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O1168 Linezolid doses should be lowered in renal impairment to improve safety

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Background: Linezolid dosing is not adjusted for renal impairment despite documentation of higher rates of hematologic toxicities associated with higher trough concentrations in this population. We routinely perform linezolid therapeutic drug monitoring and have demonstrated that trough >2 mg/L predicts efficacy while >8 mg/L predicts toxicity. The aim of this analysis was to develop a population pharmacokinetic model in order to identify optimal empiric linezolid dosing regimens for patients with varying degrees of renal impairment.

Materials/methods: Adult patients receiving intravenous or oral linezolid with at least one concentration measured were eligible for inclusion. Demographic and clinical data were obtained from the medical record and estimated glomerular filtration rate (eGFR) was calculated using the CKDEPI equation without the correction for race. Data management, exploration, and visualization were performed using R. Non-linear mixed effects modeling was executed with NONMEM 7 using the FOCE+I method. One- and two-compartment structural models with linear, Michaelis-Menten, mixed linear/Michaelis-Menten, and capacity limited clearance parameterizations were tested. Covariate-structured models were evaluated using forward selection ($\alpha = 0.05$) and backward elimination ($\alpha = 0.001$) processes with covariates standardized to their median values. The final model selected based on objective function and standard diagnostic plots was used to perform Monte Carlo Simulations (MCS) of pragmatic linezolid doses varying by 300 mg increments.

Results: A total of 603 patients contributed 1309 linezolid concentrations for analysis. Median (IQR) age, weight, body surface area (BSA), and eGFR were 64 (53, 73) years, 75 (64, 86) kilograms, 1.89 (1.71, 2.05) m^2, and 78 (49, 100) mL/min/1.73 m^2. A 1-compartment base model with linear elimination best fit the observed data. In the final model, incorporation of eGFR (in absolute units), BSA, and age reduced the between subject variability (BSV) in clearance from 67.8% to 49.9%. The BSV in volume decreased from 30.5% to 17.8% with BSA; BSV was not estimable on the absorption rate constant. Results of the MCS are provided with optimal dosing per eGFR strata highlighted in green.

Linezolid Dosage Regimen	%Probability				
	Trough Level	eGFR <30 mL/min	eGFR 30-59 mL/min	eGFR 60-89 mL/min	eGFR ≥90 mL/min
600mg Q12H	> 2 mg/L	98	86	92	79
	> 8 mg/L	65	53	40	19
300mg Q8H	> 2 mg/L	99	97	94	83
	> 8 mg/L	58	47	36	15
300mg Q12H	> 2 mg/L	90	83	74	50
	> 8 mg/L	26	18	10	03
600mg Q24H	> 2 mg/L	68	54	40	19
	> 8 mg/L	13	8	3	01

Conclusions: Standard linezolid dosing places patients with renal impairment at risk for toxicity. The lower doses identified here should be studied prospectively in this population.