

**ACUTE RENAL FAILURE IN NEONATES**

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## **Introduction**

Acute renal failure 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.<sup>1,2</sup> Acute renal failure 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.<sup>2</sup>

## **Classification of ARF**

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

1. Oligoanuric
2. Non oliguric

Based on the site of origin of insult it can be of 3 types: <sup>3</sup>

1. Pre renal (75- 80%)
2. Intrinsic renal (10-15%)
3. Post renal (5%).

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

## **Diagnosis of ARF**

### **Plasma creatinine**

ARF is traditionally suspected if

1. Plasma creatinine is more than 1.5 mg/dL for at least 24 to 48 hrs if mother's renal function is normal. <sup>2</sup>
2. Serum creatinine is raising more than 0.3 mg/dL/day
3. 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/hr after first day of life for both term and preterm neonates. One should also be aware of the fact that some term neonates may first void for the first time at around 24 hrs 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 very 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 whereas in the later it already has.

#### **Concept of acute kidney injury (AKI)<sup>4</sup>**

Several definitions have been proposed for defining acute renal failure and there is no consensus. An attempt has been made to define parameters and to bring uniformity across age the groups and various clinical situations. The product of such an attempt is the concept of acute kidney injury. This attempt needs validation before it can be put to clinical practice.

#### **The definition**

An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL ( $\geq 26.4 \mu\text{mol/L}$ ), 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 per hour 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 (supra pubic pressure) should also be avoided especially in preterm infants for the fear of VUR and rarely bladder and renal rupture.<sup>1</sup>

After confirming the absence of urine in the bladder, fluid challenge can be given. The common causes of pre renal azotemia are hypovolemia, systemic hypotension and hypoxia (in more than 80% of cases).<sup>2</sup> 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 can be given over 20 min (some authors advise 20 mL/kg over 2 hrs). If baby fails to pass urine within one hour the fluid bolus can be repeated. In spite of two fluid bolus if urine output fails to ensue, furosemide can be given in a single dose of 1 mg/kg (in a non dehydrated patient). Urine ensues in 2-3 hrs in pre renal 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). The important prerequisite is 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. Babies born at lower gestational age lose sodium in the urine due to the tubular immaturity, hence higher cutoffs must be used. A FENa of more than 6% can be used to define intrinsic ARF in babies born between 29- 32 weeks of gestation.<sup>5</sup> 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.

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

**Table 1: parameters to differentiate pre renal from intrinsic renal failure<sup>1</sup>**

Parameters	Pre renal	Intrinsic renal
U Na	≤ 20 meq/L	>50
Renal failure index*	Low < 1	High > 4
Fractional excretion of Na <sup>§</sup>	≤ 1	> 3

\* renal failure index: 
$$\frac{\text{urine Na} \times \text{plasma creatinine} \times 100}{\text{Urine creatinine}}$$

§ fractional excretion of sodium: 
$$\frac{\text{urine Na} \times \text{plasma creatinine} \times 100}{\text{plasma sodium} \times \text{urine creatinine}}$$

**Urine microscopic analysis:** 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 cysto-urethrography** 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, look for the exact etiology of renal failure. There are several causes of ARF (table 2)

Babies with ARF must be investigated not only to look for the cause and but also to look at the complications. Apart from serum creatinine and blood urea, serum electrolytes, arterial blood gas analysis, urine sodium, urine creatinine must be done. Microscopic examination of urine must be done to look 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 delineate the vascular supply of the kidney.

**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 arteriosus
- 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.

**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 etc. 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 babies under radiant warmer).<sup>6</sup> It is advisable to revise fluid

requirement every eight hourly basing on urine output. The fluid should be electrolyte free 10% dextrose water

### **Electrolyte disturbances**

#### **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, restriction of fluids will suffice. serum sodium must be monitored at least 12 hrly.
- 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 in a dose of 5 mL/kg over 4-5 hrs.
- 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 mmol/kg/day, and these must be replaced.

#### **Hyperkalemia**

Hyperkalemia ( $K^+$  more than 6.0 mEq/L): It is one of the most dangerous complications that develops in babies with ARF. ELBW babies are at higher risk of hyperkalemia. The reasons can be 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 all potassium in the fluids; several drugs are available to reverse dangerous hyperkalemia. ECG will help in diagnosing cardiac effects of hyperkalemia. 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.

**Table 3: management of hyperkalemia**

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

<sup>#</sup> 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)

### 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<sub>1</sub> and DA<sub>2</sub> 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.<sup>7</sup> This may explain the difficulty in dosing of dopamine for improving renal function. Dopamine when combined with frusemide has been shown to cause natriuresis and diuresis in preterm infants RDS and oliguria.<sup>8</sup> It may have a role in the management of indomethacin induced ARF in preterm neonates. Cochrane review concluded basing on meta-analysis of three studies that dopamine has no role in the management of acute renal failure due to indomethacin.<sup>9</sup> Over all low dose dopamine does not seem to have any role in the prevention or treatment of ARF except in the presence of 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.<sup>10</sup> 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.<sup>11</sup> Prophylactic theophylline, given early after birth, has beneficial effects on reducing the renal dysfunction in asphyxiated full-term infants.<sup>12</sup> Thus theophylline may have role in the management of renal dysfunction but data are limited, further studies are needed. Presently it has does not have any role in the management of ARF.

### **Nutrition**

The goal is to provide 100 kcal/kg/day. Proteins or amino acids can be provided in a dose of 1-2 g/kg/day<sup>13</sup>. Total parenteral nutrition can be provided if baby enteral nutrition cannot be established. If enteral feeding is possible, breast milk can 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 load can be given.

### **Acidosis**

Mild metabolic acidosis is common in babies with ARF. If  $P^H$  is  $< 7.2$  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, hyponatremia, 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.

### **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 will require dialysis ultimately).

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).<sup>14</sup> 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:*<sup>15</sup> 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 one 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 (one has to be careful while removing catheter or else you 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.

Haemofiltration and hemodiafiltration are effective in neonates with ARF in whom PD is contraindicated. The complication rates are less. Haemofiltration is particularly useful in the presence of fluid overload. Hemodiafiltration is more useful in the presence of fluid overload and azotemia with electrolyte disturbances.<sup>2</sup>

### **Outcome**

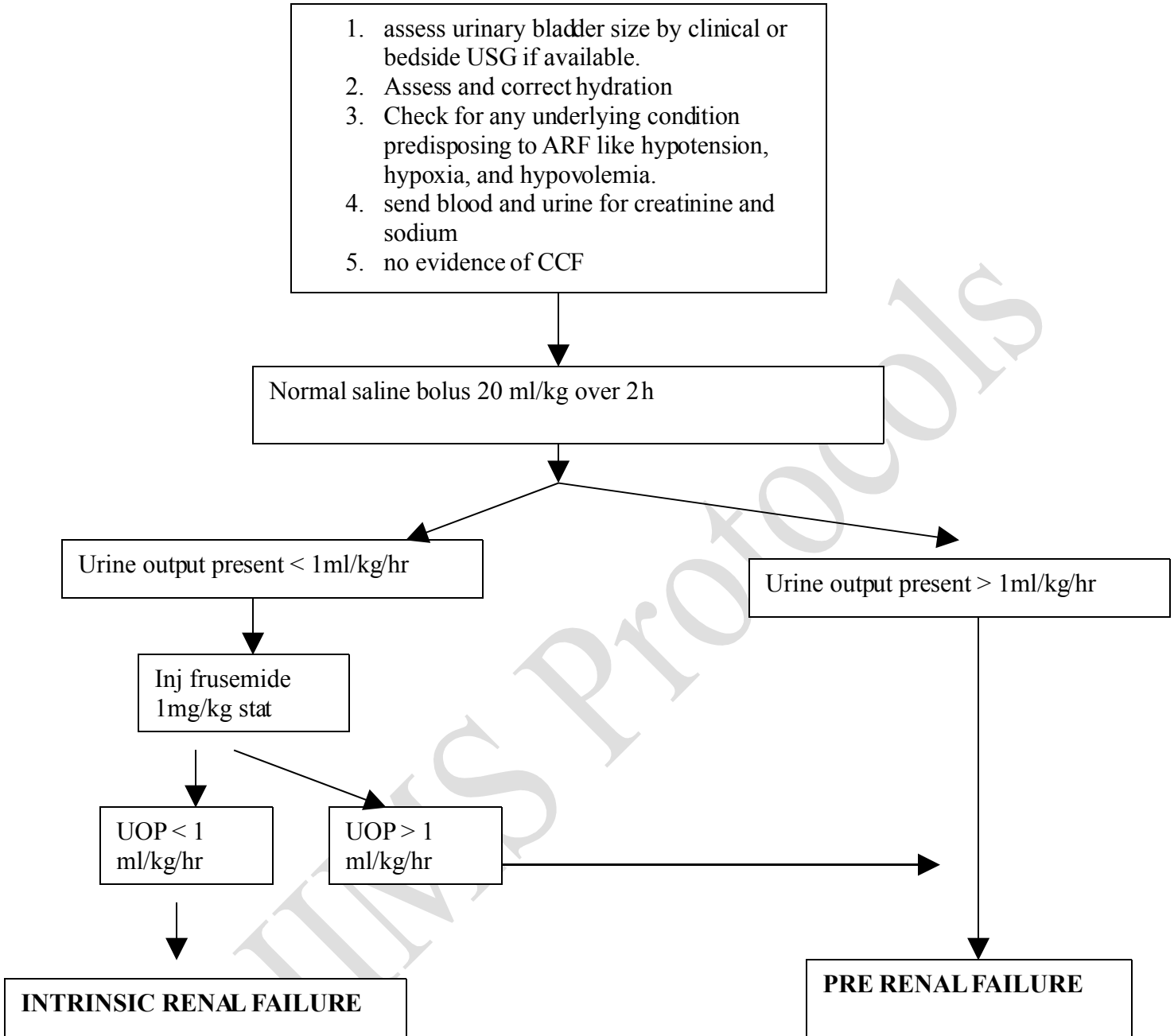
Non oliguric renal failure has a better prognosis when compared to oliguric renal failure. Mortality ranges from 25 to 78% in oligo anuric renal failure.<sup>16</sup> Long term abnormalities in GFR and tubular function are common in babies who survive the ARF and is probably secondary to hyperfiltration in the surviving nephrons. The long term consequence of such an acute insult is unknown.

### **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 random urinary protein/creatinine ratio of greater than 0.6, serum creatinine greater than 0.6 mg/dL and a tendency to obesity with a body mass index greater than the 85th percentile.<sup>17</sup>

Oliguria : urine output < 1mL/kg/hr for the past 12 hrs in a baby more than 24 hrs of age





UOP: urine output

CCF: congestive cardiac failure`

**Fig 1: evaluation of baby with oliguria:**

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