Treatment of Hardware-Associated Multidrug-Resistant *Pseudomonas aeruginosa* Meningitis

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Past Medical History

9-year-old with complex past medical history:

- Cerebral palsy
- Hydrocephalus with ventriculoperitoneal-shunt in-situ, history of multiple revisions
- Chronic respiratory failure with tracheostomy and ventilator-dependence
- Chronic aspiration, underwent esophagogastric dissociation
- Gastrostomy-Jejunostomy tube dependence
- Parenteral nutrition dependence with indwelling central line

History of Present Illness

- Admitted to the PICU with persistently elevated temperatures
- Abdominal distention and hypotension, small bowel obstruction identified
- Taken to operating room
  - Laparotomy and lysis of adhesions performed
  - Abdominal portion of ventriculoperitoneal shunt externalized
- Cultures from shunt and peritoneal fluid grew *Pseudomonas aeruginosa* and *Enterococcus faecalis*
- Neurosurgical team initially hesitant to externalize proximal portion of shunt given prior neurosurgical complications

Selected Microbiologic History

- Known respiratory colonization with *Pseudomonas aeruginosa*
  - Susceptible: piperacillin-tazobactam, ceftazidime, tobramycin
  - Intermediate: amikacin, cefepime, gentamicin, meropenem
  - Resistant: ciprofloxacin
- Prior episodes of shunt-associated meningitis
  - *Streptococcus salivarius* and *Streptococcus epidermidis* 2019
  - Methicillin-susceptible *Staphylococcus aureus* 2017

Susceptibility testing

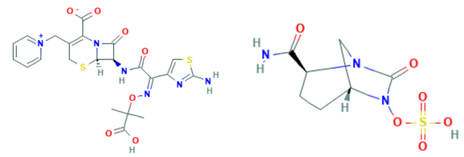
Antibiotic	MIC Interpretation	MIC Dilution	Kirby-Bauer
Amikacin	Susceptible	16	
Aztreonam*			Resistant
Cefepime	Resistant	>=64	
Cefiderocol*			Susceptible
Ceftazidime	Resistant	>=64	
Ceftazidime/Avibactam			Susceptible
Ceftolozane/Tazobactam			Susceptible
Ciprofloxacin*			Intermediate
Colistin⁺			Susceptible
Gentamicin	Intermediate	8	
Levofloxacin*			Intermediate
Meropenem	Resistant	8	
Piperacillin-Tazobactam			Resistant
Tobramycin	Susceptible	<=1	

*Susceptibility added on, available after a delay ⁺ Susceptibility sent to outside lab

Considered Treatments

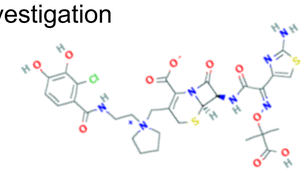
Ceftazidime-avibactam

- Four prior case reports
- Data in rabbits show ~40% CNS penetration of both components
- Only one case report of use as monotherapy
- Discomfort relying on CNS penetration of beta-lactamase inhibitor



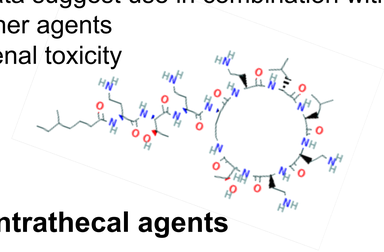
Cefiderocol

- No data regarding CNS penetration
- Company reports no known prior use for CNS infections
- 40-60% protein bound in serum, hence presumed lower CNS penetration
- Dosing in children remains under investigation



Colistin

- Longer experience with use for resistant gram negative rods
- Large molecule
- Susceptibility results not available in a timely manner
- Data suggest use in combination with other agents
- Renal toxicity



Intrathecal agents

- Controlled delivery to site of infection
- IDSA guidelines recommend considering
- Fewer systemic toxicities
- Adult data show safety and efficacy
- Risk of chemical meningitis
- Unable to give until shunt externalized
- Lack of controlled trials

Chemical structures from https://pubchem.ncbi.nlm.nih.gov/

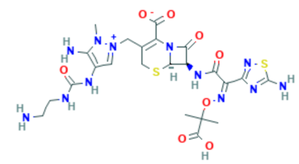
Selected Treatment

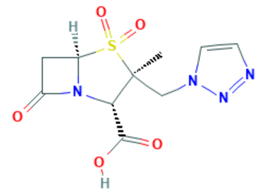
Ceftolozane-tazobactam

- Moderate size molecule
- Ceftolozane 11-21%, tazobactam 2-30% protein bound

However

- No prior report of use as monotherapy
- Unable to test ceftolozane susceptibilities alone
- Dosing in children still under investigation





Patient Outcome

- Four days of positive cultures
- Shunt externalized to external ventricular drain on day four
- Cultures cleared after shunt removal
- MRI with and without contrast without evidence of ventriculitis
- 21 days of ceftolozane-tazobactam recommended, 28 given
- 14 days of ampicillin recommended for to cover enterococcus, 21 given
- Shunt re-internalized three days after completion of anti-Pseudomonal therapy
- Remained out of hospital >30 days; no recrudescence of *Pseudomonas*

Take-Home Points

- Multiple characteristics of antimicrobials affect CSF penetration
  - Molecular size
  - Lipophilicity
  - Plasma protein binding
  - Active transport
  - Meningeal inflammation
- Data on CSF penetration of recently developed cephalosporins limited
- Comfort with beta-lactamase penetration into CNS differs between U.S. and Europe