avoid detrimental effects on human health.17

Guidance for the treatment of MRSA in man

Dilip Nathwani

The optimal antibacterial treatment of a range of MRSA infections continues to be the subject of numerous reviews and guidelines, some of which address specific sites of infection.18–20 The key challenges when tackling this particular disease area and pathogen are the complex array of diseases caused by MRSA, the variation in epidemiology and disease burden, the emergence of different strains (e.g. PVL-producing CA-MRSA) and the difficulty in establishing a rapid microbiological diagnosis combined with relatively blunt clinical instruments for predicting the likely causative pathogen to guide empirical therapy. Therefore, the decision as to whether to treat, how and with what agent, is complex, and there are a number of factors that must be considered (Figure 4).
Factors to consider before treating MRSA infections.

A strong evidence base for how best to treat serious MRSA infections in humans is generally lacking since different methodological approaches and grading systems have been used, leading to conflicting conclusions. The optimal therapy for uncomplicated or non-serious infections is usually considered to be oral therapy with a range of ‘old’ well-established antibiotics. Some are used alone or in combination with rifampicin. On the other hand, serious infections have been managed traditionally by glycopeptides such as parenteral vancomycin, which has been a well-accepted standard of care for some time. However, whether we can still confidently rely on this agent for treating severe MRSA infections such as healthcare-associated pneumonia (particularly ventilator-associated pneumonia) or complicated bacteraemia has been subject to intense study and debate over the last 10 years. For example, a consensus expert panel in 2008 tackled the question of whether vancomycin was obsolete in the treatment of MRSA infection and systematically reviewed the evidence to support this. Among a panel of experts who reviewed the evidence (n=11), 72% tended to agree (albeit with reservations) with the statement whereas among a group of 744 members of the Infectious Disease Society of America, 83% disagreed with this statement either totally or with some reservations. This clearly reflects a significant gap between how evidence is perceived by a group of (primarily US) experts and what ‘non-expert’ clinicians perceive and do in their (predominantly North American) practice.

UK Guidelines published in 2006 suggested that treatment with flucloxacillin should remain the first-line empiric treatment if the incidence of MRSA locally is low. However, depending on the severity of the infection and if MRSA is suspected based on local epidemiology and risk factors, then the use of an agent active against MRSA (vancomycin or linezolid) at the onset of infection was recommended. No distinction between the two agents was made because of a lack of unequivocal evidence of superiority of linezolid over vancomycin. In 2008 these guidelines were updated for a range of infections due to MRSA, including bone and joint, endovascular, respiratory, urinary tract, and skin and soft tissue. In spite of this, 3 years on it is still acknowledged that there is a poor evidence base for treating many infections, especially those involving bones and joints, and that the evidence for clear and unequivocal superior clinical effectiveness of newer agents such as linezolid, daptomycin and tigecycline was absent. Nevertheless, recommendations were made, primarily based on opinion and experience or evidence of equivalence, as to when certain of the new agents may be appropriate. Some older agents are also recommended but, compared with the 2006 guidance, there is a move away from the use of combination therapy.

In the absence of new clinical trial data showing clear evidence of clinical superiority, perhaps a more global assessment of the true value and consequences of new and traditional therapies is required. One such approach, increasingly recognized by health technology appraisal groups, guideline groups and quality improvement organizations, is termed GRADE. This method of providing evidence-based recommendations for clinical practice uses four domains related to the therapy or intervention (Figure 5).

For the treatment of MRSA infections, future guidelines could perhaps consider using this broad risk–benefit approach to decision making and guidance. This process may also inform the development of high-level evidence-based standards of care. Finally, on a positive note, whilst MRSA infections in humans continue to represent a significant burden, a combination of good infection control, antimicrobial stewardship and appropriate use of a range of established and new agents, should give us good reason to be optimistic about reducing its public health threat as we head towards the end of the first decade of the new millennium.

**Figure 4.** Factors to consider before treating MRSA infections.

- Is an antibacterial needed? Is it infection or colonization?
- Can simple surgical debridement be used? Is topical decolonization required?
- What is the site and severity of infection and is there a positive culture?
- If there is no positive culture, can the likelihood of MRSA be predicted?
- When are rapid diagnostic tests likely to be available and will they be helpful?
- Should a differentiation be made between community- or hospital-acquired MRSA and how likely is the presence of a PVL strain?
- What is the effectiveness of vancomycin declining and if so should the alternative new therapies be used and in which clinical settings?
- How should we measure the impact of treatment for a variety of clinical, microbiological, economic, patient-related outcomes and ecological impact (for example resistance and *C.* difficile-associated diarrhoea)?

**Figure 5.** Evidence-based recommendations for therapy or intervention.

- Balance between desirable and undesirable effects
- Quality of evidence
- Values and preferences
- Cost (resource allocation)
Points raised in discussion

- One difficulty in controlling MRSA spread in UK hospitals is that hospital bed occupancy is frequently high, thereby necessitating the strategy of isolating carriers and infected cases
- Transfer of MRSA from animals to man is currently not a major problem in the UK, although the presence of ST398 strains in pigs and calves is a potential threat, especially since such strains are frequently multiresistant. These strains do not seem to transfer between humans as readily as many epidemic strains, but they may nevertheless prove to be a reservoir of CA-MRSA
- Although infections and carriage in pets is low, the strains are often the same as those commonly found in humans, namely EMRSA-15 and EMRSA-16
- The knowledge base for the efficacy of treating MRSA infection is weak and stresses the need for larger clinical trials and better definition of key risk factors. (The point was also made that better support systems were needed and that most surveillance studies were inadequate.)

Extended-spectrum β-lactamases (ESBLs)

Extended-spectrum β-lactamases in man

Neil Woodford

Extended-spectrum β-lactamases (ESBLs) are enzymes produced by Gram-negative bacteria that inactivate oxyimino cephalosporins, conferring resistance to them. Bacteria producing ESBLs are resistant to cephalosporins such as cefuroxime, cefotaxime, ceftazidime and ceftriaxone, and, through genetically linked resistance mechanisms, they are often resistant to other antibacterials including quinolones and aminoglycosides. Most ESBL-producing organisms are thus multidrug resistant and many are only susceptible to carbapenems, along with little-used agents such as fosfomycin.

Since the start of the 21st century there has been an explosive worldwide increase in the prevalence of organisms producing ESBLs. Currently, in England, Wales and Northern Ireland, ~20000 cases of bacteraemia caused by Escherichia coli are reported per annum, of which ~12% were resistant to cefotaxime and/or ceftazidime in 2007 (Figure 6). Of these ESBL-producing isolates, most are from urinary tract infections (UTIs). To a large extent, this reflects a massive clonal spread of E. coli producing CTX-M-15 ESBL in the UK; of 1500 isolates of E. coli producing CTX-M ESBLs examined in the HPA’s Antibiotic Resistance Monitoring and Reference Laboratory, 91% contained alleles encoding group 1 enzymes (mainly CTX-M-15), with many isolates belonging to the international O25:H4-ST131 clone. The remaining isolates were mostly diverse, 8.5% producing Group 9 CTX-M enzymes, with fewer producing Group 2 enzymes and only one isolate producing a Group 8 enzyme. The O25:H4-ST131 clone producing CTX-M-15 ESBL has spread across many countries, including France, Canada, Korea, Lebanon, Portugal, Spain, Switzerland and Turkey as well as the UK. Isolates of this clone have diverse PFGE profiles, but share ~60% banding pattern similarity; they also have variable virulence factors.

The genes that encode CTX-M ESBLs escaped from the chromosomes of Klebsiella spp. However, even highly related CTX-M ESBLs may have distinct origins. For example, the genes encoding CTX-M-3 and CTX-M-15 differ by a single nucleotide, but are often found on distinct plasmid types with different flanking sequences. These clearly represent separate acquisitions from Klebsiella spp., rather than diversification by mutation after acquisition by E. coli.

Prolonged faecal carriage of ST131 clonal variants has been noted and provides the potential for persistence in community settings. Household members often share E. coli clones, which can persist. In a 3 year study of one household, 14 clones of E. coli were isolated, six of which were shared by more than one person. Four of the clones persisted in the household for 1–3 years. It is not clear whether intestinal clonal complexity is a relatively stable trait or if it varies over time, perhaps influenced by age, sex or diet. It is also not clear whether poor intestinal clonal diversity (and therefore faecal abundance of particular E. coli clones) might predict the risk of UTI.

ESBLs in animals

Chris J. Teale

Previous studies have shown that the emergence of antibacterial resistance in animals can follow a general pattern, illustrated by the use of the aminoglycosidic growth promoter nourseothricin, which was used in farm animals in the former East Germany in the 1980s. No equivalent antimicrobials were used in humans over the same period. Resistance to nourseothricin emerged and was mediated by plasmids containing a transposon which encoded the enzyme streptothricin acetylation transferase. Initially, resistance was detected in E. coli from pigs in the second year after introduction of nourseothricin, but subsequently was also detected in E. coli isolated from pig farmers. During subsequent years nourseothricin resistance was detected in E. coli isolated from humans in the wider community and then finally in Salmonella and Shigella isolates from humans. These observations strongly support the premise that resistance genes present in the commensal flora of animals can spread to bacteria which can colonize or infect humans.

E. coli carrying an ESBL were first detected in livestock in the UK in diarrhoeic calves on a Welsh dairy farm in 2004. The ESBL present was CTX-M-15 and this was located on a highly promiscuous IncK plasmid which could be detected in a large number of different strains of E. coli. Some of these strains persisted between repeat visits to the farm and were also found in adult cows.

The second case of ESBL-positive E. coli in animals in the UK also involved calves, though in this case the ESBL involved was CTX-M-15. The gene encoding CTX-M-15 was co-located on the same plasmid as the resistance genes for OXA-1 and AAC6'-Ib-cr. A plasmid bearing the same three resistance genes with the same AAC6'-Ib-cr mutation had been previously described in the literature from human sources. The most plausible explanation for these findings is that the plasmid has been transmitted to cattle either directly or indirectly from a human source, because it would seem highly unlikely for such a similar plasmid to evolve independently in the gut flora of cattle.

These findings reinforced the hypothesis that ESBL-producing E. coli can pass into the environment from humans and that animals both on farms and in the wild may subsequently be exposed to them. Recent work from Portugal has shown that such passage into the environment does occur. Epidemiological investigations on farms on which ESBL-producing E. coli have been detected have shown that cattle on some farms have a history of possible exposure to potential human sources of ESBL-positive E. coli including water courses, leaking drains or pipes, recently hospitalized farm staff and sewage sludge. Flooding events may also provide a route for the wider environmental dissemination of bacteria of human origin.

Secondary spread can occur within the animal population after initial introduction or emergence and is likely to be influenced by factors such as faecal–oral re-cycling and animal movements. The amplification which might occur as a result of secondary spread could surpass and swamp the trickle of an initial primary introduction. If elements carrying genes encoding ESBLs become established in bacteria in animals and amplification occurs on a wide scale, the consequence will be an increased occurrence in the food chain.

A wide range of ESBLs has been detected in bacteria isolated from veterinary samples across Europe, but reports of clinical infections due to ESBL-producing strains in animals have so far been very limited, with only low numbers of animals affected. Examination of bovine veterinary diagnostic samples tested at the Veterinary Laboratories Agency in England and Wales between 2006 and 2007 showed that the predominant enzymes produced by veterinary isolates were CTX-M-14 and CTX-M-15 (Table 1; C. Teale, unpublished results). Knowledge of the epidemiological aspects relating to the spread of ESBL-producing E. coli in animals may facilitate the development of possible interventions to control the further spread of resistance in the animal population and prevent entry into the food chain.

If the hypothesis regarding the importance of initial environmental transfer to the animal population is correct, then the prediction may be made that the next antibacterial resistance appearing in human strains of E. coli is likely to appear in animal strains of E. coli a short interval after its first widespread appearance in humans.

Guidance for the treatment of ESBL producers in humans

Gary L. French

Previously, ESBL producers were usually opportunistic Gram-negative bacteria such as Klebsiella pneumoniae that produced infections and outbreaks in hospitalized patients. Recently, however, ESBL-producing E. coli have appeared worldwide, often producing a CTX-M-type ESBL and causing colonizations and infections in non-hospitalized people, including those in care homes for the elderly. In some geographical areas one or two ESBL-producing E. coli clones have predominated, while in others (such as London) organisms are multilocal and the resistance determinants have appeared in other species in addition to E. coli. The risk factors and epidemiological features
of the older and newer infections caused by ESBL-producing coliforms are shown in Table 2.38

Affected patients may present from the community with unexpectedly multiresistant urinary or abdominal infection and may develop bacteraemias and/or be the source for hospital cross-infection after admission. This type of community-associated infection is more difficult to identify and control than the more familiar healthcare- or hospital-associated infection. The size of the problem is illustrated by the dramatic rise in blood isolates of $E. coli$ resistant to ceftazidime between 1994 and 2007 (Figure 6).

The key factors in controlling ESBL-producing coliforms are to have an antimicrobial stewardship system and an infection prevention and control system in place, both in hospital and in the community. A surveillance system is also needed to identify cases rapidly as they occur, and for this to be effective it is essential that the local microbiology laboratory can identify ESBLs. CTX-M enzymes may not be detected by standard laboratory tests using ceftazidime; the BSAC and HPA recommend that laboratories should routinely test isolates against both cefotaxime and ceftazidime, or against cefpodoxime, and then perform an ESBL confirmatory test on any resistant isolates.39

Antibacterial treatment policies need to take into account the fact that plasmids carrying ESBL genes often encode resistances to other antimicrobial agents including aminoglycosides, trimethoprim, sulphonamides, tetracyclines and chloramphenicol. Frequently, the host bacterium has mutated to fluoroquinolone resistance. A reduction in use of cephalosporins and quinolones can lead to a reduction in the risk of ESBL-producing coliforms. Conveniently, policies to limit the use of cephalosporins and quinolones are also commonly used to help control $Clostridium difficile$ infection.

Risk factors for sepsis need to be controlled. This includes removing urinary/vascular catheters if possible and stopping unnecessary antibiotics. Asymptomatic patients, with colonization only, do not need antibiotics and those with asymptomatic UTI can await the results from susceptibility testing of cultures. Septic patients, however, need to be treated urgently and aggressively, frequently before susceptibility results are known. In these cases initial empirical treatment should be based on recent local antimicrobial susceptibilities.

In areas where ESBL-producing coliforms are diverse and multiclonal, susceptibilities of different strains may be highly variable (Table 3)40 and only the carbapenems are (at present) reliably effective. Therefore, for serious sepsis, immediate treatment with carbapenems is advisable, which can be ‘stepped down’ or ‘de-escalated’ to simpler therapy if subsequent test results permit. Some ESBL producers are susceptible to some aminoglycosides and these are possible initial agents if local results

### Table 1. CTX-M ESBLs recovered from bovine veterinary clinical diagnostic submissions in England and Wales

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<tbody>
<tr>
<td>Confirmed ESBL</td>
<td>272 (3)</td>
<td>621 (1)</td>
<td>802 (0.9)</td>
<td>514 (1)</td>
<td>355 (1)</td>
<td>463 (2)</td>
<td>NA</td>
</tr>
<tr>
<td>CTX-M-1</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>CTX-M-3</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CTX-M-14</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>–</td>
<td>1</td>
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<tr>
<td>CTX-M-15</td>
<td>4</td>
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<td>CTX-M-20</td>
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<td>CTX-M-32</td>
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aCTX-M-14 variant.
bTotal $E. coli$ examined from bovine diagnostic samples. NA, not yet available.

### Table 2. Characteristics of infections caused by ESBL-producing bacteria38

<table>
<thead>
<tr>
<th>Virulence/place</th>
<th>Type of ESBL</th>
<th>Infection</th>
<th>Resistances</th>
<th>Molecular epidemiology</th>
<th>Risk factors</th>
<th>Newer (Escherichia coli)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older (Klebsiella spp., etc.)</td>
<td>less virulent/HCAI</td>
<td>SHV and TEM types</td>
<td>UTI, respiratory, intra-abdominal, blood</td>
<td>all $\beta$-lactams: usually quinolones and co-trimoxazole: usually aminoglycosides</td>
<td>most often clonally related</td>
<td>more virulent/community and HCAI</td>
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<td></td>
<td></td>
<td></td>
<td>usually UTIs, but also blood, gastroenteritis</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>usually not clonally related, but clonal outbreaks described worldwide, including UK</td>
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<td></td>
<td></td>
<td></td>
<td>repeat UTIs/underlying renal pathology; previous antibiotics</td>
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<td></td>
<td></td>
<td></td>
<td>(including cephalosporins and quinolones; previous hospitalization; nursing home residents; the elderly; diabetes; liver pathology</td>
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<td></td>
<td></td>
<td></td>
<td>HCAI, healthcare-associated infection.</td>
</tr>
</tbody>
</table>

Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies
Infections caused by ESBL-producing organisms are often intravenous agents, is another option, but it is not excreted in urine and is therefore not suitable for the treatment of UTI. Mecillinam and colistin have also been used to treat ESBL-producing coliforms but susceptibilities vary and there is limited information on their clinical effectiveness.

Points raised in discussion

- It was noted that selective pressure by antimicrobials to maintain resistance plasmids and/or resistant strains was an important factor, although it was noted that a number of ESBL-producing strains can be maintained in both humans and animals without any identifiable selective pressure.
- The survival of some strains of *E. coli* in the environment has been investigated; there are indications that they are quite robust and can survive various composting procedures.
- The risk of resistance determinants transferring to other related species with possible amplification was noted.
- Studies from China and India, where communities lived under poor hygiene conditions, have shown the widespread presence of resistant strains in the environment, including rivers.
- The effect of heat treatment on effluents and whether plasmin survival when the host bacterium is killed are areas for further research.
- Infections caused by ESBL-producing organisms are often multidrug resistant, often requiring prompt treatment of septic patients before susceptibility results are available; general guidelines will be of limited value since initial treatment should be based on recent local susceptibility data.

**Clostridium difficile**

**Clostridium difficile in humans**

Mark H. Wilcox

*C. difficile* is an environmental organism, and surveys have shown that it is widespread in rivers (88%), lakes (47%) and soil (21%). It is also found in the hospital environment (20%). A survey of a hospital elderly care ward has shown that spores can be found in toilets, sluice floors and commodes, and even when cleaning procedures are thorough they can be difficult to eradicate, persisting in the hospital environment and maintaining a reservoir of potential infection.

The number of death certificates mentioning *C. difficile* either as the underlying cause or as involved in the final disease has increased markedly from ∼1000 in 2001 to 8234 in 2007 in England and Wales (Figure 7). The rate of increase has, however, slowed, from 71% between 2005 and 2006 to 28% during 2006–2007. *C. difficile* infection (CDI) is still predominantly a disease of the elderly, with 3400 deaths/million population aged >85 years and only 7 deaths/million population in those aged <45 years.

Ribotype 027 is now common and appears more virulent than other strains of *C. difficile*. It is now believed that the probable reasons for this virulence are not, as had been hypothesized, the production of two toxins or a peak in toxin production or resistance to fluoroquinolones. The most likely reasons are prolonged production of toxin, the duration of germination, and increased sporulation which increases the risk of transmission.

A recent survey of cases of CDI in the community revealed that both prior treatment with antibacterials and hospitalization were important predisposing factors. For example, exposure to antibiotics in the previous 4 weeks, particularly with multiple agents (*P* <0.001), aminopenicillins (*P* <0.05) and oral cephalosporins (*P* <0.05), was significantly more frequent among cases than controls. Hospitalization in the preceding 6 months was also a significant risk factor (45% compared with 23%; *P* =0.022). However, almost half the cases had not received antibacterial therapy in the month before infection was detected and approximately one-third had neither exposure to antibacterials nor recent hospitalization. This highlights current gaps in our knowledge about the aetiology of community-associated CDI.

There is often a poor response to the treatment of severe infections. Metronidazole has commonly been the favoured treatment but reduced susceptibility is now seen and there is an increasing dependence on vancomycin, which is more effective and gives a superior microbiological response. Nonetheless, recurrence occurs in ∼20%–25% of cases. There is a poor evidence base for the effectiveness of probiotics.

The techniques used to diagnose CDI in the laboratory need to be reassessed given concerns about the accuracy of current methods. Recent advice from the Department of Health and the HPA in England recommends against use of single tests for the detection of *C. difficile* toxin.

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**Table 3. Prevalence and mechanisms of cephalosporin resistance in Enterobacteriaceae in London and South-East England**

<table>
<thead>
<tr>
<th>Organism and number of isolates examined</th>
<th>Percentage resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTX-M producers</strong></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (502)</td>
<td>FOX 89, CIP 60, GEN 60, NIT (UTI) 52, TMP (UTI) 89, MEC (UTI) 29, IPM 0, MEM 0, ETP 0.4</td>
</tr>
<tr>
<td><em>E. coli</em> (292)</td>
<td>35 91 47 25 87 7.5 0 0 0.3</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> (190)</td>
<td>42 91 80 96 91 62 0 0 0.5</td>
</tr>
<tr>
<td><strong>ESBL producers (non-CTX-M)</strong></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae (149)</td>
<td>49 68 60 38 85 49 0 0 0.7</td>
</tr>
<tr>
<td><em>E. coli</em> (89)</td>
<td>30 75 57 14 85 37 0 0 0</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> (25)</td>
<td>60 70 44 85 75 75 0 0 0</td>
</tr>
</tbody>
</table>

FOX, cefoxitin; CIP, ciprofloxacin; GEN, gentamicin; NIT, nitrofurantoin; TMP, trimethoprim; MEC, mecillinam; IPM, imipenem; MEM, meropenem; ETP, ertapenem.

*italics* indicate likely susceptibility. Tigecycline, a new broad-spectrum intravenous agent, is another option, but it is not excreted in urine and is therefore not suitable for the treatment of UTI.
C. difficile infections in animals

Ed J. Kuijper

C. difficile is a ubiquitous bacterium in the environment and has been found in calves, ostriches, chickens, elephants, dogs, horses and pigs, but its role in infection and its pathogenesis in animals are largely unrecognized and possibly underestimated. Similarly, any association between antibiotic usage and C. difficile colonization or diarrhoea in animals is less well documented than in humans.

In the past decade, two strains of C. difficile (PCR ribotypes 027 and 078) have emerged in humans. These two strains have been reported from several European countries and the USA, although the emergence of type 078 occurred relatively recently. In November 2008, a pan-European hospital-based study encompassing 106 laboratories revealed PCR ribotypes 014, 001 and 078 as the predominant types, whereas type 078 was found only sporadically in 2005. From February 2005 to February 2008, the incidence of type 078 among isolates obtained from 1687 patients increased from 3% to 13% in the Netherlands (data from the National Reference Laboratory). Compared with patients infected with type 027, patients infected with type 078 were younger and more frequently had community-associated disease.

Interestingly, type 078 has also been reported as a frequently found type in piglets. Recently, two herds of piglets suffering from diarrhoea in the Netherlands proved to be infected with C. difficile toxinotype V, PCR ribotype 078. Thirty-one isolates of C. difficile were obtained from 48 animals. C. difficile was not detected in the mother sows or in 272 healthy, weaned piglets on seven farms. None of the farm-workers and none of the family members of the farm-owners had CDI. C. difficile type 078 isolates from humans and pigs were highly genetically related by multilocus variable number tandem repeat analysis, suggesting a common origin.

It is likely that type 078 is an important pathogen of piglet diarrhoea worldwide. A study of the prevalence of C. difficile in pigs in Spain sampled 780 animals from 13 pig farms. Newborn piglets (541 samples) and 1–2 month piglets were sampled, and 25.9% of the newborns were positive irrespective of the presence of diarrhoea. In contrast none of the 239 samples from the older piglets was positive. Preliminary data suggest that all strains belong to PCR ribotype 078.

Other C. difficile PCR ribotypes are also frequently found in animals. In a Canadian study of calves from 102 dairy farms in Canada, faecal samples collected from 144 calves with diarrhoea and 134 control calves were cultured for C. difficile and tested using an ELISA for C. difficile toxins A and B. Toxins were detected in 39.6% of calves with diarrhoea but also in 20.9% of healthy controls. PCR ribotyping showed eight distinct patterns, seven of which have been identified in humans; two of these (PCR types 017 and 027) have been associated with outbreaks of severe disease. A study of the presence of C. difficile in various animals in the UK sampled neonatal pigs, male dairy calves (<2 months of age), horses and dogs. The 232 isolates obtained comprised 19 ribotypes, with the predominant one being 078 in calves and pigs.

Spores of C. difficile can also be detected in meat products. Following the emergence of type 078, a pilot study was carried out in the Netherlands by the Food and Consumer Product Safety Authority to determine the occurrence of C. difficile in 500 consumable meat samples from calves, pigs, sheep, turkey and chicken. The only positive samples were four from chicken—types 001, 003 (2) and 087. These results are clearly different from the US and Canadian experiences and need further confirmation.

Overall there is variability in the occurrence of C. difficile in different species. There is a low prevalence of human types but they have been identified in both calves and pigs. There is still much to be learned about the role of toxins and the role of animals as a possible source for human infection via direct or indirect contact, the environment or the food chain.

Guidance for the treatment of C. difficile in humans

Rod E. Warren

Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies
The diversity of techniques used for both routine isolation and typing of C. difficile was noted, yet few are suitable for use in routine laboratories. The serious deficiencies in the reliability and performance of C. difficile toxin detection kits are of particular concern for surveillance, diagnosis and management of infected persons.

- Difficulties remain in linking prior antibiotic therapy with CDI where factors such as the type of antibacterial, and the timing and duration of treatment might all have importance; some compounds, such as lincosamide, have a prolonged effect in experimental hamster models.
- The links between animals and man, particularly the potential for transmission of C. difficile from animals to food to the community, remain to be determined.
- The lack of data may mean that C. difficile infection could be unrecognized and therefore underestimated in many animals, notably pigs and cattle.
- The prevalence of C. difficile in many animal species appears to be low yet the identification in pigs of ribotype 078 with a high homology with human types is of concern and begs the question of whether these animals could be a source for human infection either directly or indirectly.
- Investigations in the Netherlands have shown a low prevalence of C. difficile in locally produced food, but little is known about food from other parts of the world.
- The true mortality in humans is uncertain since it is difficult to distinguish between whether a patient has died of or with CDI.
- The quantity of toxin produced by strains and its association with the severity of infection in both humans and animals remains unclear.
- Larger studies are required both to determine the optimum antibacterial regimen for treatment and to better define which agents provoke CDI.
- Such studies need to be of adequate duration and follow-up, particularly in populations where CDI is common.
- Better computerized support systems that link pharmacy and laboratory data are needed; currently most surveillance studies are inadequate and lack denominators and controls. Additional funding is needed to support this.

**Multidrug resistance and changing antimicrobial use in man**

Herman Goossens

The seemingly simple matter of measuring the use of antimicrobials in hospitals is fraught with problems as there are so many different methods used (Figure 8), and trying to compare these can give misleading results. Attempts to determine cause–effect relationships following changes in antimicrobial use are thus difficult and are affected by numerous confounding factors. Factors affecting the emergence and spread of multidrug-resistant organisms are complex. Their emergence can be caused by genetic recombination or mutations and their spread can be a consequence of selection. The latter may involve the amplification of a resistant strain within a colonized or infected patient receiving antibiotics. Clonal spread may then take place from a colonized to a non-colonized patient, possibly followed by the dissemination of resistance genes among bacterial strains via conjugation, transduction or transformation.

There are many confounding factors including infection control practices, colonization pressure, any underlying illness, the length of stay, the duration of treatment and also any use...
of the drug in the community or in animals. These factors complicate any attempts to determine the impact of the use of an antimicrobial. An example is afforded by the impact that the duration of treatment can have. A retrospective, cross-sectional study was carried out to estimate the probability of carbapenem resistance among Pseudomonas aeruginosa isolates from adult inpatients with respiratory tract infection.\(^8^0\) The predictors of carbapenem resistance were found to be prior receipt of mechanical ventilation for \(>11\) days and prior exposure to fluoroquinolones and to carbapenems for \(>3\) days.

Use of antimicrobials in animals can be important as shown by Johnson et al.\(^8^1\). In this study of 931 geographically and temporally matched E. coli isolates from human volunteers and commercial poultry products, drug-resistant human isolates were similar to poultry isolates but drug-susceptible human isolates differed considerably from poultry isolates.

The relationship between antimicrobial use and resistance in hospitals is complex, with no overall agreement on which methods are most appropriate for the measurement of drug use in hospitals and no agreement on how to correlate their use with selection of resistance in hospitals. There is a limited understanding of the association of exposure to antibacterials with acquisition or progression from colonization towards infection with multidrug resistance.

**Guidance for the use of antimicrobials and husbandry practices in veterinary medicine**

Susan Dawson and David J. Taylor

There are major differences between veterinary and human medicine. The most obvious is the wide range of animals that may need treatment. These are usually divided into companion animals and farm or food animals. Companion animals include horses, cats, dogs, rabbits, reptiles, fish and various other less common pets. After death, their bodies generally go to incineration or burial. Care for companion animals is intimate, and human contact extends to all age groups in the home. Antimicrobial use is not dissimilar to that in human medicine for the treatment of bacterial infections in individuals; however, for animals payment for treatment must be covered by the owner. Some pets may be insured and these policies may cover more sophisticated treatment to the limit of the policy. More elaborate operations are now available as in human medicine (hip replacement, more reconstructive work). This may require the administration of more veterinary medicines and could potentially lead to the use of more antimicrobials.

Veterinarians usually operate in small groups—there is no equivalent to the NHS for humans! Most vets specialize in treating either small companion animals, or horses, or farm animals. There is increasingly more specialization, however, for example in poultry or pigs, usually for the big producers.

Veterinary medicines are registered for use in animals by the Veterinary Medicines Directorate (VMD) in the UK or the European Medicines Evaluation Agency (EMEA). All antibacterials for veterinary use are prescription-only products which must be prescribed by a veterinary surgeon (POM-V). There is a ‘cascade’ system for the use of medicines in animals—veterinary surgeons must prescribe and use veterinary medicines where available but if no medicine is authorized they can then use a veterinary medicine authorized in the UK for another species or another condition. Failing this they may use a medicine authorized for human use in the UK or one imported from another member State.

The Responsible Use of Medicines in Agriculture alliance (RUMA) was set up 10 years ago with input from various Veterinary Associations. RUMA provides guidelines for the responsible use of antimicrobials in livestock production, with individual guidelines for all the major food-producing species. Its major aim is to highlight strategies that may reduce the need for antimicrobials, e.g. management conditions, reduction of stress. There are strict conditions for the use of antimicrobials in food-producing animals; treatment is restricted to animals on a single holding and any medicine imported from another member State must be authorized for food-producing species in the other member State. For food-producing animals, withdrawal periods are set for each medicinal product whereby that
animal, or products from that animal such as milk, cannot enter the food chain for a specified period of time.

In the EU, antimicrobial growth promoters were withdrawn in 2006 although one class continues to be administered in feed, namely the ionophores which have anti-coccidial activity. They are categorized as Zootechnical Feed Additives and fed to broiler chickens and layers to 12 weeks of age, and to rabbits. Their antimicrobial activity is incidental to their primary purpose. There are consequences to the removal of growth promoters, namely an increase in disease in some species.

The VMD reported on the annual antimicrobial usage in 2007. This revealed an overall decrease in sales of veterinary antimicrobials. The reduction was accounted for by reduced sales of tetracyclines and macrolides but an increase in sales of fluoroquinolones and cephalosporins. In spite of an increase in fluoroquinolone usage, their sales represented <1% of the total. Approximately half the total sales of therapeutic antimicrobials were tetracyclines. Eighty-seven percent of the antimicrobials were sold for use in food-producing animals. Total sales in the veterinary field are greatly biased by the weight of the type of animals treated—cows and horses require larger amounts of drugs than other smaller animals.

Cephalosporins are now used quite widely, including third- and fourth-generation compounds, but these are used mostly for cattle, pigs, poultry and horses. A short withdrawal period can give a market advantage to a particular product in cattle. For small animals, it is mostly the first- and second-generation cephalosporins that are used.

The British Small Animal Veterinary Association has issued guidelines for the use of antimicrobials for the treatment of MRSA. These state that antibacterial drugs should only be used where significant bacterial disease has been confirmed or can reasonably be suspected, and that the use of human products under the cascade system should be restricted to cases only where there is compelling evidence from culture and susceptibility testing that there is no suitable veterinary product. When selecting a drug, the likely infecting pathogen and breadth of antibacterial spectrum should be considered. Prophylactic antibacterial drugs are not indicated for routine clean surgery of <90 min.

MRSA is uncommon in animals, and those at greatest risk of infection are ill hospitalized animals, especially those with intravenous catheters, those undergoing surgery (especially with implants) and immunocompromised animals. Bacterial strains are usually of common human types and most are present on the animals on arrival but rarely persist in the hospital. There is the potential for veterinary staff to act as a reservoir of MRSA infection. Most UK veterinary isolates of MRSA are usually susceptible to routine antibacterials, including potentiated sulphonamides, tetracyclines, fusidic acid and mupirocin, although these are not all licensed for use in animals.

Vaccines for bacterial diseases such as enzootic pneumonia and proliferative enteropathy of pigs have directly reduced the need for some treatments. Similarly, vaccines for *E. coli* septicemia in poultry can reduce antimicrobial use.

**Points raised in discussion**

- Animals may present with totally different spectra of infecting organisms which are not or only very rarely found in humans. Examples are *Bordetella bronchiseptica* in dogs, non-*S. aureus* strains in canine skin infections and branchepneumonia in foals caused by *Rhodococcus equi*. Most farm animals also have a variety of non-human pathogens. Mastitis is frequently caused by coagulase-negative staphylococci, *Streptococcus agalactiae*, *Streptococcus uberis*, *Streptococcus dysgalactiae* or even *Actinomyces pyogenes*. *Pasteurella* species can cause pneumonia in cattle as can non-human species of *Mycoplasma*. Pigs are susceptible to *Mycoplasma hypopneumonae* which causes enzootic pneumonia

- Surveillance data on discontinued compounds by the Veterinary Laboratories Agency still continues for pathogens such as salmonellae and *E. coli*; there has been no major problem with resistance

- Guidelines for the use of antimicrobials in veterinary practice are not as specific as those for humans; however, some felt that most guidelines for human therapy were often inadequate

- Veterinary students are given a good background in the use of drugs, and formularies are widely available. New formularies are sent out automatically free of charge as they become available

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**Some questions that remain unresolved**

Despite considerable advances having been made in our understanding of MRSA, ESBLs and their host strains and *C. difficile*, to allow effective treatment and/or eradication, questions still remain. These include:

- Why do certain types of bacteria dominate and then decline; are certain organisms biologically fitter or better able to infect particular patients; what is the role of the host?

- What is the evidence that *C. difficile* and ESBL-producing bacteria from food-producing animals survive and infect humans?

- How can antibiotic-resistant bacteria be prevented from transferring between humans and animals?

- Can any successful farming practices that reduce the prevalence of bacterial colonization or infection be adapted for use in humans? Likewise, are there any successful strategies used in human medicine that could be modified for use in animals?

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**Transparency declarations**

G. L. F., P. A. H., D. N., M. H. W., N. W. and R. E. W. have received honoraria for conference attendance, advisory boards or consultancy from various pharmaceutical companies.

Other authors: none to declare.

**References**

Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies


75 Thomas C, Stevenson M, Williamson DJ et al. Clostridium difficile-associated diarrhoea: epidemiological data from Western


Erratum

Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies


J Antimicrob Chemother 2010; 65 Suppl 1: i3–17

The information listed for reference 13 was not the article intended. The corrected reference is given below. The authors apologize for this error.


On page i11, the heading ‘Guidance for the treatment of C. difficile in humans’ should have read ‘C. difficile in man – antibiotic provocation’.

In the second paragraph on page i12, ‘Bacillus fragilis’ should have been ‘Bacteroides fragilis’. The Journal apologizes to the author for these errors.