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Comparative nephrotoxicity rates between colistimethate sodium and polymyxin B

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Background

- The polymyxins, colistimethate sodium (CMS) and polymyxin B (PMB) are polypeptide antibiotics discovered in the 1940s.
- The use of polymyxins was initially abandoned due to nephrotoxicity and neurotoxicity concerns.
- The emergence of multidrug-resistant Gram-negative organisms has led to an increased use of the polymyxins in recent years, however, nephrotoxicity remains a concern.
- Reported rates of acute kidney injury (AKI) have ranged from 31-55% for CMS and 23-60% for PMB.
- Direct comparisons of nephrotoxicity rates between CMS and PMB are limited and have demonstrated inconsistent results.
- At OSUWMC, the use of CMS has largely been replaced with PMB since May 2014 due to preferable pharmacokinetic and pharmacodynamic properties of PMB.

Objectives

- Primary objective: To compare nephrotoxicity rates between patients who received CMS and PMB using the RIFLE criteria.
- Secondary objectives: To compare time to onset of AKI, risk factors for AKI, clinical and microbiological cure rates, hospital and infection-related length of stay (LOS), and in-hospital, attributable and 30-day mortality between patients who received CMS and PMB.

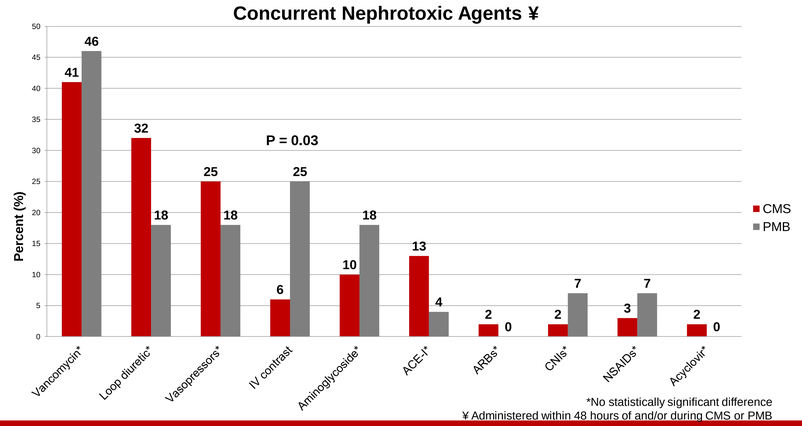
Materials and Methods

- Retrospective, single-center study of hospitalized patients who received CMS or PMB between 01/01/2012 and 09/30/2015.
- Inclusion criteria: (i) Age ≥ 18 and < 89 years, (ii) Culture with in vitro susceptibility to CMS, (iii) Receipt of intravenous (IV) CMS or PMB therapy within 72 hours of positive culture, and (iv) Receipt of IV CMS or PMB for ≥ 48 hours.
- Exclusion criteria: End stage renal disease (ESRD) or renal replacement therapy (RRT) requirement prior to CMS or PMB initiation or incarceration.
- IV CMS and PMB were dosed per institution protocol as follows:
  - CMS: 5 mg/kg x 1 loading dose, then 3.5 mg/kg every 12 hours
    Renal adjustment for creatinine clearance (CrCl)
    20-50 mL/min: 3.5 mg/kg every 24 hours
    < 20 mL/min: 3.5 mg/kg every 48 hours
  - PMB: 3 mg/kg x 1 loading dose, then 1.5 mg/kg every 12 hours
    No renal dose adjustment.
- Statistical analyses were performed using Mann-Whitney U, $\chi 2$, Student's t-test or Fisher's exact test as appropriate.
- Cox proportional hazard model was used to evaluate risk factors for AKI
- A two-tailed α of ≤ 0.05 was considered statistically significant.

Results

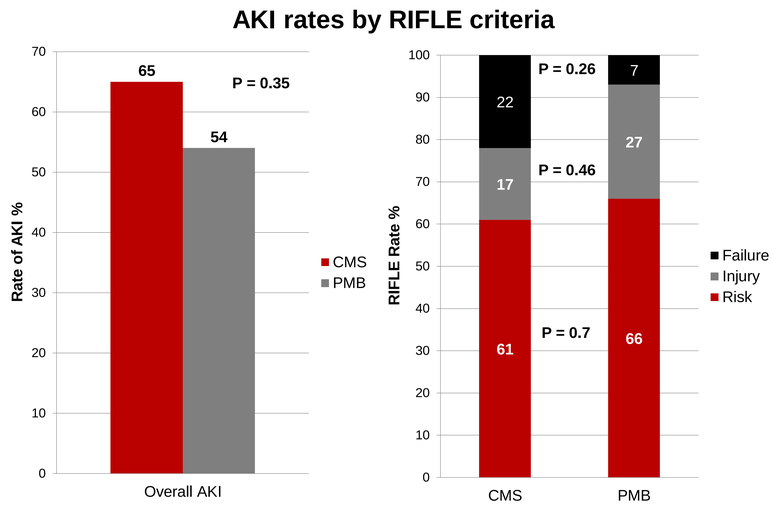
Baseline characteristics	CMS (n = 63)	PMB (n = 28)	*P*
Age (years)	51±14	51±17	0.9
Male	29 (46%)	32 (82%)	<0.01
Charlson Comorbidity Index	3 [2-5]	2 [2-6]	0.76
APACHE II#	18 [10-23]	18 [12-22]	0.94
Weight (kg)	80 [64-111]	77 [57-104]	0.6
Baseline serum creatinine (mg/dL)	0.77 [0.51-1.39]	0.71 [0.39-1.04]	0.25
Baseline CrCl (ml/min)	87 [48-166]	101 [67-260]	0.09
Hospital LOS prior to culture (days)	1 [0-6]	3 [1-10]	0.21
ICU Admission, n (%)	47 (75%)	19 (68%)	0.51
Infectious Diseases (ID) consult	53 (84%)	23 (82%)	0.77
Site of infection			
Respiratory, n (%)	33 (52%)	17 (61%)	0.46
Blood, n (%)	9 (14%)	6 (21%)	0.40
Urine, n (%)	13 (21%)	1 (4%)	**0.04**
Organism			
***Acinetobacter baumannii*, n (%)**	38 (60%)	17 (61%)	0.97
***Pseudomonas aeruginosa*, n (%)**	29 (46%)	11 (39%)	0.55
Polymicrobial n (%)	36 (57%)	18 (64%)	0.52
Therapy characteristics			
Loading dose administration, n (%)	43 (68%)	27 (96%)	**0.0026**
Mean daily dose (mg/kg/day)	5.1 ± 2.3	3.3 ± 0.4	-
Mean total daily dose (mg/day)	384 ± 192.5	261 ± 78.6	-
Time to initiation of CMS/PMB (days)	3 [1-4]	2 [1-3]	0.13
Duration of CMS/PB therapy (days)	5 [3-10]	6 [3-14]	0.34
Median number of concurrent nephrotoxic agents, n	1 [1-2]	1 [1-3]	0.83

#APACHE II was calculated within 24 hours of index culture collection



*No statistically significant difference
¥ Administered within 48 hours of and/or during CMS or PMB

Results (continued)



- RRT was initiated during therapy in 6 (10%) patients receiving CMS vs 1 (4%) patient receiving PMB (p = 0.43).
- Median time to onset of AKI was 3 [2-5] days in patients receiving CMS vs 3 [2-4] days in patients receiving PMB (p=0.71).
- Vasopressor use was an independent risk factor for AKI (HR 1.87, 95% CI 1.01-3.46).

Secondary outcomes	CMS (n = 63)	PMB (n = 28)	*P*
Clinical cure, n (%)	36 (57%)	16 (57%)	1.00
Microbiological cure, n (%)	35 (57%)	16 (57%)	1.00
Hospital LOS (days)	17 [11-28]	18 [13-37]	0.34
Infection-related LOS (days)	8 [5-12]	7 [6-16]	0.28
In-hospital mortality, n (%)	15 (24%)	4 (14%)	0.3
Attributable mortality, n (%)	17 (27%)	4 (14%)	0.18
30-day mortality, n (%)	16 (25%)	7 (25%)	0.97

Conclusions

- No difference in rates of AKI or time to AKI was demonstrated between CMS and PMB.
- PMB will continue to be the preferred polymyxin for systemic infections at OSUWMC.
- Further studies with larger cohorts are warranted to determine the comparative rates of AKI between CMS and PMB.

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