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Renal profile of sick neonates admitted to NICU of a tertiary care centre

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Abstract
Background: Sick neonates suffer from variable degree of renal impairment and AKI is a frequent phenomenon in NICU. The cause of AKI is of multi-factorial etiology and usually, there are one or more associated contributing factors. Early recognition of renal failure is important to facilitate appropriate fluid and electrolyte management & a stable biochemical milieu to prevent permanent renal damage.
Methodology: We conducted a prospective observational study at NICU of our tertiary care hospital, Nalanda Medical College & Hospital, Patna over 15 months from March 2019 to May 2020. Sick babies of gestational age ≥26 weeks and birth weight ≥800 gram admitted in NICU were included in the study & their kidney function was monitored. AKI was defined as per serum creatinine &/or urine output criteria.
Results: 459 neonates were studied out of which 57 (12.4%) suffered from AKI. Mean gestational age of neonates with AKI was 33.4 (S. D=4.4) and mean weight on admission was 2.172 Kg (S. D= 0.840 kg). Male: female ratio was 1.48:1. Out of theses neonates with AKI, a diagnosis AKI was made by 24 hours of admission in 34(59.6%) and in the rest 23 (40.4%) neonates, it occurred after 24 hours of admission. The most common type of AKI was pre-renal type which accounted for 73.7% (n=42) of cases. Intrinsic renal and post-renal causes accounted for 19.3% (n=11) and 7.02% (n=4) cases respectively. The common predisposing factors were sepsis (61.4%), asphyxia (49.1%), shock (54.4%) and dehydration (12.3%). Oliguric renal failure was seen in 25 (43.9%) cases and the underlying etiology did not play a role in the occurrence of oliguria. Out of the 57 neonates with AKI, 21 (36.9%) died. No difference in mortality was observed on the basis of sex, prematurity, SGA, birth asphyxia, dehydration, hyponatremia, hyperkalemia or metabolic acidosis. However, in this study we found a significantly higher mortality in the presence of sepsis, oliguria, higher mean serum creatinine level, and need of mechanical ventilation.
Conclusion: AKI is a common phenomenon complicating the management of sick neonates with almost 1 in every 8 neonates admitted to our NICU suffering from this condition. As pre-renal AKI was the commonest type, this underscores that prompt recognition and management of hypoperfusion can prevent progression from pre-renal to intrinsic renal type of AKI. Most of such unfortunate neonates had more than 1 predisposing factors & sepsis and perinatal asphyxia were the most common risk factors for AKI. As non-oliguric AKI was more common than oliguric AKI, there was a high probability of missing 3 out of 5 cases with AKI if the focus was only on the urine output of a sick neonate. The presence of sepsis, oliguria, higher mean serum creatinine level, and use of mechanical ventilation were more commonly associated with mortality in such neonates.

Keywords: Acute kidney injury, serum creatinine, urine output, preremal, postrenal & renal type of AKI.

1. Introduction
Acute renal failure (ARF) or acute kidney injury (AKI) is a frequent clinical condition in neonatal intensive care units (NICUs). Studies have reported AKI incidence of 6-24% of all NICU admissions [1, 2]. The most common form of AKI in neonates is prerenal failure due to renal hypo-perfusion or ischemia because of high renal vascular resistance, high plasma renin activity, low glomerular filtration, decreased intracortical perfusion rate, and decreased reabsorption of sodium in the proximal tubules in the first few days of life [3]. However, Pre-renal failure may result in intrinsic kidney failure if not treated promptly. Newborn in particular are more vulnerable to acute tubular necrosis or cortical necrosis [4].
The cause of AKI in neonates is of multi-factorial etiology and usually, there are one or more associated contributing factors [5]. Early recognition of renal failure is important in neonates to facilitate appropriate fluid and electrolyte management & a stable biochemical milieu to prevent permanent renal damage. Diagnosis of renal failure is difficult in neonates as many of the established clinical and biochemical parameters are unreliable in this age group. The short-term outcome of therapy for AKI in newborns is dependent on the underlying etiology of AKI, the involvement of other organs and the availability of renal replacement therapy. With this background, we intended to undertake the present study to study the renal profile in ill neonates, incidence of AKI and to the factors affecting its outcome.

2. Aims and Objectives
Aim: To study the renal profile of sick neonates.
Objectives: To know the incidence of acute kidney injury in ill neonates.
- To study the occurrence of AKI in relation to gender, gestational age and birth weight percentile.
- To study risk factors of AKI.
- To know the occurrence of oliguric & non oliguric type of

AKI.
- To study the outcome of neonates with AKI

3. Methodology

Study design & setting

Prospective, observational study done at NICU of a tertiary care teaching hospital, Nalanda Medical college & Hospital, Patna over 15 months from March 2019 to April 2020.

Inclusion criteria

All admitted sick neonates of gestational age ≥26 weeks and birth weight ≥800 gram. Neonates below this cut off were not included due to our experience of only rare survival of such neonates at our center.

Exclusion criteria

- Babies admitted in NICU but not sick, i.e, babies only on phototherapy, stable babies with meconium aspiration syndrome, stable premature/IUGR babies etc.
- Neonates with multiple congenital anomalies, chromosomal anomaly, antenatally diagnosed hydronephrosis, renal malformations and mothers with acute or chronic renal disease
- Neonates who were referred to other hospital were also excluded from final analysis.

Study technique

After obtaining consent and enrolment in the study as per above criteria, the neonates underwent detailed history taking, clinical examination, laboratory investigations & management based on our NICU protocol. Serum creatinine was investigated at predefined time: those admitted before 72 h of life were screened at 72 h of life and those admitted after 72 h were screened at admission. Investigations were serially repeated as and when required in the course of treatment and finally on resolution of symptoms.

Data collection

Gestational age (GA), birth weight, relevant perinatal history, findings on physical examination and systemic signs, urine output and investigations were recorded in the study performa**.** We used revised Fenton chart to classify the neonates as appropriate for GA (AGA), small for GA (SGA), and large for GA (LGA)[6]. Assessment for dehydration was done by comparing the admission weight of the neonate with respect to birth weight. Based on this, a neonate was considered dehydrated if the percentage of weight loss was >3%/day or cumulative >10% in neonates with a GA ≥34 weeks, or cumulative >15% in neonates with GA <34 weeks. To measure the urine output, we routinely weighed all wet nappies in uncatheterized neonates, subtracted the dry weight of nappies from it and calculated the urine output over a period of 24 h in the form of mL/kg/h. Measuring urine output from catheterized babies was much easy. In the present study we defined acute renal failure as:
- Ser Creatinine (SCr) rise ≥0.3 mg/dL or ≥ 50% increase from baseline over 48 hrs, OR
-Plasma creatinine more than 1.5 mg/dL for at least 48 hrs if mother's renal function was normal, OR
-urine output less than 1 mL/kg/hr for 24 hours after first day of life.

Statistical analysis

Pertinent data was recorded, tabulated and entered in Microsoft excel sheet, and then analyzed by using statistical

software "SPSS ver. 20®. Variables were expressed as mean, standard deviation and percentiles. Dichotomous variables were compared using Chi-square test whereas continuous variables were compared using Student t-test. p-value <0.05 was taken as significant.

4. Results

General characteristics of the whole study population

In our study, total 459 neonates were enrolled over the 15 months study period out of which 57 (12.4%) suffered from AKI. Table 1 depicts general characteristics of the whole study population.

Table 1: General characteristics of the whole study population

Parameter	Value
Total no. of neonates enrolled	459
Birth weight: Mean (SD)	2.092 Kg (0.741Kg)
Gestational age: Mean (SD)	35.3 (3.9) weeks
Male: Female	1.4: 1
APGAR score: Mean (SD)	7.14 (1.92)
Downe's score: Mean (SD)	3.34 (1.84)
Urea level: Mean (SD)	34.59 (18.07) mg/dl
Creatinine level: Mean (SD)	1.12 (0.74) mg/dl

General characteristics of neonates with AKI

Incidence of AKI was 12.4% (57 out of 459) in the present study. Mean gestational age of neonates with AKI was 33.4 weeks (S. D=4.4) and mean weight on admission was 2.172 Kg (S. D= 0.840 kg). Male: female ratio was 1.48:1. Out of theses neonates with AKI, a diagnosis AKI was made by 24 hours of admission in 34(59.6%) and in the rest 23 (40.4%) neonates, it occurred after 24 hours of admission.

Table 2: Characteristics of neonates with AKI (n= 57)

Parameter	Value	Percentage
Males	34	59.6
Females	23	40.4
SGA	28	49.1
AGA	25	43.9
LGA	4	7.0
Term	27	47.4
Preterm	30	52.6
Normal Birth weight	22	38.6
LBW	17	29.8
VLBW	14	24.6
ELBW	4	7.0
Age at diagnosis in days: Mean (SD)	3.9(5.4)	---
Weight at admission in gram: Mean (S.D)	2172 (840)	---
Serum creatinine in mg/dl: Mean (SD)	1.97 (1.29)	---
Dehydration	7	12.3
Metabolic Acidosis with pH<7.2)	12	21.1
Hyponatremia (Ser Na^+ <135 mEq/L)	19	33.3
Hyperkalemia (Ser K^+ >5.5 mEq/L)	23	40.4
Structural disease of kidney/urinary region	7	12.3

Predisposing factors for AKI

Among the neonates with AKI, there were multiple predisposing factors in 37 (64.9%) cases and a single predisposing factor in 20(35.1%) cases. The most common type of AKI was pre-renal type which accounted for 73.7% (n=42) of cases. Intrinsic renal and post-renal causes accounted for 19.3% (n=11) and 7.02% (n=4) cases respectively.

Table 3: Predisposing factors for AKI

Parameter	Value	Percentage
Sepsis	35	61.4
Perinatal asphyxia	28	49.1
Respiratory distress syndrome	5	8.8
Dehydration	7	12.3
Symptomatic congenital heart disease	5	8.8
Polycythemia	3	5.3
Obstruction of urogenital tract	4	7.02
Shock	31	54.4
Nephrotoxic drug	3	5.3

AKI and urine output

Oliguric renal failure was seen in 25 (43.9%) cases and the underlying etiology did not play a role in the occurence of oliguria (Table 4 and 5)

Table 4: Occurrence of oliguric and non-oliguric renal failures

Aetiology	Oliguric	Non-oliguric	Total number
Dehydration	5	2	7
Sepsis	18	17	35
Perinatal asphyxia	9	19	28
RDS	3	2	5
KUB anomaly	5	2	7
Nephrotoxic drugs	2	1	3

Table 5: Oliguria as the presenting feature in different predisposing factors

	Oliguria in the presence of risk factor	Oliguria in the absence of risk factor	p value
Sepsis	18/35= 51.4%	7/22= 31.8%	0.14
Asphyxia	9/28= 32.1%	16/29= 55.1%	0.08
Dehydration	5/7= 71.4%	20/50= 40%	0.117
KUB anomaly	5/7= 71.4%	20/50= 40%	0.117
RDS	3/5= 60%	22/52= 42.3%	0.44
Nephrotoxic drug	2/3= 66.66%	23/54= 42.6%	0.417

Prognosis

Out of the 57 neonates with AKI, 21 (36.9%) died. No difference in mortality was observed on the basis of sex, prematurity, SGA, birth asphyxia, dehydration, hyponatremia, hyperkalemia or metabolic acidosis. However, in this study we found a significantly higher mortality in the presence of sepsis, oliguria, higher mean serum creatinine level, and need of mechanical ventilation.

Table 6: Factors affecting mortality

Parameters	Improved (n=36)	Died (n=21)	p value
Male sex (n=34)	20 (55.56%)	14(66.66%)	0.413
Prematurity (n=30)	17 (47.22%)	13 (61.9%)	0.288
SGA (n=28)	15 (41.67%)	13 (61.9%)	0.144
Sepsis (n=35)	18 (50%)	17 (80.95%)	0.021
Perinatal asphyxia (n=28)	15 (41.66%)	13 (61.90%)	0.144
Dehydration (n=7)	4 (11.11%)	3(14.28%)	0.725
Oliguria (n= 25)	11 (30.55%)	14 (66.66%)	0.008
Hyponatremia (n=19)	13 (36.11%)	6 (28.57%)	0.563
Hyperkalemia (n=23)	16 (44.44%)	7 (33.33%)	0.413
Metabolic acidosis with pH<7.2 (n=12)	6 (16.66%)	6 (28.57%)	0.292
Serum Creatinine (n=57)	Mean=1.82, S. D= 0.44	Mean=2.38, S. D=0.68	0.0004
Mechanical ventilation (n=35)	18 (50%)	17 (80.95%)	0.021

5. Discussion

In the present study we intended to study the profile of renal function in sick neonates at our tertiary care centre with special emphasis on renal injury including its risk factors and outcome. The prevalence of AKI in our study was 12.4%, which was comparable to that in the study by Youssef *et al*. [7] (10.8%). However, Timovska *et al*. [8] have reported a lower prevalence of 6.5% and a Turkish study [9] reported a still lower prevalence of 3.4%. A previous study from India found the incidence of AKI in newborns to be 3.9/1000 live births and 34.5/1000 newborns admitted to the NICU [10]. Relatively higher incidence of AKI in our Indian study can be attributed to the fact that ours being a tertiary centre, many neonates were brought late and were suffering from serious ailments by the time they were brought to us. In the present study the male: female ratio was 1.5:1. Mortazavi *et al*. [11] and Airede *et al*. [12] have also reported a relatively higher incidence of AKI in male sex. The higher occurrence of AKI in boys is probably due to the higher susceptibility of boys to perinatal disorders such as sepsis and RDS. In our study, 27 (47.4%) neonates were born full term, compared to 40.7% in the study by Youssef *et al*. [7]. This can be explained by the fact that term neonates are more susceptible to suffer from perinatal asphyxia and in our study almost 50% of neonates with AKI had perinatal asphyxia as a predisposing factor. The major predisposing factors for AKI in our study were sepsis (61.4%), asphyxia (49.1%), shock (54.4%), dehydration (12.3%), RDS (8.8%) and symptomatic congenital heart disease (8.8%). Timovska *et al*. [8] have reported asphyxia, sepsis, and prematurity as the commonest risk factors for AKI. Similarly, Askenazi *et al*. [13] reported predisposing factors for AKI to be sepsis, RDS, mechanical ventilation, perinatal asphyxia, dehydration, and surgical operations in 63%, 55.6%, 51.9%, 18.5%, 14.8%, and 11.1%, respectively. Whereas, Timovska *et al*.[8] reported use of nephrotoxic drugs in 92% of neonates in their study, the corresponding figure in our study was only 5.3% due to availability and use of safer antibiotics. Also, our antibiotic use policy is to avoid nephrotoxic drugs in neonates with anticipated deranged renal function or hypoperfusion.

In the present study we found that the incidence of non-oliguric AKI was more than oliguric AKI, with 43.9% of patients being oliguric. Whereas Mathur *et al*. [14] have reported the incidence of oliguria in neonatal sepsis to be only 15% and Karlowicz & Adelman [15] have reported that non-oliguric AKI to be the commonest type of AKI associated with perinatal asphyxia in full-term infants, Mortazavi *et al*. [11] have reported that oliguric AKI is the commonest AKI in neonates (72.2%). Prompt management of hypoperfusion & shock and appropriate supportive care at our hospital may have lead to less-severe reduction in glomerular filtration rate (GFR) and better preservation of tubular function, and this partly explains the lower incidence of oliguria in the our study. In our study, pre-renal AKI was more common than intrinsic renal failure (73.7% versus 19.3%). This correlates with the findings of Durga D *et al*. [16] who reported that the most common type of AKI in neonates is pre-renal in origin, which is due to renal hypo-perfusion or ischemia. Mortality rate of neonates with AKI in our study was 36.9%. Most of the researchers have reported mortality in the range of 25-40% which is in agreement with our study [12, 17]. We found a significantly higher mortality in the presence of sepsis, oliguria, higher mean serum creatinine level and need of mechanical ventilation. This is in agreement to the study of Tellier *et al*. [18] and Esfandiar *et al*. [19] Generally speaking, the sicker the neonate the higher is the mortality. In our study, 37 patients (64.9%) had more than one associated contributing condition, and this may be an additional factor for the high mortality in our patients.

6. Conclusion

AKI is a common phenomenon complicating the management of sick neonates with almost 1 in every 8 neonates admitted to our NICU suffering from this condition. As pre-renal AKI was the commonest type, this underscores that prompt recognition and management of hypoperfusion can prevent progression from pre-renal to intrinsic renal type of AKI. Most of such unfortunate neonates have more than 1 predisposing factors with sepsis and perinatal asphyxia being the most common risk factors for AKI. As non-oliguric AKI is more common than oliguric AKI, there is propensity to miss 3 out of 5 cases with AKI if the focus is only on the urine output of a sick neonate. The presence of sepsis, oliguria, higher mean serum creatinine level, and use of mechanical ventilation are more commonly associated with mortality in such neonates.

7. Limitation

First limitation is that ours is a single-centre study and thus doesn't reflect the incidence of AKI in community or general hospitals. Second limitation is the small number of cases with AKI which prevented performing multivariate analysis for knowing the relative contribution of risk factors in the occurrence of AKI. Third limitation is that we didn't catheterize urinary bladder of the study subjects and hence urine output couldn't be measured accurately. This however, was done to prevent UTI.

8. Conflict of Interest: none

9. Financial Disclosure: The authors hereby declare that this study hasn't received any financial support.

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