Effective management of multi-drug resistant *Klebsiella pneumoniae* pyometra in a dog using cefoperazone–sulbactam and enzyme therapy: A case report

Pal M.[1*]; Aalisha A.[2]

Received: May 2025 Accepted: July 2025

Abstract

This case report describes the successful treatment of pyometra caused by multi-drug resistant (MDR) *Klebsiella pneumoniae* in a 5-year-old Labrador retriever. Antibiotic susceptibility testing revealed resistance to commonly used antibiotics, including amoxicillin-clavulanate, gentamicin, and ciprofloxacin, but sensitivity to cefoperazone/sulbactam, a third-generation cephalosporin combined with a beta-lactamase inhibitor. The therapeutic regimen involved cefoperazone/sulbactam in combination with trypsin-chymotrypsin enzyme therapy, aimed at enhancing drug efficacy by facilitating necrotic tissue clearance and promoting resolution of inflammation. This combined treatment led to complete clinical recovery, underscoring its potential as an effective alternative for managing severe open pyometra cases when surgical intervention is contraindicated.

Keywords: Cefoperazone-sulbactam, Trypsin-chymotrypsin, Pyometra, *Klebsiella pneumoniae*, Multi-drug resistant

1-MWildlife Health and Forensic Centre, College of Veterinary Science & AH, Anjora. DSVCKV, Durg, Chhattisgarh, India
2-Department of Veterinary Pharmacology and Toxicology, college of Veterinary Science & AH, Anjora, DSVCKV, Durg, Chhattisgarh, India
Corresponding author's Email: drmayankpalvet@gmail.com

Introduction

Pyometra is a potentially life-threatening condition that predominantly affects unspayed female dogs in the second half of their reproductive cycle (Frances, 2006). It is characterized by a pus-filled uterus and can lead to sepsis and multi-organ failure if not treated promptly (Azevedo *et al*., 2024). The most common pathogen associated with pyometra is *Escherichia coli*, though other bacteria, including *Klebsiella pneumoniae*, are increasingly being identified (Suresh Kumar *et al*., 2023).. The emergence of multi-drug resistant (MDR) *Klebsiella pneumoniae* in pyometra cases presents a significant challenge to treatment, especially when standard antibiotics fail (Melo *et al*., 2022). *Klebsiella pneumoniae*, a Gram-negative bacteria, is known for its ability to develop multi-drug resistance, complicating the treatment of infections it causes. Resistance to commonly used antibiotics such as amoxicillin-clavulanate, enrofloxacin, and gentamicin is of growing concern (Gariglio Clark Xavier *et al*., 2024). *Klebsiella* infections in pyometra cases can be particularly difficult to treat, especially when initial empirical therapy is ineffective. Cefoperazone-sulbactam, a beta-lactam/beta-lactamase inhibitor combination, provides broad-spectrum activity against MDR gram-negative bacteria (Sader *et al.,* 2020). Adjunctive therapy with Trypsin-chymotrypsin, a proteolytic enzyme, may further enhance treatment by breaking down necrotic tissue, reducing inflammation, and improving antibiotic penetration into infected tissues (Shah and Mital, 2018). ,Sroithongkham *et al*., 2024). This trial investigates the efficacy of this combination in managing a case of MDR *Klebsiella pneumoniae*-induced open pyometra.

Case presentation

A 5-year-old, unspayed female Labrador retriever was presented with clinical signs of open pyometra, including lethargy, anorexia, abdominal distension, melena and purulent vaginal discharge (Fig.1a and b). Upon physical examination, the dog was febrile and exhibited signs of abdominal pain.

Figure1(a): Labrador retriever (*Canis familiaris*) bitch with distended abdomen.

Figure 1(b): Purulent discharge from the vagina of a Labrador retriever (*Canis familiaris*).

The dog was stabilized with intravenous fluids and placed on broad-spectrum antibiotic therapy with cefquinone and amoxicillin-clavulanate. Despite initial treatment, her condition worsened, and pus cultures identified *Klebsiella pneumoniae* as the causative pathogen.

Sensitivity testing revealed that the *Klebsiella pneumoniae* isolate was resistant to amoxicillin-clavulanate,ciprofloxacin, ceftriaxone and gentamicin etc., but susceptible to cefoperazone/sulbactam (Table 1).

Table 1: Antibiotic susceptibility testing was performed using the disk diffusion method on pus from the uterus of a Labrador retriever (*Canis familiaris*). The antibiotics tested included.

S.NO.	Antibiotic	Sensitivity	S.NO.	Antibiotic	Sensitivity
01	Colistin	S	11	Amoxyclav	R
02	Polymixin B	S	12	Ceftriaxone	R
03	Piperacillin/tazobactam	S	13	Cefotaxime	R
04	Cefoperazone/sulbactam	S	14	Doxycycline	R
05	Fosfomycin	S	15	Gentamicin	R
06	Amikacin	S	16	Ceftazidime	R
07	Meropenem	S	17	Cefuroxime	R
08	Cefepime	S	18	Cotrimoxazole	R
09	Levofloxacin	R	19	Minocycline	R
10	Ciprofloxacin	R	20	Imipenem	R

S: Sensitivity; R: Resistant

Pus samples collected from the affected Labrador were subjected to Gram staining, which revealed the presence of Gram-negative bacilli. Further microbiological analysis identified the organism as *Klebsiella pneumoniae* (>10^5 CFU/mL).

The RFT reports showed increased blood urea, uric acid and serum creatinine, indicating towards kidney damage. The haematology reports showed increased WBC count and neutrophilia.

Treatment and discussion

This trial demonstrated the successful resolution of pyometra caused by MDR *Klebsiella pneumoniae* using cefoperazone-sulbactam in combination with Trypsin-chymotrypsin. Cefoperazone-sulbactam (Valocef®) was administered intravenously at 40 mg/kg B.D. for 14 days. (Maximum safety dose of this antibiotic taken as 200mg/kg/day (Yoneda *et al*., 1980, Imane *et al*., 2025). Cefoperazone has a long elimination half-life of approximately 2h, which allows for twice daily administration. Cefoperazone-sulbactam's broad-spectrum coverage proved effective against the MDR strain, addressing the primary infection (Sader *et al*., 2020). Trypsin-Chymotrypsin as adjunctive enzyme therapy (1 lakh AU) was given 1 tablet twice a day for 3 days and then later given once a day for 7 days. The enzyme aimed to degrade necrotic debris and fibrin, facilitating antibiotic penetration and reducing tissue inflammation (Szkopek *et al*., 2024). It shows high bioavailability without losing its biological activities as an anti-inflammatory, anti dematous, fibrinolytic, antioxidant, and anti-

infective agent. The synergistic action of Trypsin-chymotrypsin likely enhanced drug delivery to the infected uterus by breaking down necrotic material and reducing inflammatory barriers (Shah and Mital, 2018). Supportive therapy as Intravenous fluids: Ringer's lactate at 20 ml/kg/day on day 1, to address dehydration and improve systemic perfusion. From next day onwards D5 at 20 ml/kg/day for next 13 days. Gastroprotectant, Pantoprazole at 40 mg I/V for 7 days to prevent gastric irritation. Sucralfate and oxetacaine suspension 5ml twice orally for 15 days was given to treat melena (Ylhäinen *et al*., 2025). Diuretics and Kidney protectants are a very important part of supportive therapy. A combination of Spironolactone+furosemide (30:20) at 2mg/kg twice was given. Combination of Taurine(500mg) +Acetylcysteine(150mg) o.d. and a kidney detoxifier for 15 days (in this case UT-KID® 10mL orally b.d.). Diuretics and kidney-protectant drugs are crucial in the treatment of pyometra in bitches to manage the risk of kidney damage caused by endotoxemia, systemic inflammation, and reduced renal perfusion (Xavier *et al.*, 2023). Diuretics help eliminate toxins and excess fluids, preventing complications like fluid retention and edema. Kidney-protectant drugs improve renal blood flow and safeguard kidney function, ensuring systemic stability, reduce the risk of renal failure and improve the overall treatment outcome. Late diagnosis of pyometra, when kidney failure has already occurred, may result in irreversible damage to kidney (Fossum, 2008). Supportive care played a vital role in stabilizing the patient during systemic illness. Monitoring of clinical parameters (temperature, appetite, and vaginal discharge) were assessed daily.

Results

By day 3, the patient demonstrated marked improvement, with fever resolution, increased appetite, and reduced vaginal discharge. By day 5, the bitch regained energy, and purulent discharge was minimal. On day 7, hematology showed normalized WBC counts (12,000/µL) and resolved neutrophilia. Repeat cultures performed on day 10 confirmed the eradication of *Klebsiella pneumoniae*. The bitch achieved full clinical recovery by day 14 without requiring surgical intervention. At the 14-day follow-up, the dog was clinically normal, with no signs of recurrence of pyometra. Blood work performed at this time showed normal renal and hepatic function. The dog's recovery was uneventful, and no further antibiotic treatment was required.

Although surgery remains the treatment of choice for pyometra, this study highlights the potential of non-surgical medical management in cases where surgery is not feasible. The use of proteolytic enzymes like Trypsin-chymotrypsin as an adjunct to antibiotics may represent a valuable strategy in treating complicated infections (Cécere *et al*., 2024).

Implications for future management

This case underscores the growing importance of conducting bacterial culture and sensitivity testing in cases of pyometra, particularly when conventional antibiotics fail to produce the desired clinical outcome. Cefoperazone/sulbactam combined with trypsin-chymotrypsin represents a valuable treatment option for cases of pyometra caused by multi-drug resistant *Klebsiella pneumoniae*, especially when other antibiotics are ineffective.

Conclusion

The combination of cefoperazone-sulbactam and trypsin-chymotrypsin effectively managed a case of MDR *Klebsiella pneumoniae*-induced pyometra in a bitch. This approach offers a viable alternative to surgical management in selected cases, particularly when surgery is declined or contraindicated. Further studies in larger populations are recommended to standardize this protocol and evaluate its broader applicability.

References

Azevedo Moni, C., Eduarda Dias, M., Elisabete Lopes, C., Maboni Siqueira, F., 2024. Escherichia coli isolated from pyometra and cystitis in the same animal exhibit a wide phenotypic similarity. *Journal of Applied Microbiology*, 135, 5, lxae108, https://doi.org/10.1093/jambio/lxae108.

Cécere, B.G.O., Anzigliero, E.C.Z., Schonorr, A., Ribeiro, T.P., Suarez, W.H.C., Monteiro, D.P. and Da Silva, A.S., 2024. Addition of Protease Enzyme to Dog and Cat Feed and Its Influence on the Digestibility Coefficient, Immune Response, and Metabolic Biomarkers. *Food and Nutrition Sciences*, 15, 1043-1054. https://doi.org/10.4236/fns.2024.151106 7.

Fossum, T.W., 2008. Cirurgia dos sistemas reproductive e genital. In: Cirurgia de pequenos animals. 3.ed. Rio de Janeiro: *Elsevier*, pp.702-774.

Frances, O.S., 2006. Canine pyometra. *Theriogenology*, 66(**3**), 610-612.

Imane, H., Khiati Baghdad, K., and Slimani Khaled Mabrouk, S., 2025. Contributing Factors and Management of Pyometra in Dogs of Algeria. *Science line Publication World's Veterinary Journal World*, 15(**2**). 327-334. https://dx.doi.org/10.54203/scil.2025.wvj35. PII: S232245682500035-15.

Melo, R.T., Oliveira, R.P., Silva, B. F., Monteiro, G. P., Saut, J.P.E., Costa, L.R.M., Dias, S.D.C. and Rossi, D.A., 2022. Phylogeny and Virulence Factors of Escherichia coli Isolated from Dogs with Pyometra. *Veterinary Sciences*, 9(**4**), 158. https://doi.org/10.3390/vetsci9040158.

Sader, H.S., Carvalhaes, C.G., Streit, J.M., Castanheira, M. and Flamm, R.K., 2020. Antimicrobial activity of cefoperazone-sulbactam tested against Gram-Negative organisms from Europe, Asia-Pacific, and Latin America. *International Journal of Infectious Diseases*, 91, 32-37.

Shah, D. and Mital, K., 2018. The Role of Trypsin:Chymotrypsin in Tissue Repair. *Qadvances in Therapy*, 35(**1**), 31-42.

Sroithongkham, P., Nittayasut, N., Yindee, J. Nimsamar, P., Payungporn, S., Pinpimai, K., Ponglowhapan, S., and Chanchaithong, P., 2024. Multidrug-resistant *Escherichia coli* causing canine pyometra and urinary tract infections are genetically related but distinct from those causing prostatic abscesses. *Scientific Reports,* 14, 11848. https://doi.org/10.1038/s41598-024-62028-9.

Suresh Kumar, R., Rasool, A., Umamageswari, J., and Thulasiraman,, S., 2023. Ultrasonographic evaluation of canine pyometra. *Journal of Dairy, Veterinary and Animal Research*, 12(**1**), 5-6. https://www.doi.org/10.15406/jdvar.2023.12.00314.

Szkopek, D., Pierzynowski, S.G., Pierzynowska, K., Zaworski, K., Kondej, A., Wychowański, P., Konieczka, P., Seklecka, B., Donaldson, J., Jank, M. and Woliński, J., 2024. A review: Pancreatic enzymes in the treatment of chronic pancreatic insufficiency in companion animals. *Journal of Veterinary Internal Medicine*, 38(**4**). DOI: 10.1111/jvim.17096. Epub 2024 May 9. PMID: 38721836; PMCID: PMC11256127.

Xavier, R.G.C., Santana, C.H., de Castro, Y.G., de Souza, T.G.V., do Amarante, V.S., Santos, R.L. and Silva, R.O.S., 2023. Canine Pyometra: A Short Review of Current Advances. Animals (Basel). 13(**21**), 3310. DOI:10.3390/ani13213310. PMID: 37958065; PMCID: PMC10647846.

Xavier, R.G.C, Santana, C.H., Sanches da Silva, P.H., Oliveira Paraguassú, A., Rafael Nicolino, R., Maria Coletto Freitas, P., de Lima Santos, R., and Otávio Silveira Silva, R., 2024. Association between bacterial pathogenicity, endometrial histological changes and clinical prognosis in canine pyometra, *Theriogenology*, 214, pp. 118-123, ISSN: 0093-691X. https://doi.org/10.1016/j.theriogenology.2023.10.007.

Ylhäinen, A., Mölsä, S., Thomson, K., Laitinen-Vapaavuori, O., Merja Rantala, M., and Thomas Grönthal, T., 2025. Bacteria associated with canine pyometra and concurrent bacteriuria: A prospective study, *Veterinary Microbiology*, 301. https://doi.org/10.1016/j.vetmic.2024.110362.

Yoneda, T., Masatani, H., Shibata, T., Kawamura, Y., Sato, S., Iwasaki, S., Takimoto, Y., Nagasawa, M. and Takai, A., 1980. Subacute toxicity test of cefoperazone in beagle dogs with the intravenous administration for 3 months (author's transl). *Japanese Journal of Antibiotics*, 33(**10**), 1028-55.