Anti-Infective Dosing Protocol/Policy MP01 Attachment Update:

Ceftolozane-Tazobactam (C/T, Zerbaxa®)

Shawnalyn Sunagawa, PharmD
Scott Bergman, PharmD, BCIDP
On behalf of the Antimicrobial Stewardship Program
Pharmacy & Therapeutics Committee, March 2023

University of Nebraska Medical Center

Nebraska Medicine

Situation/Background

- Propose 4-hour extended infusions for all inpatient doses of C/T (similar to piperacillin-tazobactam), rather than 1-hour infusions
  - Primary use is for infections with multi-drug resistant (MDR) *Pseudomonas aeruginosa*

- C/T Restricted to ID services at Nebraska Medicine since Formulary approval in Oct 2015
  - Increases in C/T minimum inhibitory concentrations (MICs) have been noted over the last several years
  - Often no safe alternatives exist to treat these patients

ID = Infectious Diseases
Antimicrobial Stewardship Program summary of approval and restrictions, monograph:
https://www.unmc.edu/intmed/divisions/id/asp/protected-antimicrobials/ceftolozane.html

Background

FDA-Approved Indications	Dosing
Complicated Urinary Tract Infection	1.5 g q8h
Complicated Intra-abdominal Infection (in combination with metronidazole)	1.5 g q8h
Pneumonia, hospital-acquired or ventilator-associated	3 g q8h

Manufacturer labeling: Administer doses over 1 hour

IDSA Guidance for MDR Gram Negative Infections: Administer 1.5 g dose over 1 hr and 3 g dose over 3 hr

FDA = Food and Drug Administration
IDSA = Infectious Diseases Society of America
MDR = Multi-Drug Resistant (Not susceptible to antibiotics in 3 or more classes normally tested)

Assessment of Extended Infusion C/T in Patients with Varying Degrees of Renal Function

Study	Comments
Natesan, et al. 2017 Monte Carlo simulations	• Extended infusion of 4-5 hours had higher probability of target attainment (minimum goal 40% *f*T>MIC) compared to shorter infusions and continuous infusions with MIC of 4-32 mg/L • Current FDA breakpoint for susceptibility is 4 mg/L

Tamma, et al. 2021 Case series	• 28 patients with carbapenem resistant *Pseudomonas* isolates
	  • 4 patients received extended infusion
	  • Less likely to develop at least a 4-fold increase in MIC with 3 hour extended infusion *(basis of IDSA guidance)*

Montero, et al. 2022 Hollow-fiber infection model	Comparison of intermittent (1 hour), extended infusion (4 hour), and continuous infusion against XDR *Pseudomonas aeruginosa* • MIC = 2 to 16 mg/L • Extended or continuous infusion was required for bactericidal effect • Final number of bacterial colonies (mean) for intermittent infusion was 5.39 vs. 4.48 CFU/mL for extended infusion

*f*T > MIC = Fraction of time in dosing interval free drug concentrations exceed the minimum inhibitory concentration for the organism
XDR = extensively drug resistant (organism not susceptible to all but one class of antibiotic)

Assessment of Extended Infusion C/T in Patients with Varying Degrees of Renal Function

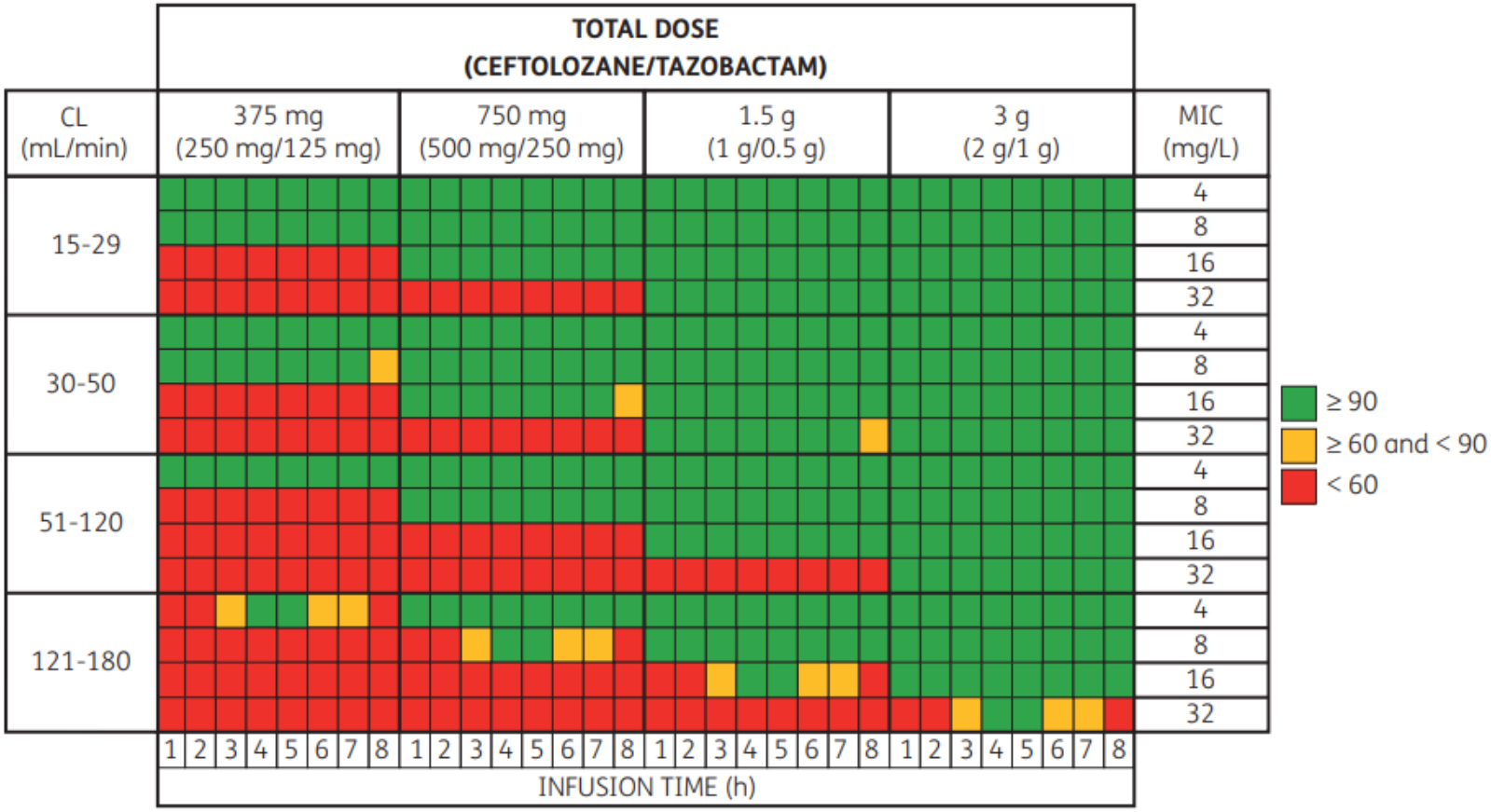

Figure 1. PTA by ceftolozane/tazobactam dose, estimated renal function category and ceftolozane/tazobactam MIC value.

PTA = Probability of Target Attainment (minimum goal of 40% Time > MIC)
Natesan, et al. 2017.

Assessment of Extended Infusion C/T in Patients on CRRT

Study	Comments

Li, et al. 2020
Review article *summarizing studies below*
	Extended infusions recommended while on continuous renal replacement therapy (CRRT)
	• CVVHD
	  • Maintenance dose = 750 mg q8h or 1.5 g q8h
	• CVVHDF
	  • Loading dose = 3 g
	  • Maintenance dose = 750 mg q8h

Aguilar, et al. 2020 Case series	Recommendations while on CVVHD (flow rates of 1-2 L/h) for MDR *Pseudomonas* infection • Prolonged 3-4 hour infusion of 1.5 g q8h dose is sufficient for achieving 3-4 times the MIC (for MIC 4 or 8) throughout the entire dosing interval
Sime, et al. 2020 Monte Carlo simulations	• Single loading dose of 3 g followed by 750 mg q8h regimen for patients on CVVHDF, regardless of flow rates • Doses as low as 750 mg q8h over extended infusion allowed for cumulative fractional response of > 85% for empiric activity against *Pseudomonas aeruginosa* when considering 40% fT > MIC • For 100% fT > MIC, required 1.5 g q8h doses
Bremmer, et al. 2016 Case study with PK/PD	• CVVHDF and treating MDR *Pseudomonas aeruginosa* bacteremia from pneumonia • 1.5 g q8h with 4 hour extended infusion duration • Dose required to achieve PK/PD target of free drug concentration > MIC throughout the dosing interval (100% fT > MIC) for MIC up to 8 mcg/mL (*Intermediate)*
Oliver, et al. 2016 Case study with PK/PD	• CVVH and treating MDR *Pseudomonas aeruginosa* pneumonia • 1.5 g q8h with 4 hour extended infusion duration • Extended infusion dosing was required to achieve PK/PD target of free drug concentration > MIC throughout the dosing interval (100% fT > MIC)

Assessment of IV Compatibilities with C/T

Drug	Compatibility & Comments
Bivalirudin, Dobutamine, Dopamine, Dexmedetomidine, Epinephrine, Fentanyl, Heparin, Norepinephrine, Phenylephrine, Vasopressin	**Yes**
Vancomycin	**Yes*** • *Compatible with conc. <15 mg/mL • Concentrations used at NM range from 3-5 mg/mL
Propofol	**No** • Separate line needed • Typical for this drug which is used in ICU patients

Assessment of Extended Infusion

- Administering doses of C/T over 4 hours will optimize PK/PD without added cost
  - Higher probability of target attainment if MICs elevated out of susceptible range
    - Ability to achieve T > MIC target for organisms with MICs up 16mg/L
  - Safe and potentially more effective for patients with varying renal function, and especially for those on CRRT
- Compatible with most common IV continuous infusion medications

T>MIC = Time above the organism's minimum inhibitory concentration
CRRT = Continuous Renal Replacement Therapy

Recommendation

Update both the 1.5 g and 3 g dose of C/T for inpatient administration over 4 hours

Indications	Dosing based on renal function				
	> 50 mL/min	**30-50 mL/min**	**15-29 mL/min**	**ESRD on HD**	**CRRT**
cUTI or cIAI	1.5 g q8h	750 mg q8h	375 mg q8h	750 mg x1, then 150 mg q8h	750 mg q8h
Systemic infection, MDR *Pseudomonas*, HAP/VAP	3 g q8h	1.5 g q8h	750 mg q8h	2.25 g x1, then 450 mg q8h	1.5 g q8h

cUTI = complicated urinary tract infection
cIAI = complicated intra-abdominal infection
MDR = multidrug resistant
HAP/VAP = hospital acquired pneumonia/ventilator associated pneumonia
ESRD on HD = End Stage Renal Disease on Hemodialysis
CRRT = Continuous Renal Replacement Therapy

University of Nebraska Medical Center

Nebraska Medicine

References

- Bremmer DN, Nicolau DP, Burcham P, Chunduri A, Shidham G, Bauer KA. Ceftolozane/Tazobactam Pharmacokinetics in a Critically Ill Adult Receiving Continuous Renal Replacement Therapy. *Pharmacother J Hum Pharmacol Drug Ther*. 2016;36(5):e30-e33. doi:10.1002/phar.1744
- Oliver WD, Heil EL, Gonzales JP, et al. Ceftolozane-Tazobactam Pharmacokinetics in a Critically Ill Patient on Continuous Venovenous Hemofiltration. *Antimicrob Agents Chemother*. 2016;60. doi:10.1128/aac.02608-15
- Aguilar G, Ferriols R, Martínez-Castro S, et al. Optimizing ceftolozane-tazobactam dosage in critically ill patients during continuous venovenous hemodiafiltration. *Crit Care*. 2019;23. doi:10.1186/s13054-019-2434-5
- Sime FB, Lassig-Smith M, Starr T, et al. A population pharmacokinetic model-guided evaluation of ceftolozane/tazobactam dosing in critically ill patients undergoing continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother.* 2019b. pii: AAC.01655-19. doi: 10.1128/AAC.01655-19.
- Chaijamorn W, Shaw AR, Lewis SJ, Mueller BA. Ex vivo ceftolozane/tazobactam clearance during continuous renal replacement therapy. *Blood Purif.* 2017;44(1):16-23. doi: 10.1159/000455897.
- Li L, Li X, Xia Y, Chu Y, Zhong H, Li J, Liang P, Bu Y, Zhao R, Liao Y, Yang P, Lu X, Jiang S. Recommendation of Antimicrobial Dosing Optimization During Continuous Renal Replacement Therapy. Front Pharmacol. 2020 May 29;11:786.
- Montero MM, Domene-Ochoa S, Lopez-Causape C, et al. Comparison of ceftolozane/tazobaxtam infusion *regimens* in a hollow-fiber infection model against extensively drug resistant Pseudomonas aeruginosa isolates. *Antimicrob Chemother.* 2022;10(3):e00892-22.
- Natesan S, Pai MP, Lodise TP. Determination of alternative ceftolozane/tazobactam dosing regimens for patients with infections due to Pseudomonas aeruginosa with MIC values between 4 and 32 mg/L. J Antimicrob Chemother. 2017 Oct 1;72(10):2813-2816. doi: 10.1093/jac/dkx221. PMID: 29091209.
- Tamma PD, Beisken S, Bergman Y, et al. Modifiable Risk Factors for the Emergence of Ceftolozane-tazobactam Resistance, *Clinical Infectious Diseases*, Volume 73, Issue 11, 1 December 2021, Pages e4599–e4606, https://doi.org/10.1093/cid/ciaa1306