Nebraska Medicine

SERIOUS MEDICINE. EXTRAORDINARY CARE.

SUPPORTING EVIDENCE FOR ALTERNATE CEFEPIME DOSING SUBSTITUTION

BACKGROUND

Cefepime (CEP) is approved by the Food and Drug Adminstration (FDA) for the treatment of febrile neutropenia, empiric therapy of uncomplicated skin and soft tissue infection (SSTI), complicated intra-abdominal infection (in combination with metronidazole), pneumonia, and urinary tract infection (UTI), due to susceptible gram-negative (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Enterobacter species,Acinetobacter spp.* etc) and gram-positive pathogens [*Streptococcus pyogenes*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae* etc] except methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus spp* (including vancomycin resistant isolates) and anaerobes.[1,2] Cefepime is also used for many non-FDA approved indications including bacteremia associated with intravascular lines (due to *Pseudomonas aeruginosa*), bacterial meningitis, brain abscess (postneurosurgical prevention), septic lateral/cavernous sinus thrombosis (with metronidazole), infective endocarditis (including culture-negative endocarditis), and peritoneal dialysis-associated peritonitis.[1]

Table 1. The manufacturer-recommended and FDA-approved dosing of CEP is as follows:[1]

	Adults and children >40kg[a]				Pediatrics >14 days and ≤40kg[ab]	
CrCl>50 ml/min or CRRT	500mg q12hr	1 g q12hr	2g q12hr	2g q8hr	50mg/kg/dose q12h (max 2g/dose)	50mg/kg/dose q8h (max 2g/dose)
Infections	Mild to moderate UTI (complicated or uncomplicated)	Community acquired pneumonia Mild to moderate UTI (complicated or uncomplicated)	Nosocomial pneumonia (or 1g q8h) Uncomplicated SSTI Complicated intra-abdominal infection Otitis externa, malignant Community acquired pneumonia (including pseudomonal) Septic lateral/cavernous sinus thrombosis Severe UTI	Bacteremia associated with intravascular line: (due to *P. aeruginosa*) Bacterial meningitis Febrile neutropenia Infective endocarditis Nosocomial Pneumonia (pseudomonal) Brain abscess Septic lateral/cavernous sinus thrombosis	Uncomplicated SSTI Pneumonia UTI (complicated or uncomplicated)	Febrile neutropenia Infective endocarditis Bacterial meningitis Pseudomonas infection
CrCl 10-50 mL/min	500mg q24hr	1 g q24hr	2 g q24hr	2 g q12hr	50mg/kg q24hr	50mg/kg q12hr
CrCl < 10 mL/min	500mg q48hr	1g q48hr	2g q48hr	2 g q24hr	50% of dose q24hr	50% of dose q24hr
Hemodialysis[c]	Dose as CrCl<10ml/min				Dose as CrCl <10 ml/min	
Peritoneal dialysis					50mg/kg/dose q48h	

[a]duration of treatment 7-10 days; [b]0-14 days old: 30mg/kg q12h; [c]administer following hemodialysis on dialysis days

ALTERNATE DOSING PROPOSAL

- Pharmacists will automatically interchange orders for standard doses of CEP to alternate doses and automatically adjust the dose of CEP for renal insufficiency as indicated in the charts below. The creatinine clearance (CrCl) will be estimated using the Cockroft-Gault equation for patients ≥18 years old and the Schwartz equation for patients < 18 years old. Renal dosage adjustments will be made in accordance with the Antimicrobial Renal Dosage Adjustment policy.

Table 2. This will translate to auto-substitution as follows:[3-7] (normal renal function)

Medication Ordered	Interchange With
Cefepime 1g q12hr	Cefepime 1g q6h
Cefepime 2g q12hr	Cefepime 1g q6hr
Cefepime 2g q8hr	Cefepime 1g q6hr
Cefepime 2g q8hr for "Neutropenic Fever"	Cefepime 2g q8hr*

This includes all adults and children > 40 kg. Children weighing 40kg or less are excluded from the automatic dosage substitution.

*Cefepime 2g q 8hrs is allowed **only in neutropenic fever**, and ordering clinicians must write the indication ("neutropenic fever") after ordering this dose. Pharmacists will also review laboratory data in patients whom 2g q8h is ordered and no indication was documented. If the Absolute Neutrophil Count (ANC) is ≤500 the 2g q8hr dose will be used. All other orders will be changed to 1g q6hr.

Table 3. Dosage adjustments for renal function:[3-7]

Clcr(ml/min)	>50ml/min/CRRT/SLED	30-50 ml/min	10-29	CrCl<10ml/min, Hemodialysis and peritoneal dialysis
Adults and Children >40kg	1g q6h	1g q8hr	1g q12hr	1g q24hr
	2g q8hr	2g q12hr	2g q12hr	2g q24hr

CRRT = continuous renal replacement therapy; SLED = slow extended dialysis

JUSTIFICATION

Internal Minimum Inhibitory Concentration (MIC) Surveillance

An internal study was conducted to review the MICs of CEP against *Pseudomonas aeruginosa* isolates. A random selection of 30 blood isolates and 12 sputum isolates were evaluated, and MICs were obtained via Sensititre susceptibility plates. According to Clinical Laboratory Standards Institute (CLSI) guidelines, the breakpoint for susceptibility of Enterobacteriaceae, *Acinetobacter* spp. and *P. aeruginosa* to CEP is ≤ 8 mg/L. The results of the internal survey are illustrated below:

	CEP
MIC_{50}	8 mg/L
MIC_{90}	16 mg/L

The MIC needed to inhibit 90% of the organisms is above the breakpoint of 8, which is very concerning due to the likelihood of target attainment given the pharmacokinetic (PK) and pharmacodynamic (PD) parameters associated with CEP. Beta-lactam agents, such as CEP, are concentration-independent antibacterial killers, and the PD parameter that correlates to optimal activity is the percent of dosing interval the free drug concentration remains above the MIC (%fT>MIC). Furthermore, CEP lacks any persistent effects [post-antibiotic effect (PAE)] that last after antimicrobial exposure to most organisms, such that once the free drug concentrations fall below the MIC, bacterial re-growth is almost instantaneous. The necessary percent of time the concentration must remain above the MIC varies depending on the type of beta-lactam antibiotic (Table 4).[8,9] The clinical implication of these findings is the potential for suboptimal dosing.

Table 4. Summary target attainments for different beta-lactam classes against different pathogens[8,9]

Pathogen	Overall (%fT>MIC)	Carbapenems (%fT>MIC)	Penicillins (%fT>MIC)	Cephalosporins (%fT>MIC)
Gram positive	20-50%	20-30%	30-40%	40-50%
Gram negative	40-70%	40-50%	50-60%	**60-70%**

Pharmacokinetic/Pharmacodynamic (PK/PD) studies

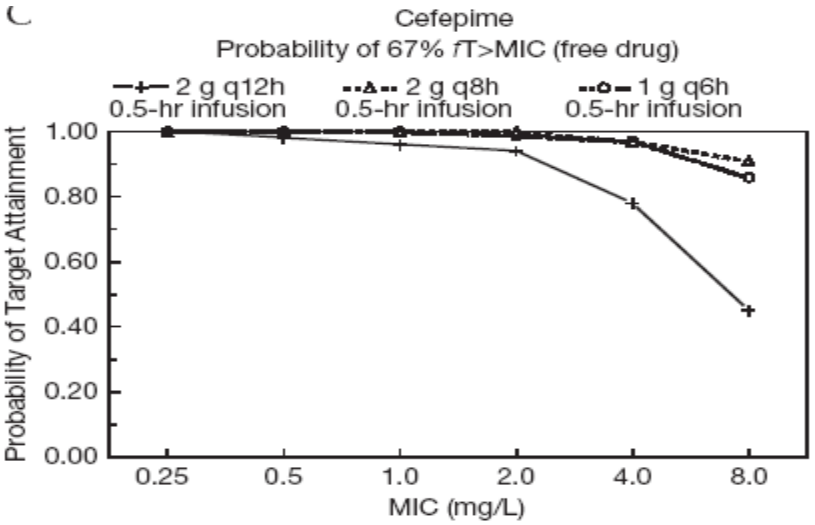
Evidence 1: Lodise TP, et al. Pharmacotherapy. 2006; 26: 1320-32[3]

An alternate dosing regimen that provides similar probability of target attainment (PTA) but with less total daily drug has been explored. Using Monte Carlo simulation, the following PTAs were achievable for varying CEP dosing regimens against *Pseudomonas aeruginosa* isolates at different MIC values.

Table 5. Cefepime target attainment versus *Pseudomonas aeruginosa*

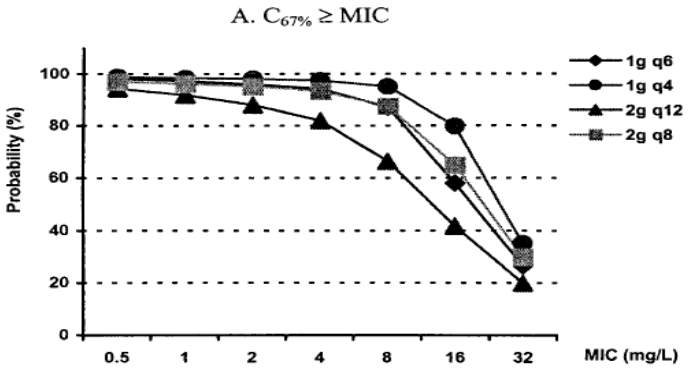
Breakpoints	S	I	R					
	≤8	16	≥32					
	MIC (mg/L)							
Regimen/infusion	Target %	0.25	0.5	1	2	4	8	16
2g q12/0.5	67	100	98	97	95	79	45	--
2g q8/0.5	67	100	100	100	100	97	91	--
1g q6/0.5	67	100	100	100	99	97	89	--

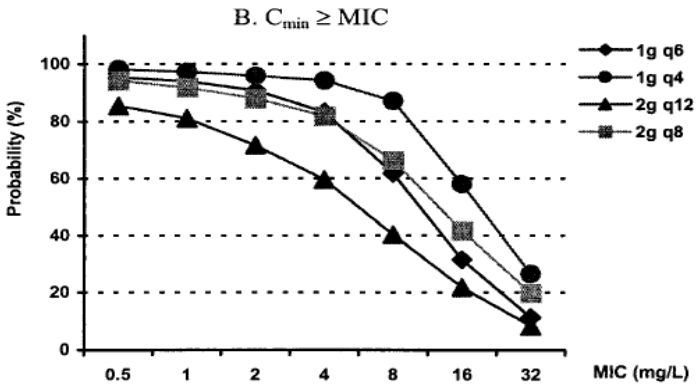
As illustrated in table 5 above, CEP 1g q6h given as a 30 minute infusion rivals the standard 2g q8h dosing with less total daily required drug. Ideally, the PTA should be 90% or more for a regimen to be considered appropriate for a given MIC. These two regimens are comparable up to the breakpoint of 8mg/L. Therefore, from a cost containment perspective, given similar PTA, CEP 1g q6h is justifiable. As shown in the figure below, which is a pictorial representation of data in Table 5, substituting CEP 1g q6h for CEP 2g q8h will not compromise PK/PD targets. Additionally, as depicted in the figure, although both CEP 2g q12h and 1g q6h result in the same total daily dose, the PTA is higher with the latter regimen.

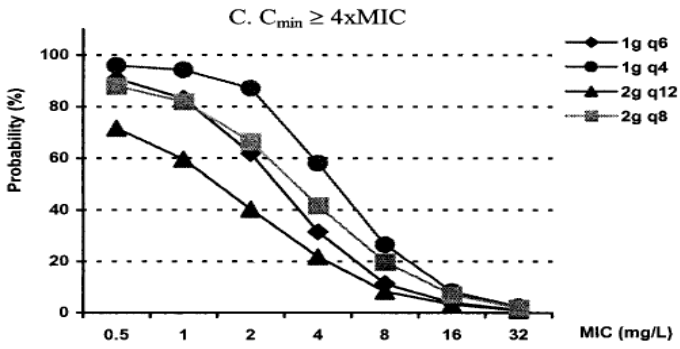


Evidence 2: Tam VH, et al. Antimicrob Agents Chemother 2003;47:1853–61[6]

- This study evaluated PK/PD of CEP in 36 adult patients admitted between October 1999 and June 2000. Patients enrolled had varying degrees of renal function.
- Monte-Carlo simulation was conducted to assess the PTA in patients with various levels of renal function (CrCl, 120, 60, and 30 ml/min) for 1,000 patients using PK information from the 36 adults.
- The PD targets chosen were a free concentration greater than or equal to the MIC for 67% of the dosing interval ($C_{67\%}$≥MIC), a C_{min} ≥MIC, and a C_{min}≥4xMIC.
- The graphs depicted below are for the PTA at CrCl of 120ml/min.
    - Doses were given over 30 min.





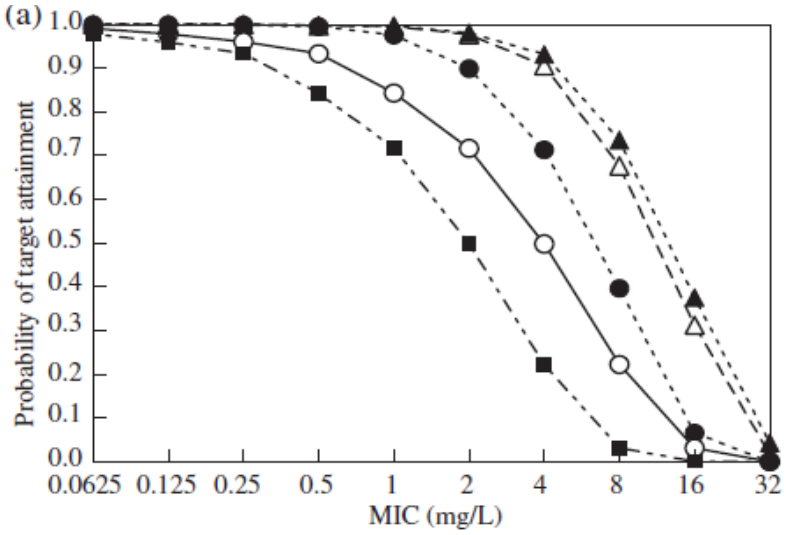


- As seen in the pictures above, the PTA is similar for CEP 2g q8h vs. 1g q6h. PTA was lowest when the dosing regimen 2g q12h was employed.

Evidence 3: Roos JF, et al. J Antimicrob Chemother. 2006 Nov;58(5):987-93[4]

- Using data from 13 ICU patients (11 males) with normal renal function, who received CEP 2 g every IV 12 h as a 30 min infusion, the researchers developed a population PK model for CEP. This PK information was then applied to simulate various CEP dosing regimens and to generate the PTA against *E. coli, K. pneumoniae, P. aeruginosa and Acinetobacter baumannii.*
- Doses simulated included: intermittent doses of 2 g q12h, 2 g q8h, 1 g q12h, 1 g q6h, or 1 g q4h given over 30 minutes; and continuous infusion regimens, 2, 4 or 6 g over 24h with a loading dose of 0.5 g.

Results:



PTA of individual regimens
Intermittent infusion only; Filled triangles=2g q8h; open triangles= 1g q4h; filled circles=1g q6h; open circles= 2g q12h; filled squares=1g q12h.

Table 6. Probabilities of PTA for intermittent administration versus continuous infusion of CEP in ICU patients (using free concentration ≥ MIC for 65% of dosing interval as target)

Dosing regimens		PTA (%)		
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
Intermittent infusion				
1g q4h	95.3	95.3	82.6	57.9
2g q8h	95.8	95.8	84.9	61.1
1g q6h	91.9	91.9	69.5	41.5
2g q12h	78.9	78.9	53.6	28.2
1g q12h	66.1	66.1	35.5	11.6
Continuous infusion with 0.5g loading dose				
2g/day	95.2	95.2	81.3	56.3
4g/day	96.9	96.9	91.7	68.5
6g/day	97.9	97.9	94.8	74.6

- The 2g q8h dose had highest PTA with *P. aeruginosa* or *A. baumannii* although no intermittent regimen resulted in a PTA ≥90%
- The continuous infusion regimens of 4g/day and 6g/day were more likely to achieve target attainment for all isolates except *A. baumannii.*

In summary, based on PK/PD data and PTA, CEP 1g q6h is attractive because it provides similar PTA as CEP 2g q8h but at reduced total daily drug. The biggest limitation with application of CEP 1g q6h is the lack of data regarding clinical outcomes as compared to a dose of 2g q8h.

PHARMACOECONOMICS

Projected expenditures for automatic interchange to CEP 1g q6h

Table 7. Cost analysis

Agent	**Dose**	**TNMC Inpatient Acquisition Cost/Day***	**FY09 =73.8 DDD/1000 PD PD=140,927= 10,400.4 DDD total**
Cefepime	1g IV q 6 h	$23.14	$240,665.26
Cefepime	2g IV q8h	$34.71	$360,997.88
Net cost		**-$11.57**	**-$120,332.62**
Cefepime	1g IV q 6 h	$23.14	$240,665.26
Cefepime	2g IV q12h	$23.14	$240,665.26
Net cost		0	0
FY09 = fiscal year 2009; DDD= defined daily doses (2gm/day for CEP) ; PD = patient days *$11.57/2gm or $5.79/gm			

CONCLUSION

The alternative CEP dosing proposal presented is extrapolated from PK/PD data and experiences at other institutions. CEP 1g q6h has been demonstrated to produce similar PTA to that of CEP 2g q8h, which is recommended for more serious infections. With limited clinical data available for this dosing option, after the dosing substitution is implemented, data would be collected to evaluate the impact on patient outcomes. Furthermore, pediatric patients weighing 40kg or less are excluded from the alternate dose proposal given the lack of data for this population.

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Prepared by: Jessica C. Njoku, Pharm.D., BCPS
Reviewed by: Elizabeth D. Hermsen, Pharm.D., M.B.A., BCPS-ID, Mark E. Rupp, M.D., Trevor C. VanSchooneveld, M.D.