The increasing prevalence of antibiotic-resistant Gram-negative bacteria is a serious concern not only for humans but also companion animals. Recent clinical attention has focused on the increasing frequency of Gram-negative pathogens responsible for hospital-acquired infections. In this group, extended-spectrum β-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae, in particular E. coli and K. pneumoniae, as well as carbapenemase-producing A. baumannii, have caused major challenges in the past decade. These three groups of organisms will be the focus of this article.

β-lactams are the most widely utilised antimicrobials worldwide for the treatment of infections in humans and animals. β-lactamase production is the most common mechanism of antibiotic resistance, particularly in Gram-negative bacilli. There are four different groups based on the Ambler molecular classification, which categorises the enzyme according to their amino acid sequence, primarily on their active site. Classes A, C and D are serine β-lactamases and Class B are metallo-β-lactamases which require a bivalent metal ion for activity, usually Zn²⁺ (Table 1).

ESBL and CMY-2-like producing Enterobacteriaceae

Two types of cephalosporinases commonly described in human and animal pathogens are ESBLs and CMY-2 like. CMY-2 type of resistance was commonly described in Salmonella and E. coli isolated from food-producing animals. CMY-2 producing E. coli is also relatively common in humans and nearly as common as ESBL producing E. coli. Nowadays, CTX-M type ESBLs are the most commonly reported β-lactamases both in human and animals. Until the year 2000, TEM and SHV type ESBLs were of great concern and mostly in E. cloacae and K. pneumoniae. However, since mid-2000s, there has been a dramatic shift into the predominance of CTX-M type ESBLs. In dogs and cats, there have been reports of infections caused by CTX-M type ESBL producing E. coli associated with human infections. ESBL producing E. coli is also relatively common in pigs in China, with the prevalence of 10.7%. The presence of this ESBL in farm animal causes a significant threat to public health.

E. coli ST131 clone

E. coli is a leading cause of urinary tract infections in humans and dogs. E. coli can be divided into four phylogenetic groups: A, B1, B2 and D. The virulent extra-intestinal pathogens are usually found in classes B2 and D. In the last decade, E. coli sequence type (ST) 131 has emerged as a pandemic uropathogenic E. coli causing community and hospital-acquired infections especially urinary tract infections. This clone potentially can harbour a variety of β-lactamase genes; however, it is most strongly associated with CTX-M-15 ESBL. In addition, the pandemic clone E. coli ST131 also belonged to the phylogenetic group B2, the highly virulent group of ExPEC. The combination of virulence and antimicrobial resistance may give E. coli ST131 a fitness advantage over other E. coli strains.
which highlights the widespread and successful dissemination of *E. coli* ST131.

*E. coli* ST131 is also represented among resistant isolates in companion and farm animals. A European study determined the presence of *E. coli* ST131 which mostly produced CTX-M-15, comprising 5.6% of ESBL-producing *E. coli* isolates recovered from companion animals. In Australia, *E. coli* ST131 accounted for 7.2% of isolates from companion animals. Transmission between dogs and cats sharing the same clone, *E. coli* ST131, has been described previously. Dogs in particular have been identified as a possible reservoir not only for ST131, but also for extra-intestinal pathogenic *E. coli* (ExPEC) in general for the transmission to other pets and humans. *E. coli* ST131 has also been reported from poultry and pig farms in Spain. In this instance, both companion and farm animals can be the reservoirs for *E. coli* ST131 and other cephalexin-resistant *E. coli*. Studies on retail meat for human consumption have found *E. coli* indistinguishable from human *E. coli* causing urinary tract infections (UTIs) and *E. coli* ST131 was isolated from chicken. Further studies are urgently needed to investigate the pathways of transmission between humans and animals to determine whether isolates found in retail meat and livestock pose an imminent threat to humans.

### Carbapenem-resistant Enterobacteriaceae (CRE)

Various *Enterobacteriaceae* confer antibiotic resistance by producing enzymes such as carbapenemases. The carbapenemase modifies the carbapenems through the hydrolysis of the antibiotic and has been defined into different classes using the Ambler classification system. The resistance in *Enterobacteriaceae* is found within Ambler class A (KPC - *K. pneumoniae* Carbapenemase), class B (metallo-β-lactamases) and class D (OXA – oxacillinases) (Table 1).

<table>
<thead>
<tr>
<th>Ambler classification</th>
<th>Description or characteristics</th>
<th>Examples of enzymes</th>
<th>Bacterial strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A (serine β-lactamase)</td>
<td>Cephalosporinases (ESBLs) Usually susceptible, except for KPC</td>
<td>TEM, SHV, CTX-M, KPC, VEB</td>
<td><em>Enterobacteriaceae</em>, <em>Pseudomonas spp.</em></td>
</tr>
<tr>
<td>Class B (metallo-β-lactamase or MBL)</td>
<td>Contain metal ion (Zn) Carbapenemases Not inhibited by clavulanic acid Inhibited by aztreonam</td>
<td>IMP, VIM, NDM</td>
<td><em>Enterobacteriaceae</em>, <em>Acinetobacter spp.</em>, <em>Pseudomonas spp.</em></td>
</tr>
<tr>
<td>Class C (AmpC β-lactamase – serine β-lactamase)</td>
<td>Resistant to clavulanic acid Intrinsic in certain species of Gram-negative</td>
<td>CMY, DHA</td>
<td><em>Enterobacteriaceae</em></td>
</tr>
<tr>
<td>Class D (serine β-lactamase)</td>
<td>Oxacillinases Susceptible to clavulanic acid</td>
<td>OXA</td>
<td><em>Enterobacteriaceae</em> (OXA-48 like), <em>Acinetobacter spp.</em></td>
</tr>
</tbody>
</table>

Note: Enzymes in bold are carbapenemases.
Carbapenem-resistant *Acinetobacter baumannii*

*A. baumannii* has gained recognition as a major nosocomial pathogen in recent years, predominantly affecting immunocompromised or critically ill patients. It causes a wide range of infections including pneumonia, bacteraemia and infections of the skin, bone, urinary tract and central nervous system. The remarkable ability of *A. baumannii* to up-regulate or acquire antibiotic resistance determinants makes the bacterium a significant nosocomial pathogen. Resistance to carbapenems has been reported worldwide, including Australia. Alteration of penicillin-binding proteins and loss of outer membrane genes subsequently leading to the over-expression of these downstream genes in *IS* elements play significant roles in the expression of various OXA genes in *A. baumannii*. *A. baumannii* can also be isolated from faeces of slaughtered pigs and cattle. These strains from animals possessed *bla*OXA-like, however, the resistance islands could not be found and none of the isolates from animals belonged to the European clones I, II and III as the common clones of human *A. baumannii* strains.

The rapid spread of multi-drug-resistant bacteria Gram-negative bacteria, especially in nosocomial pathogens; in the past decade underline the importance of infection control precautions in both human and veterinary hospitals. The possibility that farm animals may be the reservoir of resistance mechanisms and the current evidence of spread of the most recent and notorious carbapenem resistance genes demonstrate the need for increased surveillance of antibiotic usage in veterinary and farm animals as well as in humans.

**References**


Under the Microscope


Biographies

Dr Hanna Sidjabat’s research interest is in molecular epidemiology of plasmids carrying antibiotic resistance genes and genetic context of antibiotic resistance genes.

Witchuda Kamolvit MD is a PhD student studying the genome of OXA-23 producing A. baumannii from Australia and Asian countries.

Alexander Wailan BSc Hons is a PhD student studying the NDM-1 plasmid mobilisation and complete NDM-1 plasmid sequences from Australia, New Zealand and Asian countries.

Prof David Paterson’s research interest includes study of the molecular and clinical epidemiology of infections with antibiotic resistant organisms. The focus of this work is the translation of knowledge into optimal prevention and treatment of these infections.

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