

ESKAPE PATHOGENS: RESISTANCE, PERSISTENCE AND THE ONE HEALTH CHALLENGE

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Abstract

Antimicrobial resistance (AMR) is one of the major challenges threatening the effective treatment of bacterial infections in both human and veterinary medicine. Among resistant bacteria, the ESKAPE pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.—are particularly important because of their ability to evade multiple antimicrobial agents and cause difficult-to-treat infections. Their capacity to acquire resistance genes, form biofilms, persist in healthcare environments and spread through contaminated surfaces and equipment makes them an increasing concern in veterinary hospitals. The close interaction among animals, humans and their shared environment further highlights their importance from a One Health perspective. Judicious antimicrobial use, culture and susceptibility testing, strict infection-control practices, surveillance and antimicrobial stewardship are essential to limit their emergence and spread. Greater awareness of ESKAPE pathogens among veterinarians is crucial for protecting animal health while preserving the effectiveness of existing antimicrobials.

Keywords: Antimicrobial resistance, antimicrobial stewardship, ESKAPE pathogens, Multidrug resistance, Nosocomial infections, One Health.

Introduction

Antimicrobial resistance (AMR) is rapidly transforming the management of bacterial infections, making once-treatable diseases increasingly difficult to control. For decades, antibiotics have been essential in human and veterinary medicine, agriculture and food processing for treating and preventing infections. However, their widespread and indiscriminate use has accelerated AMR, making many antibiotics ineffective. Multidrug resistance (MDR) refers to resistance to at least three classes of antimicrobial agents, whereas extensively drug-resistant (XDR) bacteria remain susceptible to agents from only one or two antimicrobial classes. Pandrug-resistant (PDR) bacteria are non-susceptible to all

antimicrobial agents across all relevant antimicrobial classes, leaving extremely limited or no therapeutic options. The emergence of “superbugs” threatens modern healthcare, including surgeries, cancer treatment, caesarean sections and organ transplantation, which depend on effective antibiotics. Among the organisms of greatest concern are the ESKAPE pathogens. The name ESKAPE is formed from the first letters of six bacterial groups: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. The term ESKAPE reflects their remarkable ability to “escape” the action of multiple antibiotics due to multidrug resistance through diverse resistance mechanisms, making

infections difficult to treat and often life-threatening, particularly in immunocompromised or critically ill patients.

The World Health Organization's 2024 Bacterial Priority Pathogens List places several ESKAPE organisms in high- or critical-priority categories. This classification reflects the combination of limited treatment options and the serious infections associated with these bacteria. Although historically emphasized in human medicine, ESKAPE pathogens are increasingly relevant to veterinary practice, where antimicrobial exposure, intensive care, invasive procedures and close animal–human contact can create opportunities for resistant organisms to emerge and spread. Understanding these pathogens and adopting responsible antimicrobial use, timely diagnosis, effective infection control and One Health surveillance are therefore essential to protect both animal and public health.

How do ESKAPE pathogens escape antibiotics?

ESKAPE pathogens are particularly challenging because they can develop or acquire antimicrobial resistance through multiple mechanisms, including enzymatic destruction or modification of antibiotics, alteration of antibiotic targets, reduced bacterial-cell permeability, active efflux of antibiotics, acquisition of resistance genes and biofilm formation. Together, these mechanisms can result in multidrug-resistant infections with very limited treatment options.

The Six ESKAPE Pathogens

1. *Enterococcus faecium*

Enterococci are Gram-positive, facultatively anaerobic bacteria that commonly occur as commensals in the gastrointestinal tract of humans and animals, as well as in birds, reptiles and other organisms. They are also found in soil, water and food. Among the more than 50 *Enterococcus* species, *E. faecalis* and *E. faecium* are particularly important and have been associated with infections in food-producing animals and poultry (Makarov *et al.*, 2022). Their ability to acquire resistance to multiple antimicrobials makes them important

opportunistic and nosocomial pathogens. Vancomycin-resistant *E. faecium* (VRE) is of particular concern because vancomycin has traditionally been important for treating serious Gram-positive infections. In veterinary hospitals, resistant enterococci warrant attention because animals may carry resistant strains without showing obvious clinical disease, highlighting their potential One Health significance.

2. *Staphylococcus aureus*

Staphylococcus aureus is commonly associated with skin and soft-tissue infections, wound infections and postoperative complications. The emergence of methicillin-resistant *S. aureus* (MRSA) has made treatment considerably more challenging. In some regions, as many as 90 per cent of *S. aureus* infections are reported to be MRSA, which cannot be treated with standard antibiotics. WHO reports indicated that MRSA is circulating in every province worldwide, significantly increasing the risk of death by 64 per cent compared to drug-sensitive forms of the infection which is attributed to its antibiotic resistance (Abebe and Birhanu, 2023). Methicillin resistance is primarily associated with penicillin-binding protein 2a (PBP2a), which has low affinity for β -lactam antibiotics, allowing cell-wall synthesis to continue despite treatment. β -lactamase production can also contribute to resistance to β -lactam antibiotics. Although the treatment options for MRSA are limited, there are promising alternatives to antibiotics to combat the infections. Innovative therapeutic strategies with wide range of activity and modes of action are yet to be explored. In companion-animal practice, MRSA and other resistant staphylococci are important not only because of animal disease but also because pets live in close contact with people, highlighting their One Health significance.

3. *Klebsiella pneumoniae*

Klebsiella species are Gram-negative, non-motile, lactose-fermenting, facultatively anaerobic, rod-shaped bacteria belonging to the family Enterobacteriaceae. *K. pneumoniae* is an important veterinary pathogen associated with epidemic metritis and cervicitis in mares, pneumonia and septicaemia in foals and mastitis

in cattle. Bovine mastitis caused by *K. pneumoniae* can result in reduced milk quality, decreased production and mortality, leading to significant economic losses in the dairy industry. Companion animals such as dogs and cats may also serve as reservoirs of multidrug-resistant (MDR) *K. pneumoniae*, highlighting their potential role in the transmission of resistant bacteria (Soliman *et al.*, 2024). Of particular concern are extensively drug-resistant (XDR) hypervirulent *K. pneumoniae* (hvKP) strains with hypermucoviscous characteristics, which have been associated with severe infections, including ventilator-associated pneumonia in humans. Some strains produce extended-spectrum β -lactamases (ESBLs), which can make many commonly used β -lactam antibiotics ineffective. Carbapenem-resistant strains represent an even greater therapeutic challenge.

4. *Acinetobacter baumannii*

Acinetobacter baumannii is a Gram-negative, aerobic, non-motile, pleomorphic coccobacilli that is an important opportunistic pathogen, particularly in immunocompromised individuals and is associated with aquatic environments. It has been designated as a "red alert" human pathogen due to its broad antibiotic resistance spectrum. The virulence potential of *A. baumannii* is based on a "persist and resist" strategy, with the bacteria also resisting oxidative stress and complement-mediated killing. It has become a major concern because of its ability to persist in healthcare environments and acquire resistance to multiple antimicrobial classes. Fluoroquinolone resistance among *A. baumannii* isolates from developing countries has been reported to range from 75% to 97.7%. In 2018, WHO ranked carbapenem resistant *A. baumannii* (CRAB) as the top priority for antibiotic research and development (Abhisek *et al.*, 2025). Veterinary hospitals should therefore consider environmental hygiene, equipment disinfection and infection-control practices alongside appropriate antimicrobial therapy.

5. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a ubiquitous Gram-negative bacterium with minimal nutritional requirements, enabling it to survive in diverse environments such as water, surfaces,

medical devices and hospital waste. It is an important opportunistic pathogen associated with healthcare-associated infections (HAIs), including pneumonia, bloodstream infections, surgical-site infections (SSIs), urinary tract infections (UTIs), burn-wound infections, keratitis and otitis media (Asmare *et al.*, 2024). Its major virulence factors include elastase, alkaline protease, exotoxin A, haemolysins, phospholipase and exoenzymes. AMR can arise through loss of Outer membrane protein D (OprD), overexpression of efflux pumps, AmpC (Ampicillinase C) β -lactamase overproduction and target-site mutations, contributing to resistance against carbapenems, cephalosporins and fluoroquinolones.

6. *Enterobacter* spp.

Enterobacter spp. are Gram-negative, rod-shaped, facultatively anaerobic bacteria that occur in the environment and as part of the normal microbiota of humans and animals. They can act as opportunistic pathogens, causing bacteraemia, lower respiratory tract infections, urinary tract infections, skin and soft-tissue infections, endocarditis and surgical-site infections. Their clinical importance extends across large and companion animals, with infections reported in conditions such as mastitis in dairy cattle and urinary tract, gastrointestinal, otic and wound infections in companion animals. Some possess AmpC (Ampicillinase C) β -lactamases, which can complicate antibiotic selection. The World Health Organization's Bacterial Priority Pathogens List update, issued in 2024, has 3rd generation cephalosporin (3GC) and carbapenem-resistant Enterobacterales as critical priority pathogens due to their ability to acquire and transfer resistance genes, as well as to cause severe, sometimes untreatable infections (Fernandes *et al.*, 2026). Additional resistance mechanisms may further restrict therapeutic options. For veterinarians, this reinforces the importance of culture and antimicrobial susceptibility testing rather than relying solely on empirical treatment.

Why Do ESKAPE Pathogens Matter in Veterinary Practice?

ESKAPE pathogens are relevant to veterinary medicine because they can cause clinical disease, persist in hospital environments and carry antimicrobial-resistance determinants. Animals may also act as carriers of resistant organisms, while veterinary hospitals can provide opportunities for transmission through patients, personnel, equipment and contaminated environments. Because animals, people and the environment are interconnected, resistant ESKAPE pathogens should be considered within a One Health framework. This does not mean that every ESKAPE organism is inherently a zoonotic pathogen; rather, some strains may have animal-human transmission potential or other cross-species significance.

How Can Veterinarians Fight ESKAPE Pathogens?

Although the six ESKAPE pathogens are biologically different, they share an important characteristic: the ability to survive antimicrobial pressure and cause difficult-to-treat infections. Effective management of ESKAPE pathogens requires a multifaceted infection-control and antimicrobial stewardship approach. Antimicrobial stewardship refers to the responsible and evidence-based use of antimicrobial drugs to ensure that the right antimicrobial is used for the right patient, at the right dose, by the right route, for the right duration. Unnecessary antibiotic use should be avoided, and prolonged therapy should be regularly reassessed. Culture and antimicrobial susceptibility testing are particularly important in recurrent, severe, postoperative or non-responsive infections, as resistance cannot be reliably predicted from the organism's identity alone. Strong infection-control measures, including hand hygiene, isolation, environmental cleaning and proper equipment disinfection, are essential. Persistent infections should also prompt consideration of biofilms and infected devices or wounds. Finally, hospital

surveillance of resistant isolates can help identify emerging antimicrobial-resistance problems before they become widespread.

The Future: Beyond Conventional Antibiotics

The growing threat posed by ESKAPE pathogens has accelerated research into alternative and complementary strategies to combat antimicrobial resistance. These include bacteriophage therapy, antimicrobial peptides, anti-biofilm approaches, development of novel antibiotics, microbiome-based therapies, rapid molecular diagnostics, genomic surveillance and artificial intelligence (AI)-assisted antimicrobial discovery. Many of these approaches remain under investigation, but they demonstrate an important shift: the future of infection management may involve more than antibiotics alone. Combining these emerging tools with antimicrobial stewardship, early diagnosis and targeted therapy could improve treatment outcomes while reducing the emergence and spread of resistance. Such integrated approaches may be particularly valuable in veterinary medicine, where antimicrobial use directly intersects with animal health, food safety and One Health.

Conclusion

ESKAPE pathogens represent a major challenge because they combine opportunistic pathogenicity, environmental persistence and antimicrobial resistance. For veterinary medicine, the response cannot depend on discovering a stronger antibiotic every time resistance emerges. The more sustainable strategy is a combination of early diagnosis, rational antimicrobial use, infection prevention, environmental hygiene, surveillance and development of new therapeutic approaches. The battle against ESKAPE pathogens is therefore not simply a battle against six bacteria. It is a battle to preserve the effectiveness of antimicrobial therapy for the future.

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