

Challenges of using Ceftazidime/Avibactam in paediatrics

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Overview



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- Ceftazidime/avibactam
- Dosing
- Patient summary
- Adverse drug reactions
- Patient case
- Further areas for development

Ceftazidime/Avibactam

- Avibactam is a non β lactam β lactamase inhibitor
 - Inhibits ESBLs, KPCs, OXA -48, AMPCs
 - Does NOT inhibit metallo- β lactamases
- Licensing - Gram negative infections including MDR infections in > 18 yo
- Adult dose 2g/0.5g TDS
 - Renal dose adjustment $\text{CrCl} < 50 \text{ml/min}$
- IV infusion over 2 hours
- Paediatrics – no information on:
 - Dosing, safety and tolerability

Ceftazidime/Avibactam

- Introduced into MFT in 2017
- Medicines management – monitor outcomes of newly introduced treatments
- Ongoing work to monitor CPE outcomes within the Trust
- Around 90% of our CPEs in Manchester are KPCs

Retrospective case review



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- 7 patients over a 12 month period at Royal Manchester Children's Hospital (RMCH)
 - 9 infection episodes
 - Patients were between 16 months and 16 years at the time of treatment
- Review of – Indication, dosing strategy, infusion issues, concurrent use of TPN, adverse effects, 30 day outcomes
- In the same period 15 adult patients were treated with ceftazidime/avibactam and comparisons of rates of adverse drug reactions were made
- Initial patients – had very limited treatment options

Dosing

- Adult dosing – ceftazidime component is the same dose
- No available information on dosing of avibactam in paed
- No dosing or pk studies in paed
 - Use of 1st principles
 - Liaison with Pfizer medical information
- Dosing schedule based on dosing of ceftazidime in paediatrics
 - 50mg/kg tds (renally adjusted where necessary)

Pt	Age	Sex	Speciality	Indication	Organism ID	Duration (days)	30 day outcome
A	16y	F	Metabolics	Sepsis – urine/portacath	Klebsiella pneumoniae - KPC	8	No recurrence
B	7y 11m	F	Respiratory	Pseudomonas sputum, CXR bilateral consolidation PICU	MDR Pseudomonas	14	RIP
C	14y	M	Medicine	Wound infection	MDR Pseudomonas	14	Discharged home
D	6y	M	Medicine	Chest sepsis	Klebsiella varicola -KPC	7	Discharged home
				LRTI		7	Discharged home
E	3y 1m	F	Gastro	Line infection	Klebsiella oxytoca - KPC	14	No recurrence
F	16 m	F	Surgery	Line infection	Klebsiella pneumoniae - KPC	30	No recurrence
				KPE bacteremia		14	No recurrence
G	4y 2m	F	Gastro	Line infection	MDR enterobacter asburiae in sputum	7	Discharged home

Treatment outcomes

9 infection episodes:

8 resolutions with no recurrence within 30 days

1 RIP

Adverse drug reactions:

1 case of thrombocytopenia (platelets dropped 140 to 51)

1 case of abnormal LFTs

Hypernatraemia

- Sodium content:

Ceftazidime	104mg per 2g vial
Ceftazidime/avibactam sodium	148mg per 2g/0.5g vial
- 5 of 6 patients experienced hypernatraemia during treatment with ceftazidime/avibactam
 - 1 patient no results taken
- Compared to 1/15 adults in the same time period
- None of the patients had treatment stopped due to hypernatraemia
- Retrospective review of pip/tazo courses in the same paed patients hadn't led to hypernatraemia
 - Pip/taz contains more sodium per dose for a 20kg child than ceftazidime/avibactam

Case– Miss SO age 16 months

- Complex PMHx- spina bifida, neurogenic bladder, gastrectomy, TPN dependent
- Reason for admission– post op laparotomy, intestinal reconstruction
- Micro Hx
 - recurrent UTIs, line infections, previous CPE bacteremia -treated with temocillin and amikacin
 - Line infection – CPE treated with caz/avi for 30 days (6 months previously)
- CPE rectal screen positive but no infection concerns
- Then....
 - Temp 38.3, WCC 30 (baseline 20)
 - Started ceftriaxone and teicoplanin plus stat amikacin
 - Paired cultures and MSU
 - Blood culture positive for Klebsiella Pneumoniae carbapenemase producing strain
 - Likely UTI/abdominal source

Antibiogram - Miss SO age 16 months

Antibiotic	Sensitive?	Antibiotic	Sensitive?
Trimethoprim	S	Amoxicillin	R
Ciprofloxacin	S	Co-amoxiclav	R
Cefuroxime	R	Amikacin	S
Tigecycline	S	Piperacillin/tazobactam	R
Meropenem	R	Ertapenem	R
Ceftazidime/avibactam	S	Temocillin	R

Challenges with Miss SO

- Choice of agent
- Dosing – used 50mg/kg tds
- Hypernatraemia on previous use of ceftazidime/avibactam
- Infusion time – caz/avi = 2hours tds, & ciprofloxacin 1 hour tds
 - TPN dependent
 - Limited line access
 - No compatibility information for ceftazidime/avibactam
 - Ciprofloxacin and ceftazidime are compatible at Y site, but should we risk this?
 - Had to liaise with dieticians and gastro team
 - Can't stop and restart TPN
 - Reduce volume of TPN and give overnight with fluids in between
- Prioritisation of therapy
- Attached to IVs for 9 hours of the day + TPN over night

Outcomes Miss SO

14 days treatment

No recurrence of infection

Summary

- Importance of reflection on cases
 - Hypernatraemia trend wouldn't have been picked up in this group
 - Important to assess treatment outcomes, is the new treatment working in this group of patients?
- Importance of pharmacovigilance
- Sharing experience
- Plans for future work
 - Collaboration with Alder Hey antimicrobial pharmacist
 - Reviews of use of other new antimicrobials in paed
 - Ceftolozane/tazobactam (should reduce use of ceftazidime/avibactam)
 - Isavuconazole (used in 3 patients so far)

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