Abstract #46

Urinary NGAL is Elevated in Hospitalized Cystic Fibrosis Patients with Recent and Increased Tobramycin Exposure

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Background

- Patients with cystic fibrosis (CF) are exposed repeatedly to nephrotoxic antibiotics
- Aminoglycosides (AGs) are often used in CF because of their activity against gram-negative bacteria, particularly *Pseudomonas aeruginosa*
- AG-associated nephrotoxicity results from drug accumulation within kidney proximal tubule and occurs in ~20% of non-critically children and adolescents receiving AG ≥3 days
- Repeated AG exposure and AKI events are associated with the development of impaired kidney function and chronic kidney disease in patients with CF
- Serum creatinine (SCr) does not directly reflect kidney function and underestimates kidney injury, especially in CF patients
- Urinary biomarkers (UB) can be used for early detection of AKI, risk stratification and prediction of outcomes irrespective of SCr values
- Urinary biomarkers may also specify site and mechanism of injury
- Neutrophil gelatinase-associated lipocalin (NGAL) is reabsorbed in the proximal tubule via the same endocytic receptor as AGs (megalin) and may be elevated in AG use due to impaired proximal tubular reabsorption

Objectives

- To define potential roles of NGAL during tobramycin courses in patients with CF
- To identify factors associated with NGAL values during once daily tobramycin therapy in CF patients

Methods

- Prospective observational cohort study in patients with CF receiving once daily tobramycin for a pulmonary exacerbation from Oct 2012-Aug 2013
- **Inclusion criteria:** Subjects included in analysis if provided urine samples ≥70% of tobramycin days or sustained ≥1 day of AKI during therapy
- **Exclusion criteria:** history of lung transplant, receipt of colistimethate sodium (Colistin), receipt of immunosuppressive therapy
- NGAL & SCr measured daily while on tobramycin
- NGAL measured by commercially available ELISA (AntibodyShop, Grusbakken, Denmark) and corrected for urine creatinine concentrations
- Tobramycin measurements performed every 3 days via turbidimetric inhibition immunoassay (Dimension Vista™, Siemens Diagnostics, Tarrytown, NY)

Definitions

- AKI: Rise in SCr by 50% from baseline or ≥0.3 mg/dL within 48 hours (SCr ≥0.5 mg/dL to be considered AKI)
- Baseline SCr: lowest SCr in 6 months prior to admission

Methods (cont)

Data Analysis

- Examined the association of NGAL concentrations and clinical covariates by applying linear mixed-effects regression using restricted maximum likelihood (REML) estimation
- Used MW/Pharm (Mediware, the Netherlands) to perform population model-based Bayesian estimation of individual PK parameter estimates and exposure (AUC) in each subject on each study day based on available patient data (height, weight, gender, SCr, drug doses and levels)
- Secondary analysis, restricted to days on which tobramycin was measured (N=106), constructed nonparametric ROC curves to determine the optimal NGAL cutoff which identifies increased tobramycin exposure (AUC>125 mg*h/L)

Results

- 35 tobramycin courses were given to 26 subjects from Oct 2012-Aug 2013

Table 1. Characteristics of population during tobramycin courses[a]

Variable	Value
Demographics	
Female gender, N (%)	24 (69)
Age in years, Mean (SD)	15.4 (4.1)
Past Medical History	
CF-related diabetes, N (%)	18 (51)
History of prior AKI, N (%)	21 (60)
Tobramycin receipt within 90 days of admission, N (%)	13 (37)
Low albumin (<3.5 mg/dL), N (%)	17 (49)
Baseline SCr in mg/dL, Median (IQR)	0.4 (0.31-0.57)
Medication use	
Tobramycin duration in days, Median (IQR)	12 (8-14)
Tobramycin dose in mg/kg, Median (IQR)	12.0 (10.8-14.1)
Concomitant nephrotoxic drug administration, N (%)	21 (60)
Acute kidney injury[b]	
AKI within 48 hours of tobra start, N (%)	10 (29)
AKI sustained on/after day 3 of tobra, N (%)	4 (11)
Duration of AKI in days, median (range)	1 (1-9)
NGAL (ng/mg UCr)	
Median over all measurements (IQR)	53.2 (28.2-101.4)

[a] Summary statistics and percentages based on N=35 tobramycin courses.
[b] All AKI was KDIGO stage 1 (<100% rise in SCr from baseline).

Table 2. Factors associated with NGAL during tobramycin*

Variable	Coefficient	SE	P-value
Female gender	120.5	39.4	.018
Tobramycin AUC	1.2	0.36	.002
Days since last AG course	-.20	.07	.025
Low albumin (<3.5 mg/dL)	-120.3	45.5	.033
Homozygous delta F508 mutation	-142.4	45.8	.022

*Linear mixed effects model fit by restricted maximum likelihood (REML) estimation
Factors not associated with NGAL included age, duration of therapy, CF-related diabetes, prior AKI, receipt of concomitant nephrotoxic medications or any specific antibiotics

Results (cont)

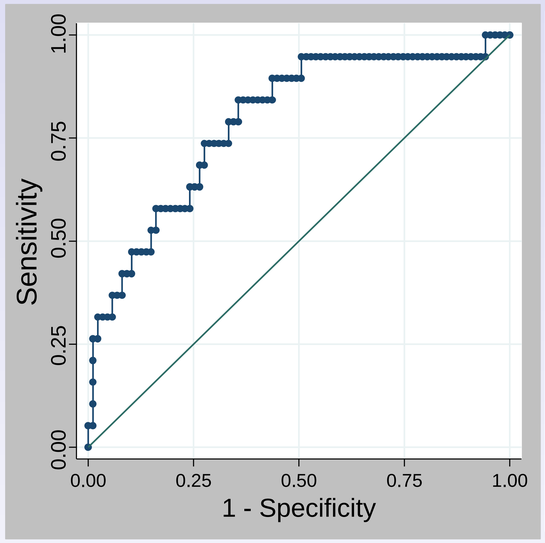

Figure 1. Receiver operating characteristic (ROC) curve for NGAL prediction of tobramycin AUC > 125mg*h/L

AUC under ROC curve = .7907

Nonparametric ROC curve restricted to days on which tobramycin was measured (N=106).

Optimal NGAL cutoff to identify AUC>125 mg*h/L by Youden's index = 64.5 ng/mg UCr (sensitivity 84.2%, specificity 64.4%)

Table 3. Sensitivity, specificity, positive and negative likelihood ratio, and Youden's Index of NGAL for prediction of tobra AUC > 125mg*h/L

NGAL (ng/mg UCr)	Sensitivity	Specificity	LR+	LR-	J-statistic
10.7	7	.06	1.06	0	.06
25.6	.95	.18	1.16	.29	.13
42.6	.89	.49	1.77	.21	.39
64.5	**.84**	**.64**	**2.36**	**.25**	**.49**
84.1	.74	.72	2.67	.36	.46
149.6	.47	.90	4.58	.59	.37
256.1	.26	.99	22.90	.75	.25

Conclusions

- We identified several factors associated with NGAL during tobramycin therapy in CF patients including increased & recent tobramycin exposure
- An NGAL above 64.5 ng/mg may detect supra-therapeutic exposure to tobramycin, as defined by an AUC above 125 mg*h/L
- Urinary NGAL measurement may provide a fast and easy adjunct to TDM

Acknowledgments

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