



Resistance against β -lactam antibiotics

Introduction

Antimicrobial resistance (AMR) has become a significant global health challenge of the 21st century. Bacterial resistance is driven by mutations, horizontal gene transfer, and environmental reservoirs of resistance genes. These natural processes are exacerbated by the use of antibiotics in both agriculture and healthcare and inadequate infection control practices. Pharmaceutical investment in antibiotic development has declined due to economic disincentives, creating a critical gap between the rapid emergence of resistance and the slow pace of new drug discovery (Figure 1)¹.

ANTIBIOTIC DISCOVERY TIMELINE



ANTIBIOTIC RESISTANCE EMERGENCE TIMELINE

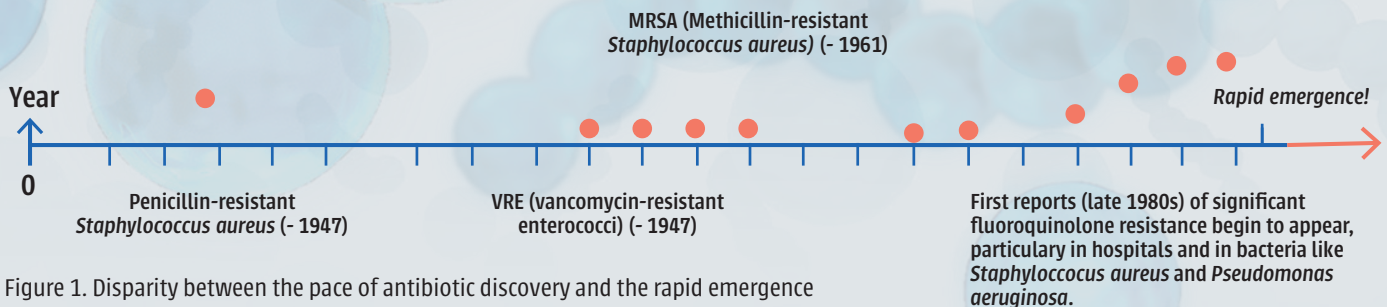


Figure 1. Disparity between the pace of antibiotic discovery and the rapid emergence of antibiotic resistance.

β -lactam antibiotics

β -lactam antibiotics comprise the antimicrobial agents that contain a β -lactam ring in their molecular formula. The core β -lactam ring acts as a structural mimic of a part of the penicillin binding proteins (PBPs). After irreversibly binding to PBPs, they stop peptidoglycan cross-linking, causing cell wall defects and, eventually, osmotic lysis of the bacteria.

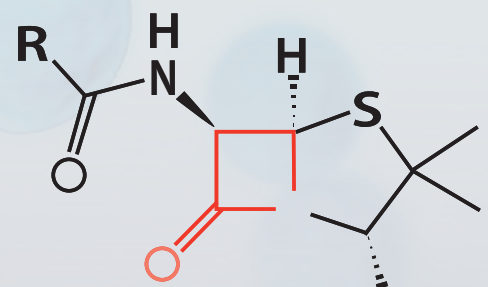


Figure 2. Molecular formula of β -lactam antibiotics with the β -lactam ring shown in red.

Penicillins were the first β -lactam antibiotics to be used clinically. An overview of most used penicillins in veterinary medicine is shown in table 1.

Table 1: Overview of different of penicillins used in veterinary medicine

Categorisation of penicillins used in veterinary medicine			
Natural penicillins β -lactamase sensitive Narrow-spectrum	Anti-staphylococcal penicillins β -lactamase resistant Narrow-spectrum	Aminopenicillins without β -lactamase inhibitors Broad-spectrum	Aminopenicillins with β -lactamase inhibitors Broad-spectrum
Penicillin G Penicillin V	Cloxacillin Oxacillin	Amoxicillin Ampicillin	Amoxicillin + clavulanic acid Ampicillin + sulbactam

Resistance mechanisms

Resistance to β -lactam antibiotics is mainly mediated by a large number of β -lactamases which differ in their abilities to hydrolyse the various β -lactam antibiotics. Other resistance mechanisms include the acquisition of PBPs with reduced affinity to β -lactam antibiotics, mutations in the PBPs, but also reduced β -lactam uptake due to alterations in the outer membrane of gram-negative bacteria or export by multidrug transporters².

Phenoxyphen® for treatment of *S. suis* infections and AMR

β -lactamase as a clinically important resistance mechanism in gram-positive bacteria is almost exclusively found in staphylococci. β -lactamases are not known to occur in *Streptococcus* species. As with methicillin resistance in staphylococci, penicillin resistance in streptococci is due to alteration of target PBPs. The molecular basis for PBP alterations, however, differs between staphylococci and streptococci³.

S. suis strains from diseased swine show generally high susceptibility against natural penicillins. Minimum Inhibitory Concentrations (MICs) were determined against *Streptococcus suis* isolates from diseased pigs in Europe (2019-2024). Most of the isolates showed a MIC of ≤ 0.0625 $\mu\text{g/ml}$ (clinical breakpoints established by CLSI: S: ≤ 0.25 $\mu\text{g/ml}$; I: 0.5 $\mu\text{g/ml}$; R: ≥ 1 $\mu\text{g/ml}$)⁴.

A recent study, comparing penicillin V with amoxicillin, shows less induction of AMR in gram-negative *Enterobacteriaceae* from the intestinal microbiome of piglets after penicillin V treatment compared to amoxicillin treatment⁵.

There is a general recommendation that responsible use principles should be adhered to in everyday practice to keep the risk of AMR as low as possible. **Narrow-spectrum penicillin with a lower risk of AMR selection, like penicillin V, should be used for first-line treatment whenever possible and where susceptibility testing suggests the likely efficacy of this approach⁶.**

References

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