Urine Biomarkers Predict Acute Kidney Injury in Newborns Admitted to Neonatal Intensive Care Unit

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BACKGROUND

- Infants admitted to Neonatal Intensive Care Unit (NICU) are at high risk to develop Acute Kidney Injury (AKI)[1]
- Urine biomarkers may be able to detect Neonatal AKI[1,2]
- Some Biomarkers Present in Urine Decrease during AKI, presumably due to consumption as part of repair/protective mechanisms. [3,4,5]

OBJECTIVE

To determine the incidence of AKI, describe differences in patient characterisics and report outcomes in sick infants admitted to level 2 or 3 NICU.

METHODS

- Between February 2010 and May 2011, we screened all infants admitted to the NICU at our institution.
- Population
  - Inclusion criteria included
    - Birth Weight > 2000 grams
    - Gestational age > 34 weeks
    - 5 minute Apgar ≤ 7.Parental Consent
    - Admission to Level 2 or 3 NICU
  - Exclusion Criteria
    - Congenital Anomalies of Kidney /Urinary Tract
- Serum creatinine (SCr) was measured daily for the first 4 days of life.
- AKI was defined as a rise in SCr of > 0.3 mg/dl or persistent SCr above 1.5 mg/dl 48 hours after birth..
- 8 Candidate biomarkers were evaluated (see Table 2)
- Descriptive statistics were performed to determine differences between groups
  - Shapiro–Wilk test and normal probability plot were used to test for normality of data.
    - Normally distributed continuous variables were compared using Student's t-test
    - Non-normal distributed continuous variables were analyzed using Mann-Whitney
  - Categorical variables were analyzed using Fisher's exact test
  - p-values < 0.05 were considered statistically significant

RESULTS

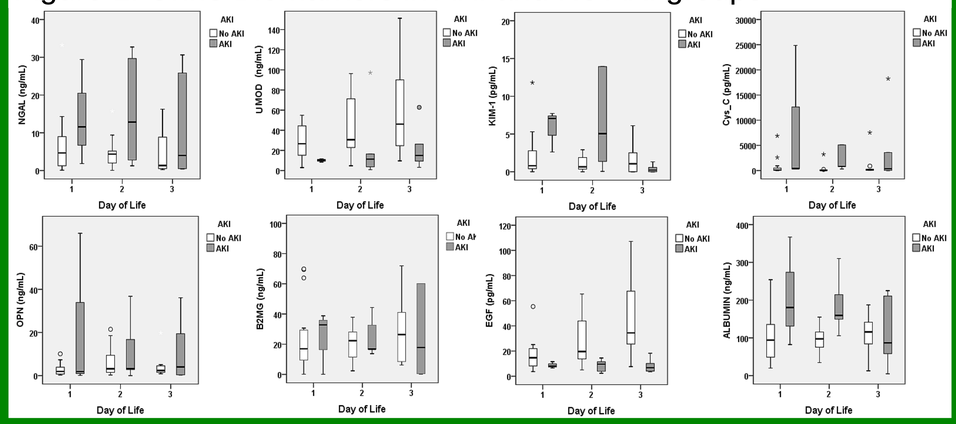
Table 1: Characteristic of Cohort by Presence of AKI

	No AKI (n = 24)	AKI (n =9)	P-value
Birthweight (gram)	2421 ± 631	3425 ± 863	<0.001
Gestational Age (wk)	35 ± 3	37 ± 3	0.1
Alive to 36 wks GA	24 (100%)	7 (77%)	0.07
1 Min Apgar*	2 (1, 6)	1 (0,5)	0.1
5 Min Apgar*	7 (4, 7)	5 (0,7)	0.06
Standard Vent	18 (75%)	6 (67%)	0.7
Indomethacin	11/21 (52.4)	3/7 (42.9)	NS
Vancomycin	14/21 (66)	7/7 (100)	NS
Aminoglycoside	21(88%)	7(78%)	0.6
Race : White	9 (38%)	5 (56%)	0.5
Black	13 (54%)	4 (44%)	
Hispanic	2 (8%)	0 (0)	
Maternal Hypertension	6 (25%)	1 (11%)	0.36
Maternal Preeclampsia	8 (33%)	0 (0%)	0.07

Table 2: Maximum Urine Biomarkers Predict AKI

	No AKI (n = 24)	AKI (n =9)	p-value	ROC AUC
NGAL (ng/mL)	2.3 (1.3, 4.2)	5.5 (2.1, 14.7)	0.12	0.68
KIM-1 (pg/mL)	1.2 (0.7,2)	2.1 (0.9,4.8)	0.25	0.63
UMOD (ng/mL)	26.2 (17.4, 39.4)	11 (5.7, 21.4)	0.03	0.23
Osteopontin (ng/mL)	2.3 (1.3, 4.2)	3.0 (1.2, 7.7)	0.64	0.64
Cystatin C (pg/mL)	89.6 (39.3,204.5)	1123 (272.4,4635)	0.004	0.82
β_2 MG (ug/mL)	10 (4.8, 21.3)	7.7 (2.3, 26.3)	0.7	0.56
EGF (pg/mL)	17.4 (12.7,23.8)	6.7 (4.0,11.3)	0.003	0.18
Albumin (ng/mL)	75.1 (54.6, 109.3)	111 (60, 201)	0.27	0.72

Figure 1: Urine Biomarkers in AKI and No AKI groups



CONCLUSIONS

1. This is the first study to evaluate the association between eight known urine biomarkers and AKI in neonates admitted to level 2 or 3 NICU without cardiac disease or who are not very-low birth weight infants.
2. Urine Cys C is higher in those with AKI
3. Urine EGF and UMOD are lower in the those with AKI
4. Other biomarkers (NGAL, OPN, Albumin, and KIM -1) had AUC ROC of 0.68, 0.64, 0.72, and 0.63 respectively. The graphical data (figure 2) suggests their potential as biomarkers of AKI.
5. Evaluation of larger cohorts are needed before we can apply these to clincal practice.

BIBLIOGRAPHY

1. Jetton, JG, Askenazi, DJ: Update on AKI in the neonate. *Curr Opin Pediatr*, 2012.
2. Askenazi, DJ, et al. : Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants. *J Pediatr,* 159**:** 907-912, 2011.
3. Tsau YK, et al.. Decreased urinary epidermal growth factor in children with acute renal failure: epidermal growth factor/creatinine ratio \Pediatr Res. 1996 Jan;39(1):20-4.
4. Chen L, Liu W. Effect of asphyxia on urinary epidermal growth factor levels in newborns. J Tongji Med Univ. 1997;17(3):144-6.
5. Kwon O, et al. Simultaneous monitoring of multiple urinary cytokines may predict renal and patient outcome in ischemic AKI. Ren Fail. 2010 Jul;32(6):699-708.

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