SPECIAL ARTICLE

RENAL DYSFUNCTION IN THE CRITICALLY ILL NEONATE--A TROPICAL PERSPECTIVE

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Rapid advances in technology and a better understanding of neonatal physiology have resulted in a vast improvement in the quality of care of critically ill neonates. While this has no doubt led to an improved survival rate in high risk neonates, two peculiar situations have arisen. Prolonged survival in high risk neonates has resulted in an increased incidence of multi-system complications, including altered renal function(1-13) which occurs in 11-23%(1,12) of these sick children. Secondly, neonates born with congenital organ insufficiency are now kept alive with artificial organ replacement therapy. In addition, the availability of ante-natal diagnostic facilities to detect several anomalies including those of the urinary tract has raised several medical and ethical issues for which no clear answers exist(14).

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Finally the etiology of renal failure in neonates in the tropics is distinctly different from that observed in the industrialized nations, as is the availability of diagnostic and therapeutic facilities(15). This review focuses on renal dysfunction in the critically ill neonate with emphasis on a tropical perspective. Although electrolyte disturbances frequently accompany renal disorders, and do come under the perview of neonatal nephrology, a detailed discussion is beyond the scope of this article and hence will not be covered.

Renal Physiology in the Neonate

Nephrogenesis in the human is complete at approximately 34 weeks of gestational age(16). The neonatal kidney is capable of maintaining water and electrolyte balance vital for growth. However neonates in general and premature neonates in particular are handicapped by the presence of significant limitations of renal function especially under conditions of stress(17,18). The GFR when indexed to body weight is lower than adults and reaches adult values by two years of age. In neonates born prior to 34 weeks of gestation the GFR is 0.1-0.5 ml/min, which reaches 5-10 ml/min in term infants. The serum creatinine at birth is identical to maternal values, and falls by 50% by the first post-natal week. This fall is delayed in pre-term neonates(16,17), and the delay is inversely proportional to the gestational age.

The traditional view that tubular maturation lags behind glomerular maturation is no longer accepted(18). Positive electrolyte balance is an important component of

growth and hence the importance of conservation by the neonatal kidney. While neonates born at 26-30 weeks are capable of reabsorbing 96% of the filtered sodium, their more mature counterparts can reabsorb 98-100%(18). Chloride handling is adequate in both term and pre-term neonates. The neonates can produce dilute urine comparable to adults (30-50 mOsm/L), the concentrating limit is 400-600 mOsm/L which is half of that observed in adults. This is primarily due to the low protein intake which leads to decreased urea concentration in the medulla(18). Although AVP secretion is adequate, high levels of PGE2 inhibit its action on the renal medulla(18). The renal vascular resistance and plasma renin activity are high in the neonate, and hence renal blood flow is lower than in older children(11). The younger nephrons in the superficial cortex are less perfused than their more mature, deeper counterparts(13). Finally it must be emphasized that only 93% of neonates pass urine within the first 24 hours of birth and 99.4% within the first 48 hours(19).

Therefore, renal adjustments in the neonate are finely balanced and a variety of pathological conditions that upset this fine balance are capable of precipitating acute renal failure.

Etiology

The etiology of acute renal failure in the tropical countries is significantly different from that observed in the West(1-12). Overpopulation, poor sanitation, poverty, ignorance and inadequate health delivery coupled with natural conditions that favour the spread of vectors and agents of disease are responsible for the unique pattern of ARF in the tropics (*Table I*). Septicemia contributes to ARF in 40-93% of cases in both developed and third world countries(1-12). Perinatal hypoxia and respiratory distress syndrome (RDS) which are the leading causes of ARF in the West(1-7) are of less importance in India(9-15). On the contrary gastroenteritis which is implicated in 60% of cases of ARF in Indian newborns(15), is uncommon in the developed countries(1-7).

TABLE I–*Etiology and Mortality in Neonatal Acute Renal Failure*

Author	Country	No.	No. Dialysed	Mortality %	Etiology				
					Sepsis and DIC	Diarrhea	Perinatal hypoxia	Congenital abnormality	Others
Griffin(7)	UK	10	10	30	4	2	-	4	-
Anand(4)	USA	14	1	36	13	-	13	-	-
Norman(1)	USA	20	?	45	9	6	16	2	3
Mathew(6)	USA	16	?	63	?	?	11	2	3
Chevalier(5)	USA	16	4	25	13	-	9	4	3
Steele(3)	Canada	12	12	75	-	-	6	4	2
Unni(9)	India	20	?	60	10	7	1	-	4
N' war(10)	India	12	-	68	5	-	2	5	-
Pereira(15)	India	20	20	75	18	12	1	-	1

TABLE II—*Etiology of Acute Renal Failure*

Pre-renal	Intrinsic renal	Post-renal
Dehydration	*All pre-renal causes*	*Urethral obstruction*
Diarrhea		Post. urethral valve
Fluid restriction	*Cong. Anomalies*	Imperforate prepuce
Gastric aspiration	Hypoplasia	Urethral stricture
Phototherapy	Agenesis	Urethral diverticulum
	Polycystic kidney	Megaurethra
Hypotension	Cystic dysplasia	
Septicemia		*Neurogenic Bladder*
Surgery	*Vascular*	
Anesthesia	Renal artery stenosis	*B/L Urethral Obstruction*
	Renal vein thrombosis	Uretrocele
Hypoxia	DIC	Megaureter
Birth asphyxia		Extrinsic obstruction
RDS	*Drugs*	Ureteropelvic obstruction
	Aminoglycosides	Pelviureteric obstruction
Hypoperfusion	Indomethacin	
CCF	Radiocontrast	
Mechanical ventilation		
	Pyelonephritis	
Hemorrhage		
Twin to twin		
Fetal-maternal		
Intra-abdominal		
Intracranial		
Third space losses		
Paralytic Ileus		

The etiology of ARF can be divided into pre-renal, intrinsic renal and post-renal causes (*Table II*). Pre-renal causes are usually completely reversible if prompt correction is instituted. The same factors can lead to intrinsic renal failure if prolonged and severe. Post-renal factors are congenital obstructive lesions at various levels in the urinary tract. It must be emphasized that, frequently the etiology is multifactorial(15) and it is difficult to implicate a single factor as the sole etiology of ARF.

Hypovolemia due to diarrheal diseases is responsible for 60% of all cases of neonatal ARF in India(15). Inadequate fluid replacement and poor hygeine are the main contributing factors. This impression is substantiated by the fact that, no case of ARF requiring dialysis was seen among 6000 babies born in a leading referral hospital in North India(15). Sepsis is frequently associated with gastrointestinal infection in neonates and is a leading cause of ARF world-wide(1-12).

Perinatal hypoxia due to birth asphyxia and RDS is by far the commonest cause of neonatal ARF in the West(1-7). Although

birth asphyxia and RDS are frequently encountered in the tropics the non-availability of advanced critical care precludes survival long enough to develop ARF. Congestive cardiac failure and mechanical ventilation are both associated with a fall in cardiac output and consequently renal hypoperfusion.

Third space losses such as in ileus also lead to decreased intravascular volume. Hypotension and renal hypoperfusion are also seen in sepsis, surgery, anesthesia and hemorrhage(17,18). The final common pathway in the pathophysiology of pre-renal insults is renal hypoperfusion, hypoxia and oliguria. Timely intervention pre-empts intrinsic ARF, while severe prolonged pre-renal insults result in ARF. Likewise the severity of the insult is the prime determinant of the renal lesion which encompass tubular, papilary and cortical necrosis(4).

Vascular lesions although uncommonly diagnosed during life are an important cause of ARF in neonates(18). Renal artery occlusion occurs due to embolization during catheterization of the umbilical artery. Systemic hypertension and hematuria are important clues to the diagnosis. Renal vein thrombosis also presents with hematuria and should be suspected in infants of diabetic mothers and those with sepsis or polycythemia. Fibrinoid necrosis due to DIC can cause tubular or cortical necrosis. Despite the widespread use of aminoglycosides in neonatal nurseries, nephrotoxicity is uncommon(15). Since immature superficial nephrons are poorly perfused toxic accumulation does not occur(13). Indomethacin used in the therapy of PDA causes ARF by inhibiting the synthesis of renal vasodilating prostaglandins.

Obstructive lesions are commonly associated with renal dysplasia and multi-system anomalies. Early diagnosis and surgical intervention have, however not been rewarding(18).

Diagnosis

The immediate challenge in a newborn with renal dysfunction is to differentiate pre-renal azotemia from intrinsic renal failure, and to rule out obstructive lesions. A history of oligohydramnios, birth asphyxia, fluid losses, voiding patterns, drug therapy and family history of renal disease should be elicited. A general physical examination should focus on the hydration status and look for congenital anomalies that are associated with renal dysfunction.

Systemic examination includes examination for abdominal masses, respiratory distress, congestive cardiac failure (CCF) and CNS dysfunction. Laboratory evaluation includes serum electrolytes, calcium, phosphate, proteins, BUN, creatinine, osmolality and glucose, arterial blood gases, coagulation profile and appropriate bacteriological cultures. Urinalysis should include sodium and osmolality. In addition chest *X*-ray and ECG are mandatory. The next step is to rule out an obstructive pathology. An abdominal ultrasound, micturating vesicourethrogram and renal scan will establish and localize the lesion. An IVP is best avoided in view of the radiocontrast nephrotoxicity and the fact that it is unlikely to give any further information(18). Similarly in patients with suspected vascular lesions arteriography or venography are not recommended since they are invasive and immediate confirmation of the diagnosis is not likely to alter the management(4). The same can be said of the renal biopsy. These latter two procedures should be reserved for a later date, in patients who make an incomplete or slow recovery.

Renal indices in the newborn have not been accurate in separating pre-renal from intrinsic renal failure(6). The neonatal kidney is a subtle "salt waster", and therefore there is a wide splay in urinary indices, with a great degree of overlap between values in normal, pre-renal and intrinsic renal failure. The distinction is further blurred in premature infants. With these limitations the only two indices found to be reliable in the diagnosis of established ARF are FENa (UNa/PNa × PCr/UCr × 100) greater than 2.5 and renal failure index (UNa × PCr/UCr) greater than 3. These indices are, however, valid only if evaluated prior to fluid or diuretic therapy. Unfortunately most patients referred to tertiary care centers would have already received fluid and/or diuretic therapy prior to referral.

Finally a fluid and diuretic challenge with 20 ml/kg of normal saline over 60-90 min followed by 1 mg/kg of furosemide, will improve the urine output in pre-renal azotemia. Alternatively 0.5-1.0 g/kg of mannitol as a 20% solution can be run over 30 minutes. The latter is preferred in low birth weight neonates and patients with CCF who are intolerant to large fluid volumes. If urine output does not improve after these measures a diagnosis of intrinsic ARF is established and appropriately managed.

Management

The diagnosis of intrinsic ARF is established in neonates who continue to be oliguric despite correction of pre-renal factors and exclusion of obstructive lesions. In these patients and those awaiting surgical correction of their urinary tract anomalies, the principals of management are directed towards sustaining fluid and electrolyte balance maintaining growth and preventing complications during the interim period.

Fluid Balance: Fluid overload is commonly encountered in neonates with ARF due to the absence of renal excretion and due to the overzealous attempts to correct presumed pre-renal factors. The consequences include edema, CCF, hypertension, hyponatremia, encephalopathy and seizures(20). Therefore, fluid management should be guided by 1-3 hourly estimates of fluid losses and 12 hourly body weight measurement(18,20). Insensible losses should be replaced with 10% dextrose(18), while renal and non-renal losses should be replaced with fluids containing sodium concentration similar to that of the fluid lost(20). Hyponatremia is usually dilutional and requires fluid restriction and not sodium replacement(20). However, symptomatic hyponatremia and levels less than 120 mEq/L should be corrected with 3% NaCl infusion(20). The target in neonates with ARF should be a daily weight loss of 0.5-1.0% of body weight(18).

Hyperkalemia: Neonates in general tolerate hyperkalemia better than adults. Although we observed hyperkalemia in 60% of neonates with ARF(15), EKG changes were present in only one. Therefore, serum potassium levels of 6-7 mEq/L can be managed with oral or rectal cation exchange resins (sodium polysterene sulphonate-Kayexalate) which exchange 1 mEq of potassium for every 2-3 mEq of sodium. This is administered in doses of 1 mg/kg every 3-6 hours. In neonates with ECG changes of hyperkalemia or potassium levels greater than 7 mEq/L more aggressive management is indicated (*Table III*).

Hypocalcemia and Hyperphosphatemia: Elevated serum phosphorus levels are

TABLE III – *Management of Hyperkalemia in Neonatal ARF*

Potassium Level (mEq/L)	ECG Changes	Management
6-7	Absent	Cation exchange resin 1 g/kg/24 h in 3 to 4 divided doses orally or retention enema 3-6 hourly
> 7	Present or absent	10% calcium gluconate 1 ml/kg IV slowly over 5-10 minutes (In presence of cordiotoxicity) 7.5% $NaHCO_3$ 1 ml/kg IV over 10-15 minutes
		Insulin-glucose infusion Glucose 0.8 g/kg/hour Insulin 1 unit/4g of glucose
		Dialysis

managed with low phosphorus formulas and oral aluminium hydroxide (Aludrox Wyeth), 50-150 mg/kg/day in three divided doses. Although lowering of serum phosphorus itself may normalize serum calcium levels, supplemental calcium (10-20 mg/kg/day) or vitamin D may be required in refractory cases or patients with symptomatic hypocalcemia.

Acidosis: Severe uncompensated metabolic acidosis was a consistent feature in our experience with neonates with ARF(15). While mild acidosis may not require therapy, moderate to severe cases require correction with $NaHCO_3$, 1-3 mEq/kg. Refractory acidosis and, fluid overload that precludes $NaHCO_3$ therapy are indications for dialysis.

Hypertension: Hypertension is usually mild and is due to fluid overload. Fluid restriction usually ameliorates this problem. However, severe hypertension warrants treatment with diazoxide (2-3 mg/kg over 30 minutes), sodium nitroprusside (0.5 μg/kg minute) or hydrallazine (0.15-0.5 mg 6 hourly). Persistent hypertension requires treatment with oral hydrallazine, propranolol or alpha methyl dopa and investigation for conditions like renal artery stenosis.

Dialysis: While the indications for dialysis vary from center to center, we have used the following: anuria more than 48 hours, serum creatinine greater than 3 mg/dl, hyperkalemia (serum K^+ >6.5 mEq/L or ECG changes), severe uncompensated metabolic acidosis (pH <7.20), fluid overload, and metabolic encephalopathy(15). Peritoneal dialysis has been the mainstay of renal replacement therapy in neonates. While western authors recommend continuous dialysis with 20 ml/kg exchanges until recovery(3), we feel that this is associ-

TABLE IV – *Prognostic Variables in Neonatal ARF*

Variable	Died (n=15)	Survived (n=5)
Weight (kg)	2.0 ± 0.6	1.8 ± 0.7
Non-oliguric ARF	3 (20%)	1 (20%)
Septicemia	13 (87%)	5 (100%)
Hemoglobin (g/dl)	15.4 ± 3.5	15.6 ± 3.9
Neutrophil count (10^9 /L)	10.3 ± 5.9	13.2 ± 4.7
Serum potassium (mEq/L)	5.7 ± 1.6	6.0 ± 1.2
Blood urea (mg/dl)	149 ± 60	155 ± 47
Serum creatinine (mg/dl)	5.1 ± 1.9	5.4 ± 0.7
Serum bicarbonate (mEq/L)	4.7 ± 2.8	7.7 ± 4.7
Arterial blood pH	7.05 ± 0.09	7.13 ± 0.05

None of the differences were significant p>0.05.

ated with a high risk of infection in Indian conditions. Therefore, we recommend intermittent dialysis of 20-30 cycles of 20-50 ml/kg with a dwell time of 20-30 minutes. This may be repeated every 48-72 hours until recovery. This is well tolerated and relatively free from complications, although hypothermia, transient hemorrhage and peritonitis are potential complications(15). The advent of slow continuous ultrafiltration (SCUF), continuous arteriovenous hemofiltration (CAVH) and continous arteriovenous hemodialysis (CAVHD) have promised to revolutionize the management of neonatal ARF and facilitate liberal fluid and nutritional therapy(21). The high cost, requirement of trained personnel, continuous monitoring, accurate replacement fluids and arteriovenous access devices preclude their use in the developing countries at least in the near future.

Prognosis

Oliguria usually lasts for a week and diuresis heralds the onset of recovery. Several prognostic variables have been used to predict survival in neonates with ARF. We have, however, been unable to define any reliable prognostic indicator in high risk neonates with ARF(15) (*Table IV*).

Hence despite spectacular advances in critical care, the mortality in neonates with ARF continues to range from 25-78%.

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