IREDELL HEALTH SYSTEM

Meropenem (Merrem) Alternative Dosing Substitution in Adult Patients	
Pharmacy Department	
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EXECUTIVE SUMMARY

1. Use of a meropenem alternate dosing scheme optimizes the probability that drug concentrations will remain above the pathogen's minimum inhibitory concentration (MIC) for an appropriate period of time (known as "target attainment").
2. The goals of the alternative dosing scheme are to optimize treatment outcomes while curtailing resistance to meropenem and reducing cost.
3. ASET recommends implementing the alternative dosing protocol in all adult patients to realize both clinical and economic advantages.

BACKGROUND

Meropenem is a formulary carbapenem antibiotic used at Iredell Memorial Hospital for the treatment of moderate-to-severe infections, including sepsis, lower respiratory tract, urinary tract, complicated skin and skin structure, bone and joint, and intra-abdominal infections. Meropenem is often effective against multi-drug resistant organisms, including *Pseudomonas*, *Acinetobacter*, and extended-spectrum beta-lactamase (ESBL) producers.

Increasing antimicrobial resistance and the resulting increased mortality has led to the reevaluation of the optimal method to administer antibiotics. Studies have shown that for β-lactams (including meropenem), the best predictor of bacterial killing is the time during which the free drug concentration exceeds the minimum inhibitory concentration of the organism (%fT>MIC). Specifically, maximal bactericidal effect is achieved when free drug concentration exceeds the MIC by approximately four-fold for 40% of the dosing interval.

Traditionally, meropenem has been dosed 1g IV q8hrs (30-minute infusion) 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 meropenem with the goal of optimizing its clinical utility. Additionally, in an era of cost constraints and resistance development, it has become imperative to maximize effectiveness while minimizing drug exposure and reducing adverse events.

JUSTIFICATION

Pharmacodynamic studies: Pharmacodynamic targets of 40% fT>MIC have been identified as optimal for meropenem. Using Monte Carlo simulation, the following probabilities of target attainment were achievable for meropenem against *Pseudomonas* isolates at different MIC values.

Table 1. Monte Carlo simulation studies [1,2]

% of meropenem target attainment against *Pseudomonas aeruginosa* by regimen and MIC[†]

Regimen/infusion time (hrs)	MIC (mg/L)						
	S				I	R	
	0.25	0.5	1	2	4	8	16
	Percent of target attainment						
1g q8/0.5*	**100**	**99-100**	**95-99**	**85-93**	**65-70**	**32**	**7**
1g q8/1	100	99	96	86	70	37	9
1g q8/3	100	100	100	100	93-99	62	15
500mg q6/0.5**	**100**	**100**	**100**	**100**	**72**	-	-
500mg q8/1	100	97	90	65	32	-	-
500mg q8/3	100	100	100	100	80	-	-

[†] 40 percent of free-drug concentration exceeding the minimum inhibitory concentration

* Current treatment approach

** Proposed treatment approach

The proposed dosing regimen of 500mg q6h resulted in a greater likelihood of target attainment than traditional dosing of 1g q8h at all MICs ≤ 4 mg/L. None of the regimens are reliable at an MIC ≥ 8 mg/L, which would be resistant for *Pseudomonas*, *Enterobacteriaceae*, and *S. pneumoniae* and according to the most recent Clinical Laboratory Standards Institute (CLSI) breakpoints. Thus, 500mg q6hr is a logical dosing alternative for susceptible MICs because it provides a higher probability of PD target attainment without the need for extended-infusion with less total drug (2g/d) as compared to the traditional dose of 1g q8hr.

Clinical studies: The clinical relevance of these finding has also been investigated.

Study 1: Arnold HM, et al. *Pharmcotherapy*. 2009; 29(8): 914-2.[3]

- Design: retrospective single cohort study comparing clinical outcomes of patients receiving alternative dosage of meropenem (500mg q6h) to patients receiving imipenem (500mg q6h) or the traditional dosage of meropenem (1g q8h) after failure of or intolerance to cefepime for treatment of febrile neutropenia
- 127 patients were included in the study
- 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
- No statistically significant differences found for any of the outcomes between the alternative dose of meropenem and the traditional dose or between the alternative dose of meropenem and imipenem

Results:

Outcome	**IMI (n=40)**	**TRAD-MEM (n=29)**	**ALT-MEM (n=58)**	**Significance**
Need for add'l antibiotics, n (%)	8 (20)	5 (17)	8 (14)	p=0.71
Median time to receipt of add'l antibiotics, days (range)	5 (1-12)	2 (1-22)	1 (1-6)	ALT vs TRAD MEM: HR 0.645; CI 0.208-1.998
Median time to defervescence, days	2	2	3	ALT vs TRAD MEM: HR 0.881; CI 0.511-1.519
Median treatment duration, days (range)	10 (10-32)	8 (3-25)	8 (3-35)	ALT vs TRAD MEM: HR 1.124; CI 0.685-1.845
In-hospital mortality, n (%)	2 (5)	2 (7)	4 (7)	p=0.82
30- day mortality (%)	5 (13)	2 (7)	8 (14)	p=0.64
Vancomycin and aminoglycosides were add'l antibiotics; TRAD-MEM = traditional meropenem 1g, IV q8h ; ALT-MEM= alternative meropenem 500mg IV q6h; IMI= imipenem 500mg q6h				

Conclusions: This study provides support for the alternative meropenem dosing as equally effective compared to traditional dosing.

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

- Design: retrospective cohort study with a cost-minimization analysis involving 100 patients treated with meropenem 1g q8h or 12 hours (traditional dosing regimen) and 192 patients treated with meropenem 500mg q6 or 8 hours (alternative dosing regimen) 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 and included all pathogens isolated and not specifically the isolates treated with meropenem. Concomitant therapy was allowed in both groups and consisted of vancomycin, fluoroquinolones, aminoglycosides, metronidazole and linezolid. No significant differences were observed in prescribed concomitant therapies between the cohorts.

Results:

Outcome	**TRAD-MEM (n=100)**	**ALT-MEM (n= 192)**	**Significance**
Median MEM related length of stay, days (range)	7 (1-44)	9 (1-67)	p=0.141
Median duration of therapy, days (range)	5 (2-22)	4 (1-27)	p=0.055
Median time to defervescence, days (range)	3 (1-22)	1.5 (1-10)	p<0.0001
Therapy success, %	90.9	92.1	p=0.72
In-hospital mortality, n (%)	8 (8%)	22 (11.5%)	p=0.238
Median antibiotic cost/pt for duration of treatment	$439.05	$234.08	p<0.0001
TRAD-MEM= traditional meropenem; ALT-MEM= alternative meropenem			

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:

- Duration of therapy, concomitant antimicrobial therapy, clinical success rates, length of stay, and in-hospital mortality rates were similar between the two groups.
- Median time to resolution of symptoms was significantly shorter and the median cost of antibiotic therapy was significantly lower in the alternative meropenem group.
- Cost-minimization analysis revealed a decrease in drug acquisition costs (level 1 cost) when the alternative dosing strategy was used.

Study 3: Kotapati S, et al. *Am J Health Syst Pharm*. 2004; 61; 1264-71.

- Design: retrospective review of 85 patients treated with meropenem to evaluate the clinical and economic benefits of meropenem dosage strategies of 500 mg q6h vs. 1g q8h based on pharmacodynamics concepts.
- Clinical outcomes: rate of response and treatment success or failure, infection-related length of stay, meropenem-related length of stay
- Microbiological outcomes: successes or failures at the end of therapy or discharge
- 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 cost plus meropenem-related length of stay costs

Results:

Outcome	**ALT-MEM (n=45)**	**TRAD-MEM (n=40)**	**Significance, p value**
Clinical success, n (%)	28 (78%)	32 (82%)	0.862
Microbiologic success, n (%)	19 (63%)	19 (79%)	0.334
Meropenem-related LOS, days (range)	7 (4.8-13)	7.5 (4-10)	0.891
Level 1 cost, $ (range)	567 (292-1,213)	982 (600-1,719)	0.009
Level 2 cost, $ (range)	1,035 (563-1,582)	1,787 (903-2,622)	0.008
Level 3 cost, $ (range)	19,934 (11,895-27,513)	16,087 (9,969-23,274)	0.42

Conclusion: Meropenem 500 mg q6h yielded similar clinical outcomes to a regimen of 1000mg q8h and reduced the daily drug acquisition cost associated with antibiotic therapy.

ECONOMIC EVALUATION:

Evidence 1: See study by Patel and colleagues above. A reduction of $204.97/patient, or nearly 50% was realized. **Note that these data were based on acquisition cost for branded Merrem®. Generic meropenem was not.**

Evidence 2: See study by Kotapati and colleagues above. Median level 1 and 2 costs significantly lower for the 500-mg group. Level 3 costs did not differ significantly between groups.

Evidence 3: IMH-specific evidence (based on acquisition of generic meropenem]

Agent	**Dose**	**IMH Inpatient Acquisition Cost/Day**
Meropenem	1g q8h	$23.94
Meropenem	500mg q6h	$15.76

EXTENDED INFUSION MEROPENEM: In a recent meta-analysis, the authors noted a reduced mortality among patients receiving β- lactam agents administered by continuous infusion or extended infusion compared to those receiving intermittent infusions.[7] For inpatient use, this approach may be less resourceful than other methods to improve the pharmacodynamics of meropenem due to the drug's short stability. Thus, lowering the dosage and administering the drug more frequently over a 24-hour period can achieve similar pharmacodynamics exposure and theoretically reduce costs. It is recommended that the use of extended infusion meropenem be advocated for more severe infections, such as those in patients with cystic fibrosis, multi-drug resistant *Pseudomonas* and *Acinetobacter*, infections of the central nervous system (CNS) and necrotizing fasciitis.[8]

ALTERNATE DOSING PROPOSAL:

Patient Population Impacted: Adult patients hospitalized at Iredell Health System

Procedure: Orders for traditional doses/administration of meropenem for adults will be interchanged with alternate dosing. Pharmacists may automatically interchange traditional dosing meropenem orders and adjust the dose of meropenem as indicated in the guideline for renal adjustment in Table 2. Orders will be adjusted by the pharmacist per protocol.

The prescriber must be contacted if orders need to be adjusted based on indication (i.e. from alternate dosing indication to extended-infusion indication).

If there is any question about the indication for meropenem, the prescriber should be contacted for clarification.

Table 2. Dosing of meropenem in adult patients[5,6,7,8]:

Indication	Dosing Based on Creatinine Clearance	
• Pneumonia • Intra-abdominal infection • Neutropenic fever • Infections caused by ESBLs or Ceftriaxone-resistant organisms	**(30-min infusion)**	
	> 50 mL/min	500 mg q6h
	25-49 mL/min	500 mg q8h
	10-24 mL/min	500 mg q12h
	< 10 mL/min, hemodialysis (HD)	500 mg q24h (give dose after HD)
	Continuous renal replacement therapy (CRRT)	500 mg q6h
• *Pseudomonas* infection (susceptible to meropenem) • *Acinetobacter* infection (susceptible to meropenem)	**(3-hr infusion)**	
	> 50 mL/min	1 g q8h
	25-49 mL/min	1 g q12h
	10-24 mL/min	500 mg q12h
	< 10 mL/min, hemodialysis (HD)	500 mg q24h (give dose after HD)
	Continuous renal replacement therapy (CRRT)	1 g q12h
• CNS infections • Necrotizing fasciitis • Bone/Joint Infection	**(3-hr infusion)**	
	> 50 mL/min	2 g q8h
	25-49 mL/min	2 g q12h
	10-24 mL/min	1 g q12h
	< 10 mL/min, hemodialysis (HD)	1 g q24h (give dose after HD)
	Continuous renal replacement therapy (CRRT)	2 g q12h

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