Nephrotoxicity associated with intravenous (IV) polymyxin B (PMB) once versus twice daily dosing

Nabeela Ahmed PharmD, Marco R. Scipione PharmD, John Papadopoulos PharmD, Daniel Eiras MD, Yanina Dubrovskaya PharmD

Contact Information:
Nabeela Ahmed, PharmD
NYU Langone Medical Center
550 First Avenue
New York, NY 10016
Email: nabeela.ahmed@nyumc.org

NYU Langone MEDICAL CENTER

 # 1804

NYU Langone Medical Center , New York, NY

ABSTRACT (REVISED)

Background: Nephrotoxicity is a known adverse effect of PMB. Animal data suggests that once daily dosing may be associated with decreased rate, severity and more gradual onset of nephrotoxicity compared to divided dosing. Clinical data evaluating the effect of PMB dosing frequency on nephrotoxicity is limited.

Objective: Compare rate of acute kidney injury (AKI) with PMB once vs. twice daily dosing.

Methods: In a single center, retrospective study we evaluated adult patients with Creatinine Clearance (CrCl) ≥30 mL/min who received ≥48h of PMB therapy. Nephrotoxicity was defined as development of AKI using RIFLE criteria.

Results: A total of 173 patients were included (once daily n=141, twice daily n=32). Median age was 68 years (IQR 56-79), CrCl was 65 mL/min (IQR 44-91), mAPACHE II score was 14 (12-16), PMB duration of therapy was 6 days (IQR 4-11), 59% of patients received concomitant nephrotoxic agents, and these were comparable between once and twice daily dosing. Overall, rate of AKI was 43% with once vs. 22% with twice daily dosing, P=0.04 with most cases being Risk category by RIFLE (18 vs. 16%, P=0.9). No patients met ESRD. In-hospital mortality was 19% with once vs. 28% with twice daily dosing, P=0.4. Time to AKI onset (7 vs. 8 days) and peak serum creatinine (SCr) (8 vs. 8 days) was similar with once vs. twice daily dosing. In multivariate model, severe sepsis (OR 4.2, 95% CI 1.6-11.3, P=0.005), receipt of >2 concomitant nephrotoxic agents (OR 2.6, 95% CI 1.0-6.7, P=0.045), PMB duration of therapy >10 days (OR 2.6, 95% CI 1.0-4.5, P=0.02) and total dose >1,500,000 units/day (OR 2.1, P=0.05) were identified as an independent predictors of AKI, but not once daily dosing (OR 2.6, 95% CI 0.9-7.1, P=0.075).

Conclusion: Observed nephrotoxicity was higher in the once daily group, however these events were multifactorial and most patients had recovery of renal function.

BACKGROUND

- Animal models suggest that once daily dosing may be associated with decreased rate, severity and more gradual onset of nephrotoxicity compared to divided dosing
- Clinical data evaluating the effect of PMB dosing frequency on the rate of nephrotoxicity is very limited
- Previously at our University Medical Center, we used a twice daily dosing regimen of PMB. Starting from January 2009 we implemented PMB once daily dosing protocol

PMB Dosing Protocol

Twice daily (2008-2009)	
CrCl >50 mL/min	CrCl 20-50 mL/min
15-25,000 units/kg[a]/day	50-75% of normal dose

Once daily (2009-present)	
CrCl >80 mL/min	CrCl 30-80 mL/min
Loading dose 25,000 unit/kg[a] x day 1	
25,000 units/kg[a]	15,000 units/kg[a]

[a] based on **actual body weight**; adjusted body weight should be used in patients with BMI ≥30kg/m²

OBJECTIVE

- To compare the rate of nephrotoxicity with PMB once vs. twice daily dosing
- To determine rate of in-hospital mortality and identify risk factors and time to AKI

METHODS

Study Design

- IRB approved single center retrospective cohort study (01/01/2008-10/31/15)

Inclusion Criteria	Exclusion Criteria
≥18 years old Received PMB for ≥48 hours Baseline CrCl ≥30mL/min First treatment course of PMB	Hemodialysis (HD) or continuous renal replacement therapy (CRRT) prior to initiation of PMB therapy

Definition of Nephrotoxicity - RIFLE criteria[1]

Risk	Increased SCr level x 1.5
Injury	Increased SCr level x 2
Failure	Increased SCr level x 3
Loss	Persistent acute renal failure for >4 weeks
End Stage Renal Disease (ESRD)	ESRD >3 months

[1] *Bellomo R. et al. Crit Care 2004; 8:R204-2012.*

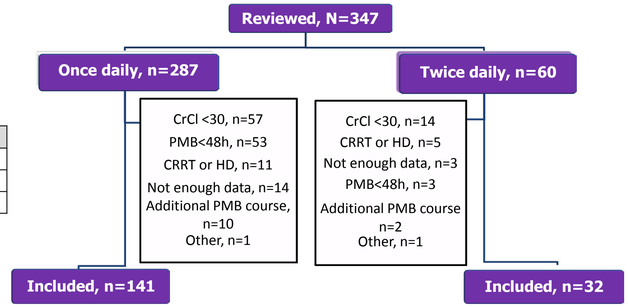
*To qualify for the Risk category, two consecutive SCr elevations of 1.5 times the baseline SCr were required

Definition of Nephrotoxicity – Time to onset

Time to onset	First date RIFLE criteria met (regardless of severity)
Time to peak SCr	Highest SCr during PMB therapy

Statistical Analysis

- All continuous variables presented as median (Interquartile Range [IQR])
- Chi-square or Fisher's exact tests, Mann-Whitney U test
- Multivariate logistic regression



RESULTS

Table 1. Clinical and treatment characteristics

	Once daily n=141	Twice daily n=32
Age, years	66 (56-79)	71 (56-81)
Male gender [a]	89 (63)	12 (38)
Total body weight, kg	73 (59-90)	70 (57-84)
Ideal body weight, kg [b]	62 (55-71)	54 (52-66)
Body mass index, kg/m2	26 (22-31)	25 (21-30)
Length of hospital stay, days	25 (14-40)	26 (18-51)
Length of intensive care unit stay, days (n=73)	18 (6-38)	30 (14-71)
In-hospital mortality	27 (19)	9 (28)
Comorbidities, n (%)		
Cardiovascular disease	84 (60)	14 (44)
Diabetes mellitus	29 (21)	5 (16)
Malignancy	25 (18)	8 (25)
Cirrhosis	16 (11)	1 (3)
Solid organ transplant	5 (4)	1 (3)
Charlson Comorbidity Index	2 (1-3)	2 (1-3)
Clinical Characteristics at PMB Initiation		
mAPACHE II score	14 (12-16)	15 (12-17)
Serum creatinine (SCr), mg/dL	0.9 (0.7-1.2)	0.8 (0.5-1.1)
Creatinine clearance (CrCl), mL/min	65 (43-90)	64 (44-94)
Concomitant nephrotoxic agents, n (%)	81 (57)	21 (66)
Vancomycin	53(38)	14(44)
Aminoglycosides	32 (23)	12 (38)
Diuretics	41 (29)	10 (31)
IV Contrast	15 (11)	3 (9)

[a] *P*=0.014; [b] *P*=0.029

Table 2. PMB Treatment and dosing

	Once daily n=141	Twice daily n=32
Duration, days	6 (4-11)	7 (4-12)
Total dose per ideal BW, units/kg/day [a]	25,078 (21,797-28,443)	18,767 (15,174-23,760)
Total dose per total BW, units/kg/day [a]	21,930 (17,479-25,054)	16,253 (12,594-19,861)
Total daily dose >1,500,000 units [a]	81 (57)	4 (13)

[a] *P*=0.0005; [b] *P*=0.036

Figure 1. Rate of nephrotoxicity

Table 3. Severity of nephrotoxicity by RIFLE criteria

	Once daily n=141	Twice daily n=32
Risk	26 (18)	5 (16)
Injury [a]	22 (16)	0 (0)
Failure	13 (9)	1 (3)
Loss	0 (0)	1 (3)

[a] *P*=0.015

Figure 2. Time to nephrotoxicity

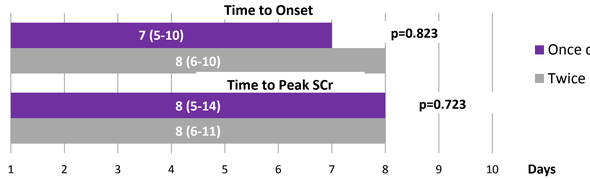


Table 4. In-hospital mortality

	Once daily n=141	Twice daily n=32
In-hospital mortality	27 (19)	9 (28)

Table 5. Risk factors for nephrotoxicity

	AKI n=68	No AKI n=141	Univariate Analysis		Multivariate Analysis	
			Odds Ratio (OR) 95% CI	P-value	OR 95% CI	P-value
Severe sepsis	17 (25)	9 (9)	3.6 (1.48-8.54)	0.006	4.2 (1.56-11.33)	0.005
Once daily dosing	61 (90)	80 (76)	2.7 (1.10-6.71)	0.042	2.6 (0.91-7.11)	0.075
PMB duration >10 days	26 (38)	21 (20)	2.5 (1.25-4.91)	0.014	2.6 (1.18-5.61)	0.018
Dose >1,500,000 units/day	40 (60)	44 (42)	2.1 (1.13-3.92)	0.027	2.1 (1.02-4.45)	0.046
Charlson comorbidity index >2	26 (38)	24 (23)	2.1 (1.07-4.08)	0.045	2.1 (0.99-4.33)	0.05
Received >2 nephrotoxic agents	35 (56)	44 (42)	2.0 (0.87-4.66)	0.100	2.6 (1.02-6.71)	0.045

CONCLUSION

- Rate of nephrotoxicity was **43%** with once daily vs. **22%** with twice daily dosing
  - Once daily dosing was not an independent predictor of nephrotoxicity
- Nephrotoxicity was multifactorial
  - Risk factors included PMB longer duration, higher doses, and receiving >2 other nephrotoxic agents concomitantly
- Nephrotoxicity was reversible as most patients recovered their renal function to baseline
- Need further confirmation of our results in a prospective study with matched cohorts