Nephrotoxicity Associated with Colistin Therapy: A Comparative Analysis of Older and Younger Adults

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Abstract

Objectives. Colistin has become the mainstay for the treatment of infections due to carbapenem-resistant (CR) Gram-negative bacilli (GNB). Recent evidence has confirmed high rates of nephrotoxicity in the 30-50% range among patients receiving colistin. However, no analyses have analyzed nephrotoxicity due to colistin in older adults, and none have determined the independent impact of age on nephrotoxicity. The objective of this analysis was to determine the independent effect of increased age (>=65 years old) on the incidence of colistin nephrotoxicity and mortality.

Methods. This was a sub-analysis of a previously described cohort of 126 patients treated with colistin from 2005-2009. The cohort was divided into older pts (>= 65 yrs) and younger pts (< 65 yrs). Data collected included patient demographics, comorbidities, colistin dosage, duration of therapy, and incidence and degree of acute kidney injury as defined by the RIFLE criteria. A propensity score was developed measuring the likelihood of a subject to be ≥ 65 years old. To evaluate the independent impact of age on toxicity and mortality, a multivariate analysis was performed analyzing the impact of older age on risk for nephrotoxicity and mortality after controlling for the propensity score.

Results Of the 126 patients in the cohort, 50 (40%) were older and 76 (60%) were younger. Nephrotoxicity occurred in 21 (42%) of older patients and 33 (43%) of younger patients (p = 0.88). 41 (33%) of patients died, including 17 (35%) older adults and 24 (32%) younger adults (p= 0.72). Older patients were more likely to have received a loop diuretic, >= 3 concomitant nephrotoxins, have a higher Charlson comorbidity index, a history of peripheral vascular disease and myocardial infarction. They were less likely to have diabetes, reside in an intensive care unit, and to receive high dose colistin therapy. After controlling for the propensity score based on theses variables, age >=65 was not associated with increased risk of nephrotoxicity (OR 0.77, 95% CI 0.32 – 1.88) or mortality (1.07, 95% CI 0.43 – 2.72).

Conclusions: Age >= 65 was not independently associated with increased risk for colistin associated nephrotoxicity or mortality. When older adults require colistin therapy for CR-GNB it is imperative that that clinicians are equally as aggressive with regards to dose and concomitant antimicrobial agents as they would be in younger patients so as to optimize colistin therapy.

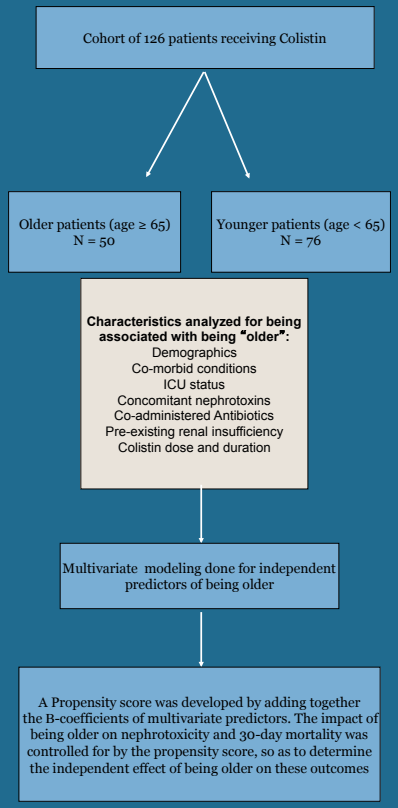
Introduction

- Colistin, a polymyxin antimicrobial, has recently been reintroduced into practice for its activity against multi-drug resistant Gram-negative organisms
- Colistin utility is often limited by high rates of nephrotoxicity
- Multiple analyses have determined "age" as being a risk factor nephrotoxicity in either bivariate or multivariate analyses
- No analyses have determined the independent effect of age on colistin-related nephrotoxicity, after appropriately controlling for factors associated with increased age

Purpose:

The primary aim of this analysis was to determine the independent impact of older age (defined as ≥65 years of age) on the development of nephrotoxicity among patients receiving intravenous colistin.

Methods



Results

Bivariate analysis Demographics and Co-morbidities

	Older (%) N=50	Younger (%) N=76	P value
Diabetes Mellitus	25 (50)	23 (30)	0.026
Peripheral Vascular Disease	8 (16)	1 (1)	0.002
Myocardial Infarction	11 (22)	4 (5)	0.005
ICU status	33 (66)	61 (80)	0.07
Mechanical ventilation	31 (62)	47 (62)	0.99
Renal insufficiency prior to colistin	17 (34)	15 (20)	0.07
Charlson Score*	4 (3-5)	2 (1-4)	<0.001
Charlson Score ≥ 3	38 (76)	36 (47)	0.001
Colistin dose** (mg/kg/d/IBW)	4.28 ± 1.87	4.74 ± 1.86	0.16
Colistin dose >4 mg/kg/d/IBW)	24 (48)	47 (61)	0.15

* Median (interquartile range)

** Mean ± SD

Bivariate analysis: Selected concomitant agents

	Older (%) N = 50	Younger (%) N = 76	P value
Vasopressors	10 (20)	9 (12)	0.21
Aminoglycosides	15 (30)	27 (36)	0.52
Furosemide	38 (76)	32 (42)	<0.001
Rifampin	30 (60)	45 (59)	0.93
Number of concomitant nephrotoxins			0.18
0	6 (12)	22 (29)	
1	15 (30)	24 (32)	
2	21 (42)	21 (28)	
≥ 3	8 (16)	9 (12)	

Multivariate Analysis: Independent Predictors of Being "Older"

	B-coefficient	Odds ratio (95% Confidence Interval)
Furosemide	2.63	13.8 (4.14-46.0)
≥ 3 concomitant nephrotoxins	1.31	3.72 (0.9 – 15.8)
Peripheral Vascular Disease	2.32	10.2 (1.0- 101.1)
Location outside the ICU	1.19	3.29 (1.1 – 10.1)
DM	0.58	2.13 (1.01 - 4.5)
Charlson score ≥ 3	1.50	4.49 (1.4 - 14.3)
Dose < 4 mg/kg/day/IBW	1.84	6.3 (1.7 -22.8)

Multivariate model controlled for baseline renal insufficiency and history of myocardial infraction

Unadjusted outcome measures

	Older (%) N=50	Younger (%) N = 76	Odds Ratio (95% Confidence Interval)
Nephrotoxicity	21 (42)	33 (43)	0.94 (0.46 – 1.94)
30 day mortality	17 (35)	24 (32)	1.15 (0.54 – 2.47)

All values listed as n (%)

Adjusted Outcomes: Propensity-Score Adjusted Effect of Age ≥ 65 on nephrotoxicity and mortality

	Odds Ratio (95% Confidence Interval)
Nephrotoxicity	0.77 (0.32 – 1.88)
30 day mortality	1.07 (0.43 – 2.72)

Conclusions

- Age ≥ 65 was not independently associated with increased risk for nephrotoxicity or mortality
- "Older" patients often have many risk factors for developing colistin-associated nephrotoxicity and this should be taken into account when determining optimal dosing regimens
- If risk factors for nephrotoxicity are not present in older adults receiving colistin, clinicians should be equally aggressive with regards to dose and administration of concomitant nephrotoxic agents as they would be when treating younger patients