

# Treating Carbapenemase-Producing *Enterobacterales* Urosepsis with Ceftazidime/Avibactam in Pregnancy

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## Background

Urinary tract infection (UTI) in pregnancy has maternal, fetal and neonatal implications including maternal sepsis, preterm birth and placental hypoperfusion. Carbapenemase-producing *Enterobacterales* (CPE) infections are associated with a higher rate of mortality than non-CPE infections<sup>1</sup>. CPE are resistant to beta-lactam antibiotics, with therapeutic options limited in pregnancy due to a lack of safety data including the use of ceftazidime/avibactam. This case describes the use of an antimicrobial with no published human pregnancy safety data to treat CPE urosepsis in pregnancy.

## Case Presentation & Progress

### Presentation

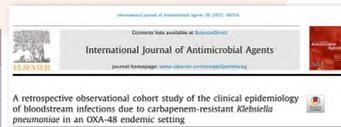
HK presented to the Maternal Fetal Assessment Unit at 23+5 weeks' gestation with symptoms of urosepsis, on a background of recurrent UTIs, duplex left kidney and a partial nephrectomy, performed in India.

### Cultures

Urine culture and sensitivities identified an OXA-48 carbapenemase-producing *Klebsiella pneumoniae* isolate that was only susceptible to four antimicrobials (Table 1). HK was diagnosed was multi-drug resistant (MDR) urosepsis.

Table 1: OXA-48 CPE Antibiogram

Drug	Interpretation	MIC (mg/L)
Meropenem	Resistant	>32
Ceftolozane/tazobactam	Resistant	>256
Ceftazidime/avibactam	Susceptible	1.5
Colistin	Susceptible	0.5
Fosfomycin	Susceptible	24
Cefiderocol	Susceptible	0.25



Whole Genome Sequence Analysis of the First Australian OXA-48-Producing Outbreak-Associated *Klebsiella pneumoniae* Isolates: The Resistome and *In Vivo* Evolution

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### First Admission Progress and Discharge

HK received a 10-day course of ceftazidime with avibactam 2.5g eight-hourly and was discharged at 25+4 weeks' gestation. Methenamine hippurate 1g 12-hourly was prescribed as prophylaxis for the remainder of pregnancy.

### Readmission

HK represented with urosepsis at 36 weeks' gestation and was recommenced on ceftazidime/avibactam. Therapy continued until delivery.

### Discharge

Mother and baby were discharged after four days, with maternal and neonatal follow-up plans in place.



### Urology Follow-Up

Two months post-discharge, HK reported she had not had any UTIs since delivery. Baby of HK was well and reported nil complications since delivery.

## Gestation

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### Empirical Therapy

After urine and blood cultures had been taken, HK was empirically treated with ceftriaxone per local guidelines<sup>2</sup>. HK showed no clinical improvement; thus, ceftriaxone was changed to meropenem, whilst awaiting sensitivities.

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### Direct Therapy and Implications in Pregnancy

Pharmacy supported the clinical decision that ceftazidime/avibactam was the most appropriate antimicrobial.<sup>3,4</sup> Despite a lack of safety data for this combination, ceftazidime has not been associated with an increased risk of birth defects or adverse pregnancy outcomes<sup>5</sup> and avibactam showed no embryofetal toxicity in rats at 9 times the human dose and in rabbits at 2 times the human dose. At higher doses, anomalies such as delayed ossification of several bones were observed.<sup>6</sup> Ceftazidime/avibactam showed a dose related (3 times the human dose) increase (less than 10%) in the incidence of renal pelvic and ureter dilation in rat pups.<sup>6</sup>

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### Delivery

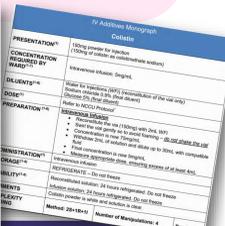
Baby of HK was delivered by non-elective caesarean section at 37+3 weeks' gestation.



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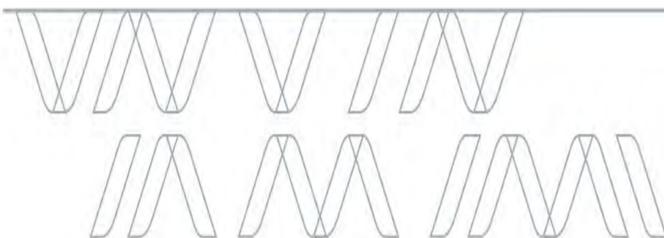
### Neonatal Management

Baby of HK was born well, however developed symptoms of early-onset sepsis. Empirical treatment with IV benzylpenicillin & IV colistin commenced, under microbiology consultation. A neonatal medication protocol was drafted with special considerations for the complex dosing of this rarely used drug in neonates.<sup>8</sup> After 48 hours of intravenous antibiotics, Baby HK had clinically improved, and her septic screen results were negative.



## Conclusion

CPE are resistant to all beta-lactam antibiotics and therapeutic options are further limited in pregnancy due to a lack of safety data about newer, broad-spectrum antimicrobials used for MDR isolates. This case showed no association between ceftazidime/avibactam use in pregnancy and adverse outcomes.



## References

1. Australian Commission on Safety and Quality in Health Care. Information for clinicians: Carbapenem Resistant Enterobacteriaceae [Internet]. Darlinghurst, NSW: Australian Commission on Safety and Quality in Health Care; Nov 2013 [cited 28 Oct 2022]. <https://healthpoint.hdwa.health.wa.gov.au/policies/Polices/NMAHS/WNHS/WNHS.IG.InfectionsObstetricGynaecologyAntibioticTreatmentUrinaryTractInfection.pdf>
2. Taslan AT, et al.; Study Group for Carbapenem Resistance (SCARE). A retrospective observational cohort study of the clinical epidemiology of bloodstream infections due to carbapenem-resistant *Klebsiella pneumoniae* in an OXA-48 endemic setting. *Int J Antimicrob Agents*. 2022 Apr;59(4):106554.
3. Espedido BA, Steen JA, Ziochos H, Grimmond SM, Cooper MA, Gosbell IB, van Hal SJ, Jensen SO. Whole genome sequence analysis of the first Australian OXA-48-producing outbreak-associated *Klebsiella pneumoniae* isolates: the resistome and *in vivo* evolution. *PLoS One*. 2013;8(3):e59920.
4. The Royal Women's Hospital. Ceftazidime. In: Pregnancy and Breastfeeding Medicines Guide [Internet]. Parkville (Victoria): The Royal Women's Hospital; 2021.
5. Truven Health Analytics. Ceftazidime/avibactam. In: Micromedex [Internet]. Greenwood Village (CO): Truven Health Analytics; cited 2022 October 31.
6. Ilhan O, Bor M, Ozdemir SA, Akbay S, Ozer EA. Efficacy and Safety of Intravenous Colistin in Very Low Birth Weight Preterm Infants. *Paediatr Drugs*. 2018 Oct;20(5):475-481. doi:10.1007/s40272-018-0301-5. PMID: 30073562