UC Davis Health Antimicrobial Stewardship Program

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The UC Davis Antimicrobial Stewardship Program (ASP) was first established in 1986 and then expanded in pediatrics in 2011 and hospital wide in 2013 in response to the growing challenge of antibiotic resistance. Due to increasing antibiotic resistance, patients are at a higher risk for adverse effects and poor outcomes and treatment strategies become more complex.

Antibiotics are life-saving drugs, and their use has important implications for patient care and public health. With this in mind, the UC Davis Health ASP strives to ensure all patients receive optimal antibiotic therapy when indicated. We thank you for your support in putting this very important program into action.

Image: Stained Pseudomonas aeruginosa colony biofilm grown in the laboratory. https://news.harvard.edu/gazette/story/2017/11/photos-reveal-strange-beauty-of-microbes/

In This Issue

Aspiration Pneumonitis

Diagnosis

- Aspiration pneumonitis is an abrupt chemical injury caused by inhalation of sterile gastric contents.
  - It can progress quickly to a decline in respiratory status followed by rapid improvement within 48 hours of the insult.
  - Chest x rays can look like multifocal pneumonia is present.
- Patients with aspiration events are usually unlikely to produce significant sputum, making the utility of sputum cultures low.
  - Sputum Gram-stain and cultures should be considered when the diagnosis is unclear, if purulent sputum is being produced, or if antibiotic treatment is initiated in a hemodynamically unstable patient.

Treatment

- **Hemodynamically stable patients with aspiration events**
  - Antibiotics are not warranted, and supportive care is the mainstay of therapy.
  - Prophylactic antibiotics have not been shown to be helpful in preventing the development of pneumonia after aspiration events.

- **Hemodynamically unstable patients with aspiration events**
  - Treat with regimens for community-acquired pneumonia (CAP) (e.g., ceftriaxone) if the event occurred within 72 hours of admission to hospital.
  - Treat with regimens for heathcare-acquired pneumonia (HAP) (e.g., cefepime) if the event occurred 72 hours after admission to hospital.
    - Coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) can be considered if the patient has known history of MRSA colonization or infection, intravenous drug use, a recent stay in a nursing home or skilled nursing facility, or prolonged hospitalization with unknown MRSA colonization status
  - It is not necessary to add additional anaerobic or atypical coverage.
  - Reassess at 48 hours.
    - If clincial symptoms resolve, antibiotics can be discontinued.
    - If no or minimal improvement & bacterial pneumonia is suspected, treat for 5–7 days.

- **Patients with aspiration events not treated initially with no improvement in 48–72 hours**
  - A small proportion of patients (10–20%) may develop bacterial pneumonia 48–72 hours after an aspiration event.
  - If there is no improvement or there is clinical worsening within the first 48–72 hours, consider a course of antibiotic therapy (as above).

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Cefepime Neurotoxicity: the Devil's in the Levels

UC Davis Health

Antibiotic Stewardship Newsletter May 2023

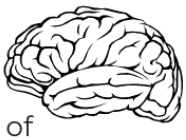
Risk Factors for Cefepime Induced Neurotoxicity (CIN)

Impaired Renal function:
Cefepime is primarily cleared by the kidneys. Patients with reduced renal function are at a higher risk of renal accumulation.

Critical illness:
Patients that are critically ill often require higher doses and prolonged durations of cefepime.

Elderly patients:
especially those that are frail, are at a higher risk of CIN.
This is likely due to reduced renal function and overestimation of renal function based creatinine.

Neurological conditions:
Intracranial tumors & CNS infections can increase permeability of the blood-brain barrier, increasing cefepime levels in CSF.



Low protein:
Chronic illnesses associated with low albumin or serum protein increase free fraction of cefepime.

Many antibiotics have side effects that include encephalopathy, neuropathy, or even seizures, but cefepime has come under increased scrutiny as reports of cefepime-induced neurotoxicity (CIN) come to light. Unfortunately, there is a lack of high-quality large-scale RCTs to help us tease out many aspects of CIN, but a comprehensive review of the data that is available can help us discern which patients are at risk of CIN and appropriately approach cases of suspected CIN.

Mechanistically, CIN is not well understood. The commonly accepted theory is that cefepime, along with other beta-lactam antibiotics, competitively binds GABA-A receptors and activates excitatory N-methyl-D-Aspartate (NMDA) receptors, causing neuronal excitability, myoclonus, and non-convulsive status epilepticus [1–4]. While many patients with CIN have shown abnormal EEG findings, this does not fully explain the constellation of symptoms described as CIN in published reports, including altered mental status, encephalopathy, and movement difficulty [1–3,5,6].

Due to a lack of high-quality prospective studies, there are other limitations to what we know about CIN, including disagreement about its prevalence. Current estimates of CIN frequency land between 0.002% to 2.6% of patients prescribed cefepime [7–9].

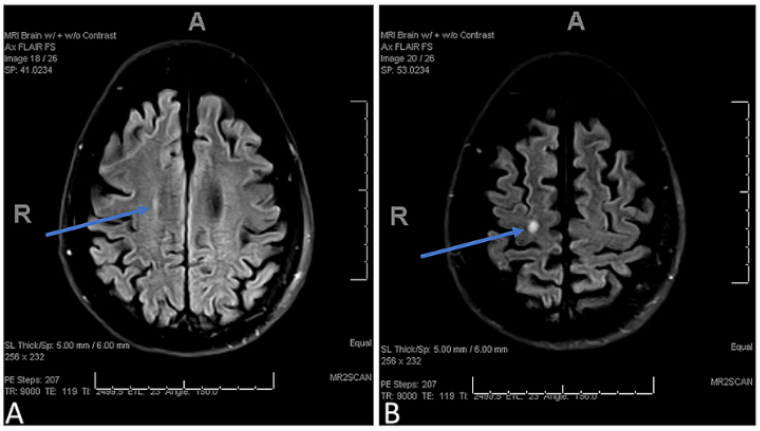
Systematic reviews agree on common variables associated with an increased risk of CIN, including renal dysfunction, advanced age, critical illness, low protein or albumin, and pre-existing neurological disease (see left panel) [7,10].

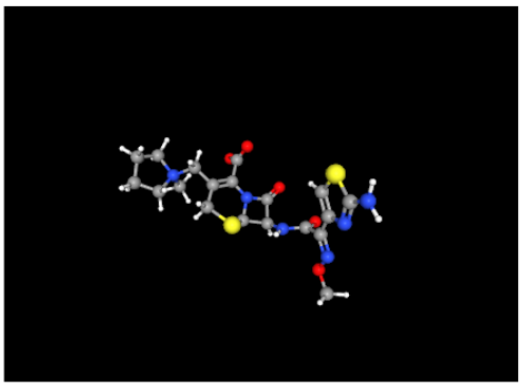
Unfortunately, in attempting to apply this model to therapeutic drug monitoring (TDM), there is a lack of consensus on the what cefepime concentrations are a determinant for CIN. Reports range from 20 to 49 mg/L [11–14].

One predictive model of CIN using Bayesian population pharmacokinetic simulations to assess various dosing schemes and renal dispositions. They found that a combination of cefepime 2 grams given every 8 hours and an apparent CrCl around 60 mL/min had the greatest probability of neurotoxicity [11]. The study illustrates that patients who are near renal dose adjustment cut-offs, especially those prone to over-estimated clearance based on Scr, are at an increased risk of cefepime accumulation and CIN.

Cefepime TDM, the use of cystatin C-based eGFR measurements, or assessing clearance based on other antibiotic pharmacokinetics (such as clearance of vancomycin for example) may aid in personalizing the patient's cefepime dosage based on clearance.

Abbreviations: Scr (serum creatinine), CrCl (creatinine clearance), eGFR (estimated glomerular filtration rate.





Figure, left: Axial FLAIR MRI. (A, B) Right centrum semi-ovale with hyperintense demyelinating lesion without enhancement in a patient with CIN. Source: A Case of Cefepime-Induced Neurotoxicity: Rena Function Missing in Action. Right: Cefepime 3D molecular structure. Source: pubchem.ncbi.nlm.nih.gov/compound/cefepime#section=3D-Conformer

In one of the most thorough CIN TDM studies published, Lau et al. found that a cefepime trough of 36 mg/L was the most sensitive and specific cut-off for predicting CIN regardless of multiple factors including renal function [12]. Lau's group went on to utilize a Monte Carlo simulation of cefepime concentrations to study the probability of attaining adequate time over the MIC (8 mg/L for *P. aeruginosa)* to optimize bacterial killing while still avoiding CIN. They found that a trough of 49 mg/L is an appropriate target in the context of difficult-to-treat infections [13]. In this situation, the risk of CIN should be weighed against the risks of inadequately treating infection and may benefit from engaging an infectious disease specialist to assess if another agent may be more appropriate.

While there is no agreed-upon goal cefepime trough, TDM of cefepime can be helpful in the context of a patient who becomes altered while on cefepime therapy in order to determine if CIN is likely. In this situation, first address modifiable factors contributing to altered mental status, such as ICU delirium or polypharmacy. If the patient has an increased risk for CIN (renal dysfunction, critical illness, CNS infection, or malignancy), and it appears likely that CIN is the culprit, it would be advantageous to engage Infectious Diseases pharmacy specialists who can assist with cefepime TDM and guide alternate antibiotic selection. Discontinuation of cefepime should resolve altered mentation, and a high cefepime trough help to confirm that CIN was the likely culprit.

A common question that we encounter is whether we can safely use cefepime in patients with renal dysfunction. The vast majority of case reports of CIN involve inappropriately dosed cefepime relative to true clearance (inaccurate estimation of renal function per Cockroft-Gault) [15,16]. Patients that are on maintenance hemodialysis are represented in a quorum of CIN case reports, and multiple studies have investigated who is at risk within this population. It appears the anuric patients with low albumin or protein, those with prolonged courses, elderly patients, and those that are dosed aggressively are the most at risk [17–20] .

Many providers believe that using piperacillin-tazobactam is a safer alternative for patients on hemodialysis. However, there are multiple case reports of patients in this population who experience neurotoxic effects on piperacillin-tazobactam [21–24]. Additionally we have reported reduced rates of *P. aeruginosa* susceptibility to piperacillin-tazobactam in the 2021 UC Davis Antibiogram. Overall, there is no strong evidence to suggest that piperacillin-tazobactam is more appropriate in patients on hemodialysis and the decision around which agent to use should be made on a case-by-case basis.

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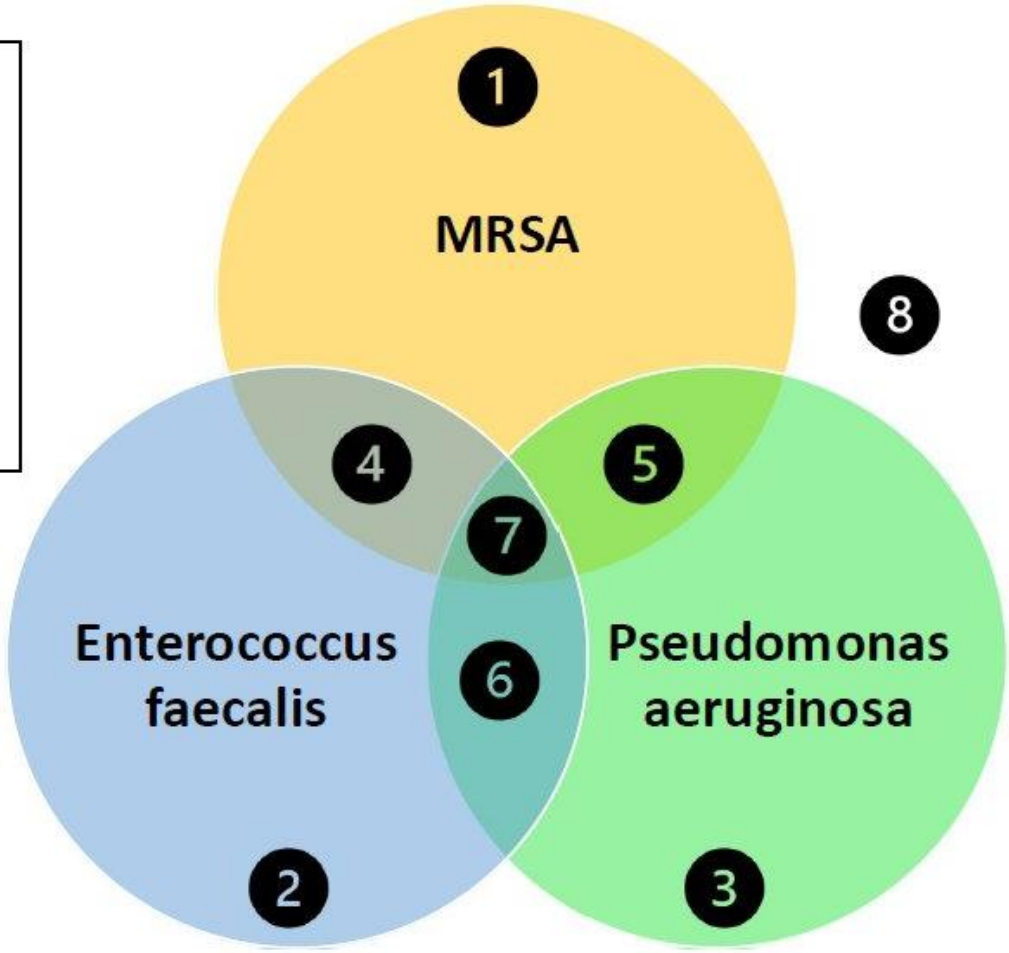
Antibiotic Escape Room!

You're trapped!

You are given a list of 6 antibiotics. Use your knowledge of spectrum of activity. Some numbers may be used once, more than once, or not at all.

What is the 5-digit code (A-B-C-D-E) to escape?

A. Ampicillin
B. Aztreonam
C. Ertapenem
D. Piperacillin-tazobactam
E. Vancomycin



answer on last page...

Created by: Dr. Shaqil Peermohamed MD MPH FRCPC
Twitter: @shaq_MD

Test Your Knowledge

Would you like to win a $10 gift certificate to Starbucks? Complete the following post-newsletter quiz and submit to hs-ASP@ucdavis.edu to be entered into a raffle for a free lunch!

1. A 63-year-old female is hospitalized for acute kidney injury secondary to viral gastroenteritis. On hospital day 4 she sundowns overnight, vomits, and aspirates. She is placed on 3L supplemental oxygen via nasal cannula, and a CXR is performed revealing multifocal infiltrates. She is tachycardic but remains otherwise hemodynamically stable and afebrile. What empiric antibiotic course is most appropriate for this patient?

a. Cefepime + Vancomycin for possible HAP

b. Cefepime + Vancomycin + Metronidazole for possible HAP and anaerobic coverage

c. None. Observe patient and manage symptomatically

2. True or False: When aspiration pneumonitis is complicated by aspiration pneumonia, anaerobic coverage is necessary.

3. The following day the patient's altered mental status resolves. She remains afebrile. By the following morning (approximately 36 hours after her aspiration event) she is back on room air. Aside from a non-productive cough she has no complaints. How long should any empiric antibiotics that were started be continued?

a. Stop them now as she has significantly improved within 48 hours of the aspiration event

b. Complete a 5-day course for uncomplicated CAP

c. Complete a 7-day course for uncomplicated HAP

4. True or False: Elderly patients with critical illness and high cefepime doses relative to their renal function are at the greatest risk for cefepime induced neurotoxicity (CIN).

Answers to last Newsletter's quiz: 1. B, 2. F, 3. B, 4. F

ASP Gold Star Winners for May & June

The following staff have been recognized by the ASP team for their dedication to combatting antimicrobial resistance and commitment to the principles of antimicrobial stewardship:

- David Pritchard (MICU)

Quick Antibiotic Fact:

Piperacillin-Tazobactam

An anti-pseudomonal beta-lactam that also has significant anaerobic activity, it comes with a large amount of Na^{++} so use cautiously in patients with heart disease.

Contact Us

The Antimicrobial Stewardship Program team members

Adult ASP Physicians:

Stuart Cohen, MD
Archana Maniar, MD
Sarah Waldman, MD
Scott Crabtree, MD
Natascha Tuznik, DO
Christian Sandrock, MD
Larissa May, MD
Alan Koff, MBBS

Pediatric ASP Physicians:

Natasha Nakra, MD
Jean Wiedeman, MD
Ritu Cheema, MD
Elizabeth Partridge, MD

ASP Pharmacists:

Monica Donnelley, PharmD
Nicola Clayton, PharmD
TJ Gintjee, PharmD

Antibiotic questions? Contact us.

https://health.ucdavis.edu/antibiotic-stewardship/

See the On-Call Schedule for the ASP attending/fellow of the day

Contact the ASP Pharmacist at 916-703-4099 or by Vocera "Infectious Disease Pharmacist"

Escape Room answer: 2-3-8-6-4