Meropenem Extended vs. Standard Infusion Dosing Protocol in Critically Ill Patients

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ABSTRACT (REVISED)

Background: Due to altered pharmacokinetics/ pharmacodynamics (PK/PD) in critically ill patients, extended infusion (EI) administration of β-lactams (BL) provides better target attainment in this population. To optimize meropenem (MER) dosing, our antimicrobial stewardship program (ASP) implemented a MER EI protocol (EIP) in an 18–bed medical intensive care unit (MICU) in March 2014.

Objective: To compare outcomes with MER EIP vs. standard infusion protocol (SIP).

Methods: In a retrospective study, we evaluated adult patients in MICU with severe sepsis and septic shock who received MER for ≥72 h administered as EIP 1 g over 3 h Q8H with a total daily dose (TDD) 3 g (1/2015-1/2017) vs. SIP 500 mg over 30 min Q6H with TDD 2 g (1/2012-1/2014).

Results: A total of 148 were included (EIP n=52, SIP n=96). Age, weight, comorbidities, severity of illness (median mAPACHE II 18 vs. 19, *P*=0.6; SOFA 5 vs. 6, *P*=0.5) and vasopressor use (75 vs. 79%, *P*=0.5) were comparable between groups. Serum creatinine (SCr) was lower in EIP group (median 1.1 vs. 1.4 SI, *P*=0.05) and SIP group required higher rates of renal dose adjustment at MER initiation (65 vs. 39%, P=0.004). Gram-negative (GN) pathogens (MIC≤0.25 mcg/mL, 94%) were identified in 44% of patients in EIP vs. 38% in SIP group, *P*=0.5. ICU mortality (median time to death 9 days) was lower (19 vs. 37%, *P*=0.047) and clinical response was higher (83 vs. 46%, *P*=0.038) in EIP vs. SIP group. Total pressor days on MER were shorter (2 vs. 3 days, P<0.01) and white blood cell normalization rate was higher (87% vs. 51%, *P*<0.01) in EIP vs SIP group, whereas there was no difference in days of mechanical ventilation, duration of MER therapy and ICU stay. After controlling for renal dose adjustment and severity of illness scores in a multivariate model, CLD (OR 3.3, 95% CI 1.36-7.77, *P*=0.008) and MER SIP (OR 1.2, 95% CI 1.05-5.79, *P*=0.045) were independent predictors of ICU mortality.

Conclusion: In this cohort of MICU patients with severe sepsis or septic shock and highly susceptible GN pathogens, there was reduced mortality and improved clinical response in MER EIP group, suggesting MER 500 mg over 30 minutes (TDD 2 g) might not be optimal dosing in this critically ill patient population.

BACKGROUND

- Critically ill patients have altered PK/PD
  - Increased Vd, augmented renal clearance, impaired target tissue penetration and altered protein binding
- Larger drug exposures up to 100% *f*T>MIC may be necessary for maximum bactericidal activity of BL
- Clinical data evaluating the effect of MER EIP in critically ill patients is limited
- In March 2014, MER pilot was implemented in our 18-bed MICU to optimize dosing

Empiric coverage in MICU Patients with Severe Sepsis and Septic Shock

MER SIP over 30 min (2012-2014)[a]		
CrCl >50 mL/min	CrCl 30-50 mL/min	CrCl 10-29 mL/min
500 mg q6h **TDD: 2 g**	500 mg q8h	500 mg q12h

Pilot MER EIP over 3h (2015-2017)		
CrCl >50 mL/min	CrCl 30-50 mL/min	CrCl 10-29 mL/min
1 g q8h **TDD: 3 g**	1 g q12h	500 mg q12h

[a] Patients in **SIP group** with BMI >30 kg/m^2 and CrCl >50 mL/min received MER 1 g infused over 30 min every 8 h. Renal adjustments were 1 g over 30 min every 12 h for CrCl 30-50 mL/min and 500 mg over 30 min every 12 h for CrCl 10-29 mL/min.

Disclosure: The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities.

OBJECTIVE

- To compare ICU mortality and clinical response in patients with severe sepsis and septic shock in the MICU who received MER EIP vs. SIP

METHODS

Study Design

- IRB approved single center retrospective cohort study (01/2012-01/2017)

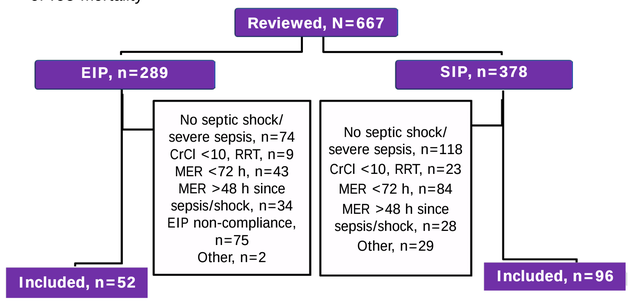
Inclusion criteria	Exclusion criteria
▪ ≥18 years old ▪ Received MER for ≥72 hours ▪ Baseline CrCl ≥10 mL/min ▪ Severe sepsis or septic shock admitted to the MICU	▪ MER started >48 h since severe sepsis/septic shock onset ▪ MER-intermediate/resistant pathogens ▪ Renal replacement therapy (RRT) at MER initiation ▪ Comfort care at MER initiation ▪ EIP non-compliance

Definitions

Clinical response at the end of therapy (EOT)	▪ Had improvement in clinical parameters without escalation of therapy
Microbiological response at EOT	▪ Clearance of previously positive culture by EOT ▪ Evaluated only in patients with initial and subsequent cultures

Statistical Analysis

- All continuous variables presented as n (%) or median (Interquartile Range [IQR])
- Chi-square or Fisher's exact tests for categorical and Mann-Whitney U test for continuous variables
- Stepwise (forward selection) multivariate logistic regression to identify predictors of ICU mortality



RESULTS

Table 1. Baseline and clinical characteristics

	EIP, n=52	SIP, n=96
Age, years	68 (57-78)	68 (56-78)
Male gender	26 (50)	56 (58)
Actual weight, kg	79 (58-87)	74 (61-90)
BMI, mg/m^2	26 (22-32)	27 (23-29)
Comorbidities	50 (96)	95 (99)
Diabetes mellitus (DM)	11 (21)	16 (17)
Malignancy	16 (31)	32 (33)
Structural lung disease	11 (21)	13 (14)
Chronic liver disease (CLD)	8 (15)	22 (23)
Chronic kidney disease (CKD)	5 (10)	18 (19)
SCr at MER start, mg/dL	1.1 (0.7-2.1)	1.4 (0.9-2.5)
CrCl calculated by Cockroft-Gault equation [a]	53 (33-95)	38 (25-74)
CrCl >125 mL/min	7 (14)	5 (5)
Albumin	2.29 (2.1-2.5)	2.47 (2.1-2.8)
mAPACHE II at MER initiation	18 (15-22)	19 (15-23)
SOFA score at MER initiation	5 (3-8)	6 (4-7)
Pitt bacteremia score at MER initiation, n=19	3 (1-4)	1.5 (0.25-3.75)
ICU length of stay, days	13 (7-17)	10 (6-16)
MER Treatment Characteristics		
Required pressors	39 (75)	79 (79)
Norepinephrine (NE)	31 (80)	70 (89)
MER dose renally adjusted [b]	20 (39)	62 (65)
Concomitant antibiotics	33 (64)	44 (46)
Aminoglycosides	26 (50)	36 (38)
Combination duration of therapy (DOT)	1 (1-3)	1.5 (1-3.8)
Time to MER start from ICU admission	2 (1-5)	2 (1-4)
MER DOT	8 (5-13.5)	7.5 (5-12)
Microbiological characteristics		
Positive culture during therapy	27 (52)	51 (53)
Patients with Gram negative pathogens	23 (44)	36 (38)
Documented MIC of GN pathogen, mcg/mL, n=55	≤0.25 mg/L, n=20	≤0.25 mg/L, n=35

[a] *P*=0.032, [b] *P*=0.004

Figure 1. Gram negative pathogens

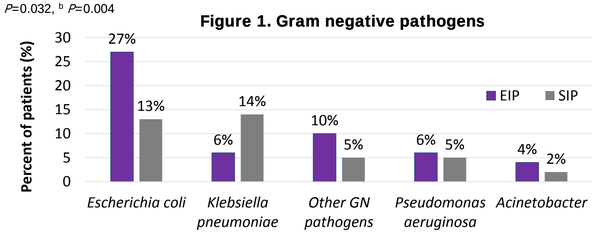


Figure 2. ICU mortality

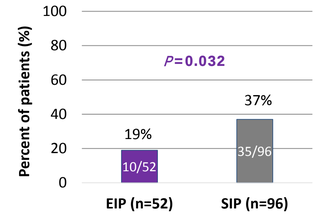


Figure 3. Clinical response

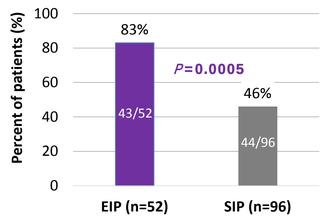


Table 2. Clinical and microbiological characteristics

	EIP, n=52	SIP, n=96
Time to death since ICU admission	13 (9-16)	10 (6-15)
Time to death from MER start	9 (7-15)	9 (5-11)
Febrile at MER start	20 (39)	43 (45)
Defervesced	19/20 (95)	38/43 (88)
Total pressor days on MER, n=118 [a]	2 (1-4)	3 (2-6)
WBC normalized [b]	33/38 (87)	33/65 (51)
Days of mechanical ventilation from MER start, n=69	7 (4-11), n=29	6 (4-9), n=40
Extubated during MER course	24/29 (83)	35/40 (88)
Microbiological response at EOT, n=48 (repeat cultures)	4/20 (20)	7/28 (25)

[a] *P*=0.038; [b] *P*=0.001

Table 3. Predictors of ICU mortality

	Died n=45	Did not die n=103	Univariate Analysis		Multivariate Analysis	
			Odds Ratio (OR) 95% CI	P-value	OR 95% CI	P-value
Albumin	2.34 (2.1-2.5)	2.4 (2.1-2.8)	-	0.249	-	-
MER renally adjusted	28 (62)	54 (52)	1.5 (0.07-3.1)	0.271	-	-
CLD	17 (38)	13 (13)	4.2 (1.8-9.7)	0.001	4.2 (1.82-9.72)	0.001
MER SIP	35 (79)	61 (59)	2.4 (1.1-5.4)	0.032	2.4 (1.08-5.39)	0.047
MER combination therapy	23 (51)	55 (53)	0.91 (0.45-1.84)	0.938	-	-
Required pressors	39 (87)	79 (77)	2.0 (0.75-5.22)	0.244	-	-
SOFA >6	21 (47)	27 (26)	2.5 (1.2-5.12)	0.016	-	-
APACHE >20	21 (47)	34 (33)	1.8 (0.87-3.63)	0.116	-	-

CONCLUSION

- In this small cohort of MICU patients with severe sepsis or septic shock and Gram negative pathogens with low MIC:
  - MER EIP was associated with lower ICU mortality and higher clinical response rates
- This finding suggests that MER 500 mg over 30 min (TDD 2 g) might not be optimal dosing in this patient population