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USE OF PİPERACİLLİN/TAZOBACTAM İN *PSEUDOMONAS AERUGİNOSA* INFECTİONS İN DOG AND CATS

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Abstract

Pseudomonas aeruginosa (P. aeruginosa), although rarely encountered as a pathogen in healthy animals, can cause severe infections in immunocompromised animals, resulting in high morbidity and mortality. Due to the natural resistance mechanisms possessed by this bacterium, its susceptibility to many antibiotics is reduced, and during treatment it can also develop resistance to antibiotics to which it was initially susceptible. In infections caused by multidrug-resistant *P. aeruginosa* isolates, combination antibiotic therapies are recommended to increase treatment success and to prevent or reduce the development of resistance. Piperacillin/tazobactam, a penicillin/beta-lactamase inhibitor combination, exhibits high in vitro efficacy against *P. aeruginosa* due to its resilience against beta-lactam resistance mechanisms. This review aims to evaluate the effectiveness of piperacillin/tazobactam in *P. aeruginosa* infections.

Key words: *Pseudomonas aeruginosa*, piperacillin, tazobactam, antibiotic susceptibility,

INTRODUCTION

Pseudomonas aeruginosa is an environmentally ubiquitous bacillus that functions as an opportunistic pathogen capable of colonizing the skin and mucosal surfaces of mammals. In cats and dogs, this microorganism has been implicated in cutaneous, systemic, and urinary tract infections, as well as in the development of lesions including ulcers, hemorrhagic crusts, and erythematous papules (Hillier A. et al., 2006). Moreover, *P. aeruginosa* is associated with a range of infectious conditions such as otitis externa (Ramanarayana P. et al., 2022; Robinson V.H. et al., 2019), rhinosinusitis (Sharma D. et al., 2019), and periodontal disease (Riggio M.P. et al., 2011) (Da Silva L.C.A. et al., 2016). Due to its persistent environmental presence and significant potential for transmission to mammalian hosts, infections caused by this bacterium are closely linked to the "One Health" concept. This review aims to assess the clinical indications and therapeutic effectiveness of piperacillin/tazobactam in veterinary medicine.

Etiology

The term *Pseudomonas* originates from the Greek words *"pseudes,"* meaning false, and *"mona,"* meaning unit or single entity (Bağcıgil A.F. et al., 2024). *P. aeruginosa* is a gram-negative, non–spore-forming, aerobic bacillus classified within the family *Pseudomonadaceae*. This microorganism demonstrates a remarkable ability to survive under unfavorable environmental conditions and is widely distributed in nature, particularly in soil and aquatic habitats. It is most frequently identified as a pathogen in animals with compromised immune function (Ekselli S., 2019; Güven Ö. et al., 2008; Koçhan A. et al., 2017). As an opportunistic pathogen, *P. aeruginosa* is capable of inducing infections with a broad spectrum of clinical manifestations, largely attributable to the production of multiple virulence factors (Zeyrek S., 2019). In addition, its presence on the skin and in the feces of healthy animals indicates that immunosuppressive conditions or disturbances in the normal microbiota play a critical role in facilitating infection. Although infections are generally sporadic, this bacterium can give rise to a wide range of disease conditions across numerous animal species, including cattle, sheep, goats, pigs, dogs, cats, and reptiles (Ekselli S., 2019).

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Transmission

Pseudomonas infections exhibit increased colonization rates, particularly in environments such as animal shelters where dogs and cats are housed together, intensive care units, and clinical settings involving mechanical ventilation, cancer chemotherapy, or the use of broad-spectrum antimicrobial agents (Bonten M.J., 2002). These conditions substantially increase the risk of developing invasive infections. In the presence of immunosuppression, the bacterium initially breaches anatomical and physiological defense mechanisms, enabling adhesion and successful colonization. Following this stage, bacterial proliferation occurs within the affected tissue or organ until a critical population density is reached, thereby creating favorable conditions for infection. Once this threshold is exceeded, local tissue invasion commences, and if host defenses fail to control the process, overt clinical disease ensues (Stover C.K. et al., 2000).

Clinical Symptoms

The clinical manifestations of *Pseudomonas* infections differ according to the extent, localization, and severity of lesions present in affected animals. Infections caused by this organism typically arise following disruption of tissue integrity; however, because it rarely infects healthy tissues, it is regarded as a high-risk pathogen. A notable example includes an eight-year-old, 6.3-kg, male mixed-breed dog treated at Kangwon National University Animal Hospital that developed acute pneumonia after undergoing a successful kidney transplantation. Analysis of bronchoalveolar lavage samples confirmed infection with multidrug-resistant *P. aeruginosa* (Park K.M. et al., 2013).

Although *P. aeruginosa* infections in animals are typically sporadic, certain cases may progress to acute disease accompanied by septicemia. This pathogen is capable of causing wound infections across all animal species and is associated with a wide range of clinical conditions, including mastitis, uterine infections, enteritis, arthritis, respiratory tract disease, and botryomycosis in cattle (Leitner G. et al., 2007); pneumonia, mastitis, fleece rot, and pulmonary abscesses in sheep and goats (Kelly P. et al., 2016); otitis externa, urinary tract infections, corneal ulceration, pneumonia, endocarditis, and deep pyoderma in dogs and cats (Płókarz D. et al., 2022); metritis, abortion, corneal ulcers, and abscess formation in horses (Andrew S.E. et al., 2019); and septicemia in poultry (El-Sukhon S.N. et al., 2002). The most distinctive pathological finding associated with *P. aeruginosa* infections is the presence of nodular lesions that frequently lead to suppurative inflammation within affected tissues (EFSA AHAW Panel, 2022).

In a study carried out in Poland by (Płókarz D. et al., 2022), involving a total of 271 animals comprising 212 dogs and 59 cats, the demographic features of the study population as well as the anatomical sources of *P. aeruginosa* isolates obtained from cats were evaluated. The findings indicated that 83% of the isolates recovered from cats were derived from the respiratory tract, whereas this proportion was limited to 17% in dogs. Additionally, the authors suggested that cats may represent a more appropriate experimental model for human cystic fibrosis when compared to dogs.

Notably, within the same study, 118 of the *P. aeruginosa* isolates obtained from dogs originated from the ear and external auditory canal, with additional samples collected from the skin and respiratory tract. In contrast, isolates from cats were predominantly recovered from the nasal cavity (44 samples) as well as from the respiratory and oral cavities (49 samples) (Płókarz D. et al., 2022).

Antibiotic Resistance

Pseudomonas aeruginosa is regarded as one of the most difficult gram-negative pathogens to treat in both human and veterinary medicine, largely due to its inherent multidrug resistance mechanisms and its remarkable capacity to adapt to diverse environmental conditions (Bonten M.J., 2002; Ekselli S., 2019; Jawetz E. et al., 2010; Lister P.D. et al., 2009). The antimicrobial resistance profile of this organism is generally classified into three principal categories: intrinsic (natural), acquired, and adaptive resistance mechanisms (Güven Ö. et al., 2008; Koçhan A. et al., 2017; Mayer K.H. et al., 1995).

1. Intrinsic (natural) resistance mechanisms: The outer membrane of *P. aeruginosa* is characterized by inherently low permeability, which limits the intracellular penetration of numerous β-lactam and fluoroquinolone antibiotics (EFSA AHAW Panel, 2022; Hillier A., 2006). Additionally, decreased expression or complete loss of porin proteins—most notably OprD—constitutes a critical factor contributing to carbapenem resistance (Langendonk R.F. et al.,

2021; Lister P.D. et al., 2009; Płókarz D. et al., 2022). Another major intrinsic mechanism involves multidrug efflux systems, particularly MexAB-OprM, MexXY-OprM, and MexCD-OprJ, which actively transport antimicrobial agents out of the bacterial cell. These pumps confer broad resistance to aminoglycosides, quinolones, macrolides, and β-lactam antibiotics (Gilardi G.L., 1991; Hattab J. et al., 2021; Park K.M. et al., 2013).

2. Acquired resistance mechanisms: *P. aeruginosa* is capable of gaining additional resistance determinants through horizontal gene transfer via plasmids, transposons, and integrons (Jawetz E. et al., 2010; Koçhan A. et al., 2017; Mayer K.H. et al., 1995). This process is particularly relevant to the acquisition of genes encoding β-lactamases. Enzymes such as extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and carbapenemases—including metallo-β-lactamases of the VIM, IMP, and NDM families—play a pivotal role in the emergence of multidrug resistance in this species (Kelly P. et al., 2016; Langendonk R.F. et al., 2021; Ramanarayana P. et al., 2022; Robinson V.H. et al., 2019). These enzymes hydrolyze key antimicrobial agents, including piperacillin, ceftazidime, and carbapenems, thereby compromising their therapeutic efficacy (Lister P.D. et al., 2009; Płókarz D. et al., 2022; Šeol B. et al., 2002). Furthermore, resistance to aminoglycosides such as gentamicin and tobramycin may arise through the production of aminoglycoside-modifying enzymes (AMEs) (Leitner G. et al., 2007; Riggio M.P. et al., 2011).

3. Adaptive resistance mechanisms: The ability of *P. aeruginosa* to form biofilms provides substantial protection against antimicrobial agents (Güven Ö. et al., 2008; Lister P.D. et al., 2009; Sebola D. et al., 2020). Bacteria embedded within biofilms exhibit reduced susceptibility to antibiotics as a result of diminished metabolic activity, increased cell density, and restricted drug penetration (El-Sukhon S.N. et al., 2002; Park K.M. et al., 2013). This adaptive strategy significantly impairs treatment outcomes in veterinary clinical conditions such as chronic otitis externa, urinary tract infections, and wound infections (Jawetz E. et al., 2010; Koçhan A. et al., 2017; Stover C.K. et al., 2000). In addition, quorum sensing systems enable bacterial cell-to-cell communication, regulating biofilm development and the coordinated expression of virulence factors (Güven Ö. et al., 2008; Langendonk R.F. et al., 2021; Zeyrek S., 2019).

Recent veterinary investigations have documented a rising prevalence of multidrug-resistant (MDR) *P. aeruginosa* strains isolated from dogs and cats, with reported resistance rates to β-lactam antibiotics ranging between 40% and 70% (Jawetz E. et al., 2010; Lister P.D. et al., 2009; Sharma D. et al., 2019; Zeyrek S., 2019). This increasing resistance burden not only restricts available therapeutic options but also highlights the clinical relevance of broad-spectrum β-lactam/β-lactamase inhibitor combinations, such as piperacillin/tazobactam, in veterinary practice (Langendonk R.F. et al., 2021; Lister P.D. et al., 2009).

Antibiotic Selection

β-lactam antibiotics are among the most frequently selected agents for the treatment of *P. aeruginosa* infections and include piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, and carbapenems (Gilardi G.L., 1991; Jawetz E. et al., 2010; Mayer K.H. et al., 1995). These antimicrobial agents exert their bactericidal effect by binding to penicillin-binding proteins (PBPs), thereby inhibiting transpeptidase activity essential for peptidoglycan synthesis in the bacterial cell wall. Disruption of cell wall integrity ultimately results in cell lysis and bacterial death (Güven Ö. et al., 2008; Langendonk R.F. et al., 2021; Lister P.D. et al., 2009).

Piperacillin is a broad-spectrum ureidopenicillin that demonstrates strong affinity for PBP-3 in *P. aeruginosa* (Jawetz E. et al., 2010; Stover C.K. et al., 2000). Nevertheless, resistance to piperacillin may arise through the production of β-lactamases. To counteract this mechanism, tazobactam acts as an inhibitor of serine-type β-lactamases, thereby preventing enzymatic degradation of piperacillin and enhancing its antibacterial activity. Numerous in vitro and in vivo studies have documented a synergistic effect of the piperacillin–tazobactam combination against *P. aeruginosa* isolates (Gilardi G.L., 1991; Jawetz E. et al., 2010; Lister P.D. et al., 2009; Sebola D. et al., 2020).

Veterinary clinical investigations indicate that piperacillin–tazobactam is particularly effective in managing conditions such as otitis externa, pyoderma, skin and soft tissue infections, and urinary tract infections in dogs (Hattab J. et al., 2021; Hillier A., 2006; Koçhan A. et al., 2017). In the study conducted by Hattab J. et al. (2021), *P. aeruginosa* was isolated from 24 samples obtained

from 300 dogs presenting with suspected pyoderma, otitis, or urinary bladder infections, and resistance to piperacillin–tazobactam was reported to be only 8.3%. Consistently, a study performed in South Africa by Sebola D. et al. (2020) demonstrated that multidrug-resistant *P. aeruginosa* strains retained relatively high susceptibility to this antimicrobial combination.

In routine clinical application, the effectiveness of piperacillin–tazobactam should be assessed in relation to its pharmacokinetic characteristics, local antimicrobial resistance patterns, and the potential presence of bacterial biofilms (Ekselli S., 2019; Langendonk R.F. et al., 2021; Robinson V.H. et al., 2019). These factors play a decisive role in determining therapeutic outcomes. Moreover, the broad antimicrobial spectrum of this combination and its comparatively low resistance rates support its use as either an alternative or a preferred treatment option for *P. aeruginosa* infections (Jawetz E. et al., 2010; Langendonk R.F. et al., 2021; Lister P.D. et al., 2009; Zeyrek S., 2019).

CONCLUSIONS

The treatment of *Pseudomonas aeruginosa* infections remains a challenging and complex process today. This difficulty arises from the multifactorial nature of the bacterium's intrinsic, acquired, and adaptive antibiotic resistance mechanisms. The combination of different resistance mechanisms leads to the emergence of multidrug-resistant (MDR) strains, rendering conventional antibiotics insufficient for the effective treatment of infections. *P. aeruginosa* also has the potential to rapidly develop new resistance mechanisms against novel antibiotics, highlighting the serious risks posed to animal health by the excessive and indiscriminate use of antibiotics.

Veterinary clinical studies and isolated strains support the efficacy of piperacillin/tazobactam in *P. aeruginosa* infections. Accordingly, these findings indicate that piperacillin/tazobactam is an effective therapeutic option for both acute and secondary chronic infections. Moreover, data from human and animal studies demonstrate that this combination is a clinically reliable option in the management of *P. aeruginosa* infections, given the bacterium's ability to resist β-lactamase production and other resistance mechanisms.

In conclusion, considering the antibiotic resistance of *P. aeruginosa* and the clinical severity of infections, the targeted and controlled use of piperacillin/tazobactam is regarded as a critical strategy to enhance treatment success and prevent the development of resistance. Accordingly, in veterinary practice, the use of piperacillin/tazobactam should be guided by bacteriological and clinical data to ensure its appropriate and effective application.

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