Meropenem Assessment Before and After Implementation of Standard Dosing Regimen

Connor Chan, B.Sc., B.Sc.(Pharm); Vincent H. Mabasa[1], B.Sc.(Pharm), ACPR, PharmD; Ivy Chow[1], B.Sc.(Pharm), ACPR, PharmD

[1] Pharmacy Department, Burnaby General Hospital, Fraser Health Authority, British Columbia, Canada

BACKGROUND

- Meropenem, a broad-spectrum carbapenem antibiotic, exhibits time-dependent bactericidal activity in-vivo
  - Maximize time that drug concentration exceeds MIC
- Traditional dose is 1g IV Q8H : alternative dose of 500mg IV Q6H explored to optimize pharmacodynamic profile
  - Four studies showed similarity in %-time above MIC
  - Three clinical trials showed similar clinical success rate and mortality rate
  - Largest trial showed shorter infection resolution time (*1.5 days*) with alternative dosing
  - Potential for significant cost savings
- Limitations to current clinical literature:
  - Single-centered, not statistically powered, and exclusion of patients with eGFR < 25mL/min

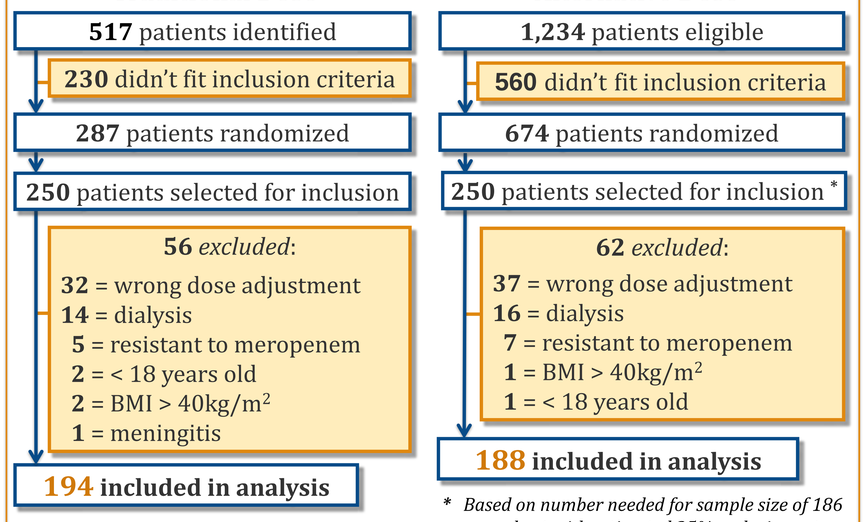
OBJECTIVES

- To characterize the effect of meropenem dosing regimen on clinical outcomes within Fraser Health
- To quantify any difference in cost between dosing regimens

METHODS

- **Design:** Multi-centered, retrospective cohort study with a superiority design
- **Inclusion criteria:** Inpatients receiving ≥ 72 hours of meropenem therapy between July '06 and Aug '09
- **Exclusion criteria:** Age < 18 years, BMI > 40kg/m^2, infections requiring higher meropenem concentrations (*meningitis, cystic fibrosis*), dialysis patients, meropenem-resistant infection prior to therapy, and/or no renal dose adjustment within 48 hours
- **Sample size:** 186 per cohort needed for 80% power
  - 91% historical success rate, 10% predicted difference
- **Outcomes:**
  - **Primary:** Clinical success rate
  - **Secondary :** 30-day mortality, meropenem-related length of stay, treatment duration, time to defervescence
- **Definitions:**
  - **Dose:** traditional = 1g IV Q8H, alternative = 500mg IV Q6H
  - **Clinical success:** normalization, or trend towards normalization, of white blood cells (< *11 × 10^9/L*), neutrophils (< 8 × 10^9/L), and temperature (< *37.5^{o}C*) with improvement in infectious signs and symptoms (*i.e. radiographic improvement, less dyspnea, etc.*)
  - **Meropenem-related length of stay***:* time from initiation of meropenem treatment to discharge

Figure 1 –Selection of Study Participants



* *Based on number needed for sample size of 186 per cohort with estimated 25% exclusion rate*

Table 1 – Baseline Characteristics

	Traditional Dose (N = 194)	Alternative Dose (N = 188)
Age *(years)*	64.9 ± 14.5	66.1 ± 17.3
Weight *(kg)*	73.4 ± 25.3	72.8 ± 18.7
Male	99 *(51.0%)*	96 *(51.1%)*
eGFR *(ml/min)*	67.6 ± 30	68.4 ± 33
Comorbidities:		
Cardiovascular Disease	103 *(53.1%)*	114 *(60.6%)*
Cancer	71 *(36.6%)*	57 *(30.3%)*
Diabetes	55 *(28.4%)*	59 *(31.4%)*
Lung Disease	38 *(19.6%)*	38 *(20.2%)*
Source of Infection:		
Blood	76 *(39.2%)*	70 *(37.0%)*
Lung	76 *(39.2%)*	71 *(37.8%)*
Urinary Tract	**53 *(27.3%)*** ‡	**71 *(37.8%)*** ‡
Abdomen	50 *(25.8%)*	42 *(22.3%)*
Microbiology:		
Escherichia coli	35 *(18.0%)*	43 *(22.9%)*
Pseudomonas sp.	10 *(5.2%)*	15 *(8.0%)*
Enterococcus sp.	13 *(6.7%)*	17 *(9.0%)*
Polymicrobial	22 *(11.3%)*	22 *(11.7%)*

‡ *Represents a p-value < 0.05*

Table 2 – Clinical Success Rate

	Traditional Dose (N = 194)	Alternative Dose (N = 188)	95% CI
Clinical Success	162 *(83.5%)*	152 *(80.8%)*	0.88 – 1.07
Complete vs. Partial Success	102 *(52.6%)*	94 *(50.0%)*	0.77 – 1.17

Table 3 – Secondary Clinical Outcomes

	Traditional Dose (N = 194)	Alternative Dose (N = 188)	95% CI
30 Day All-Cause Mortality	18 *(9.2%)*	27 *(14.4%)*	0.85 – 2.85
30 Day Infection-Related Mortality	9 *(4.6%)*	12 *(6.4%)*	0.55 – 3.48
Duration of Therapy	6.9 days	6.9 days	-0.73 – 0.71
Meropenem-Related Length of Stay	24.5 days	27.7 days	-5.11 – 9.63
Time to Defervescence	2.2 days	2.1 days	-0.41 – 0.37

Table 4 – Cost Analysis

	Traditional Dose	Alternative Dose
Cost per Patient per Visit	$ 355.90	$222.23
Total Treatment Cost per Cohort	$69,058.08	$41,778.60

DISCUSSION

- No statistical differences in baseline characteristics (*with the exception of urinary tract infections*), clinical success (*both overall and complete vs. partial*), or secondary outcomes between dosing regimens
- Non-significant trend in higher all-cause mortality with alternative dose due to higher malignancy-related death
- No differences observed within intensive care, virulent infection (*i.e. pseudomonas*), or hospital site subgroups
- Savings of $133.67 per patient and $27,279.48 per cohort (*with cost pro-rated to April 20th, 2015*) in favor of alternative dosing
- Historical savings of $79,417.44 per cohort (*brand name prior to 2012*)

LIMITATIONS

- Retrospective study design
- Limited resources for ideal design (*non-inferiority with nested superiority study*) – sample size would be over 10,000 patients per cohort
- Temporal variance in treatment over study period

CONCLUSION

- Meropenem 500mg IV Q6H did not differ from 1g IV Q8H in terms of clinical outcomes (*i.e. **not** superior*), but did demonstrate significant cost savings

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