Acute Renal Failure Management in the Neonate

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Drs Chua and Sarwal did not disclose any financial relationships relevant to this article.

Objectives

After completing this article, readers should be able to:

1. Define the types and delineate the causes of acute renal failure (ARF) in neonates.
2. Describe the laboratory tests and imaging studies used to diagnose ARF.
3. Explain the roles of fluid balance, diuretics, dopamine, and nutrition in the management of neonatal ARF.
4. Describe the approaches to treating hyponatremia, hyperkalemia, calcium–phosphorus perturbations, acidosis, and hypertension in ARF.
5. Review the outcome and prognosis for ARF in neonates.

Introduction

Acute renal failure (ARF) is a very common problem in the neonatal intensive care unit. The newborn kidney has a very low glomerular filtration rate (GFR) that is maintained by a delicate balance between vasoconstrictor and vasodilatory forces. (1) Although sufficient for growth and development under normal conditions, the low GFR of the newborn kidney limits postnatal renal functional adaptation to endogenous and exogenous stresses. (2) This limited response predisposes the newborn to the development of ARF and is even more pronounced in the low birthweight infant (ie, <2,500 g due to preterm birth or intrauterine growth restriction). (3) Given this predisposition, early identification of ARF in the neonate is essential to preserving renal function.

Incidence

The true incidence of neonatal ARF is difficult to ascertain, but studies have reported that 8% to 24% of newborns admitted to the neonatal intensive care unit present with ARF. These percentages are likely an underestimation because many cases of nonoliguric neonatal ARF, which occurs commonly in sick neonates, are excluded. (1)

Definition

ARF is defined as a sudden decrease in GFR that results in the progressive retention of creatinine and nitrogenous waste products and the inability to regulate fluid and electrolyte homeostasis. The definition of ARF in neonates is less precise because the serum creatinine shortly after birth is a reflection of maternal renal function, usually less than 1.0 mg/dL (88.4 mcmol/L), which subsequently declines over time. As a result, the clinical presentation, gestational age, and maternal serum creatinine must be taken into consideration when diagnosing ARF in the neonate. Most investigators consider newborns to have ARF when the serum creatinine is 1.5 mg/dL (132.6 mcmol/L) or greater in the presence of normal maternal renal function. Acute renal insufficiency should be suspected when the plasma creatinine concentration increases in both preterm and term neonates or fails to decrease in the first week after birth in term neonates. (4)

As in older children and adults, ARF in neonates can be oliguric/anuric (defined as urine output of <1.0 mL/kg per hour or lack of urine output by 48 h of age) or nonoliguric. The type as well as the degree of renal injury generally dictates whether an infant experiences oliguric or nonoliguric renal failure. In the setting of normal urine output, ARF could be missed if the serum creatinine is not measured.

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Table 1. Causes of Acute Renal Failure in Neonates

Prenatal Injury/Vascular Damage

- Maternal use of:
  - Angiotensin-converting enzyme inhibitors
  - Angiotension II receptor antagonists
  - Nonsteroidal anti-inflammatory drugs

Congenital Renal Diseases

- Renal agenesis
- Renal dysplasia/hypoplasia
- Autosomal recessive/dominant polycystic kidney disease
- Finnish-type congenital nephrotic syndrome

Postnatal Renal Diseases

- Prerenal
  - Decreased true intravascular volume
    - Perinatal hemorrhage
    - Dehydration
    - Third space losses (sepsis, traumatized tissue, necrotizing enterocolitis)
    - Gastrointestinal losses
    - Hypoalbuminemia
  - Decreased effective intravascular volume
    - Congestive heart failure
    - Pericarditis, cardiac tamponade
- Intrinsic Renal
  - Acute tubular necrosis
    - Perinatal asphyxia
    - Ischemic/hypoxic insults
    - Drug-induced
      - Aminoglycosides
      - Intravenous contrast media
      - Nonsteroidal anti-inflammatory drugs (indomethacin)
      - Angiotensin-converting enzyme inhibitors (captopril, enalapril)
      - Amphotericin B
  - Interstitial nephritis
  - Vascular lesions
    - Renal artery thrombosis
    - Renal vein thrombosis
    - Cortical necrosis
  - Infectious causes
    - Sepsis
    - Pyelonephritis
    - Syphilis
    - Toxoplasmosis
    - Candidiasis
- Postrenal/Obstructive
  - Obstruction in a solitary kidney
  - Bilateral ureteral obstruction
    - Bilateral fungal bezoar
  - Urethral obstruction
    - Posterior urethral valves
  - Neurogenic bladder due to myelomeningocele

Causes

The underlying cause of ARF varies. Fetuses can suffer nephrologic insult due to maternal medications. Congenital renal diseases, such as autosomal recessive/dominant polycystic kidney disease or bilateral renal hypodysplasia, can lead to ARF. In addition, perinatal asphyxia or hemorrhage at birth can result in a hypoxic event that leads to the development of ARF. Postnatally, the causes of ARF can be divided into prerenal, intrinsic renal, and postrenal (or obstructive), with prerenal disease accounting for 85% of the cases. (5) Potential causes of neonatal ARF are listed in Table 1. (5)(6)

In prerenal failure, inadequate renal perfusion leads to decreased renal function in an otherwise intrinsically normal kidney. Re-establishing normal renal perfusion results in the return of normal renal function. The primary clinical conditions that lead to prerenal failure are those associated with systemic hypotension, hypovolemia, or hypoxia.

Intrinsic renal disease implies that renal failure is associated with damage to the kidneys. Prerenal disease can lead to intrinsic renal disease if renal perfusion is not restored. Intrinsic ARF in the neonate can be caused by a variety of perinatal disorders, including perinatal asphyxia, hypoxic-ischemic events, drug toxicity, and sepsis. In addition, vascular lesions such as renal artery thrombosis or renal vein thrombosis are important causes of ARF in the neonatal period. Renal artery thrombosis can be a complication of umbilical artery catheterization and should be considered in the differential diagnosis of ARF in a sick neonate, especially in the presence of hypertension. Renal vein thrombosis, which may present with an abdominal

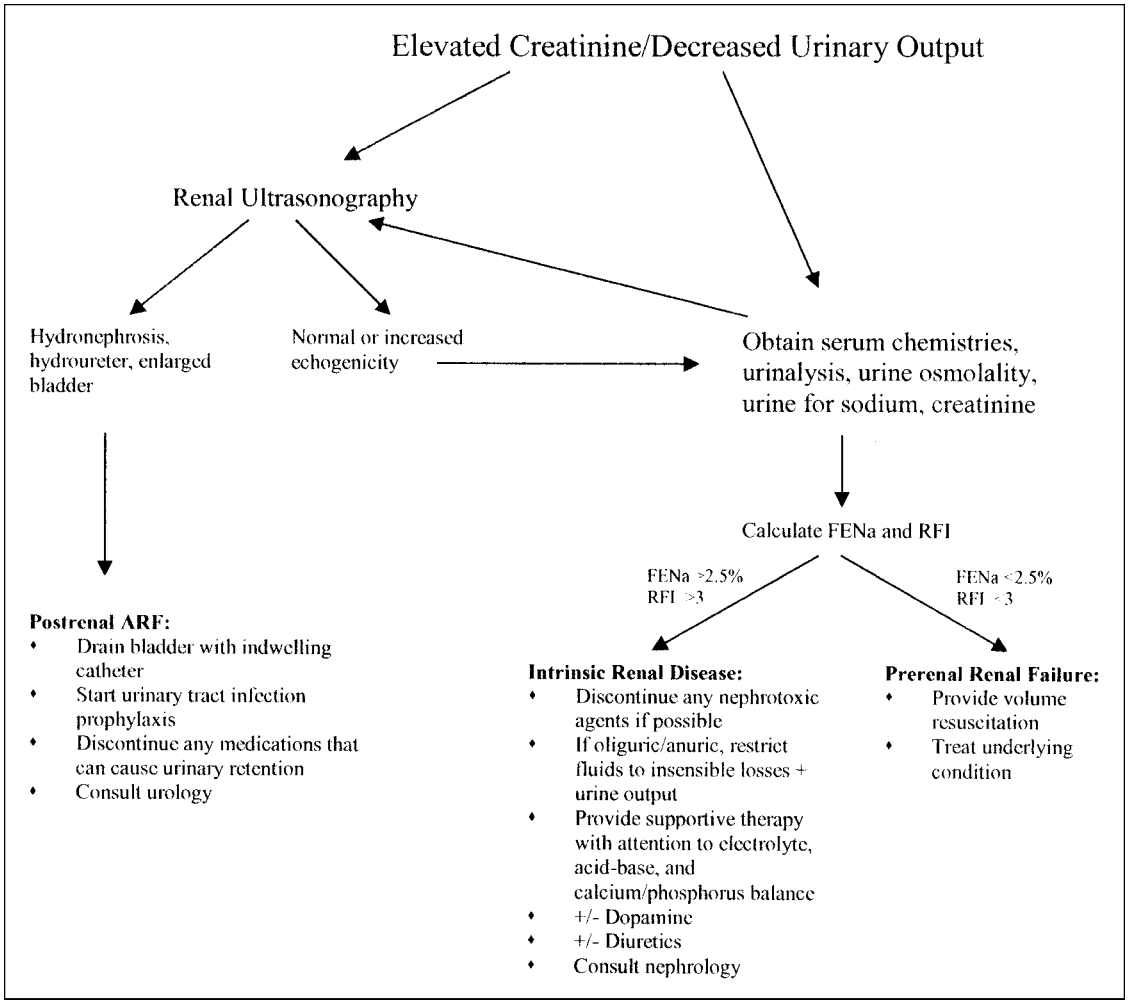

Figure. Algorithm for management of acute renal failure. FENa=fractional excretion of sodium, RFI=renal failure index

mass and gross hematuria, can be due to severe dehydration, disseminated intravascular coagulation, or poor circulation. The use of contrast agents also has resulted in ARF in neonates, given their low GFR, underscoring the importance of adequate hydration when imaging with contrast media is indicated.

Postrenal ARF occurs following obstruction of urinary flow after the urine has been produced by the kidneys. As a result, obstruction must affect both kidneys unless the patient has a solitary kidney. In males, urethral obstruction with posterior urethral valves can result in postrenal ARF.

Diagnosis

The first step in the evaluation of a neonate who has ARF is differentiating between prerenal, intrinsic renal, and postrenal disease (Figure). Often the clinical findings suggest the underlying cause. Laboratory studies should be obtained to aid in the diagnosis and management. They should include a complete blood count with red cell morphology, coagulation studies, chemistry panel (including sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total protein, albumin), urinalysis, urine culture, random urinary protein/creatinine ratio, and arterial blood gas. Urinary studies, such as urinalysis, urine osmolality, urine-to-plasma creatinine ratio, urinary sodium concentration, fractional excretion of sodium (FENa), and renal failure index (RFI), can be useful in differentiating between prerenal and intrinsic renal disease (Table 2). (7) Single FENa measurements, however, should be used with caution in very preterm infants because of the variability of their values in the first 5 days after birth. (4)

Table 2. Diagnostic Indices in Neonatal Acute Renal Failure

	Prerenal	Intrinsic Renal
Urine osmolality (mOsm [mmol]/kg water)	>400	<400
Urinalysis	Normal	>5 red blood cells/ high-power field
Urine sodium (mEq/L) [mmol/L]	31±19	63±35
Urine/protein creatinine ratio	29±16	10±4
Fractional excretion of sodium (%)	<2.5	>2.5
Renal failure index	<3.0	>3.0

The FENa and RFI can be calculated by the following equations:

$$\text{FENa (\%)} = (\text{urine sodium}/\text{serum sodium})/(\text{urine creatinine}/\text{serum creatinine}) \times 100$$

$$\text{RFI} = (\text{urine sodium}/\text{urine creatinine}) \times 100$$

Differentiating between intrinsic renal and postrenal disease in neonates is achieved best through renal ultrasonography and voiding cystourethrography. Ultrasonography with Doppler interrogation can provide information regarding the presence or absence of kidneys, size, presence or absence of hydronephrosis, bladder distention, and blood flow to the kidneys. Voiding cystourethrography can identify lesions of the lower urinary tract that cause obstruction, such as posterior urethral valves.

Medical Management

In the setting of prerenal renal failure, the underlying condition should be treated and volume resuscitation implemented to restore renal perfusion. In postrenal disease, obstruction may be relieved by primary surgical repair or via temporary drainage with an indwelling catheter.

After the diagnosis of intrinsic renal failure is determined, attention is directed to management of the complications that accompany ARF, including fluid and electrolyte abnormalities, calcium/phosphorus perturbations, acidosis, and hypertension. The goal is to limit or prevent further renal injury. Medication lists of neonates who have ARF should be reviewed to adjust doses as indicated. In addition, attempts should be made to withdraw nephrotoxic drugs if possible.

Fluid Balance

The ultimate goal in fluid management is to achieve or maintain a state of euvolemia. Because the insensible water losses of neonates vary, it is imperative to weigh the neonate every 12 hours to aid in management of fluid status. In addition, intake and output should be documented strictly. In the presence of hypovolemia, the fluid deficit should be corrected by administration of 20 mL/kg over 1 to 2 hours of an isotonic saline solution. An additional fluid challenge may be necessary to achieve euvolemia, depending on the level of dehydration. If the infant has euvolemia or hypervolemia, fluids should be restricted to allow for only insensible losses plus replacement of urine output.

Diuretics

The use of diuretics has not been shown to alter the course of ARF, but conversion of oliguric to nonoliguric renal failure can aid in fluid management. (8)

Furosemide therapy (1 to 2 mg/kg per dose) can increase urine flow rate, which decreases intratubular obstruction. In addition, furosemide inhibits Na^+K^+ATPase, which limits oxygen consumption in already damaged tubules. Because administration of furosemide has been associated with ototoxicity, (8) its use should be discontinued if no effect is noted. Although mannitol has been used in children and neonates who had prerenal ARF in the past, it has been shown to cause or exacerbate ARF in adults. (9) In addition, the administration of hypertonic mannitol to low-birthweight infants can increase the risk of intracranial hemorrhage. (10) Given these findings, the routine use of mannitol in neonates who have ARF should be avoided.

Dopamine Administration

Neonates who have hypotension and fail to respond to volume resuscitation often require inotropic and systemic vasoactive support. The use of "renal" dose dopamine (1 to 3 mcg/kg per minute) to improve renal perfusion following an ischemic insult is a very common practice in intensive care units. Dopamine increases renal blood flow by promoting vasodilatation and improves urine output by promoting natriuresis. Despite these effects, no definitive studies show that "renal" dose dopamine decreases the need for dialysis or improves survival in patients who have ARF. (11)(12)

Table 3. **Management of Hyperkalemia**

Intervention	Dose	Mechanism
Sodium bicarbonate	1 mEq/kg IV over 10 to 30 min	Shifts potassium into cells
Calcium gluconate (10%)	0.5 to 1.0 mL/kg IV over 5 to 10 min	Stabilizes cardiac membrane potential
Insulin/Glucose	Glucose 0.5 g/kg; insulin 0.1 U/kg IV over 30 min	Stimulates cellular uptake of potassium
Sodium polystyrene sulfonate	1 g/kg PO or PR in sorbitol	Exchanges sodium for potassium across colonic mucosa
Furosemide (if not anuric)	1 to 2 mg/kg IV	Increases urinary excretion of potassium

IV=intravenous; PO=oral, PR=rectal

Hyponatremia

Hyponatremia in neonatal ARF frequently is dilutional and treated best with fluid restriction rather than provision of supplemental sodium. Serum sodium concentrations less than 125 mEq/L (125 mmol/L), however, can be associated with seizures and lethargy. Accordingly, administration of hypertonic saline may be warranted to treat or avoid symptomatic hyponatremia by increasing the serum sodium concentration to 130 mEq/L (130 mmol/L).

The amount of sodium needed to correct the hyponatremia can be estimated from the following formula, in which 0.6 represents total body water: (13)

$$\text{Amount of sodium (mmol)} = [\text{desired sodium} - \text{actual sodium (mmol/L)}] \times 0.6 \times \text{weight (kg)}$$

Serum sodium concentrations should be corrected cautiously (maximum daily correction of 8 to 10 mmol/L per day) to avoid the development of neurologic sequelae.

It is also important to remember that neonates can have high urinary losses of sodium due to immature kidneys or obstructive lesions. In these situations, increased sodium supplementation in feedings or parenteral nutrition may be indicated. (14)

Hyperkalemia

Hyperkalemia is a common complication in ARF as the kidney tightly regulates potassium balance and excretes 90% of dietary potassium intake. As in older children and adults, hyperkalemia can be life-threatening and lead to cardiac arrhythmias, cardiac arrest, and death in neonates. Given these complications, an electrocardiogram should be obtained in the setting of hyperkalemia. Tall, peaked T waves are the first manifestation of cardiotoxicity, followed by prolongation of the PR interval, flattening of P waves, and widening of QRS complexes, which subsequently can lead to ventricular tachycardia and ventricular fibrillation. Therapies for hyperkalemia and their mechanisms of action are listed in Table 3. The use of intravenous calcium gluconate, sodium bicarbonate, insulin, and glucose is only temporizing and does not remove potassium from the body. Sodium polystyrene sulfonate, administered orally, via nasogastric tube, or rectally, is a resin that exchanges sodium for potassium in the gastrointestinal tract and results in potassium removal. Sodium polystyrene sulfonate must be used cautiously because of potential complications, including hypernatremia and constipation. In addition, this therapy has been associated with intestinal necrosis. (15) In the absence of anuria, furosemide can be used to increase the urinary excretion of potassium. If the patient is unresponsive to these therapies and continues to have hyperkalemia or develops life-threatening hyperkalemia, renal replacement therapy is indicated.

Calcium–Phosphorus Perturbations

Hyperphosphatemia and hypocalcemia can develop in neonates who have ARF. Because hypophosphatemia occurs frequently in neonates, (16) the manifestation of hyperphosphatemia in neonates who have ARF may take longer compared with older children who have ARF. Treatment of hyperphosphatemia consists of dietary phosphorus restriction, using low-phosphorus formulas as well as the addition of phosphorus binders such as calcium carbonate to the formula to bind phosphorus and prevent gastrointestinal absorption. (17) Aluminum-containing phosphorus binders no longer are recommended because of the risk of aluminum toxicity. (18)

Symptomatic hypocalcemia should be corrected using intravenous 10% calcium gluconate at a dose of 0.5 to 1 mL/kg in 5 minutes.

Table 4. Composition of Maternal Human Milk and Renal Infant Formula

Formula	kcal/mL (kcal/oz)	Protein (g)	Carbohydrate (g)	Fat (g)	Sodium (mEq)	Potassium (mEq)	Calcium (mg)	Phosphorus (mg)
Human milk (preterm)	0.67 (20)	14	66	39	11	15	248	128
Human milk (mature)	0.69 (20)	10	72	39	7	13	280	147
Renal formula	0.67 (20)	15	69	38	7	15	378	189

Acid-Base Balance

Metabolic acidosis is encountered commonly in neonatal ARF because the kidney excretes net acids generated by intermediary metabolism. When neonates exhibit severe acidosis, defined by a plasma bicarbonate concentration of 12 mEq/L (12 mmol/L) or less or plasma pH below 7.20, acidosis should be corrected by the administration of intravenous or oral sodium bicarbonate. The addition of sodium bicarbonate to the maintenance fluids, oral supplementation of sodium bicarbonate, or maximizing the sodium acetate in parenteral nutrition often can provide the necessary bicarbonate supplementation to attenuate the acidosis caused by the ARF. It is important to note that treatment of acidosis decreases the amount of ionized calcium. Therefore, when correcting acidosis, attention to the serum ionized calcium level is essential to prevent the development of tetany or seizures.

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.

Nutrition

Attention to nutrition is essential in ARF management to prevent excessive tissue breakdown. If the infant is tolerating oral feedings, maternal human milk or a renal formula that has a low renal solute load and low phosphorus should be used (Table 4). Infants who have oliguria frequently cannot receive adequate calories with maternal human milk or formula alone because of the need for fluid restriction. Therefore, high-caloric additives that have low osmolality may be required to provide sufficient calories. (19) If oral feedings are not tolerated, nutrition should be administered intravenously with a goal of providing a minimum of 50 kcal/kg per day and 1 to 2 g/kg per day of protein. Caloric needs rarely are met in an infant who has oliguria, which can result in a 0.2% to 1% loss of body weight per day beyond the first week after birth. (4)

Renal Replacement Therapy

When conservative measures fail to control the complications of ARF, renal replacement therapy is indicated. Indications for initiation of acute renal replacement therapy include severe metabolic acidosis, electrolyte abnormalities (such as hyperkalemia), intoxications, fluid overload, and symptomatic uremia. The various methods of available renal replacement therapy include peritoneal dialysis, hemodialysis, and hemofiltration with or without dialysis. Although the use of hemofiltration is increasing and peritoneal dialysis is decreasing in the pediatric population, the preferred method of dialysis in the neonatal period continues to be peritoneal dialysis. (20) Further details of renal replacement options with a review of advantages and disadvantages is discussed in other articles in this issue (Neonatal Hemodialysis and Continuous Renal Replacement Therapy, Neonatal Peritoneal Dialysis).

Outcome/Prognosis

Oliguria in neonatal ARF may last up to 3 weeks. An increase in urine output generally is the first indication of renal recovery. Occasionally, polyuria with increased sodium and potassium losses may occur during the recovery phase. For this reason, serum electrolyte concentrations should be monitored closely. (19)

The outcome in neonatal ARF depends on the underlying cause and the extent of organ damage. (6)(19) Neonates who develop nonoliguric ARF have better survival rates than those who suffer from oliguric ARF. The overall mortality rate in oligo-anuric neonatal ARF ranges from 25% to 78%. Recovery from ARF in the neonate is unrelated to nonrenal factors such as age at diagnosis, birthweight, Apgar scores, or requirement for ventilatory support. Blood urea nitrogen, peak serum creatinine, and urine flow rate have been reported to be inadequate discriminators of renal outcome. (20) Abit-

bol and associates (21) reported on the long-term follow-up of extremely low-birthweight infants who had neonatal ARF and found 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 (53 mcmol/L), and a tendency to obesity with a body mass index greater than the 85th percentile. Loss of renal mass and nephrocalcinosis were not prognostic indicators.

Newborns who have ARF are predisposed to the development of chronic renal failure in the future and, therefore, need lifelong monitoring of blood pressure, urinalysis, and renal function.

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NeoReviews Quiz

4. A 24-hour-old preterm neonate is suspected of having oliguric renal failure. Based on measurements of urinary sodium and creatinine concentrations as well as serum sodium and creatinine concentrations, the fractional excretion of sodium is calculated to be 1.2%. Of the following, the *most* likely cause of renal failure in this infant is:

   A. Aminoglycoside toxicity.
   B. Hypovolemia.
   C. Pyelonephritis.
   D. Renal vein thrombosis.
   E. Urethral obstruction.

5. Hyperkalemia, a common complication of acute renal failure, can produce life-threatening cardiac arrhythmia and warrants serial monitoring by electrocardiography. Of the following, the *first* electrocardiographic manifestation of cardiac toxicity from hyperkalemia is:

   A. Flattening of P waves.
   B. Peaking of T waves.
   C. Prolongation of PR intervals.
   D. Suppression of ST segments.
   E. Widening of QRS complexes.

6. Recovery from acute renal failure in neonates depends on the underlying cause and the extent of organ damage. Of the following, the *first* indication of renal recovery from acute renal failure in neonates is a:

   A. Decrease in blood urea nitrogen.
   B. Decrease in serum creatinine.
   C. Decrease in serum potassium.
   D. Increase in serum sodium.
   E. Increase in urine output.