UWTASP tele-antimicrobial stewardship program | echo

April 1, 2025

Agenda

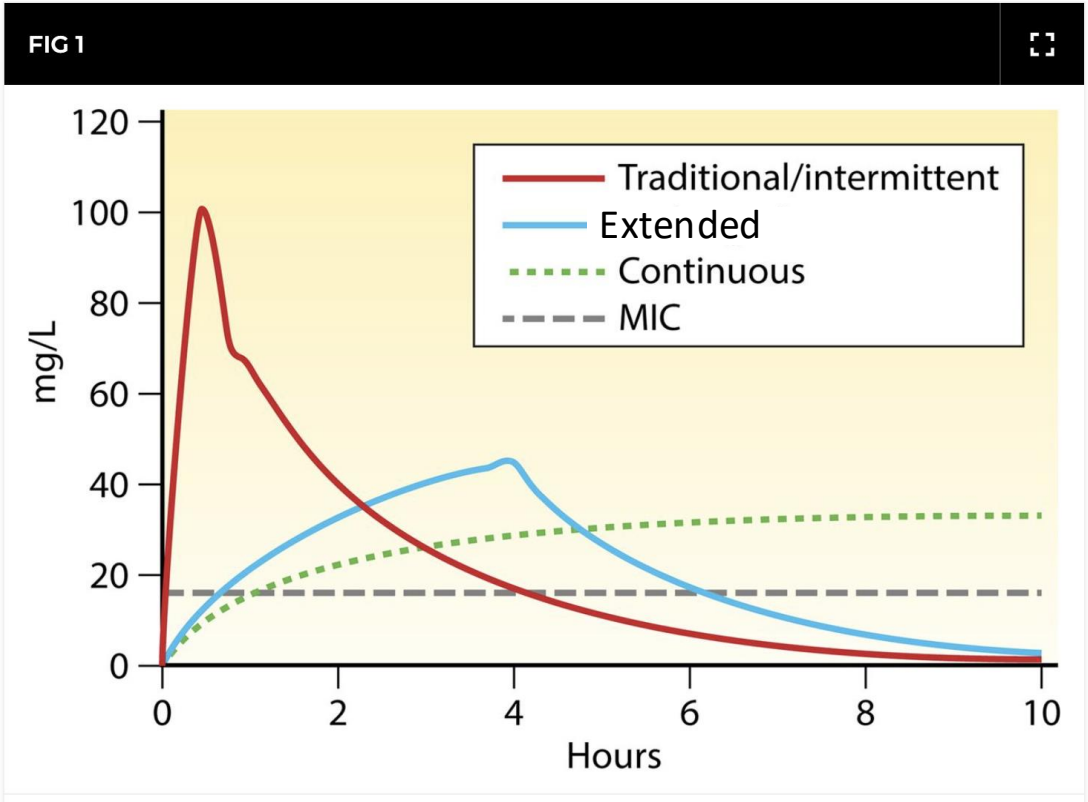
- Sydney Kruse, PharmD: *Time Matters: Prolonged Infusion Strategies for Beta-Lactam Antibiotics*
- Case Discussions
- Open Discussion

Lecture Objectives

- Explain the theory of prolonged infusion beta-lactam antibiotics
- Evaluate the BLING III trial and understand how it fits into the broader literature surrounding prolonged infusions
- Illustrate challenges and considerations for implementation of a prolonged infusion protocol

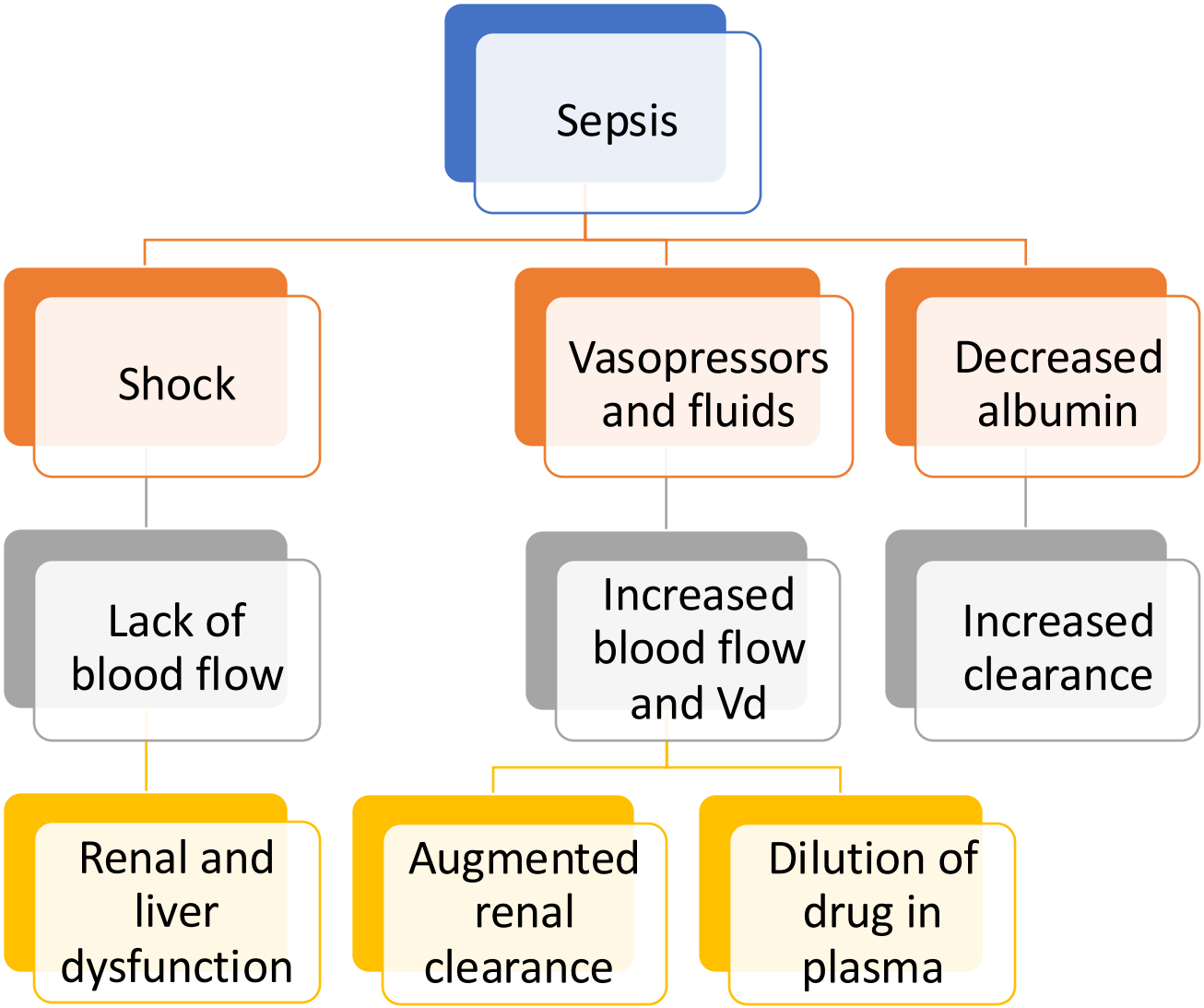
Prolonged Infusion of Beta-Lactam Antibiotics Optimizes PK/PD

- Beta-lactams exhibit time-dependent killing of micro-organisms (fT>MIC)
  - PK/PD Target is ~50% fT> MIC
- Maximal killing occurs at consistent free antibiotic concentrations 4-5X above the MIC

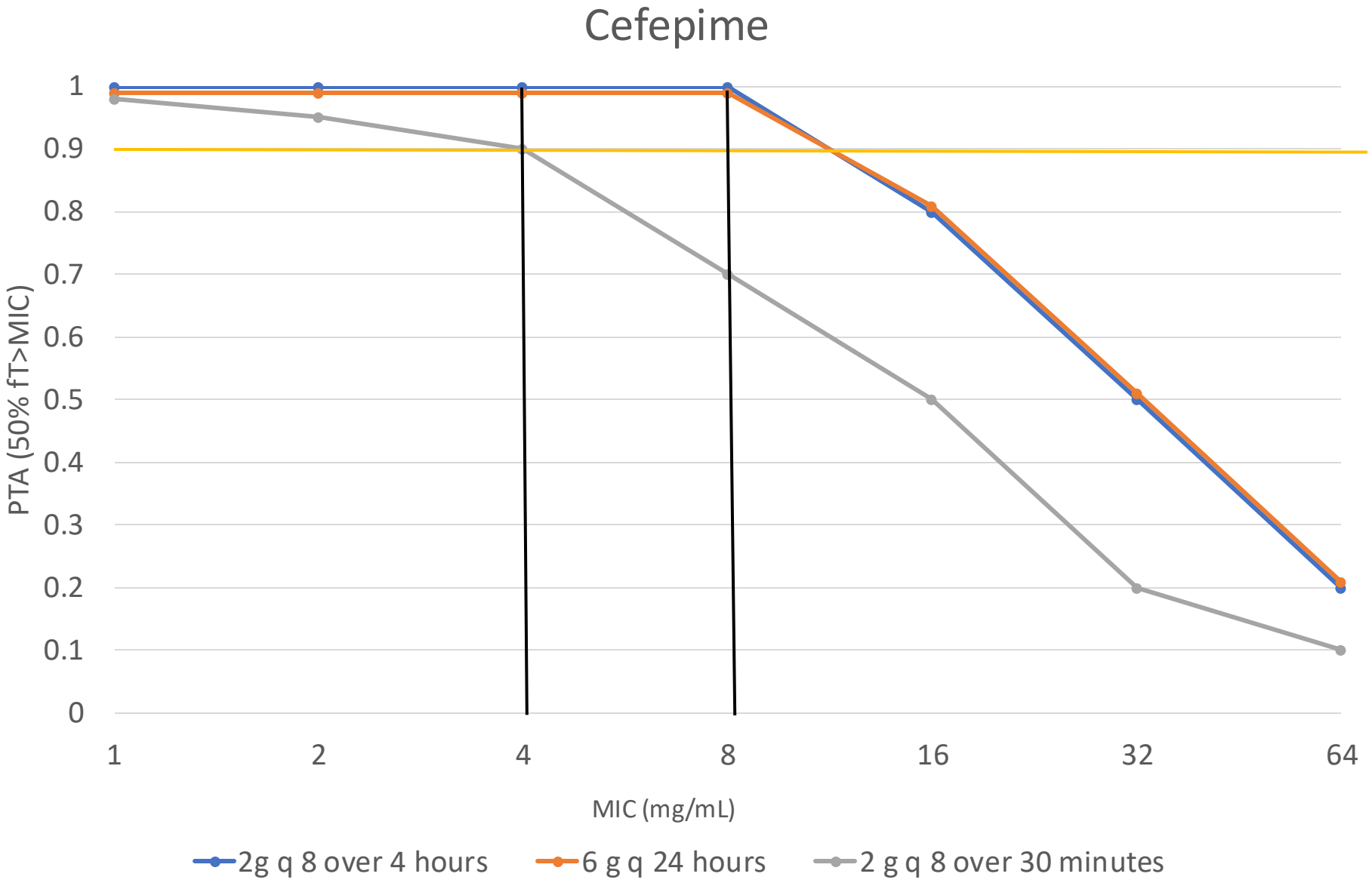


Grupper M, Kuti JL, Nicolau DP. *Clin Microbiol Rev*. 2016;29(4):759-772
Turnidge JD. *Clin Infect Dis*. 1998;27(1):10-22. doi:10.1086/514622

Changes in PK/PD in Critically Ill Patients with Sepsis



Veiga RP, Paiva JA. *Crit Care.* 2018;22(1):233
Tilanus A, Drusano G. Open Forum Infect Dis. 2023;10(7):ofad305.



PTA: probability of target attainment

Goutelle S, Jullien V, Bru JP, et al. *J Antimicrob Chemother*. 2023;78(11):2762-2769

BLING III Trial

The BLING III Randomized Clinical Trial

Purpose: To evaluate CI vs II β-lactam administration in the critically ill

Methods: International, open-label, randomized clinical trial of adult ICU patients with a documented site or strong suspicion of infection and organ dysfunction

Intervention: CI vs II piperacillin/tazobactam or meropenem

Primary Outcome: All-cause mortality at 90 days

Dulhunty JM, Brett SJ, De Waele JJ, et al. *JAMA*. 2024;332(8):629-637.

Baseline Characteristics

	Continuous Infusion (n = 3498)	Intermittent Infusion (n = 3533)
Age, Mean SD, y	59.3 (16.4)	59.6 (16.1)
Sex, Male, no. (%)	2308 (66)	2300 (65.1)
APACHE II score ± SD	19.6 ± 7.6	19.5 ± 7.4
Inotropes/vasopressors in the 24 h prior to randomization, no./total (%)	2481/3496 (71.0)	2482/3532 (70.3)
Pulmonary infection, no./total (%)	2062/3494 (59.0)	2119/3532 (60.0)
Piperacillin/tazobactam at eligibility, no. (%)	2739 (78.3)	2766 (78.3)

Dulhunty JM, Brett SJ, De Waele JJ, et al. *JAMA*. 2024;332(8):629-637.

Results

Outcome	Continuous infusion (n = 3498)	Intermittent infusion (n = 3533)	Absolute difference (%)
Primary outcome			
All-cause mortality at day 90, no./total (%)	864/3474 (24.9)	939/3502 (26.8)	-1.9 (-4.9 to 1.1)
Adjusted analysis			**-2.2 (-5.5 to 1.1)**
Secondary outcomes			
Clinical cure at day 14, no./total (%)	**1930/3467 (55.7)**	**1744/3491 (50.0)**	**5.7 (2.4 to 9.1)**
New acquisition, colonization, or infection with an MRO or C. *difficile*, No./total (%)	253/3498 (7.2)	266/3522 (7.5)	-0.3 (-1.9 to 1.4)
Adverse events: 10 (0.3%) CI vs 6 (0.2%) II			

Dulhunty JM, Brett SJ, De Waele JJ, et al. *JAMA*. 2024;332(8):629-637.

Number Needed to Treat

- Number Need to Treat (NNT) is a way to assess the benefit of treatment

- NNT = 1/absolute risk reduction (ARR)
  - ARR of mortality from BLING III was 2% (0.02)

- 1/0.02 = 50

- **50 patients need to be treated with a continuous infusion to avoid 1 death**

Dulhunty JM, Brett SJ, De Waele JJ, et al. *JAMA*. 2024;332(8):629-637.

Limitations

Limitations:

- Most patient on piperacillin/tazobactam
- Caution to generalizing to places with higher antimicrobial resistance

Key take aways:

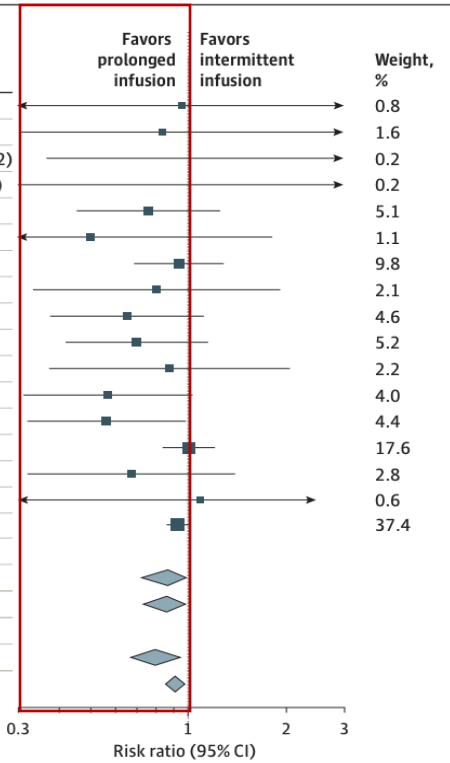
- The CI group had numerically lower mortality rate and improved clinical cure when compared to II
- Not statically significant but may have clinical significance based on NNT of 50 patients.

Dulhunty JM, Brett SJ, De Waele JJ, et al. *JAMA*. 2024;332(8):629-637.

2024 Systematic Review and Meta Analysis

Figure 1. All-Cause 90-Day Mortality for the Comparison Between Prolonged Infusions of β-Lactam Antibiotics vs Intermittent Infusions

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.20 to 0.19)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.33 to 0.23)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (-0.02 to 0.22)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (-0.12 to 0.79)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.16 to 0.04)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.28 to 0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.10 to 0.07)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.61 to 0.36)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.69 to 0.02)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.27 to 0.04)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.29 to 0.21)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.36 to 0.00)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.31 to -0.01)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (-0.08 to 0.08)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.37 to 0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.28 to 0.30)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.04 to 0.00)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Hartung-Knapp-Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



The black boxes represent point estimates, and the areas of the boxes are proportional to the weight of the studies. The weights displayed are based on bayesian analysis with vague priors. The whiskers represent CIs. Width of the diamonds represents the trials' pooled estimate CI, and the middle point represents the point estimates.

[a]Credible intervals are presented for bayesian analysis.

Abdul-Aziz MH, Hammond NE, Brett SJ, et al. *JAMA.* 2024;332(8):638–648.

Current and Future Operations

How Does UW Medicine Administer Beta-Lactams?

Piperacillin/tazobactam is administered as an extended infusion over 4 hours

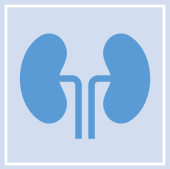
Cefepime and meropenem are administered over 30 minutes

Newer BL/BLIs are administered as EI via MDRO order panel

On the Horizon at UW Medicine

Prolonged infusion are recommended by the IDSA and international recommendations endorsed by ACCP, BSAC, CFF, ESCMID, IDSA, SCCM, and SIDP

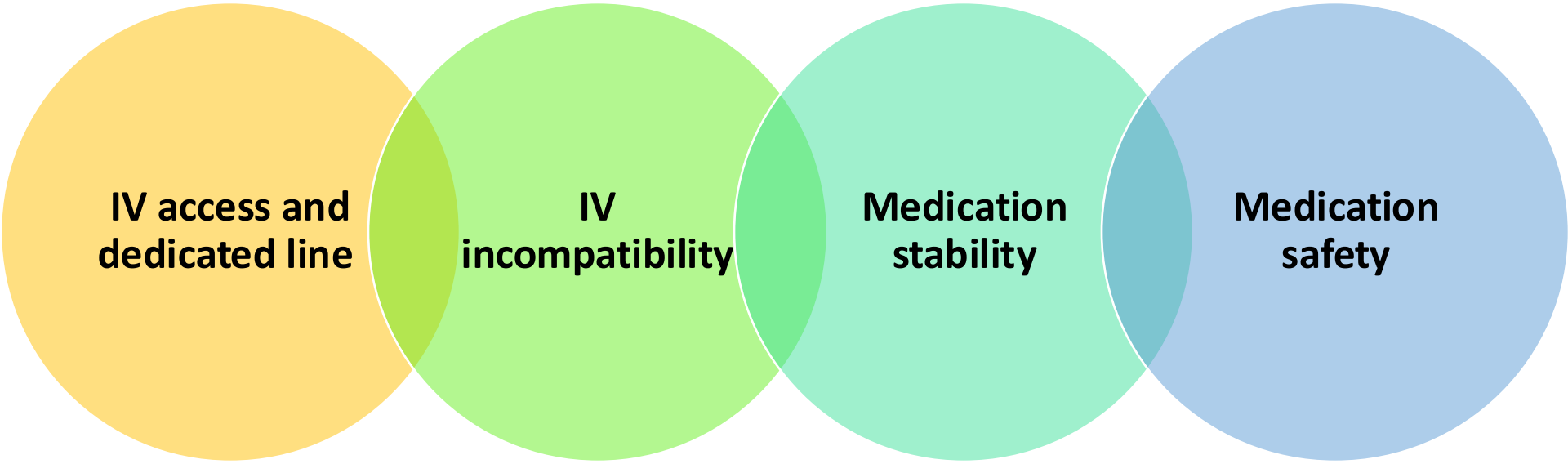
Implementing more routine use of extended infusions for severe pseudomonal infections



Includes bacteremia, pneumonia, CNS infection, intra-abdominal, and complicated skin and soft tissue infection

Tamma PD, et al. Clin Infect Dis. 2021 Apr 8;72(7):1109-1116

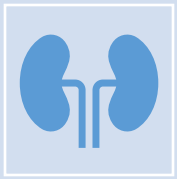
Potential Issues Associated with Prolonged Infusion Beta-Lactam Antibiotics



Considerations for Implementation of Prolonged Infusion Beta-Lactam Protocol

- Severity of illness of patients
- Local resistance patterns
- Hospital resources
- Cost

Prolonged Infusion Beta-Lactam Conclusions



Prolonged infusions are safe, effective, and optimize PK/PD of beta-lactam antibiotics

Logistical challenges exist with prolonged infusions

Individual institutional factors play a role in implementation of a prolonged infusion strategy

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