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Acute Renal Failure in Neonates

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ABSTRACT

Acute renal failure (ARF) is a common condition seen in neonatal intensive care units. It is broadly classified into prerenal, intrinsic renal and post renal failure. There is no consensus on the definition of neonatal ARF. Of utmost importance is to differentiate prerenal from intrinsic renal failure. The most common causes of neonatal ARF are hypovolemia, hypotension and, hypoxia. Among several indices that are available for differentiating prerenal failure from intrinsic renal failure, fractional excretion of sodium is the preferred index. Diagnostic fluid challenge with or without frusemide is a bed side method for differentiating prerenal failure from intrinsic renal failure. Babies with ARF have to be monitored for several metabolic derangements like hyponatremia, hyperkalemia, hypocalcemia, and acidosis and have to be managed accordingly. Fluid balance should be precise in order to avoid fluid overload. It is difficult to provide adequate calories due to fluid restriction. Dialysis has to be instituted to preempt complications. Peritoneal dialysis is the easiest and safest modality. These babies need long term follow up as they are prone for long term complications. **[Indian J Pediatr 2008; 75 (4) : 385-391]** *E-mail : arvindbagga@hotmail.com*

Key words : *Acute renal failure; Neonate, Hyperkalemia; Dialysis*

Acute renal failure (ARF) is a frequent clinical condition in neonatal intensive care unit. There is wide variation in the incidence of ARF across studies. It affects approximately 1-24% of newborns in the NICU.[1,2] ARF is an acute reduction in glomerular filtration rate (GFR) with both failure to remove solutes and water leading to concurrent net solute and water retention – oligoanuric renal failure.[2]

Classification of ARF

Based on the urine output, it can be of two types:

(i) Oligoanuric *(ii)* Non oliguric

Based on the site of origin of insult it can be of 3 types: [3]

(i) Prerenal (75- 80%) *(ii)* Intrinsic renal (10-15%) *(iii)* Post renal (5%).

Persistence of insult can convert pre renal or post renal failure to intrinsic renal failure.

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DIAGNOSIS OF ARF

Plasma creatinine

ARF is suspected if

- Plasma creatinine is more than 1.5 mg/dL for at least 24 to 48 hrs, if mother's renal function is normal.[2]
- Serum creatinine is increasing by 0.3 mg/dL/day
- Serum creatinine fails to fall below maternal plasma creatinine within 5-7 days

The above definitions can be used with a reasonable degree of accuracy in term neonates. In preterm neonates, the physiological decline in plasma creatinine can extend over 2-3 weeks. In fact the plasma creatinine can rise transiently and then decline. The plasma creatinine remains elevated due to reabsorption of creatinine across permeable tubules.

Urine output

Oliguria: It has been defined as urine output less than 1 mL/kg/h after first day of life for both term and preterm neonates. One should also be aware of the fact that some term neonates may void for the first time at around 24 h of life.

ARF can also present with normal renal output in one third of the cases. This can happen especially in

asphyxiated neonates. Hence it is essential to monitor plasma creatinine apart from urine output. The common clinical scenario that leads to suspicion of renal failure is oliguria. In face of such an event it becomes extremely important to differentiate prerenal and intrinsic renal failure as in the former the damage to the kidneys is yet to begin where as in the later it already has.

Concept of acute kidney injury (AKI)[4]

Several definitions have been proposed for defining ARF and there is no consensus. An attempt has been made to define parameters and to bring uniformity across age groups and various clinical situations. The product of such an attempt is the concept of acute kidney injury.

An abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/Kg/h for more than six hours).

Pre renal *vs* intrinsic renal failure

Several methods have been developed to differentiate them; the sheer number reflects the importance. When a baby has not passed urine in the past 12 hrs, the first and the foremost thing is to look for distended bladder. Palpation of the abdomen, ultrasound of the abdomen (if available at bed side) can be employed to look for distended bladder. It is better to avoid catheterization of the bladder in order to prevent infection but it may be necessary in sick babies. In such situations it has to be done under strict asepsis. Compression of the bladder (suprapubic pressure) should be avoided especially in preterm infants for the fear of VUR and rarely bladder and renal rupture.[1]

After confirming the absence of urine in the bladder, fluid challenge should be given (Fig. 1). The common causes of prerenal azotemia are hypovolemia, systemic hypotension and hypoxia (in more than 80% of cases).[2] It is essential to look for signs of fluid excess and fluid deficit. In the absence of obvious sign of fluid overload or congestive cardiac failure, a normal saline bolus of 10 mL/kg should be given over 20 min (some experts advise 20 mL/kg over 2 h). If baby fails to pass urine with in one hour the fluid bolus should be repeated. In spite of two fluid bolus if urine output fails to ensue, frusemide should be given in a single dose of 1 mg/kg (in a non dehydrated patient). Urine output ensues in 2-3 hrs in prerenal failure. If this fails it is intrinsic renal failure.

Role of indices

Differentiation of pre renal and intrinsic renal can be done basing on urinary indices. Several indices have been proposed to differentiate them. Most important among them would be urine sodium, renal failure index (RFI) and fractional excretion of sodium (FENa) (Table 1). The important prerequisite is that the urine sample for measuring indices must be obtained prior to fluid and diuretic challenge. This is difficult to obtain in many babies as the babies are oliguric and results are not available immediately and hence practically they are of limited utility. Among the various indices available FENa is the preferred index. FENa more than 2.5 to 3.0% is found to be associated with intrinsic ARF. Preterm babies lose sodium in the urine due to the tubular immaturity, hence higher cutoffs must be used. An FENa of more than 6% can be used to define intrinsic ARF in babies born between 29- 32 weeks of gestation.[5] Urine sodium more than 50 mEq/L is suggestive of intrinsic ARF whereas urine sodium less than 20 mEq/L is seen in pre renal failure.

Table 1. Parameters to Differentiate Prerenal from Intrinsic Renal Failure[1]

Parameters	Prerenal	Intrinsic renal
UNa	≤ 20 mEq/L	>50
Renal failure index*	Low < 1	High > 4
Fractional excretion of Na$	≤ 1	> 3

$$*\text{Renal failure index} = \frac{\text{urine Na} \times \text{plasma creatinine}}{\text{urine creatinine}} \times 100$$

$$\$\text{Fractional excretion of sodium} = \frac{\text{urine Na} \times \text{plasma creatinine}}{\text{plasma sodium} \times \text{urine creatinine}} \times 100$$

The renal failure index (RFI) can also be used. RFI more than 4 in term and more than 8 in preterm babies less than 32 weeks is suggestive of intrinsic ARF.

Urianalysis: The presence of granular casts, hyaline casts, RBC, proteins and tubular cells suggests an intrinsic cause.

Ultrasonography and Doppler: Useful in ruling out congenital anomalies like polycystic kidneys, dysplasia of kidneys and obstructive causes of renal failure like posterior urethral valves. Renal doppler studies are helpful in diagnosing vascular thrombosis.

Voiding cystourethrography : Can identify lesions of the lower urinary tract that cause obstruction, such as posterior urethral valves.

Etiology of renal failure

Having differentiated prerenal from intrinsic renal failure, evaluate for the exact etiology of renal failure. There are several causes of ARF (Table 2)

Table 2. Etiology of Neonatal Renal Failure

I. Congenital malformations
- Renal agenesis
- Renal hypoplasia/dysplasia
- Cystic diseases of kidney *e.g.*, autosomal recessive polycystic kidney

II. Acquired renal disorders
- Acute tubular necrosis
  - Perinatal asphyxia
  - Perinatal hypoxia due to respiratory distress syndrome, traumatic delivery
  - Sepsis
  - Hypovolemia due to dehydration, severe patent ductus arteriousus
- Vascular
  - Arterial thrombosis or embolism or stenosis
  - Venous thrombosis
- Drugs: maternal use of ACE inhibitors, indomethacin
  Baby: indomethacin, tolazoline, aminoglycosides

III. Urinary tract obstruction
Posterior urethral valves
Pelviureteric obstruction, ureterovesical obstruction

ACE: angiotensin converting enzyme.

Babies with ARF must be investigated not only for evaluating the cause and but also for complications. Blood levels of creatinine urea, electrolytes, pH bicarbonate and urinary levels of sodium and creatinine must be done. Microscopic examination of urine must be done for RBC, granular or hyaline casts. Urine culture must be done especially in cases of obstructive lesions where babies are prone for urinary tract infection. Ultrasound imaging of the kidneys is useful in evaluating congenital lesions and obstructions. Doppler can define the vascular supply of the kidney.

MANAGEMENT OF RENAL FAILURE

Fluid management

Fluids must be restricted to insensible water loss (IWL) along with urinary loss. The urinary loss must be replaced volume for volume. The insensible water loss in a term neonate is 25 mL/kg/day. In preterm neonates this can vary widely depending on gestation, postnatal age, use of radiant warmers, phototherapy. It can vary from 40-100 mL/kg/day. IWL can be assumed to be 40 mL/kg/day in preterm infants for calculating fluids in neonates (adequate care must be taken to reduce IWL by using caps, socks, cling wrap, oil especially for preterm babies under radiant warmer).[6] It is advisable to revise fluid requirement every eight hourly basing on urine output. The fluid should be electrolyte free, 10% dextrose water.

Hyponatremia

Babies can have hyponatremia in oliguric renal failure.

- Hyponatremia is due to dilution secondary to water retention, hence has to be corrected with fluid restriction. In most of the cases, there is no sodium deficit.
- If serum sodium is between 120-135 mEq/L,

Table 3. Management of Hyperkalemia

Medication	Level of K^+ at which it is instituted	Dose	Mechanism	Onset of action
Calcium gluconate	ECG changes suggestive of hyperkalemia	0.5 to 1 mL/kg over 5-10 min	Modifies myocardial excitability	5-10 min
Sodium bicarbonate	K^+ - 6.0-6.5 mEq/L	1 mEq/kg over 10-30 min	Intracellular uptake of K^+	30 min
Glucose and insulin	K^+ - 6.5-7.5 mEq/L	0.5 g/kg/h of glucose and 0.2 U of regular insulin per g of glucose over 2 h	Intracellular uptake of K^+	30 min.
Salbutamol IV infusion*	K^+ - 6.5-7.5 mEq/L	4 µg/kg over 20 min	Intracellular uptake of K^+	Min
Cation exchange resin (Na/Ca polystyrene sulfonate)**	K^+ more than 6.0 mEq/L	1 g/kg intrarectally q 6 h	Exchange of K for Na or Ca^{2+}.	1-2 h
Exchange transfusion	K^+ more than 7.5 mEq/L	Washed RBC reconstituted with 5% albumin	Uptake of K^+ by RBC.	Minutes
Peritoneal dialysis	K^+ more than 7.5 mEq/L	Use a dialysate with low K^+ concentration	Dialysis	Minutes

*Administration of salbutamol can cause a transient increase in serum K concentration, so it should not be used as the first line medication. Salbutamol aerosol is not very effective in neonates.
**Oral administration of polystyrene resin should be avoided in VLBW infants and those with poor peristalsis (gastric bezoars after oral administration and cecal perforation after enema, other complications like hypernatremia, fluid retention can occur)

restriction of fluids will suffice. serum sodium must be monitored at least 12 hourly.

- If hyponatremia is associated with symptoms like seizures, or if hyponatremia is less than 120 mEq/L it requires prompt correction with 3% hypertonic saline at a dose of 5 mL/kg over 4-5 h.
- Hyponatremia unresponsive to above therapy is an indication for dialysis.
- Babies with non-oliguric ARF may have very large urinary sodium losses of up to 10 mEq/kg/day, and these must be replaced.

Hyperkalemia

Hyperkalemia (K^+ more than 6.0 mEq/L) is one of the most dangerous complications that develops in babies with ARF. Extremely low birth weight (ELBW) babies are at higher risk of hyperkalemia. The reasons are multifactorial. Reduction in glomerular filtration rate, urinary potassium secretion, acidosis, immature tubular response to aldosterone all contribute to the development of hyperkalemia.

The first step in the management of hyperkalemia is to stop administration of potassium in the fluids; various medications are available to reverse dangerous hyperkalemia. ECG will help in diagnosing cardiac effects of hyperkalemia (Table 3). If ECG changes are evident calcium gluconate 10% is given. This will decrease the myocardial excitability but will not lower the potassium levels. This should immediately be followed by methods to decrease the potassium levels. Hyperkalemia which is unresponsive to medications is one of the most common indications for instituting dialysis.

Hypocalcemia

Hypocalcemia can develop in babies with ARF. It may result from hyperphosphatemia and skeletal resistance to parathyroid hormone. Symptomatic hypocalcemia should be corrected by infusing 10% calcium gluconate at a dose of 0.5-1 mL/kg over 5-10 min under cardiac monitoring.

Role of dopamine

Renal blood flow increases with low dose of dopamine; action is *via* DA_1 and DA_2 receptors. There is a definite role of dopamine in babies who are hypotensive, who are in congestive cardiac failure, as these babies will need inotropic and vasoactive support. Preterm infants are hypersensitive to alpha receptors and hence even low doses of dopamine can cause vasoconstriction and raise renal vascular resistance.[7] This may explain the difficulty in dosing of dopamine for improving renal function. Dopamine when combined with frusemide has been shown to cause natiruresis and diuresis in preterm infants RDS and oliguria.[8] Cochrane review concluded that dopamine has no role in the management of ARF due to indomethacin.[9] At present low dose dopamine does not seem to have any role in the prevention or treatment of ARF except as on intrope in patients with hypotension or congestive cardiac failure.

Role of theophylline

Adenosine antagonists are able to reverse the intra-renal vasoconstrictor state of ARF. Low dose theophylline (0.5-1mg/kg) has been shown to prevent hypoxia induced renal insufficiency in newborn rabbits.[10] The mechanism is adenosine antagonism and not by cyclic AMP phosphodiesterase antagonism. In vasomotor nephropathy of very preterm infants with respiratory distress syndrome, early theophylline administration improves renal function during the first two days of life.[11] Prophylactic theophylline, given early after birth, has beneficial effects on reducing the renal dysfunction in asphyxiated full-term infants.[12] Thus theophylline may have role in the management of renal dysfunction but data are limited, further studies are needed. Presently it has no role in the management of ARF.

Nutrition

The goal is to provide 100 kcal/kg/day. Proteins or amino acids are provided in a dose of 1-2 g/kg/day.[13] Total parenteral nutrition can be provided if enteral nutrition cannot be established. If enteral feeding is possible, breast milk should be used. Caloric density can be increased by adding corn oil, medium chain triglycerides or maltodextrins. If breast milk cannot be given low phosphate formula milk with low renal solute load can be given.

Acidosis

Mild metabolic acidosis is common in babies with ARF. If pH is less than 7.2 sodium bicarbonate can be used for correction of acidosis. It is given in a dose of 1-2 mEq/kg over 3-4 hrs. But this should be done carefully as it can cause fluid overload, hypernatremia, intracranial hemorrhage and intracellular acidosis. Babies with persistent acidosis require dialysis.

Hypertension

Fluid overload in neonatal ARF can result in mild hypertension, which can be controlled with fluid restriction and antihypertensive agents. The development of severe hypertension in the setting of neonatal ARF should raise the suspicion for renal artery or venous thrombosis.

Drug dosage modification

Dosage of the drugs has to be modified in babies with ARF as the major pathway of excretion of several drugs is kidneys. In ARF such drugs can accumulate and can cause toxicity. For modifying drug dosage, the creatinine clearance has to be calculated.

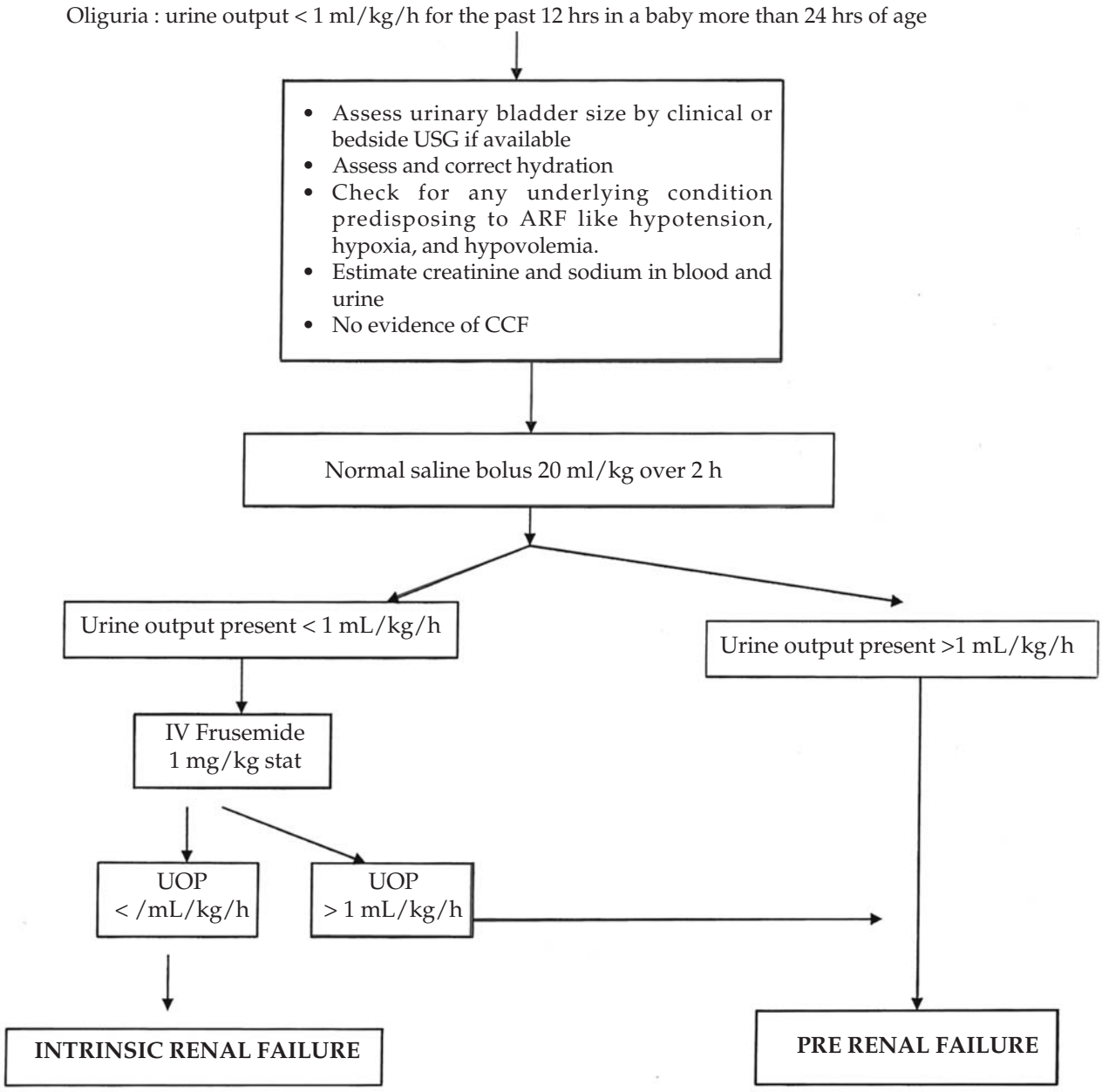

Fig. 1. Evaluation of Baby with Oliguria. UOP : Urine output CCF : congestive cardiac failure

$$\text{Creatinine clearance} = \frac{k \times \text{length in cm}}{\text{Serum creatinine}}$$

where k in

Term babies is 0.44

Preterm babies is 0.33

Basing on creatinine clearance the dosage of the drugs have to be modified.

Renal replacement therapy

Before instituting dialysis, it is always better to consider the prognosis of the condition. The common indications for renal replacement therapy are fluid overload, hyperkalemia, hyponatremia and severe metabolic acidosis which are unresponsive to medical management. Dialysis has to be instituted to preempt complications in renal failure. A newborn who is anuric and is having metabolic complications will ultimately require dialysis (*e.g.,* hyperkalemia in anuric baby is unlikely to respond to medical management alone and require dialysis).

Dialysis and filtration techniques are the available modalities. Dialysis is a process of removal of plasma solutes by diffusion down their concentration gradients across a semi permeable membrane. The membrane may

be a synthetic one (hemodialysis) or peritoneum separating the splanchnic blood from fluid instilled into the peritoneal space (peritoneal dialysis).[14] Filtration involves removal of protein free plasma water across a membrane by convection. The filtered water contains other plasma solutes at a concentration similar to plasma and can be thought of as glomerular filtrate equivalent. Hemodiafiltration involves both dialysis and filtration.

PD has major advantages as the access is relatively easy and is technically simple. Peritoneal dialysis has to be done only under strict aseptic conditions.

Peritoneal dialysis catheters: [15] PD catheters are made up of soft silastic, which is smooth silicone polymer of methyl-silicate, either in curled or straight configurations. Most of the catheters have side holes that allow for easy ingress and egress of fluid regardless of the catheter position in the peritoneum. Permanent catheters have cuffs. Pig-tail catheters and straight catheters without cuffs have been used in neonates who are anticipated to need PD access for a brief period of time. Straight Tenckhoff and coiled Tenckhoff catheters are available. Coiled Tenckhoff catheters are useful for chronic dialysis.

Procedure

The catheter is inserted into the peritoneal cavity and connected to a three way cannula. The common sites of insertion are in the midline below the umbilicus, right or left lower quadrant of the abdomen. Urinary bladder must be emptied before insertion of the catheter. The dialysate fluid is connected to a pediatric burette set and its terminal end is connected to one of the ports of three way cannula. The remaining port of the three way is connected to a intravenous (IV) set, the end of which is let into a sterile container (empty IV fluid bottle). The abdomen is distended with 20 mL/kg of peritoneal dialysis fluid. 20-30 mL/kg of dialysis fluid is infused over 10 min. A dwell time of 20-30 min is used before draining the fluid over 10 min. The dwell time can be reduced in case of respiratory compromise. A total of 20-40 cycles can be used or it can be continued till the desired effect is obtained. Blood sugar, serum electrolytes have to be monitored every 6 hourly and serum creatinine every 24 hourly.

The common dialysate fluid contains 1.7% dextrose with lactate. If higher gradient is required as in case of fluid overload 3% solution can be used. This can be prepared by adding 25 mL of 50% dextrose to one liter of 1.7% PD fluid. In case of liver failure lactate free bicarbonate containing fluid has to be used. If baby becomes hypokalemic during the procedure, add 1.5 mL of KCl to one liter of dialysate fluid. At the end of the procedure the catheter can be removed and the tip and the fluid are sent for culture.

PD is invasive procedure and complications can occur. Hyperglycemia can occur due to absorption of dextrose from PD fluid especially in cases where higher concentrations of dextrose are used. Bleeding, perforation of abdominal viscera, peritonitis, adhesion of catheter tip to omentum (Be careful while removing catheter or else will be delighted to see omentum!) PD cannot be done in babies with necrotizing enterocolitis, babies who underwent abdominal surgery and in those with severe respiratory compromise as it may worsen with abdominal distension.

Hemofiltration and hemodiafiltration are effective in neonates with ARF in whom PD is contraindicated. The complication rates are less. Hemofiltration is particularly useful in the presence of fluid overload. Hemodiafiltration is more useful in the presence of fluid overload and azotemia with electrolyte disturbances. [2]

Outcome

Non oliguric renal failure has a better prognosis when compared to oliguric renal failure. Mortality ranges from 25 to 78% in oligoanuric renal failure.[16] Long term abnormalities in GFR and tubular function are common in babies who survive ARF and is secondary to hyper-filtration in the surviving nephrons. The long term consequence of such an acute insult is not known.

Follow up

All babies who develop ARF need follow up. Adequacy of growth and nutrition, blood pressure, and renal function status has to be monitored. Newborns who have ARF are predisposed to the development of chronic renal failure in the future. Long-term follow-up of extremely low birth weight infants who had neonatal ARF has shown that prominent risk factors for progression of renal disease at 1 year of age included a spot urinary protein/creatinine ratio of greater than 0.6 and serum creatinine greater than 0.6 mg/dL.[17]

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