Clinical Management

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CRE Case Presentation

Clinical synopsis

- A 38-yo male pt was transported to MetroHealth ED following head trauma which resulted in a large temporal bone fracture, subdural & subarachnoid hemorrhage
- He underwent urgent craniectomy followed by several neurosurgical procedures
- Lengthy hospitalization with prolonged mechanical ventilation, tracheostomy/gastrostomy, discharge to long term care
- Outcome: poor neurologic status, intractable pain, and spastic paresis; an intrathecal baclofen pump was placed
- Readmitted with fever 39.8 C, witnessed aspiration, altered mental status, seizures (See timeline)
- PMHx: alcohol dependence, history of pancreatitis, HTN, history of pancreatitis
- PSHx: Craniectomy and numerous neurosurgical revisions
- No known drug allergies

Physical Exam and Initial Workup

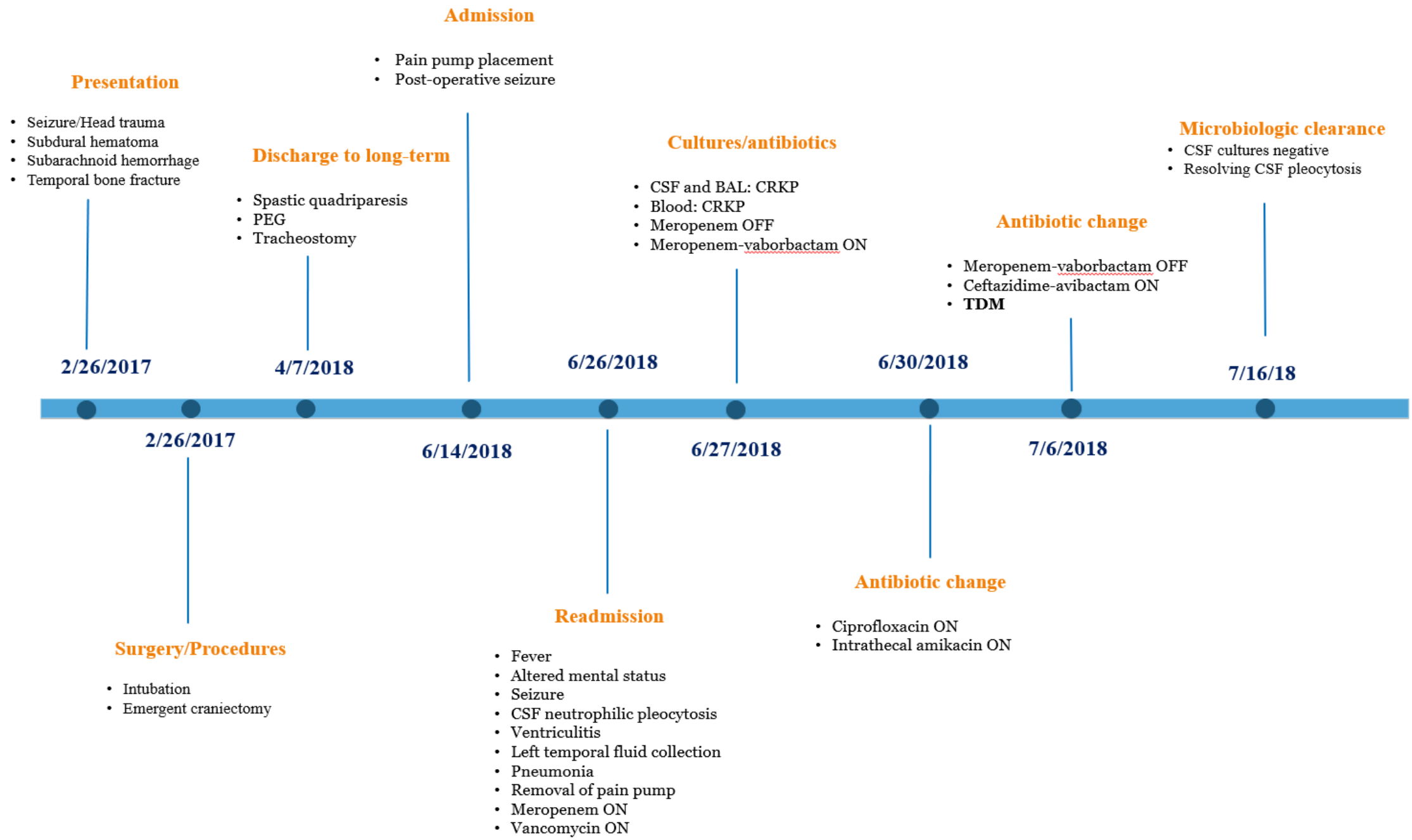
- Temp 39.7, HR 120 bpm, RR 18, BP 105/74
- Significant distress, diaphoresis, shaking chills
- Right sided rhonchi
- No erythema, swelling, purulence at the operative site
- Neuro: moving all extremities, baseline spasticity

- Blood and urine cultures were collected
- Lumbar puncture: CSF cell count, differential, culture
- Meropenem and Vancomycin started empirically
- CT head
- Intrathecal pump removal

Case summary- Background

- A challenging case of **post-neurosurgical meningitis** caused by KPC-*KP* compelled us to measure the pharmacological properties of CZA in the treatment of this syndrome.
- **Therapeutic drug monitoring (TDM)** was employed to measure and guide the correct dosing of CZA .
- We sought to determine if the different components of this formulation achieve adequate bactericidal and bacteriostatic levels in the human CSF

Timeline depicting case progression, antibiotics, and TDM initiation (dates in mm/dd/yyyy format)



Lab results

- WBC count 21K (86% PMNs)
- CSF neutrophilic pleocytosis
  polymorphonuclear cells)
- Elevated CSF protein (>200 m
- Low CSF glucose level (< 20 r
- CT head: diffusely inflamed v
  temporal fluid collection
- CT chest: Right upper and m
- Blood cultures 4/4: *Klebsiella*
- CSF cultures: *Klebsiella pneu*
- Drainage of temporal lobe abscess: Cultures as ab
- Discuss points:
  - Additional antimicrobial susceptibility testing
  - Additional workup ?

Amikacin	R
Ampicillin	R
Amox/Clavulanate	
Aztreonam	
Ceftriaxone	
Ceftazidime	
Cefotaxime	
Cefazolin	
Ciprofloxacin	
Cefepime	
Cefuroxime	
Nitrofurantoin	
Gentamicin	
Imipenem	
Levofloxacin	
Meropenem	
Piperc/Tazobact	
Trimeth/Sulfa	
Tetracycline	

Other susceptibility tests

07:56 Tue Dec 18 LTE 97%

Back Ceftazidime-avibactam

Peak Serum Level[3] (µg/mL)	Ceftazidime: 90.4 Avibactam: 14.6 (SS)
Protein Binding (%)	Ceftazidime: <10 Avibactam: 5.7-8.2
Average Serum Half-life[4] (T½, hr)	Ceftazidime: 2.8 Avibactam: 2.7
CSF/Blood Penetration[6] (%)	See Ceftazidime page Avibactam: no data
Biliary Penetration	See Ceftazidime page Avibactam: no data
Therapeutic Levels in CSF[7]	See Ceftazidime page Avibactam: no data
Volume of Distribution[8] (Vd)	Ceftazidime: 17 L (Vss) Avibactam: 22.2 L (Vss)
Area Under Curve[9] (AUC)(µg*hr/mL)	Ceftazidime: 291 (AUC_{0-8}) Avibactam: 38.2 (AUC_{0-8})
Cytochrome P450 Interaction	None known

/mL

/mL

s?

Ceftazidime-avibactam PK/PD CSF data

- Due to its microbiological activity, Ceftazidime-avibactam (CZA) is often used to treat *KPC-KP* bloodstream and urinary tract infections
- However, clinical experience with CNS infections is lacking
- Limited pharmacologic data available
- In a rabbit model, both ceftazidime and avibactam exhibited ~ 38% CSF penetration.
- Experimentally, CZA decreased CSF bacterial loads by a mean of 5.66 log10 CFU over 8 hours

Few published cases

- **Case report of a 27-year-old patient with post-neurosurgical meningitis and extra-axial fluid collection secondary to KPC-2 producing *K. pneumoniae.* Successful treatment accomplished with CZA monotherapy (MIC 1 µg/ml) dosed at 2.5 g every 6 hours for a total of 14 days**

Ceftazidime/avibactam use for carbapenem-resistant *Klebsiella pneumoniae* meningitis: a case report

Amanda Holyk ✉, Valerie Belden, Jonathan J Lee, William Musick, Ryan Keul, Gavin W Britz, Jiejian Lin

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 1, 1 January 2018, Pages 254–256, https://doi.org/10.1093/jac/dkx358
Published: 10 October 2017

Ceftazidime-Avibactam for the Treatment of Post-Neurosurgical Meningitis Caused by a *Klebsiella pneumoniae* carbapenemase (KPC)-Producing *Klebsiella pneumoniae*

Sophie Samuel, PharmD, Nancy J. Edwards, MD, Laura J Rojas, MSc, Susan D. Rudin, BS, Steve H. Marshall, MS, Ignacio De Cicco, MD, Robert A. Bonomo, MD, Cesar Arias, MD, PhD, FIDSA, Truc T. Tran, PharmD

β-lactam TDM

- β-lactam TDM has not been widely investigated
- PK variability can be huge, especially in critical illness, renal dysfunction, obesity, and burns
- TDM may be useful in these populations and for poorly susceptible organisms
- In vitro and animal data support a PD target of 40-70% for the time that the free (or unbound) antimicrobial concentration should be maintained above the MIC (f_T>MIC)
- Given that bacterial regrowth will occur as the β-lactam concentration falls below the MIC and that maximal bactericidal activity is reported at concentrations four to five times the MIC, a PD target of 50–100% f_T>4-5 times MIC has been suggested for severe infections or for perceived poor antimicrobial penetration into infected tissues
- Otherwise, 40–100% f_T>MIC is considered sufficient

Methods-

- Bacterial identification was confirmed using MALDI-TOF.
- Further testing to characterize the isolate included PCR for bla_{KPC}, bla_{NDM}, and bla_{OXA48}.
- MIC determination of CZA and susceptibility testing were performed using broth microdilution and disc diffusion assays, respectively.
- Quantifying ceftazidime and avibactam concentrations was performed using liquid chromatography-tandem mass spectrometry (Keystone Bioanalytical, North Wales, PA).
- TDM was employed by dosing CZA at 2.5g administered as a 2-hour infusion Q8H with a total daily dose of 7.5g.
- CSF sample #1 was obtained after three completed CZA doses and represented a 10-minute post-infusion level.
- Follow-up CSF and blood samples (#2, #3, and #4) were simultaneously collected after 11 completed CZA doses. These represented 64-minute post-infusion levels.

Results- Work done at the Lab

- PCR testing revealed that KPC KP harbored the bla_{KPC} gene;
- bla_{NDM} or bla_{OXA48} alleles were not detected
- MLST revealed a non-ST-258 strain (uncommon to Cleveland)
- The CZA MIC was **0.75 µg/mL** while that of Meropenem-vaborbactam was **4 µg/mL**
- Positive blood and CSF cultures were sterilzed in 10 days after CZA added (timeline).
- TDM data indicates that:
  - *i*) similar amounts of CZA penetration are present (61 vs. 19 µg/mL) in humans
  - *ii*) at 60 min post infusion, [CZA] in CSF was > 20X MIC.
  - iii) Using the serum $t_{1/2}$ of CZA as 160 min, we estimate that at the end of the dosing interval, we achieve a CSF level of CZA at 3 µg/mL .

Results

Table 1. Ceftazidime/avibactam concentrations in CSF and Blood samples

	Concentration (ug/mL)	
Sample Name	Ceftazidime	Avibactam
CSF #1	19.007	4.242
CSF #2	17.27	3.917
CSF #3	17.244	4.099
CSF #4	19.727	4.148
Blood	61.273	13.085

- The results showed....

Whole genome sequencing (WGS) of isolate **Wild type OMPs, KPC-3, SHV-187**

- Other notes and lessons learned from WGS
- This isolate was uniquely devoid of outer membrane porin (OMP) gene mutations.
- No mutations (e.g. *ramR* inactivation) leading to overexpression of AcrAB-TolC
- $bla_{\text{KPC-3}}$ detected by PCR and confirmed by WGS
- Relatively higher MIC (4 µg/mL) to MV remains unexplained

Patient outcome and key features

- Central nervous system infections with Carbapenem-Resistant *K. pneumoniae* (CRKP) are particularly challenging to manage
- The complexity in selecting an effective antibiotic with adequate CNS penetration is further limited by a lack of clinical experience with newer agents such as CZA
- Measuring CZA concentration levels in CSF was achieved in a patient with complicated CNS infection
- A novel CZA TDM method was successfully applied to demonstrate that CZA achieves and maintains therapeutic CSF concentrations that exceed the MIC by >ten-fold
- Microbiologic and clinical cure was achieved, CSF pleocytosis resolved gradually
- Additional studies are needed to further optimize CZA dosing and establish a therapeutic target for CNS infections

Conclusion: A novel method

- This report describes for the first time the measurement of CZA concentration levels in CSF of a patient suffering from *KPC-KP* nosocomial meningitis.
- The first application of TDM for CZA in CSF
- Demonstrated that CZA achieves levels greater than the MIC by 20 x in the first 60 min
- Our data give confidence in this agent to treat *KPC KP*.
- Further clinical studies are required to assess the complete profile of CZA in CSF
- Specifically, further studies that measure CZA levels throughout the dosing interval
- Complexities related to patient discomfort/frequent lumbar punctures
- Patients with lumbar drains may represent suitable candidates

- 70 year old man with coronary artery disease, abdomen aortic aneurysm s/p open repair 2007, incisional hernia repair with mesh and now with pseudoaneurysm aorta
- Extensive travel including New York, LA, Amsterdam and Egypt within the prior year
  - Hospitalized 1/2017 with similar symptoms in Cairo, Egypt – treated for intestinal blockage
- Admitted 4/2017 with abdomen pain and CT imaging consistent with acute cholecystitis
  - Open cholecystectomy – gallbladder found to be gangrenous
  - ERCP and stent for bile leak
  - Drain placement for biloma with development of sepsis at time of procedure

BLOOD CULTURE: Klebsiella pneumoniae x 2 sets

- CTX-M (ESBL) and OXA (Carbapenemase) resistance markers detected by DNA

Klebsiella pneumoniae

MIC		
Amikacin	<=4 mcg/mL	Sensitive
Amoxicillin + Clavulanate	>16 mcg/mL	Resistant
Ampicillin	>16 mcg/mL	Resistant
Ampicillin + Sulbactam	>32 mcg/mL	Resistant
Aztreonam	>32 mcg/mL	Resistant
Cefazolin	>16 mcg/mL	Resistant
Cefepime	>16 mcg/mL	Resistant
Ceftazidime	>16 mcg/mL	Resistant
Ceftazidime/avibactam	<=4 mcg/mL	Sensitive
Ceftriaxone	Resistant	
Cefuroxime	>16 mcg/mL	Resistant
Ciprofloxacin	>2 mcg/mL	Resistant
Colistin	<=0.5 mcg/mL	
Ertapenem	>4 mcg/mL	Resistant
Gentamicin	<=2 mcg/mL	Sensitive
Levofloxacin	>4 mcg/mL	Resistant
Meropenem	>16 mcg/mL	Resistant
Piperacillin/tazobactam	>128 mcg/mL	Resistant
Tobramycin	<=2 mcg/mL	Sensitive
Trimethoprim/Sulfa	>4 mcg/mL	Resistant

- Bile also with *Klebsiella pneumoniae* and *Enterococcus faecalis*
- Successfully treated with ceftazidime/avibactam, metronidazole x 4 weeks and vancomycin x 2 weeks