THE NEBRASKA MEDICAL CENTER

SUPPORTING EVIDENCE FOR MEROPENEM THERAPEUTIC INTERCHANGE AND DOSING SUBSTITUTION POLICY

BACKGROUND:

Meropenem is a member of the antibiotic class of carbapenems, which are broad-spectrum antibiotics that possess activity against several drug-resistant organisms. Notably, the carbapenems maintain activity against extended-spectrum beta-lactamase (ESBL)-producing organisms. Additionally, the spectrum of activity of the carbapenems, excluding ertapenem, includes *Pseudomonas aeruginosa*. Meropenem is FDA-approved for the treatment of the following infections due to susceptible gram-positive, gram-negative, and anaerobic organisms: uncomplicated and complicated skin and skin structure infections, intra-abdominal infections, complicated appendicitis and peritonitis, and bacterial meningitis (≥ 3 months of age only).[1]

ALTERNATE DOSAGE PROPOSAL:

- Pharmacists will automatically interchange imipenem medication orders to meropenem and automatically adjust the dose of meropenem 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.

Auto-substitution guidelines:

Adults (≥18 years of age) and Children >50kg:

IF THIS IS ORDERED	THIS WILL BE PROVIDED
Meropenem 1g q8hr	Meropenem 500mg q6hr*
Meropenem 1g q12hr	Meropenem 500mg q8hr*
Meropenem 500mg q8hr	Meropenem 500mg q8hr*
Meropenem 2g q8hr*	Meropenem 2g q8hr*
Imipenem/cilastatin 500mg q6hr	Meropenem 500mg q6hr*
Imipenem/cilastatin 500mg q8hr	Meropenem 500mg q8hr*
Imipenem/cilastatin 1g q8hr	Meropenem 500mg q6hr*
Imipenem/cilastatin 750mg q12hr	Meropenem 500mg q8hr*
Imipenem/cilastatin 250mg q6hr	Meropenem 500mg q8hr*

***For patients with a diagnosis of meningitis, cystic fibrosis or with microorganisms with a meropenem/ imipenem MIC of 4mg/L, the meropenem dose should be adjusted to 2 g q8hr. These are the only indications for which this dose is appropriate.**

Examples: 1) Prescriber orders meropenem 1g q8hr in a patient with meningitis. Dose should be automatically adjusted by the pharmacist to 2g q8hr. 2) Prescriber orders meropenem 2g q8hr in a patient with sepsis of unknown source. Dose should be automatically adjusted by the pharmacist to 500mg q6hr. 3) Prescriber orders meropenem 500mg q6hr for empiric treatment of nosocomial pneumonia. Previous sputum culture yielded *Acinetobacter* with a meropenem MIC of 4 mg/L. Dose should be automatically adjusted by the pharmacist to 2g q8hr and modified to 500mg q6hr if the new culture yields an organism with a lower MIC. **If there is any question about the indication for meropenem, the prescriber should be contacted for clarification.**

Neonates & Pediatrics (<50kg):

Type of Infection	IF ORDERED	PROVIDED		
	Imipenem (mg/kg)	Meropenem (mg/kg)		Max dose
Sepsis and other indications	15-25 q6hr	Neonates 7 days & under	20 q12hr	--
		Neonates over 7 days/Children	20 q8hr	500 mg
Meningitis, cystic fibrosis, microorganisms with reported meropenem MIC of 4 mg/L		Neonates 7 days & under	40 q12hr	--
		Neonates over 7 days/Children	40 q8hr	2 g

Guidelines for renal adjustment*:

Renal function	≥50 ml/min	25 – 49 ml/min	10-24 ml/min	<10 and HD or PD
Adults and children >50kg	500mg q6hr	500mg q8hr	500mg q12hr	500mg q24hr
	500mg q8hr	500mg q12hr	250mg q12hr	500mg q24h
	2g q8hr	2g q12hr	1g q12hr	1g q24hr
Pediatrics (over 7 days old and <50kg)	Normal dose q8hr	Normal dose q8hr	Normal dose q12hr	Normal dose q24hr

HD = hemodialysis; PD = peritoneal dialysis
*No clear recommendations for neonates 7 days & under.
Adapted from references[2-4,5,6]

JUSTIFICATION:

The justification for this protocol is provided by four types of data: 1) internal minimum inhibitory concentration (MIC) surveillance, 2) pharmacokinetic/pharmacodynamic (PK/PD) studies, 3) clinical outcome studies, and 4) pharmacoeconomics.

Internal MIC Surveillance

An internal study was conducted to compare the MICs of meropenem and imipenem/cilastatin against *Pseudomonas aeruginosa* isolates. A random selection of 30 blood isolates and 12 sputum isolates were selected, and MICs were obtained via Sensititre susceptibility plates. According to Clinical Laboratory Standards Institute (CLSI) guidelines, the breakpoint for susceptibility of the Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp. is ≤ 4 mg/L for both meropenem and imipenem. The results of the internal survey are illustrated below:

	Imipenem	Meropenem
MIC_{50}	1 mg/L	≤1 mg/L
MIC_{90}	8 mg/L	4 mg/L

The data revealed more potent activity for meropenem versus imipenem against *P. aeruginosa* isolates at The Nebraska Medical Center. This finding is important because meropenem, like all beta-lactams, exhibits concentration-independent antibacterial activity. Additionally, beta-lactams produce minimal or are devoid of persistent effects [post-antibiotic effect (PAE)] that last after antimicrobial exposure to most organisms. This thus allows for bacterial re-growth once the free drug concentrations fall below the MIC. Similar to all beta-lactams, the PD parameter that correlates to meropenem activity is the percent of time the free drug concentration remains above the MIC of the organism (%fT>MIC). However, the necessary percent of time the concentration must remain above the MIC varies depending on the type of beta-lactam antibiotic (see table below).[7,8]

Summary target attainments for different beta-lactam classes against different pathogens				
Pathogen	Overall (%T>MIC)	Carbapenems (%T>MIC)	Penicillins (%T>MIC)	Cephalosporins (%T>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

Traditionally, meropenem has been dosed 1 g IV q 8 hrs for serious infections. However, application of the PK/PD properties of meropenem to create alternative dosing strategies results in equivalent or even greater clinical success. Several studies have explored the PK/PD parameters of beta lactam agents with the goal of enhancing the duration of drug exposure, i.e. %fT>MIC.

Evidence 1: Monte Carlo simulation studies

Using Monte Carlo simulation, the following probabilities of target attainment were achievable for meropenem against *Pseudomonas* isolates at different MIC values.

Meropenem target attainment (*Pseudomonas aeruginosa only)*								
	MIC (mg/L)							
Regimen/infusion time (hrs)	Target %fT>MIC	0.25	0.5	1	2	4	8	16
1g q8/0.5[9,10]	**40**	**100**	**99-100**	**95-99**	**85-93**	**65-70**	**32**	**7**
1g q8/1[9]	40	100	99	96	86	70	37	9
1g q8/3[9,10]	40	100	100	100	100	93-99	62	15
500mg q6/0.5[10]	**40**	**100**	**100**	**100**	**100**	**72**	**--**	**--**
500mg q8/1[10]	40	100	97	90	65	32	--	--
500mg q8/3[10]	40	100	100	100	100	80	--	--

Ideally, the probability of PD target attainment should be 90% or more for a regimen to be considered appropriate for a given MIC. Based on data presented in the table above, none of the regimens are reliable at an MIC of 8 mg/L or above, which would be non-susceptible according to CLSI breakpoints. The proposed dosing regimen of 500mg q6hr resulted in a greater likelihood of target attainment than traditional dosing of 1g q8hr at all MICs ≤4 mg/L. However, at an MIC of 4 mg/L, the probability of target attainment remains less than desirable, providing support for the recommended regimen of 2 g IV q 8 hrs for organisms with a documented MIC of 4 mg/L. For all other susceptible MICs, 500mg q 6 hrs is the most logical dosing alternative because it provides high probability of PD target attainment, does not require extended infusion, which can be logistically challenging, and uses less total drug as compared to the traditional dose of 1 g IV q 8 hrs.

Evidence 2: Cheatham SC, et al. *Pharmacotherapy.* 2008;28:691-8.[5]

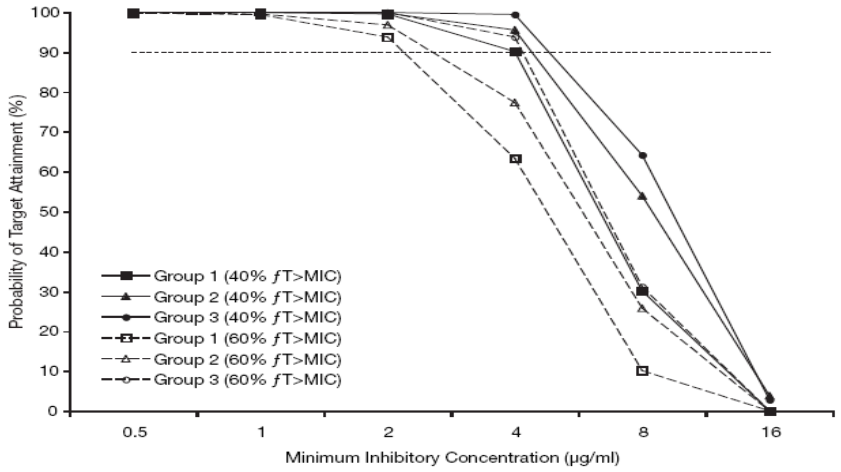
- Design: prospective, open-label, steady state PK/PD study of meropenem in 20 adult patients with suspected or documented bacterial infections
- Patients received meropenem 500mg every 6 (creatinine clearance [CrCl] > 60 ml/min), 8 (CrCl 40-60 ml/min), or 12 (CrCl 10-39 ml/min) hours

Results:

Cumulative Fraction of Response (CFR) for Meropenem at 40% and 60% fT>MIC against Gram-negative pathogens:

Organism	**500mg q6hr (CrCl > 60 ml/min)**		**500mg q8hr (CrCl 40-60 ml/min)**		**500mg q12hr (CrCl 10-39 ml/min)**	
	40%	**60%**	**40%**	**60%**	**40%**	**60%**
Escherichia coli	100	100	100	100	100	100
Klebsiella pneumoniae	97.3	97.2	97.4	97.3	100	97.2
Enterobacter spp	99.6	99.6	99.7	99.7	100	100
Serratia marcescens	99.6	99.6	99.6	99.6	100	100
Citrobacter spp	100	99.7	100	99.9	100	100
Pseudomonas aeruginosa	90.3	87.4	92.4	89.5	92.5	90.4
Acinetobacter spp	82.4	78	84.5	80.3	85.2	82.3

Probability of Target Attainment (PTA) of ≥90% at various meropenem MICs:



Conclusions:

- From a PK/PD standpoint, this study provides evidence to defend the proposed alternative dosage regimens. At a meropenem-susceptible breakpoint of 4 mg/L and with desired %fT>MIC of 40%, all 3 groups achieved optimum PTA of over 90%.
- Based on PK parameters obtained, all patients achieved adequate drug exposures.
- CFR was desirable for all pathogens at various %fT>MIC except for *Acinetobacter spp* and *P. aeruginosa* with %fT>MIC of 60%. This raises the question as to whether these dosing regimens are insufficient for patients with infections due to *Acinetobacter spp,,* thus warranting more aggressive dosing. Ultimately, other factors will need to be considered such as the pathogen MIC, patient's immune status, and severity of illness.

Evidence 3: Kuti JL, et al. *Pharmacotherapy* 2004;24:8–15.[3]

- In this Monte Carlo simulation, meropenem 500mg q6hr vs. imipenem 500mg q6hr were compared against populations of *Enterobacteriaceae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa.*
- Probabilities of attaining targets of 30%, 50%, and 100% fT>MIC were calculated.

Results: %fT>MIC exposure was greatest against *Enterobacteriaceae* and less for *A. baumannii* and *P. aeruginosa* for both agents.

- Probabilities of target attainment for 30% and 50% T>MIC were similar between drugs for most bacteria.
- At 100% T>MIC, meropenem target attainments were greater than those of imipenem against *Enterobacteriaceae* and *P. aeruginosa;* however, imipenem attainment was higher for *A. baumannii*

Probabilities of Achieving Pharmacodynamic Targets for Each Bacterial Population

Organism	**30% fT>MIC**		**50% fT>MIC**		**100% fT>MIC**	
	MEM (%)	IMI (%)	MEM (%)	IMI (%)	MEM (%)	IMI (%)
Escherichia coli	100	100	100	100	100	94
Klebsiella pneumoniae	100	100	99	100	99	91
Enterobacter cloacae	100	100	100	100	95	71
Serratia marcescens	99	99	99	99	97	57
Acinetobacter baumannii	83	89	79	88	31	60
Pseudomonas aeruginosa	93	92	87	87	47	27
MEM = meropenem; IMI = imipenem						

Conclusion: There were comparable target attainment rates at 30% and 50% fT>MIC for meropenem 500 mg every 6 hours and imipenem 500 mg every 6 hours. Based on this information, meropenem 500mg q6hr can comfortably be interchanged for imipenem 500mg q6hr. However, this regimen may be suboptimal for *Acinetobacter* isolates.

Clinical outcomes studies:

Study 1: Arnold HM, et al. *Pharmacotherapy.* 2009 Aug;29(8):914-23.[2]

- Design: retrospective single cohort study comparing clinical outcomes of patients receiving alternative dosage of meropenem to patients receiving imipenem or the traditional dosage of meropenem after failure of or intolerance to cefepime for treatment of febrile neutropenia.
- 127 patients were included in the study, of which 40 received imipenem 500mg q6 hours between September 1, 2005, and August 31, 2006; 29 received the traditional dosage of meropenem 1 g q8 hours and 58 received an alternative dosage of meropenem 500 mg q6 hours between September 1, 2006, and August 31, 2007.
- Primary outcomes: time to defervescence, need for additional antibiotics, time to receipt of additional antibiotics.
- Secondary outcomes: treatment duration, seizure rate, in-hospital mortality and 30 day mortality.

Results:

Outcome	**IMI (n=40)**	**TRAD-MEM (n=29)**	**ALT-MEM (n=58)**	**Significance**
Need for additional antibiotics (%)	8 (20)	5 (17)	8 (14)	0.71
Median time to receipt of additional antibiotics (days)	5 (1-12)	2 (1-22)	1 (1-6)	ALT-MEM vs. IMI: HR 0.652, CI, 0.244–1.738 ALT vs. TRAD MEM: HR 0.645,CI, 0.208–1.998
Median time to defervescence (days)	2	2	3	ALT-MEM vs. IMI: HR 0.912, CI, 0.574–1.451; ALT vs. TRAD MEM: HR 0.881,CI, 0.511–1.519
Median treatment duration (days)	10 (10–32± 5.9)	8 (3–25± 6.5)	8 (3–35 ± 8.1)	ALT- MEM vs. IMI: HR 1.331, CI, 0.85–2.066 ALT vs. TRAD MEM: HR 1.124, CI, 0.685–1.845
Seizure rate (%)	0	0	0	N/A
In hospital mortality (%)	2 (5)	2 (7)	4 (7)	0.82
30 day mortality (%)	5 (13)	2 (7)	8 (14)	0.64
Vancomycin and aminoglycosides were additional antibiotics; TRAD-MEM= traditional meropenem; ALT-MEM= alternative meropenem; IMI= imipenem				

- No statistically significant differences were found for any of the outcomes between the alternative dose of meropenem and the traditional meropenem dose or between the alternative dose of meropenem and imipenem.

Conclusions:

- This study not only provides further support for the alternative meropenem dosing and automatic substitution for imipenem but also provides evidence for application in febrile neutropenic patients, especially for neutropenic fever that is unresponsive to cefepime.

Study 2: Patel GW, et al. *Pharmacotherapy.* 2007 Dec;27(12):1637-43.[4]

- Design: retrospective cohort study with a cost-minimization analysis involving 292 patients treated with meropenem 1 g q8 or 12 hours (traditional dosing regimen) between 1/1/04-9/30/04 and 192 patients treated with meropenem 500 mg q6 or 8 hours (alternative dosing regimen) between 10//1/04-9/30/05; to determine if an alternative dosing strategy provides clinical outcomes similar to those of the traditional regimen while decreasing cost to institution.
- Primary outcomes: meropenem-related length of stay, in-hospital mortality, time to defervescence, and success or failure of therapy.
- Secondary outcomes: economic analysis by cost-minimization analysis taking into account meropenem dosage, dosing interval, number of IV doses given, duration of therapy and drug acquisition cost
- Patients were not significantly different at baseline, and microbiology data consisted of both gram-positive and gram-negative pathogens. Concomitant therapy was allowed in both groups and consisted of vancomycin, fluoroquinolones, aminoglycosides, metronidazole and linezolid. These did not significantly impact study outcomes (p-value range; 0.089-0.946)

Results:

Parameter	TRAD-MEM	ALT-MEM	P value
Median MEM related length of stay (days)	7 (1–44)	9 (1–67)	0.141
Median duration of therapy (days)	5 (2–22)	4 (1–27)	0.055
Median time to defervescence (days)	3 (1–22)	1.5 (1–10)	p<0.0001
Therapy success (%)	90.9	92.1	0.72
In-hospital mortality (%)	8	11.5	0.238
Median antibiotic cost/pt for duration of treatment	$439.05	$234.08	<0.0001
TRAD-MEM= traditional meropenem; ALT-MEM= alternative meropenem; IMI= imipenem			

Therapy failure:

- Result of multivariate analysis showed polymicrobial infection (p=0.013) and sepsis (p=0.015) were associated with an increased failure rate. However alternative dosage regimen was not associated with increased failure rate (p=0.628)

Conclusion:

- In this large retrospective cohort study, duration of therapy, concomitant antimicrobial therapy, clinical success rates, length of stay, and in-hospital mortality rates were similar between the two groups.
- However, the median time to resolution of symptoms was significantly shorter and the median cost of antibiotic therapy was significantly lower in the alternative meropenem group.
- Antibiotic cost containment (~2 fold savings) in this study provides an additional argument for the alternative meropenem dosage regimen in light of similar clinical outcomes across different doses.
- Extensive exclusion criteria threaten external validity of results of this study.

Pharmacoeconomics:

Evidence 1: See study by Patel and colleagues above. A reduction of $204.97/patient, or nearly 50%, was realized.

Evidence 2: Kotapati S, et al. *Am J Health Syst Pharm*. 2004 15;61:1264-70.[6]

- Design: retrospective review of 85 patients treated with meropenem to evaluate the clinical and economic benefits of meropenem dosage strategies of 500mg q6hr vs. 1g q8hr based on pharmacodynamic concepts
- Cost outcomes included:
    - Level 1 cost: drug acquisition cost for meropenem
    - Level 2 cost: Level 1 cost plus all costs associated with concomitant antibiotics and the treatment of adverse events.
    - Level 3 cost: level 1 and level 2 costs plus meropenem related length of stay costs.

Results:

Clinical, Microbiological and Economic Outcomes of Evaluable Patients:

Outcome	ALT-MEM (n=45)	TRAD-MEM (n=40)	P value
Clinical success (%)	78	82	0.862
Microbiologic success (%)	63	79	0.334
Meropenem-related length of stay (days)	7 (4.8-13)	7.5 (4-10)	0.891
Level 1 cost ($)	576 (295-1,213)	982 (600-1,719)	0.009
Level 2 cost ($)	1,035 (563-1,582)	1,797 (903-2,622)	0.008
Level 3 cost ($)	19,934 (11,895-27,513)	16,087 (9,969-23,274)	0.42
TRAD-MEM= traditional meropenem; ALT-MEM= alternative meropenem; IMI= imipenem			

Conclusion:

- Without compromising desired clinical outcomes, significant cost reduction can be realized with alternative meropenem dosage implementation.

Evidence 3:

Agent	Dose	TNMC Inpatient Acquisition Cost/Day
Imipenem	500 mg IV q 6 hrs	$ 82.68
Meropenem	1 g IV q 8 hrs	$ 90.27
Meropenem	500 mg IV q 6 hrs	$60.20

An automatic therapeutic interchange from imipenem 500 mg IV q 6 hrs to meropenem 500 mg IV q 6 hrs saves $22.48/day, and an automatic dose substitution of meropenem 500 mg IV q 6 hrs for meropenem 1 g IV q 8 hrs saves $30.07/day.

References:

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