28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

O0806 Body composition measures improve estimation of aminoglycoside clearance: a semi-mechanistic pharmacomorphomic analysis

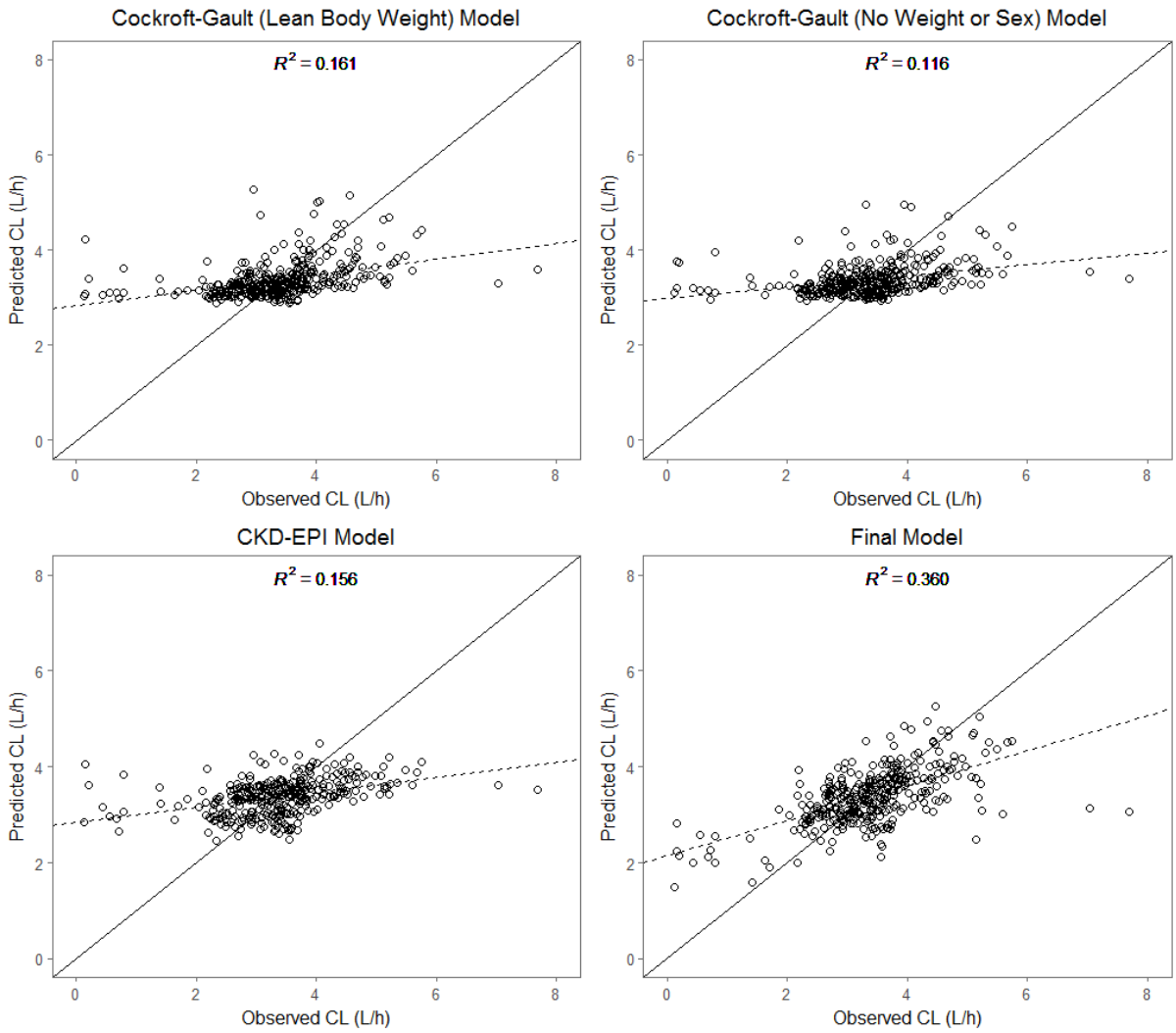
Ryan Crass*[3], Brian Ross[1 2], Brian Derstine[1 2], June Sullivan[1 2], Grace Su[1 4 5], Stewart Wang[1 2], Manjunath Pai[3]

[1]University of Michigan, Morphomics Analysis Group, Ann Arbor, United States, *[2]Michigan Medicine, Department of Surgery, Ann Arbor, United States*, *[3]University of Michigan College of Pharmacy, Department of Clinical Pharmacy, Ann Arbor,* , *[4]Michigan Medicine, Department of Internal Medicine, Ann Arbor, United States*, *[5]VA Ann Arbor Health Systems, Department of Medicine, Ann Arbor, United States*

Background: Alternate body weight metrics and estimates of kidney function (Cockcroft-Gault, MDRD, CKD-EPI) are currently used to empirically dose aminoglycosides. An optimal dosing approach across the distribution of underweight to morbidly obese patients has been elusive. We evaluated whether radiologically-derived body composition measures (morphomics) can improve the prediction of aminoglycoside pharmacokinetics.

Materials/methods: This single-center, retrospective study included adult patients treated with amikacin, gentamicin, or tobramycin with at least three serum drug concentrations and computed tomography (CT) imaging available. Patients with imaging artifacts or unstable kidney function were excluded. Volume of the central compartment (Vc) and total body clearance (CL) were computed by Bayesian analysis using ADAPT 5. Morphomic data were extracted from CT images (*Antimicrob Agents Chemother*. 2017, PMID: 28807918). Bivariable and multivariable linear regression was used to determine the relationships between pharmacokinetic parameters (Vc, CL) and measures of body size (n=7), morphomic measurements (n=29), and estimates of kidney function (n=8).

Results: A total of 363 patients with a median (min, max) of 4 (3, 16) aminoglycoside samples were analyzed. The majority of patients received tobramycin (n=268) followed by gentamicin (n=67) and amikacin (n=28). The median (min, max) age, height, and weight of included patients was 57 (21, 93) years, 170 (142, 203) cm, and 80 (42, 187) kg. Aminoglycoside Vc was not correlated to any body size metric or morphomic measurement, such as body depth, fat volume, fascial volume, or muscle volume. As illustrated in the figure below, the Cockcroft-Gault lean body weight (R^2, 0.16) and CKD-EPI (R^2 0.16) equations predicted CL, but this relationship was driven primarily by age and creatinine with only a small effect of weight and sex (R^2, 0.12). In multivariable analysis, substitution of a morphomic measurement of muscle volume for the weight and sex terms in the Cockcroft-Gault equation significantly improved CL estimation (R^2, 0.31, plot not shown) with model fit further refined by inclusion of an indicator variable for amikacin (R^2, 0.36).



Conclusions: Muscle volume measurement improves the prediction of aminoglycoside CL over standard metrics, and has the potential to improve the precision of empirical dosing.