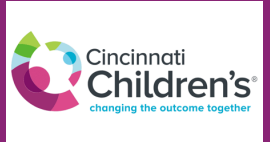# Addition of Urine NGAL to Serum Creatinine Improves Prediction of Cefepime Clearance in Pediatric ICU Patients at High Risk of AKI

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## Introduction

- Cefepime (FEP) is commonly used for empiric treatment of sepsis in the critically ill children in our pediatric intensive care unit (PICU).
- FEP primarily undergoes renal clearance (CL), requiring dose-adjustment with changing kidney function.
- Serum creatinine (SCr) is used to estimate glomerular filtration rate (eGFR), but changes in tubular injury biomarkers, e.g., urine neutrophil gelatinase-associated lipocalin (uNGAL) may precede SCr elevation during AKI.
- uNGAL is ordered in our PICU in patients at high risk of AKI based on a renal angina index (RAI, AKI risk score) of ≥8.[1]
- **Knowledge gap:** It is unknown if uNGAL can predict changes in FEP CL before changes in SCr.
- **Study aim**: determine if uNGAL can improve prediction of FEP CL in patients at risk of AKI in the PICU.

## Methods and Materials

- Prospectively enrolled patients admitted to the PICU with RAI of ≥8, given cefepime, & not on extracorporeal therapy.
- Cefepime concentrations were measured from scavenged residual blood samples using HPLC.
- Analyzed cefepime concentrations using pharmacokinetic (PK) modeling software (MwPharm++) and a pediatric FEP PK model[2] to estimate cefepime CL.
- Used linear regression to compare uNGAL, SCr-eGFR and SCr-defined AKI (KDIGO criteria) as predictors of cefepime CL normalized to body surface area (BSA) before/after hour 48 of PICU admission (b48h/a48h).
  - SCr-eGFR: bedside Schwartz for patients <18; race-neutral CKD-EPI equations for patients ≥18

## Results

- 20 patients (mean 11.6y, 50% female) were included. 15 (75%) had concentrations available after 48h.
- 12 (60%) had SCr-defined AKI on PICU admission and 10 (50%) had elevated uNGAL using threshold of 150 ng/mL.
- In univariate analyses, SCr-eGFR correlated with cefepime CL b48h (adjusted [a]$r^2$=0.65) and a48h ($ar^2$=0.67) (**Figure 1**)
- uNGAL values were skewed so geometric inverse was used; 1/uNGAL was associated with cefepime CL b48h ($ar^2$=0.43) and a48h ($ar^2$=0.50) (**Figure 2**).
- In multivariable regression, combining SCr-eGFR and 1/uNGAL improved model performance: $ar^2$=0.70 b48h and 0.72 a48h (**Table, right panel**).
- Elevated uNGAL was associated with a ~40% decrease in FEP CL after controlling for SCr-AKI (**Table, right panel**).

## Additional Results

**Figure 1**: Regressions of BSA-normalized Cefepime CL vs SCr-eGFR before hour 48 of PICU admission (red) and after hour 48 PICU admission (orange)
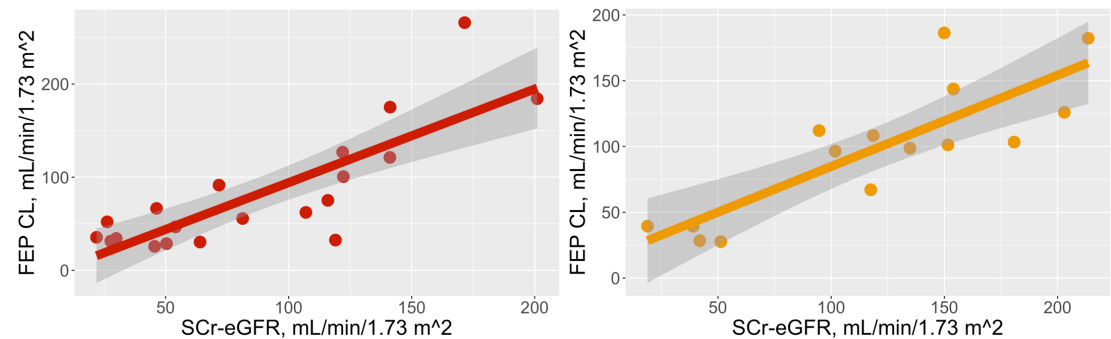


**Figure 2**: Regressions of BSA-normalized Cefepime CL vs 1/uNGAL before hour 48 of PICU admission (green) and after hour 48 of PICU admission (blue)
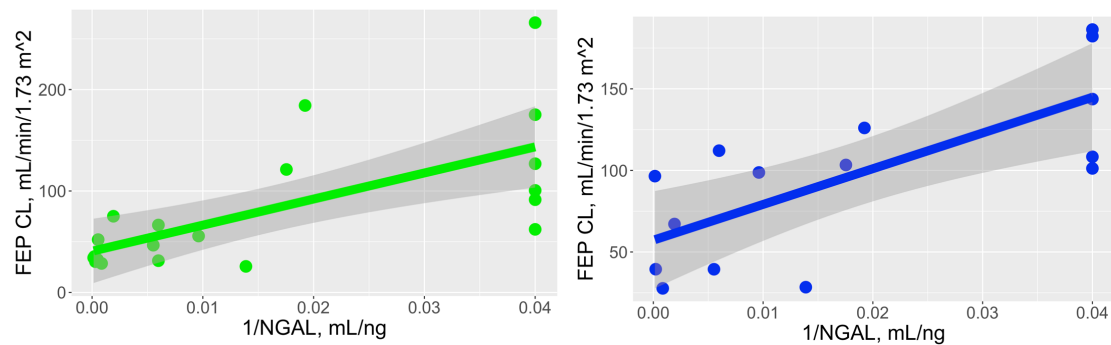


**Table**: Results of regression models of predictors of cefepime CL.

| Simple Regression Models | Coefficient | Adjusted $r^2$ |
|---|---|---|
| **SCr before 48h*** | | |
| Intercept | -6.4 | 0.65 |
| SCr-eGFR | 1.01*** | |
| **SCr after 48h*** | | |
| Intercept | 15.4 | 0.67 |
| SCr-eGFR | 0.694*** | |
| **1/uNGAL before 48h** | | |
| Intercept | 40.7* | 0.43 |
| 1/uNGAL | 2570** | |
| **1/uNGAL after 48h** | | |
| Intercept | 57.2** | 0.50 |
| 1/uNGAL | 2190** | |

| Multiple Regression Models | Coefficient | Adjusted $r^2$ |
|---|---|---|
| **SCr eGFR and 1/uNGAL Before 48h*** | | |
| Intercept | -5.61 | 0.70 |
| SCr-eGFR | 0.787*** | |
| 1/uNGAL | 1140• | |
| **SCr eGFR and 1/uNGAL After 48h*** | | |
| Intercept | 18.1 | 0.72 |
| SCr-eGFR | 0.512** | |
| 1/uNGAL | 1030* | |
| **SCr-AKI and uNGAL ≥150 Before 48h** | | |
| Intercept | 139*** | 0.43 |
| SCr-AKI | -46.2* | |
| uNGAL ≥150 ng/mL | -59.2* | |
| **SCr-AKI and uNGAL ≥150 After 48h•** | | |
| Intercept | 130*** | 0.24 |
| SCr-AKI | -23.3 | |
| uNGAL ≥150 ng/mL | -47.1• | |

• p<0.10, *p<0.05, **p<0.01, ***p<0.001

**Simple regression equations**: Cefepime CL = intercept + predictor*coefficient.
**Multiple regression equations**: Cefepime CL = intercept + first predictor*coefficient + second predictor*coefficient_2.

## Discussion/Conclusions

- uNGAL concentrations at PICU admission are associated with decreased cefepime CL before & after 48h post-admission.
- Addition of uNGAL to SCr-eGFR-based models may improve prediction of cefepime CL; study enrollment is ongoing.

## References

1. Goldstein SL, et al. *Kidney Int Rep*. 2022;**7**(8):1842-9.
2. Shoji K, et al. *Antimicrob Agents Chemother*. 2016;**60**(4):2150-6.

## Acknowledgments

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