Amoxicillin Clavulanate 875/125 mg given three times a day -- So crazy it just might work!

YoungYoon Ham, PharmD BCIDP

Disclosure Statement

- None of the planners for this activity have relevant financial relationships to disclose with ineligible companies.

Learning Objectives

- Compare the PK/PD rationale for twice- vs three-times-daily dosing of amoxicillin-clavulanate
- Select appropriate patients for three-times-daily dosing of amoxicillin-clavulanate based on clinical factors

Pre-Test Questions

Which of the following best explains why three-times-daily dosing of amoxicillin-clavulanate may be preferred over twice-daily dosing for certain infections?

A. It increases peak serum concentrations (Cmax)

B. It prolongs time above the minimum inhibitory concentration (Time above MIC)

C. It reduces renal clearance of the drug

D. It improves clavulanate bioavailability

Pre-Test Questions

A 58-year-old patient presents with community-acquired pneumonia and is prescribed amoxicillin-clavulanate. The patient has normal renal function and no history of intolerance. Which of the following is the most appropriate dosing strategy to optimize pharmacodynamic exposure?

A. 875 mg/125 mg twice daily

B. 500 mg/125 mg twice daily

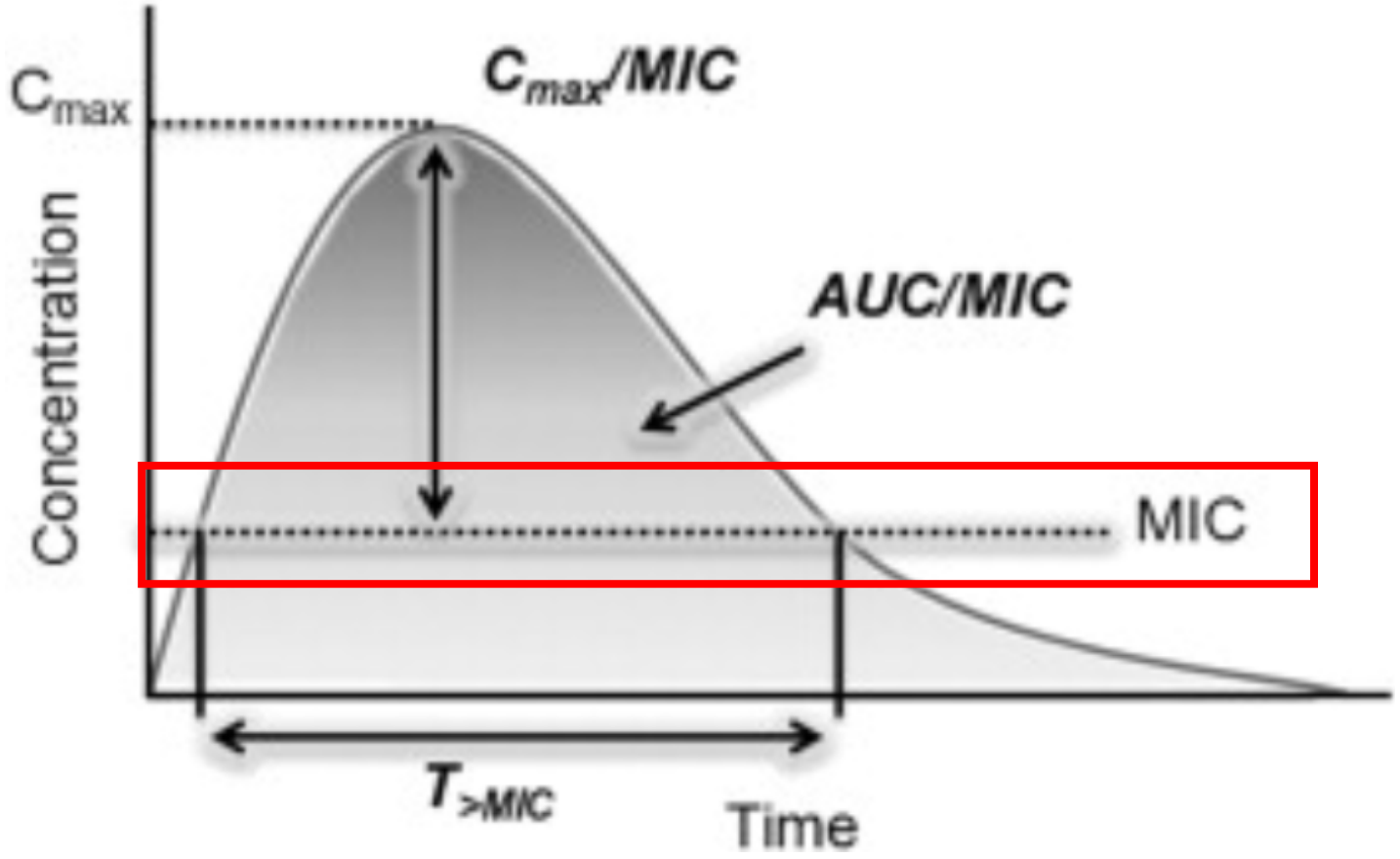
C. 500 mg/125 mg three times daily

D. 875 mg/125 mg three times daily

Back to basics…

- Amoxicillin is a penicillin (beta lactam) antibiotic
- It has some gram-negative activity on its own, but over the years, resistance has gone up
  - Beta lactamase production
- Clavulanic acid is a suicide inhibitor that permanently binds to beta lactamase, giving amoxicillin its activity back

PK/PD of amoxicillin



40 to 50 percent of the dosing interval

Asín-Prieto E, et al. *Journal of Infection and Chemotherapy*. 2015;21(5):319-329. doi:10.1016/j.jiac.2015.02.001

Amoxicillin Pharmacokinetics

- Bioavailability: 77-93%
- Volume of distribution: 0.30 L/Kg
- Protein binding: 20%
- Half-life: approximately 1 hour

Akhavan BJ, et al. Amoxicillin. In: *StatPearls*. StatPearls Publishing; 2026. Accessed April 14, 2026. http://www.ncbi.nlm.nih.gov/books/NBK482250/

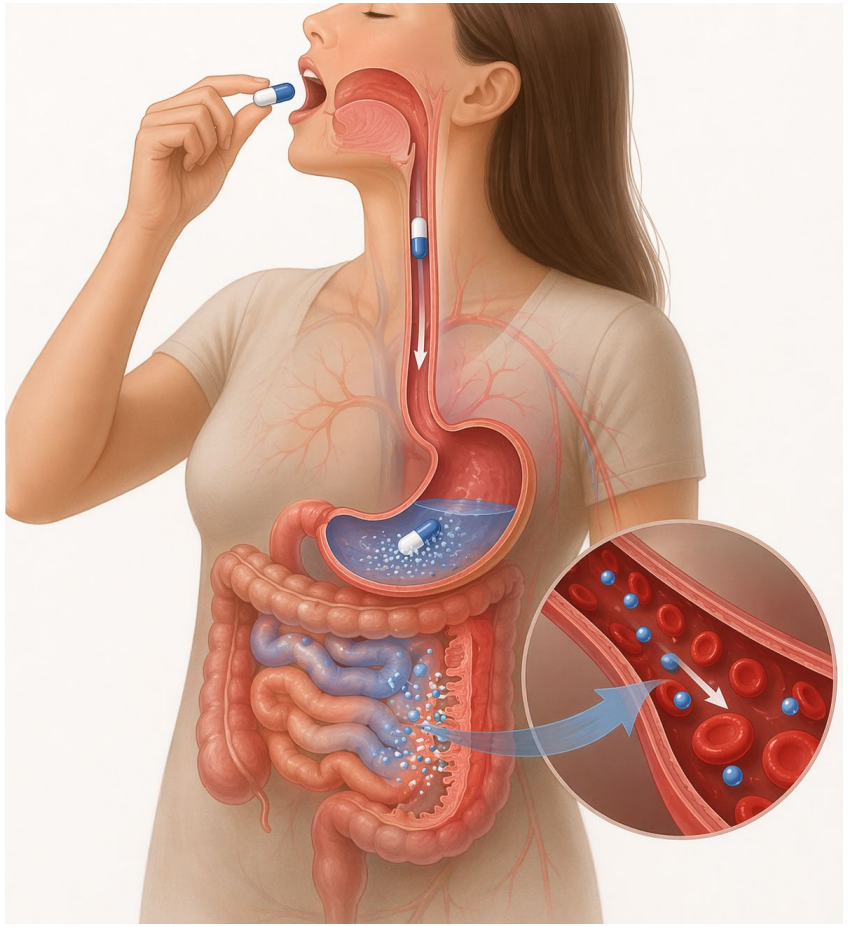
Huttner A, et al. *Clinical Microbiology and Infection*. 2020;26(7):871-879. doi:10.1016/j.cmi.2019.11.028

Fun math!

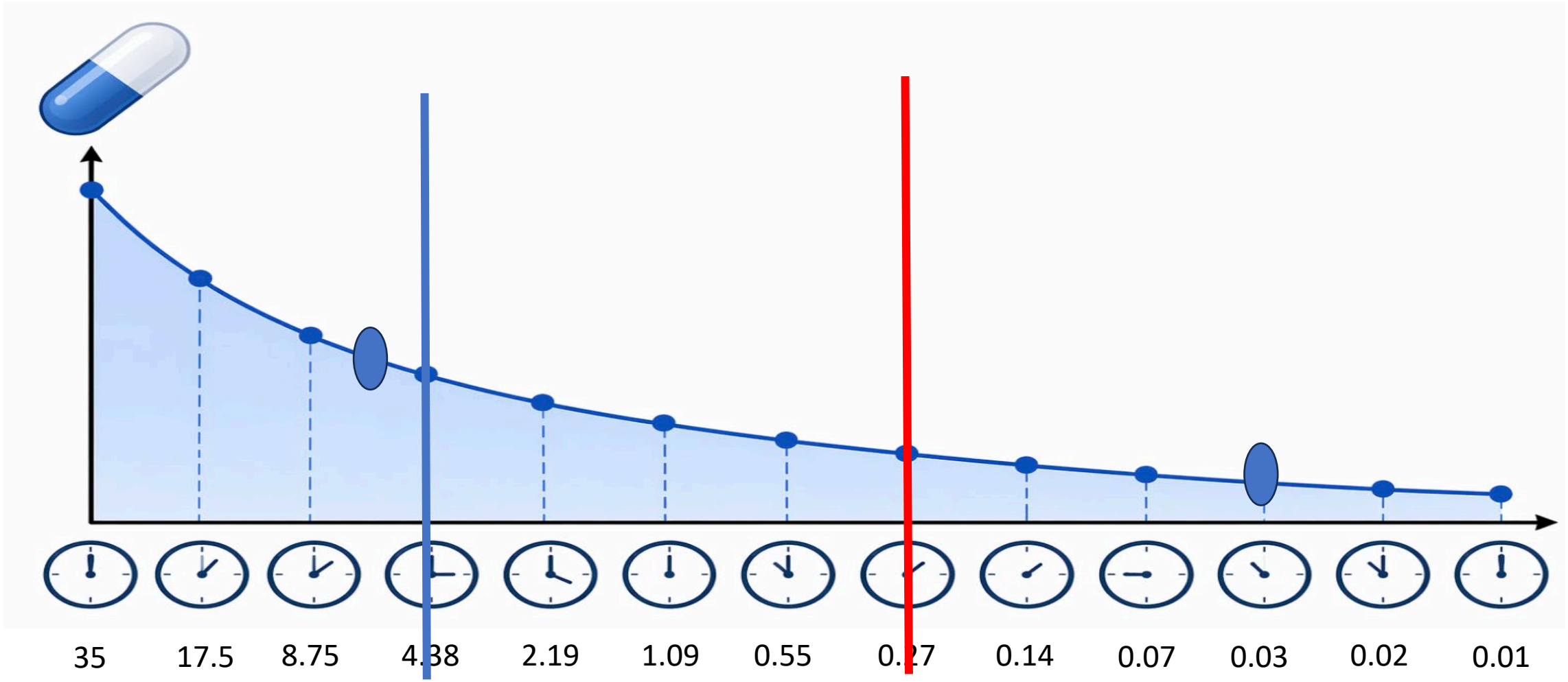
- 70 kg patient/normal renal function
- 875 mg amoxicillin

- 85% bioavailable = 744 mg
- 0.3 L/kg*70 kg = 21 L
- 744 mg/21 L = 35 mg/L

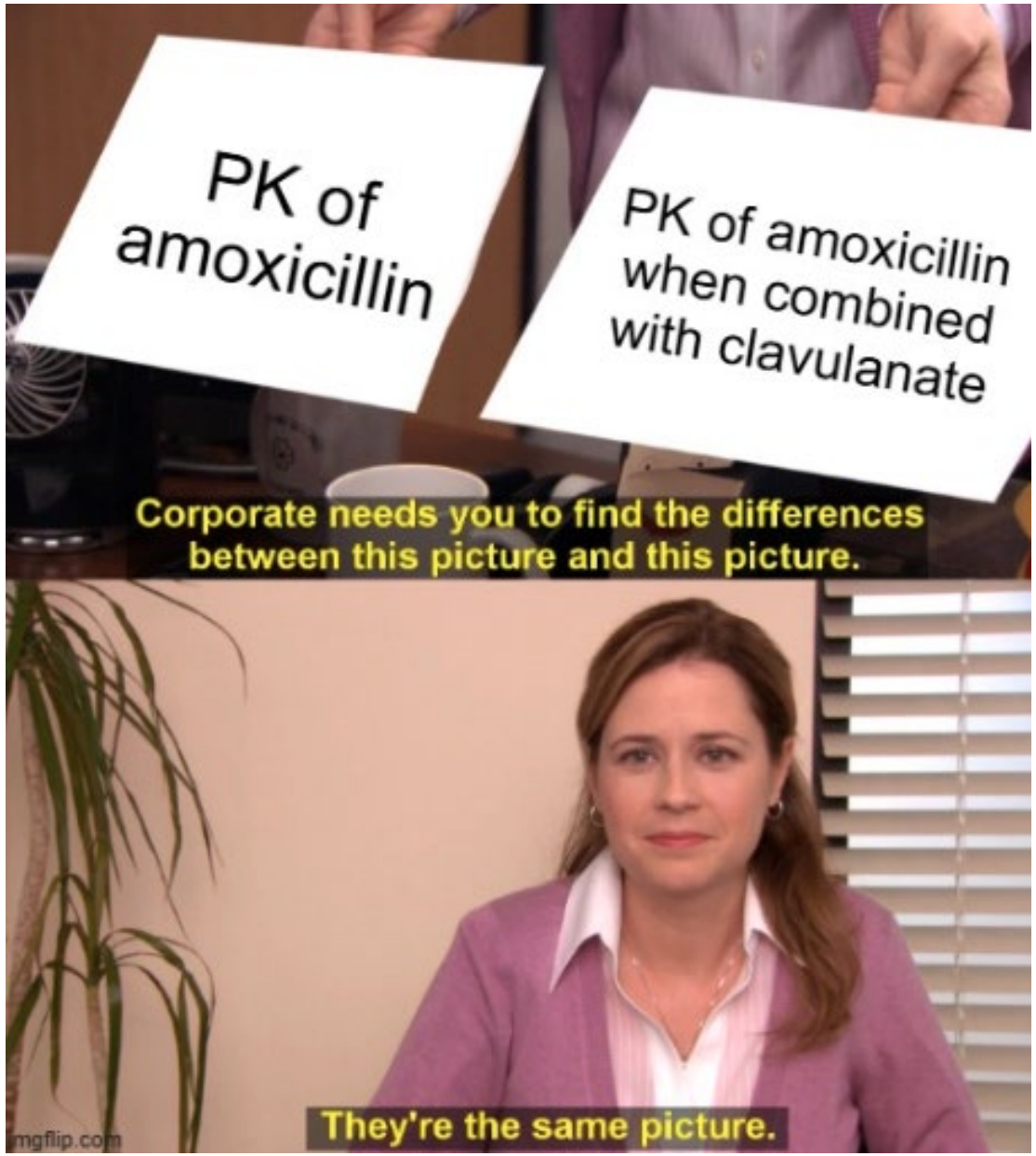
- Let's say that's the level at Cmax...



More fun math!



PK/PD of amoxicillin in amoxicillin-clavulanate



So when does BID make sense?

- Cystitis
  - High urine concentration overwhelms the PK problems
- Mild, superficial infections
  - SSTI
  - Sinusitis
  - Maybe not really bacterial anyway?
- Beta Streptococcus (the lettered streps)
  - But you don't need the clav for that!

Deep Thoughts…

- 500/125 mg TID is a common dose, which has the same amount of clavulanate
- Sometimes kidney dysfunction is helpful!
- Common indications for TID dosing
  - Pneumonia
  - Intraabdominal infections
  - Pyelonephritis
- Not at any dose for gram negative bacteremia unless basically sterile
  - Yes, I know there is data out there

Post-Test Questions and Answers

Which of the following best explains why three-times-daily dosing of amoxicillin-clavulanate may be preferred over twice-daily dosing for certain infections?

A. It increases peak serum concentrations (Cmax)

B. It prolongs time above the minimum inhibitory concentration (Time above MIC)

C. It reduces renal clearance of the drug

D. It improves clavulanate bioavailability

Post-Test Questions and Answers

Which of the following best explains why three-times-daily dosing of amoxicillin-clavulanate may be preferred over twice-daily dosing for certain infections?

A. It increases peak serum concentrations (Cmax)

B. It prolongs time above the minimum inhibitory concentration (Time above MIC)

C. It reduces renal clearance of the drug

D. It improves clavulanate bioavailability

Post-Test Questions and Answers

A 58-year-old patient presents with community-acquired pneumonia and is prescribed amoxicillin-clavulanate. The patient has normal renal function and no history of intolerance. Which of the following is the most appropriate dosing strategy to optimize pharmacodynamic exposure?

A. 875 mg/125 mg twice daily

B. 500 mg/125 mg twice daily

C. 500 mg/125 mg three times daily

D. 875 mg/125 mg three times daily

Post-Test Questions and Answers

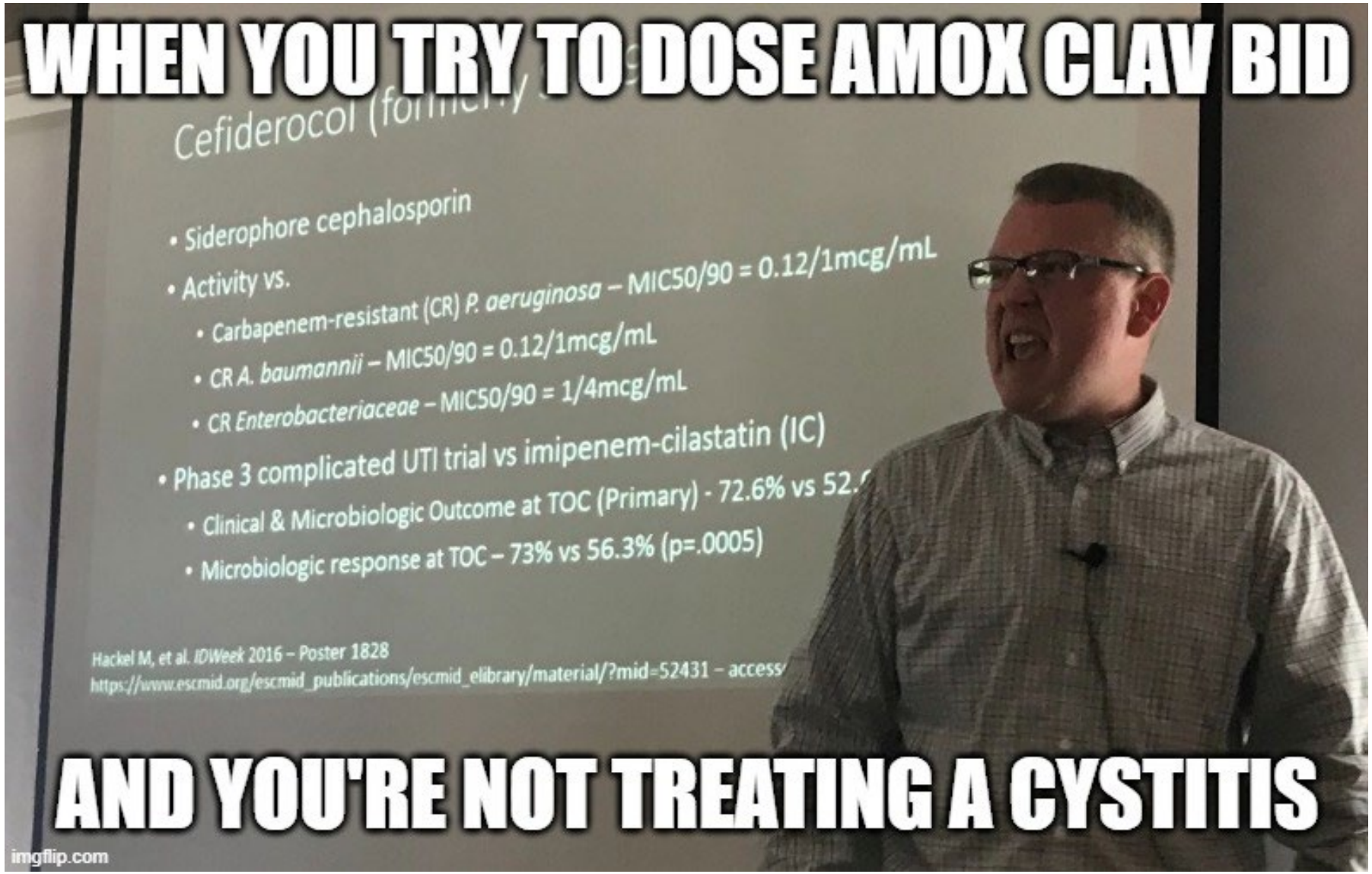
A 58-year-old patient presents with community-acquired pneumonia and is prescribed amoxicillin-clavulanate. The patient has normal renal function and no history of intolerance. Which of the following is the most appropriate dosing strategy to optimize pharmacodynamic exposure?

A. 875 mg/125 mg twice daily

B. 500 mg/125 mg twice daily

C. 500 mg/125 mg three times daily

D. 875 mg/125 mg three times daily



All credit and thanks to Jim Lewis, PharmD FIDSA