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Clinical and laboratory characteristics of acute kidney injury in infants with diarrhea: a cross-sectional study in Bangladesh

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Abstract

Objective: We described the clinical and laboratory characteristics of acute kidney injury (AKI) in infants with diarrhea.

Methods: This medical record analysis was conducted in Dhaka Hospital of the International Centre for Diarrheal Disease Research Bangladesh from January to December 2015. Infants with elevated serum creatinine (>50 μmol/L) constituted cases (n = 146). We randomly selected 150 infants with normal creatinine levels as the controls. Both groups had diarrhea. Events occurring from admission to discharge were analyzed and compared to assess differences in characteristics of the groups.

Results: Among the 146 patients with AKI, 130 (89%) were discharged after recovery. Logistic regression analysis, adjusting for potential confounders (such as oral rehydration salt intake at home, convulsions, abnormal mentation, and hypoxemia) showed that infants with AKI were

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independently associated with hypernatremia (odds ratio (OR) = 8.66, 95% confidence interval (CI) = 3.88–19.22), sepsis (OR = 4.71, 95% CI = 2.07–10.73), and severe dehydration (OR = 3.76, 95% CI = 1.78–7.95). Persistently elevated creatinine was associated with radiological pneumonia (OR = 2.16, 95% CI = 1.09–4.31) and sepsis (OR = 2.24, 95% CI = 1.14–4.40).
Conclusion: Dehydration, sepsis, and hypernatremia were found to be associated with AKI in diarrheal infants. After proper correction of dehydration, persistently elevated creatinine could be associated with sepsis and pneumonia.

Keywords
acute kidney injury, infants, diarrhea, dehydration, creatinine, Bangladesh

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What is known about this subject?

1. Acute kidney injury (AKI) is a common clinical event with severe consequences.
2. In the pediatric intensive care unit (PICU), AKI occurs in nearly 10% of all patients, and evidence suggests that many deaths in children are owing to AKI.
3. The treatment for AKI is limited to a great extent by delayed diagnosis.

What are the new findings and/or what is the impact on clinical practice?

1. This is a report from a unique dataset of infants with diarrhea, where recognition by family members of diminished urine output in infants with ongoing diarrhea would have been difficult and challenging.
2. Clinical features of hypernatremia, sepsis, and severe malnutrition to some extent, should lead to screening of infants for AKI, thereby preventing infants deaths owing to AKI.
3. Even after proper correction of dehydration, persistently elevated creatinine could be associated with sepsis and radiological pneumonia.

Introduction

Acute kidney injury (AKI) can be defined as an abrupt or rapid decline in renal filtration function, which is usually evidenced by a marked rise in serum creatinine concentration and/or decrease or absence of urine production.[1] To detect AKI, various parameters can be used, such as estimated creatinine clearance or estimated glomerular filtration rate. Among these, elevated serum creatinine (>1.5 times the reference value) can be used for clinical and epidemiological study purposes.[2] The use of different definitions of AKI has led to wide variation in the estimated prevalence (7% to 25%)[3] and mortality rate of AKI.[2] Epidemiological studies also demonstrate differing etiologies and risk factors of AKI, based on different settings and populations.[4–7]

Diarrhea remains the second leading cause of death globally among children under age 5 years, accounting for 9% of the 5.6 million deaths in children under 5 years of age worldwide during 2016.[3,8] Scaling up of oral rehydration therapy, health education, and vaccination programs has been undertaken, to reduce mortality.[9]

Despite attention to and prioritization of improving the rate of treatment for diarrhea, identifying diarrhea-related morbidity remains an unresolved global issue, the focus on which may help to address undiagnosed causes of death in children under 5 years old. Dehydrating diarrhea may act as a precipitating factor for the development of AKI by causing hypoperfusion kidney injury.[10]

Among several causes of AKI, our study focused on prerenal causes. Prerenal AKI occurs owing to reduced perfusion or hypovolemia for any reason (bleeding or gastrointestinal, cutaneous, or urinary losses), such that it is regarded as "volume responsive".[11] Creatinine measurement is inexpensive and easy to perform, with rapidly available results. However, this method has limitations as a marker of renal function, which is why the National Institute of Health Care and Excellence guideline recommends that creatinine measurement be accompanied by observation of urine output. Following an abrupt decrease in the functioning of the kidney, creatinine may gradually accumulate, meaning that serum creatinine readings will take several days to reflect a new state.

Although primary care professionals are seeing increasingly more children with AKI,[13] a recent review highlighted the paucity of related data in low- and middle-income countries.[3] One nationwide study from a developing country reported diarrhea and sepsis as top risk factors in community-acquired AKI;[13] however, the epidemiology and outcomes of AKI have not yet been studied in a special situation like diarrhea and malnutrition. Nonetheless, there is a lack of consensus regarding the management of AKI with diarrhea. If factors associated with AKI in infants with diarrhea are identified, this will facilitate early intervention against the development of AKI, which may reduce morbidity and mortality in these infants. Thus, the aim of our study was to describe the clinical and laboratory characteristics and associated features of AKI in infants with diarrhea.

Materials and methods

Ethical considerations

This study was approved by the Research Review and Ethical Review Committees of icddr,b. This is a medical chart analysis, which did not involve direct patient participation. Data were deidentified before analysis; in this way, anonymity was well preserved. Written or verbal informed consent were therefore not required.

Study site and population

The study was conducted in Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), which is the largest hospital specializing in the treatment of diarrheal diseases in the world. Dhaka Hospital provides care and treatment for over 140,000 patients of all ages annually. In 2015, the total number of patient visits was 138,341, and 59% of patients were children under age 5 years. Pediatric patients are from urban and peri-urban areas and lower middle-income families. A description of the hospital has been provided elsewhere.[14]

Study design and data source

This was a retrospective cross-sectional study conducted from January to December 2015 at Dhaka Hospital of the icddr,b. Eligible patients were of either sex, age 0 to 12 months, hospitalized with diarrhea, and had serum creatinine measurement data because of poor or absent urine output or clinical features of hypernatremia, hypokalemia, or sepsis in the intensive care unit (ICU) or longer-stay

unit of the hospital. We enrolled all infants with serum creatinine levels >1.5 times the age-specific upper cut-off level. For comparison, we selected age- and sex-matched hospitalized infants with normal creatinine levels using simple random sampling. Demographic features, laboratory measurements, and information of hospital course that included medication exposures, length of hospital stay, and survival/death were the variables of interest retrieved from the database. Study definitions of the different clinical conditions are given in Box 1.

Routine patient care

On arrival at the hospital, a patient is seen by a triage nurse who takes a quick history and assesses dehydration. Subsequently, the patient is seen by a physician for further evaluation, initial management, and necessary examinations. The physician then

Box 1. Study-related case definitions

Clinically suspected hypernatremia (12)	Hypernatremia in children is an electrolyte imbalance commonly observed at Dhaka Hospital (11, 24). Before measuring serum electrolytes, patients with hypernatremia can be identified based on history and clinical presentation, for example: History: excessive intake of oral rehydration saline compared with fluid loss Symptoms: excessive thirst, hyper-irritability, inconsolable crying, convulsions (11, 19, 24) Signs: Abnormal mentation, exaggerated deep tendon reflexes, non-pitting edema Laboratory confirmation: serum sodium ≥150 mmol/L
Sepsis (17)	Sepsis defined according to the following, in the absence of dehydration: • Presence of signs and symptoms of inflammation and infection **plus** • Hyperthermia or hypothermia (temperature >38.5°C or <35.0°C, respectively) **plus** • Tachycardia (heart rate: neonates 180 beats per minute (bpm), infants >160 bpm, children age 1–5 years >140 bpm, age >5 years >90 bpm) **plus** • Bounding pulse **or** altered mental status **or** hypoxemia in the absence of pneumonia **or** abnormal white blood count (>12×10^9 cells/L or <4×10^9 cells/L or band and neutrophil ratio ≥0.1) **or** increased serum lactate level (17)
Oliguria and anuria	Oliguria defined as urine output <1 mL/kg per hour in infants; in children and adults, urine output <0.5 mL/kg per hour for >6 hours (19, 25) Anuria defined as no urine output >12 hours
Treatment of dehydrating diarrhea	WHO guideline for treating dehydrating diarrhea (26)
Severe pneumonia (WHO classification) (15)	Infants with age-specific fast breathing and severe lower chest wall indrawing, with any feeding difficulty or abnormal mentation or convulsion or grunting Suspected patients confirmed with chest X-ray

evaluates the patient for complications and other health problems associated with diarrhea, such as electrolyte imbalance, sepsis, pneumonia and malnutrition (Box 1). Assessment of dehydration is diligently performed at each point and rehydration is continued until the cessation of diarrhea. The hospital provides treatment and logistics for patient care at no cost.

Physicians order serum creatinine measurement in patients with poor or absent urine output for >8 hours or with a suspected electrolyte imbalance, such as hypernatremia (Box 1). Correction of dehydration is started before a blood sample is collected for serum creatinine measurement. Among infants diagnosed with AKI, after proper resuscitation and management of underlying conditions, serum creatinine measurement is repeated, usually after ~24 hours, to ensure correction of dehydration. Protocolized treatment is offered for infants with severe acute malnutrition[4] as well as severe pneumonia and other associated complications, as defined by the World Health Organization (WHO).[15]

Identification and outcome of AKI

AKI was defined as an increase in serum creatinine >1.5 times from age specific normal reference value. For infants aged 1 to 12 months, the normal range of serum creatinine is 18 to 35 μmol/L.[15] Any infants having spot serum creatinine >50 μmol/L were identified as a case of AKI. It should be mentioned that blood for serum creatinine measurement was collected after rehydration of the patient. The primary outcomes were normalization of serum creatinine, outside referral, or death.

Data analysis

Data were retrieved from the electronic medical record system. After the deidentification process, the data were entered into IBM SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Epi Info version 7.0 (USD Inc., Stone Mountain, GA, USA) and Stata 13 (StataCorp LLC, College Station, TX, USA) were used in the analysis. Differences in proportion were compared using the chi-square test or Fisher's exact test, as appropriate. Differences in means were compared with the *t*-test for normally distributed data, and differences in medians were compared using the Mann–Whitney test for data that were not normally distributed. The odds ratio (OR) with 95% confidence interval (CI) was calculated to identify the factors associated with AKI; a p-value <0.05 was considered statistically significant. Bivariate analysis was conducted for all explanatory variables (age, sex, vomiting, fever, convulsions, history of scanty urine, receiving oral rehydration salt solution at home, feeding practices, dehydration at admission, abnormal mentation, chest indrawing, abdominal distension, hypotension, hypoxemia, nutritional edema, urinary tract infection (UTI), severe acute malnutrition, sepsis, and discharged alive) to identify those factors associated with infants with AKI. Logistic regression analysis was performed to identify characteristics that were significantly associated with AKI in infants after adjusting for covariates and confounders using appropriate statistical testing.

Results

During the study period 1857 infants (age 0–12 months) were admitted for diarrhea-related complication in the longer stay and intensive care units. Among them, 731 infants were tested for serum creatinine. Of these, 146 (20%) patients had serum creatinine >1.5 times higher than the normal reference value. Among the remaining patients with normal creatinine levels, we selected a similar number (n = 150) of infants using computer-generated random sampling,

Table 1. Comparison of baseline characteristics among infants with and without acute kidney injury (AKI).

Characteristics	With AKI n=146 (%)	Without AKI n=150 (%)	Difference (AKI vs. no AKI) OR (95% CI)	p-value
Age, months (median, IQR)	3.0 (2.0,7.0)	5.5 (3.2,8.0)	–	–
Male sex	86 (59)	90 (60)	0.96 (0.60–1.52)	0.85
Vomiting	85 (58)	86 (57)	1.03 (0.65–1.64)	0.88
Fever	72 (49)	77 (51)	0.92 (0.58–1.45)	0.73
Convulsion	33 (23)	14 (9)	2.83 (1.44–5.56)	0.002
History of scanty urine	22 (15)	18 (12)	1.3 (0.67–2.54)	0.44
Receiving ORS at home	124 (85)	98 (62)	3.4 (1.98–6.05)	<0.001
Dehydration at admission	125 (86)	91 (61)	3.86 (2.19–6.80)	<0.001
Abnormal mentation (irritability/lethargy)	88 (60)	53 (35)	2.78 (1.73–4.45)	<0.001
Chest indrawing	70 (48)	64 (43)	1.24 (0.78–1.95)	0.21
Abdominal distension	19 (13)	25 (17)	0.75 (0.39–1.43)	0.24
Hypotension	22 (15)	12 (8)	2.04 (0.97–4.29)	0.07
Hypoxemia	28 (19)	13 (9)	2.5 (1.2–5.04)	0.01
Nutritional edema	17 (12)	8 (5)	2.24 (0.98–5.60)	0.40
Urinary tract infection	37 (25)	18 (12)	2.40 (1.34–4.61)	0.003
Severe acute malnutrition	86 (59)	78 (52)	1.32 (0.84–2.09)	0.24
Sepsis	49 (34)	11 (7)	6.38 (3.16–12.90)	<0.001
Discharged alive	130 (89)	145 (97)	0.28 (0.10–0.77)	<0.01

Values are n (%), unless otherwise specified.
OR: odds ratio. CI: confidence interval. IQR: interquartile range; ORS, oral rehydration salt.

irrespective of seasonality, sex, or sociodemographic characteristics. The mean serum creatinine in the AKI and non-AKI groups was $91.5 \pm 44.9\,\mu mol/L$ and $24.3 \pm 6.8\,\mu mol/L$, respectively.

The differences in baseline characteristics among diarrheal infants with and without AKI are shown in Table 1. In bivariate analysis, infants with diarrhea and AKI more often presented at a younger age, with convulsions, abnormal mentation, hypoxemia, sepsis, hypernatremia, UTI, and had mixed feeding practices (not exclusively breastfed), in comparison with infants without AKI.

In logistic regression analysis, after adjusting for likely confounders (Table 2), children with AKI were significantly associated with hypernatremia (OR = 8.66, 95% CI = 3.90–19.22; $p < 0.001$), sepsis (OR = 4.71, 95% CI = 2.07–10.73; $p < 0.001$), and some were associated with severe dehydration (OR = 3.76, 95% CI = 1.78–7.95; $p = 0.001$). Blood culture was done for 230 patients; among them, only 17 bacterial isolates were found (Table 3). No cases of hemolytic uremic syndrome were diagnosed.

Among the infants with AKI, repeat serum creatinine showed normalization of creatinine in 85 (58%) infants. The remaining infants were referred to other hospitals with pediatric nephrology services. It was not possible to determine outcomes in these referred patients, despite estimating the long-term consequences of prerenal AKI. This comparison was also made between infants with AKI on admission whose creatinine normalized and those with elevated creatinine throughout their stay in the hospital. The results showed that persistently elevated creatinine was associated with severe pneumonia (with radiological opacity) (OR = 2.16, 95% CI = 1.09–4.31;

Table 2. Independent predictors of developing acute kidney injury among infants with diarrhea.

Predictors	Unadjusted OR (95% CI)	Unadjusted p value	Adjusted OR (95% CI)	Adjusted p-value
ORS intake at home	3.4 (1.98–6.05)	<0.001	1.5 (0.64–3.57)	0.34
Convulsion	2.83 (1.44–5.56)	0.002	0.87 (0.36–2.11)	0.75
Abnormal mentation	2.78 (1.73–4.45)	<0.001	1.50 (0.81–2.80)	0.19
Hypoxemia	2.5 (1.2–5.04)	0.01	2.10 (0.83–5.30)	0.10
Sepsis	6.38 (3.16–12.90)	<0.001	4.71 (2.07–10.73)	0.001
Dehydration at admission	3.86 (2.19–6.80)	<0.001	3.76 (1.78–7.95)	0.001
Hyponatremia	0.58 (0.36–0.92)	0.02	0.75 (0.40–1.40)	0.37
Hypernatremia	8.96 (4.3–18.47)	<0.001	8.66 (3.88–19.22)	0.001

Adjustment variables: oral rehydration salt intake at home, convulsions, abnormal mentation, and hypoxemia.
ORS, oral rehydration salt; OR, odds ratio; CI, confidence interval.

Table 3. Bacterial isolates from infants with and without acute kidney injury (AKI).

Bacterial isolate (n)	With AKI	Without AKI
Staphylococcus aureus (3)	√ √ √	–
Staphylococcus haemolyticus (2)	√ √	–
Streptococcus pneumonia (2)	√	√
Salmonella paratyphi A (2)	√	√
Shigella flexneri (1)	–	√
Escherichia coli (1)	√	–
Acinetobacter (1)	–	√
Enterobacter species (1)	√	–
Pseudomonas species (2)	√√	–
Acinetobacter (1)	√	–
Cryptococcus (1)	–	√

√ indicates number of isolates present in blood culture samples; – indicates the absence of isolates.

p = 0.025) and continued fever (OR = 2.24, 95% CI = 1.14–4.40; p = 0.017) (Table 4).

Discussion

Our study focused on infants with AKI, which is a serious complication of dehydrating diarrhea. Dehydration in diarrheal illness is considered a major prerenal cause of AKI; however, reports are scarce from other diarrheal settings. In our hospital, the prevalence of AKI among infants with diarrhea was 16%, and 42% of them were referred to other facilities owing to persistently elevated creatinine. However, we could not track the outcomes of these patients using the database as this was a retrospective review.

Dehydration has been reported as an independent predictor of AKI in diarrheal infants. Our observation of an association of diarrheal diseases with dehydration is consistent with previous reports.[16]

Sepsis has been recognized as a major precipitating cause of AKI.[17] The pathophysiology may be explained by a unique constellation of hemodynamic, inflammatory, and immune mechanisms.[18] In logistic regression analysis, we found that sepsis was independently associated with AKI. It is important to note that patients with sepsis-associated AKI have much higher mortality than those with non-sepsis-associated AKI.[13] However, we were unable to provide supporting evidence based on our data as we observed few deaths in our series. This is likely owing to the fact that we referred critically ill patients to a specialized hospital before we could observe the final outcome. The role of diarrheal pathogens in developing AKI and the pathogenesis are not yet known, which calls for further prospective research to address this question.

Table 4. Comparison of independent predictors among infants with and without normalization of creatinine during hospitalization.

Characteristics	Persistently elevated creatinine n = 61 (%)	Normalized creatinine n = 85 (%)	Difference (elevated vs. normalized creatinine) OR (95% CI)	p-value
Repeated convulsions	24 (28)	9 (15)	2.27 (0.97–5.32)	0.054
Poor feeding practices	58 (68)	32 (52)	1.95 (0.99–3.84)	0.053
Sepsis	49 (58)	23 (38)	2.24 (1.14–4.40)	0.017
Radiologic pneumonia	60 (71)	32 (52)	2.17 (1.09–4.31)	0.025
Persistent hypernatremia	37 (43)	20 (33)	1.58 (0.79–3.13)	0.189
Persistent hyponatremia	21(25)	28 (46)	0.38 (0.19–0.78)	0.007

OR, odds ratio; CI, confidence interval.

Our study showed that children with AKI were eight times more likely to present with hypernatremia. Previous case reports from Bangladesh have confirmed this finding.[5,11,19] Several factors may contribute to hypernatremia, first, owing to hypernatremic dehydration and second, owing to the inability to excrete a sodium load owing to prerenal failure.[2,12] In hypernatremic dehydration, well-described fluid shifts occur from the intracellular to the extracellular space, to maintain intravascular volume.[16,20] The degree of dehydration in these children is often underestimated, contributing to late presentation and/or recognition.[19] Late recognition of dehydration may also lead to higher incidence of AKI.[11] The literature suggests that hypernatremia can present with irritability, hyperpyrexia, and convulsions, which may explain the clinical presentations of the children in our study.[14,19,21]

Among the infants with AKI on admission, a comparison was made based on repeated measurement pf creatinine levels during the hospital course. Continued fever was found to be significantly associated with persistently elevated creatinine, which might indicate the presence of infection in these infants. Although childhood pneumonia often causes elevation of serum creatinine owing to bacteremia or sepsis,[21,22] the association with persistently elevated creatinine was a new observation of our study, which warrants further prospective research. This observation is important in light of previous reports of the progression of approximately 10% of cases of childhood AKI to chronic kidney disease (CKD) within 13 years after hospital discharge and warrants long-term follow-up of these patients, to prevent CKD.[23]

The limitation of our study is the retrospective nature of data collection, which prevented us from obtaining additional information that could be useful in explaining the etiology of AKI. One important early feature of suspected AKI in young infants is diminished urination; however, with ongoing watery diarrhea, caregivers are often unable to detect this and thus fail to report this in a timely manner, which may delay the diagnosis. Moreover, data on rehydration fluids used before hospitalization could not be retrieved; the availability of these data might have affected our findings.

However, the strength of our study is that this is a report from a unique dataset of infants with diarrhea, in a setting where recognition by family members of a

diminished urine output in infants with ongoing diarrhea would have been fairly challenging. Clinical features of hypernatremia and sepsis and a history of poor feeding practices should lead to earlier screening of suspected infants for AKI, thereby saving many lives.

Conclusions

The findings of our study emphasize the importance of the early identification of simple clinical predictors of AKI and their prompt management, which may help to prevent AKI-related consequences in infants with diarrhea.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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