Neonatal Kidney Dysfunction

48

David Askenazi, Stefano Picca, and Isabella Guzzo

Kidney Function in Neonates

At birth, the kidney replaces the placenta as the major homeostatic organ, maintaining fluid and electrolyte balance and removing harmful waste products. In a healthy term neonate, dynamic changes to renal blood flow occur which lead to alterations in glomerular filtration rate (GFR) over the first few months of life. Tubular development is intact such that conservation or elimination of electrolytes and water are efficient and adequate. Alternatively, the glomerular, tubular and vascular regulation of the kidney in premature infant are abnormal compared to the healthy term counterpart. Describing the "normal" renal physiology in preterm neonates is difficult (as one can argue they are all abnormal); understanding how a term neonate maintains renal blood flow, glomerular filtration and tubular function is critical to extrapolation of how the premature infant's underdeveloped/immature kidneys function. As we describe neonatal homeostasis, we will contrast the physiology of the "normal" healthy term infant to those of premature infants, understanding that the degree of immaturity and the neonatal course will affect the ability of premature infants "normal" homeostasis.

Healthy term infants are ready to maintain homeostasis of water, electrolytes, and acid/base. In addition, they function to metabolized drugs/toxins, and eliminate waste products. As the clinician has an integral role in prescribing fluids, electrolytes, drugs and nutrition, proper homeostasis in sick term/near term newborns and premature infants depends on the clinicians' ability to appropriately prescribe fluids, nutrition and electrolytes. Infants who lack ability to remove uremic toxins and maintain appropriate fluid balance rely on nephrology teams who can support the kidney with dialytic therapies designed to maintain homeostasis.

D. Askenazi (✉)
Department of Pediatrics,
University of Alabama at Birmingham,
1600 7th Ave South, Louder Bldg. 502,
Birmingham, AL 35233, USA
e-mail: daskenazi@peds.uab.edu

S. Picca • I. Guzzo
Dialysis Unit, Department of Pediatrics,
Bambino Gesù Children's Research Hospital IRCCS,
Piazza S. Onofrio 4, Rome 00165, Italy
e-mail: stefano.picca@opbg.net;
isabella.guzzo@opbg.net

Renal Blood Flow in Newborns

Starting with delivery and umbilical cord clamping, major hemodynamic changes occur in renal blood flow which drive changes in neonatal glomerular filtration rate. The proportion of cardiac output distributed to the kidney changes abruptly. Fetal kidneys receive approximately 2.5–5 % of cardiac output at birth [1], which increases to 6 % by 24 h of life [2, 3], steadily escalates to 10 % at 1 week of life, and attains 15–18 % at 6 weeks of

D.F. Geary, F. Schaefer (eds.), *Pediatric Kidney Disease*, DOI 10.1007/978-3-662-52972-0_48

life [4] as it approaches the fractional cardiac output to the kidneys observed in adults (approximately 20–30 %). These dynamic changes in renal blood flow are driven by both increased systemic blood pressure and a substantial decrease in renal vascular resistance. The abrupt and significant drop in renal vascular resistance is due to a redistribution of renal blood flow within the kidney, changes in the number of vascular channels and changes in glomerular arterial resistance [5]. Initially, renal blood flow primary extends to the outer cortex which over time distributes to medullary sections over the first few months of life [6].

The auto-regulatory mechanisms which control renal blood flow are driven by both the myogenic reflex of vascular smooth muscles and the tubule-glomerular feedback system. These reflexes aim to maintain constant renal blood flow by sensing vascular endothelial stretch and distal tubular fluid flow respectively. Nitric oxide, angiotensin II, adenosine, bradykinins, and endothelin play a central role in maintaining adequate blood flow.

The renin angiotensin system is active throughout fetal development and contributes to normal fetal maturation. Congenital abnormalities (i.e., defects to angiotensin II receptors) and secondary abnormalities (i.e., maternal use of angiotensin converting enzyme inhibitor) can significantly affect kidney development. Prostaglandins (potent vasodilators) also serve to increase renal blood flow by active vasodilation of afferent arterioles. These agents are increased in times of stress and help counteract vaso-constrictive effects of angiotensin II and catecholamines. Prostaglandins and inhibitors of prostaglandins are commonly prescribed in neonatal medicine to maintain patency, or electively close patent ductus arteriosus; respectively. Such dynamic changes in renal blood flow, alterations in hemodynamics, and medications to promote vasoconstriction/ vasodilation will greatly affect glomerular filtration rate in neonates.

Glomerulogenesis

Renal development commences during the fifth week of gestation with partially functional temporary organs (the pronephros and metanephros). The first nephrons are formed by about the eight week of gestation and increase over time, such that by 14 weeks gestation, four glomerular generations are presents. By 36 weeks post gestation, about 12–13 generations of glomeruli are present [7]. The juxtamedullary nephrons develop initially, with superficial ones following. Nephrogenesis continues until 36 weeks of gestation at which time the number of nephrons, 1.6–2.4 million, approximates that of an adult [8]. Autopsy studies suggest that the extrauterine environment is not amenable to neoglomerulogenesis leading to low nephron number in premature infants [9]. Thus, the premature infant may be programmed for low nephron endowment, and subsequent chronic kidney disease.

In individuals with a lower number of nephrons, single-nephron hyperfiltration can increase total GFR to a similar level as attained by those with normal numbers of glomeruli. However, the impact of low nephron endowment may become problematic over time as single nephron hyperfiltration may cause dynamic changes leading to glomerulosclerosis and ultimately progressive loss of kidney function, especially in the context of other risk factors for CKD such as acute kidney injury, hypertension, diabetes, and other primary renal diseases.

Glomerular Function Rate (GFR)

GFR is the most useful measurement of kidney function. GFR is measured indirectly through the concept of clearance (the equivalent volume of plasma from which a substance would have to be totally removed to account for its rate of excretion in urine per unit time). Clearance is calculated by dividing the excretion rate of a substance by its plasma concentration ($C_x = U_x \times V$); where U_x and P_x are urine and plasma concentrations of substance x and V is urine flow rate. C_x is expressed as milliliters per minute and is usually normalized to standard 1.73 m^2 idealized adult body surface area [10]. GFR is the best clinical test to estimate functional renal mass which can assist the clinician in prescribing fluids/electrolytes, determine disease progression, and appropriately prescribe medications excreted by the kidney.

The gold standard method for GFR measurement is inulin clearance. Tables 48.1 and 48.2 summarize studies conducted to estimate GFR (measured by inulin clearance) in healthy term and preterm infants, respectively. Dependent on degree of prematurity, GFR steadily improves from 10 to 20 ml/min/1.73 m^2 during the first week of life to 30–40 ml/min/1.73 m^2 by 2 weeks after birth concomitant with alterations in renal blood flow. Thereafter GFR improves steadily over the first few months of life [11, 12]. Serum creatinine (SCr) is the most common method to estimate GFR and monitor renal function but has significant shortcomings (see Chap. 3). There are several specific problems with using SCr in neonates: SCr in the first few days of life reflects mother's and not the infant's renal function. Moreover, GFR in term and preterm infants is generally very low and there is a very wide distribution of normal serum creatinine values which vary greatly dependent on level of prematurity and age [13] (Fig. 48.1). Finally, bilirubin levels in premature infants rise in the first several days and return to normal after a few weeks. If the colorimetric Jaffe method of SCr is used this may have tremendous impact on the interpretation of SCr [14].

Attempts to estimate GFR using SCr in neonates have suggested the following formula for children less than 1 of age [15]:

Table 48.1 Formal GFR measurements for term neonates during the first 2 years of life

Term infants	
Age	ml/min/1.3 m^2
1–3 days	21 ± 5
4–14 days	37 ± 7
1–3 months	85 + 35
4–6 months	87 ± 22
7–12 months	96 + 2
1–2 years	105 ± 17

Data from Schwartz and Furth [11]

Table 48.2 Formal GFR measurements for preterm neonates during the first 4 months of life

Premature infants	
Age	ml/min/1.73 m^2
1–3 days	14.0 ± 5.0
1–7 days	18.7 ± 5.5
4–8 days	44.3 ± 9.3
3–13 days	47.8 ± 10.7
1.5–4 months	68.4 ± 16.6

Data from Schwartz and Furth [11]

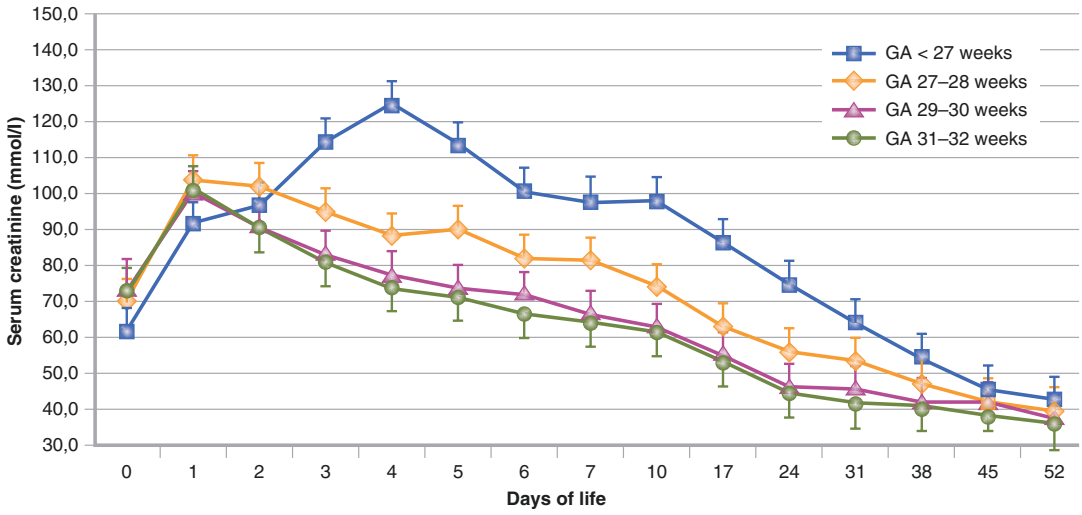

Fig. 48.1 Serum creatinine values over time by gestations age categories (Used with permission of Springer Science + Business Media from Gallini et al. [13])

$$k * SCr / height\ (cm);$$

where k = 0.33 for low birth weight and 0.45 for normal birth weight infants

However, caution should be used when applying this equation in clinical practice for several reasons. At best the formula represents a mean estimate and the true GFR may be off in either direction by 20% or more. In addition, the k coefficients were derived using the Jaffe calorimetric method to measure SCr. As most hospitals now only use the enzymatic equation, the coefficients may no longer be applicable.

Cystatin C has been extensively studied as a measure of GFR and a marker of acute kidney injury. Since Cystatin C is not influenced by the maternal serum level and is highest at birth, it may be better suited than SCr to monitor renal function in infants. Cystatin C concentrations significantly decrease during the first 3 days of life and are independent of gestational week, birth weight and maternal renal function status in very low birth weight infants [16]. Cystatin C does not differ between males and females and is not influenced by gestational age. Thus, cystatin C seems to have many properties of an ideal marker of renal function in this age group [17]. However, as only a few studies on this topic have been conducted so far and no studies link cystatin C levels with short and long-term outcomes in this population, further research is needed before adopting Cystatin C as a primary marker of renal function in neonates.

Water, Electrolyte and Acid-Base Disorders in Neonates

Metabolic Acidosis

Neonates typically show a certain degree of acidosis depending on gestational and postnatal age [18]. In full-term neonates, after completion of nephrogenesis at the 34th week of gestation [19], the mechanisms devoted to maintain acid base (AB) equilibrium are still immature. This immaturity concerns both the capacity of H^+ excretion and the HCO_3^- reabsorption threshold [20, 21]. Moreover, the ability of excreting large amounts of acid through ammoniagenesis is impaired in the newborn baby, due to the decreased presence of enzymes necessary for ammoniagenesis, like glutaminase [22]. Finally, neonatal nutrition involves a two to three times higher protein load than older children with consequently higher acid production. In premature infants, this unfavorable condition is even worsened by the inability to efficiently acidify urine with further acid retention and consequently increased risk of metabolic acidosis. In fact, in preterm infants, plasma bicarbonate levels are lower than in full term neonates for the first 3 weeks of life due to the lower renal threshold for bicarbonate (see Chap. 36). This predisposes preterm neonates to condition known as late metabolic acidosis, which is further promoted by milk formulas containing casein, by parenteral nutrition (especially in TPN containing arginine HCl), and by withdrawal of milk alimentation (and consequently alkali intake), e.g., during episodes of diarrhea.

The acid-base disturbances seen in the NICU occur in an organism with immature homeostatic mechanisms. According to the classic metabolic acidosis classification based on the anion gap, we can take into account a number of clinical situations leading to metabolic acidosis. The anion gap attests the balance (or unbalance) between acid accumulation and loss of base equivalents. It is calculated by: $Na^+ - (Cl^- + HCO_3^-)$ in mEq/L. Metabolic acidosis with a normal anion gap (<16 mEq/L) is seen in neonates with intestinal or renal HCO_3^- losses, which can be due to either proximal or distal renal tubular acidosis (see Chap. 36). Also, the use of the carbonic anhydrase inhibitor acetazolamide in pregnancy has been associated with metabolic acidosis in preterm neonates [23, 24].

The most common conditions causing an anion gap >16 mEq/L in neonates are renal failure, inborn errors of metabolism (IEM) or lactic acidosis [25]. In renal failure, the impairment of acid load elimination increases HCO_3^- consumption while in IEM (in particular in organic acidurias [26]. HCO_3^- stores are depleted by the increased production of organic acids. Small bowel drainage following surgical procedures

may also induce large HCO_3^- losses. In necrotizing enterocolitis (NEC) acidosis is associated with progressive systemic shock and lactic acidosis [27]. In VLBW infants, metabolic acidosis on the first day of illness is more common in infants with perforated NEC compared to infants without perforation [23].

The treatment of metabolic acidosis in neonates firstly relies on the diagnosis and treatment of the underlying cause. The treatment of renal tubular acidosis with $NaHCO_3$ in critical children is controversial [28]. Only one randomized trial study examining potential benefits of $NaHCO_3$ in asphyxiated newborn infants is available showing no influence on the outcome [29], while no advantage of this treatment has been found in adult patients. Potential hazards of $NaHCO_3$ supplementation in infants include risk of sodium overload and hypernatremia, hypokalemia and hypocalcemia. Moreover, the use of $NaHCO_3$ in infants has been associated with a number of adverse events like intracranial hemorrhage, deterioration of cardiac function and myocardial injury [30, 31]. A recent survey in Canadian NICUs showed that $NaHCO_3$ is most frequently administered in septic shock whereas its use is much less frequent in cardiac arrest [32]. In neonates $NaHCO_3$ should be given only after establishment of adequate ventilation and circulation and should be restricted to severe acidosis with life-threatening hyperkalemia. In neonatal resuscitation, a dose of 1–2 mEq/kg of a 0.5 mEq/mL solution may be given by slow intravenous push (over at least 2 min) after adequate ventilation and perfusion have been established [33]. In infants with renal failure, titration of acid/base balance using sodium citrate is necessary to maintain appropriate metabolic control and growth.

Metabolic Alkalosis

Metabolic alkalosis is almost invariably accompanied by hypokalemia and can be classified on the base of chloride urine concentration. In critical infants, low urinary Cl^- concentration (expressed as Cl^- <10 mEq/L or, more precisely, as Cl^-/Creatinine ratio <10 in mol/mol) suggests that the kidneys are avidly holding on to chloride, thus, ruling out chloride loss from the kidneys as the etiology. Low urine chloride metabolic alkalosis may be present as a consequence of loss of gastric secretions (vomiting, nasogastric suction), secretory diarrhea or after rapid correction of hypercapnia, and chronic diuretic which cause low total body chloride). In contrast, metabolic alkalosis with high urine chloride suggests inappropriate losses of chloride from the kidney from primary chloride losing tubulopathies (Bartter syndrome, Gitelman syndrome) and, more frequently, the use of diuretics. If metabolic hypochloruric alkalosis is present in context of systemic hypertension, defects in regulation of aldosterone and renin should be sought (Fig. 48.2).

A peculiar low-chloride associated clinical situation is that of infants after cardiopulmonary bypass surgery. In these patients, metabolic alkalosis is associated with younger age, preoperative ductal dependency and hemodilution [34]. Volume and chloride depletion have been advocated as possible causes [35]. Metabolic alkalosis is also reported in up to 18 % of infants referred to surgery for pyloric stenosis [36].

Hyperkalemia

Hyperkalemia may represent a life-threatening condition in the NICU. It is the most common electrolyte disorder associated to heart conduction problems [37]. Non-oliguric hyperkalemia of the newborn is defined as a plasma potassium level >6.5 mmol/L in the absence of acute renal failure [38]. In neonates, spurious hyperkalemia has to be initially excluded since mechanical trauma to red blood cells during venipuncture with consequent release of intracellular potassium is particularly frequent in neonates and prematures. The hemolytic Index is useful in detecting spurious hyperkalemia in infants [39]. Once spurious hyperkalemia is ruled out, a number of causes of true hyperkalemia have to be considered. Hyperkalemia may be induced by increased intake, intra-extracellular potassium

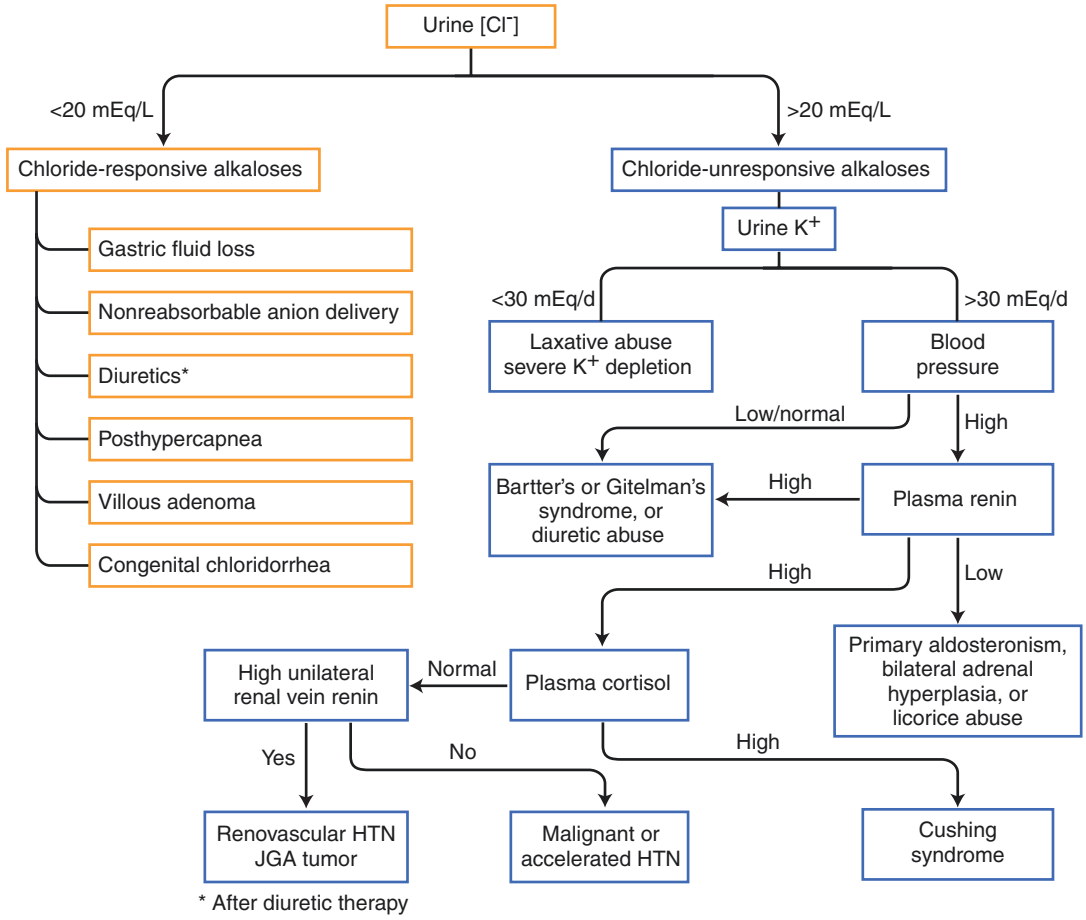

Fig. 48.2 Clinical decision tree diagram for metabolic alkalosis (Used with permission of Elsevier from DuBose TD. Disorder of Acid Base Balance. Brenner and Rector's the Kidney, 595–639. Elsevier; 2012)

redistribution and decreased elimination. Increased intake in critical infants may be seen with acute potassium load and blood transfusion. Acute load is infrequent in non-oliguric infants and it is usually consequent to dosing errors or the administration rate of intravenous potassium containing solutions. Potassium concentration in transfused blood may be as high as 50 mmol/L, so that even small amounts may induce severe hyperkalemia in small infants. This renders the use of fresh blood in newborns mandatory [39]. The most common cause of intra-extracellular potassium redistribution hyperkalemia in critical infants is metabolic acidosis. In this condition, potassium moves from the intracellular compartment in order to maintain electroneutrality, after H^+ ions have accumulated in the intracellular space.

Hyperkalemia is frequent in preterm neonates. It presents as a sudden rise of serum potassium in the first 72 h of life of preterm neonates with a gestational age <28 weeks and may cause heart conduction impairment that may result in sudden death. This condition results from potassium loss from the intracellular space, together with the immature renal excretion of potassium and aldosterone unresponsiveness. Management of hyperkalemia is mandatory when symptoms and/or EKG alterations are present. The latter include tall, peaked T waves with narrow base, prolonged PR interval, decreased or disappearing P wave, widening of QRS, amplified R wave, ventricular

fibrillation or asystole. There are three main approaches to the treatment of hyperkalemia: (1) antagonizing the membrane actions of hyperkalemia, (2) driving potassium into cells, and (3) removing potassium from the body. First, stabilization of myocardial function may be obtained by Ca^{2+} infusion. Calcium inactivates sodium channels and increases membrane excitability in 2–3 min. Its effect lasts for 30–60 min, so that an alternative therapy is required after that time. Calcium is given by slow intravenous injection over 5–10 min: 0.11 mmol/kg (0.5 ml/kg of calcium gluconate 10%). Potassium can be driven into intracellular space by insulin in exchange with sodium. I.v. insulin is used with glucose for emergency treatment of hyperkalemia at the dose of intravenous solution of insulin (0.1–0.6 units/kg/h in neonates) with glucose infusion of 0.5–1 g/kg/h (5–10 ml/kg/h of glucose 10%). The effect starts in 15 min and can last for hours. Blood glucose levels must be carefully monitored to avoid both hypo-and hyperglycemia [40]. Intravenous sodium bicarbonate reverses potassium ions from the extra- to the intracellular compartment to maintain electro-neutrality. A half correction of the base excess (0.3 × weight × BE) over 10–15 min can be administered and the rest given in the next 12–24 h. The main constraint of sodium bicarbonate use is sodium and volume overload especially when renal impairment is present. β-2 adrenergic agonists increase sodium-potassium ATPase activity and potassium is driven back into cells. Salbutamol can be nebulised or given by intravenous infusions [41]. Finally, removal of potassium is generally obtained by diuretics and cation exchange resins. Furosemide can be administered in 1 mg/kg dosage and repeated in case of need. Since the efficacy of diuretics depends on GFR, higher dosage may be required in renal failure. Calcium or sodium polystyrene sulfonate (Kayexalate®, Concordia Pharmaceuticals, Oakville, Ontario, Canada) binds potassium by exchanging it with sodium in GI tract so that potassium is eliminated in the stool. In adult patients with life-threatening hyperkalemia, the role of exchange resins has been questioned [42]. In neonates, potassium elimination can be enhanced by ion resins, but hyperkalemic neonates may develop gastrointestinal obstruction and/or perforation following oral or rectal administration of exchange resins [43]. Moreover, in a comparative study in hyperkalemic preterm neonates cation-exchange resin did not induce a better outcome of all-cause mortality than glucose and insulin [44]. Given the above considerations, combined insulin/glucose infusion should be preferred over treatment with rectal cation-resin for acute hyperkalemia in preterm infants [45]. Low potassium formulas are available for children who have poor potassium elimination. In addition, premixing formula with sodium polystyrene sulfonate (Kayexalate®), allowing the resin to settle and providing the supernatant for nutrition, efficiently lowers the oral potassium load without risking bowel obstruction/perforation.

Hypokalemia

True, not alkalosis induced hypokalemia (<3.5 mmol/L) in critical infants may develop as a consequence of potassium loss due to intestinal problems (vomiting, nasogastric suction, diarrhea), renal conditions (diuretic use, recovery from acute kidney injury) or insufficient potassium intake, mainly coming from unbalanced parenteral nutrition. Congenital conditions if untreated can be lethal during the first weeks or months of life. These include congenital chloride diarrhea (a rare autosomal recessive disease characterized by chronic secretory diarrhea), and some inherited conditions like Bartter syndrome, Gitelman syndrome, and related syndromes (see Chap. 33).

In neonates, potassium replacement must be managed with extreme caution, given the rapid change of kalemia induced by small amounts of potassium. Intravenous potassium treatment should only be given for immediately life-threatening emergencies over several minutes while severe hypokalaemia may be treated with an infusion of 0.2–0.5 mmol/kg/h to a maximum of 1 mmol/kg. Non-emergencies are best treated using oral supplements if possible, otherwise as small dosages as low as 0.03–0.07 mmol/kg by

slow injection. During potassium administration, very frequent monitoring of plasma levels has to be established as well as continuous EKG monitoring while correction occurs [46].

Hypernatremia

Changes in sodium concentration are common in critical neonates, due to the small patient volume and the body fluid changes occurring in the perinatal period. Hypernatremia (>145 mmol/L) must always be considered in relation to the water content and is traditionally classified as hypo-, normo- or hypervolemic. Hypovolemic hypernatremia is often seen when fluid restriction is required and water loss exceeds that of sodium. Other frequent causes of hypovolemic hypernatremia are losses through the gut or the kidney (like watery diarrhea, water loss in post-obstructive polyuria). Hypernatremia is more frequent in VLBW infants in which water loss through lungs and the immature skin may reach 150 ml/kg/day, thus exposing the preterm to hypernatremia due to free water deficit, especially in the first hours of life. Moreover, renal sodium handling is inversely related to creatinine clearance in the first 2 weeks of life. After 4–5 days from birth sodium balance becomes negative with a sudden decrease of fractional excretion, thus enabling the neonatal kidney to spare sodium. This occurs also in preterm babies [47]. A particular case is that of critical infants with severe hypoperfusion and acidosis requiring large amounts of sodium bicarbonate. In this case, often a capillary leak syndrome is present with leak of albumin, sodium and water to the interstitium in a mixed hypovolemic-sodium retaining situation in which sodium is in a third space. Hypervolemic hypernatremia in the NICU is frequently induced by administration of large amounts of sodium with drugs and blood products.

Management of hypernatremia in critical infants is usually an urgent treatment. Respiratory distress, necrotizing enterocolitis, and patent ductus arteriosus are associated with hypernatremia and volume expansion [48, 49]. Correction of hypernatremia basically consists in free water administration with correction velocity being the crucial issue. There is evidence that plasma both sodium changes and velocity of these changes are associated with neurological outcome [50]. The rule is to reduce natremia at a speed not >0.5–1.0 mmol/L/h. If plasma sodium is very high (>160 mmol/L), it is advisable to administer a 0.9 % saline solution in order to reduce natremia slowly.

Hyponatremia

Hyponatremia (<130 mmol/L) is associated with cerebral edema and permanent neurologic sequelae especially in preterm neonates [51, 52]. In critical neonates, hyponatremia is most frequently seen as a consequence of diuretic use, surgical procedures, diarrhea/vomiting and third space loss. A particular neonatal issue is hyponatremia during therapeutic hypothermia. In these patients, hyponatremia has been related to water loss as a consequence of cooling induced skin vasoconstriction [53]. Total body fluid overload will also cause hyponatremia.

Diuretics are commonly used to treat infants with oxygen-dependent chronic lung disease [54] and congenital heart defect [55]. In acute situations, high-dose diuretics may be required and this may cause hyponatremia which, in turn, hampers the response to the diuretic. Hypokalemia, alkalosis, and calcium wasting can be part of this picture. During surgery, standard neonatal intensive care guidelines recommending hypotonic i.v. infusions containing 20–40 mmol of sodium are often followed [56]. However, these guidelines may not meet metabolic and volume needs in the perioperative period and hyponatremia may result in up to 60 % of patients [51, 56, 57]. Careful monitoring of sodium levels and the use of balanced sodium solutions are mandatory in these patients [57]. During neonatal sepsis, capillary leak may take place and large amounts of sodium together with water and albumin are displaced into the interstitium with severe edema poorly responding to diuretics [58].

Replacement of sodium loss in volume depletion must take into account the variation of sodium plasma levels since, if a patient is seizing with a serum sodium <120 mol/L, 3 % saline can be given. In patients that are clinically stable, use of isotonic saline can improve sodium concentrations. Like in hypernatremia, correction velocity must not be >1 mmol/kg/h. Careful attention to fluid shifts and serial electrolyte monitoring is essential.

Hypocalcemia

Normal levels of serum calcium are normally achieved during the second week of life when PTH secretion from parathyroid glands can efficiently respond to hypocalcemic stimuli [59]. Before then, normal neonates spontaneously lean towards hypocalcemia. Actually, a physiologic fall in serum calcium concentration, after calcium supply from the placenta suddenly stops, occurs in the first 24 h of life. PTH is then stimulated but its action becomes valid from 2 to 3 days of life onward [60] . The kidney plays a key role in calcium homeostasis and, although the timing of the action of PTH on renal calcium excretion in neonates is not certain, calciuria increases after the second week of life [61].

NICU infants may develop hypocalcemia (<8.8 mg/dl or ionized calcium <4.9 mg/dl) for a number of reasons. When PTH secretion from immature parathyroid glands is insufficient, a prolongation or a worsening of hypocalcemia occurs (early onset neonatal hypocalcemia) [59]. Under these circumstances, hypocalcemia is rarely symptomatic but EKG alterations (Q-T prolongation) may be present [59]. Preterm infants and children of diabetic mothers [62] are more exposed to the risk of hypocalcemia. Approximately 50 % of infants of mothers who have diabetes show hypocalcemia [50].

The etiology of neonatal hypocalcemia is multifactorial. It is probably due to loss of calcium and magnesium with urine, resulting in reduced placental transfer and decreased neonatal secretion of PTH. Another risk factor for early onset hypocalcemia is maternal calcium ingestion during pregnancy, inducing inhibition of the neonate's PTH response and consequent hypocalcemia [63]. Hypocalcemia starting after 5–10 days of age is due to resistance of renal tubule cells to PTH leading to renal retention of phosphorus and hypocalcemia (late onset neonatal hypocalcemia) [59].

Overt hypoparathyroidism in neonates occurs in case of dysgenesis of the parathyroid glands. The most common cause is the DiGeorge syndrome, in which a maldevelopment of the third and fourth branchial pouches occurs. The phenotype is characterized by hypocalcemia caused by parathyroid gland hypoplasia, defective T-lymphocyte function and impaired cell-mediated immunity caused by impaired thymic differentiation and conotruncal defects of the heart or aortic arch. The syndrome is associated with microdeletions of chromosome 22q11.2 and some neonates may have isolated hypoparathyroidism. Also in the CATCH 22 syndrome (cardiac anomaly, abnormal facies, thymic aplasia, cleft palate, hypocalcaemia with deletion on chromosome 22) the loss of genes in the 22q11 region results in haploinsufficiency for genes located in this region and is associated with contiguous gene deletion syndromes that include not only the DiGeorge syndrome but also the overlapping conotruncal anomaly and velocardiofacial syndromes [59, 64].

In NICU patients, acquired hypocalcemia is frequently drug induced. Aminoglycosides, often used in NICU, can increase renal calcium loss and induce hypocalcemia in neonates [65]. Anticonvulsants such as phenytoin or phenobarbital are potential inducers of inducers of cytochrome P450 (CYP450), causing increased vitamin D degradation. Also, the prolonged use of anticonvulsant in the mother during pregnancy can induce hypocalcemia in the newborn [66]. Renal excretion of calcium is notably enhanced during treatment with loop diuretics. This concerns particular populations like infants with heart problems or after cardiosurgery. Ionized calcium also can be reduced in infants treated with sodium bicarbonate, which increases calcium binding to albumin.

Urgent treatment of neonatal hypocalcemia is based on i.v. calcium supply. Calcium gluconate and calcium chloride are both available at 10 % concentration. Both preparations have to be administered via a central vein. Although there is no proven superiority of one form over the other for the treatment of ionized hypocalcemia [67], calcium chloride appears to be more irritating for vessels and gluconate should be preferred in neonates. Calcium chloride contains three times more elemental calcium than gluconate (272 vs 90 mg in 10 ml at 10 %, respectively). Serum calcium levels should be corrected by continuous intravenous infusion of calcium (at 1–3 mg of elemental calcium/kg body weight/h) under strict monitoring of ionized calcium levels, in order to avoid complications as such as bradycardia and arrhythmia or vessel necrosis.

Hypercalcemia

Neonatal hypercalcemia is much less frequent than hypocalcemia. Infants normally show higher total (8.8–11.3 mg/dl) as well as ionized calcium levels (1.19–1.40 mmol/L) than older children or [57]. Hypercalcemia is often asymptomatic. Hypercalcemic infants can show irritability, dizziness and arterial hypertension. It is not infrequent that hypercalcemia is discovered after diagnosis of nephrocalcinosis or lithiasis.

Hypercalcemia in NICU infants is almost always iatrogenic [59]. Vitamin D and calcium supplementation are often cause of hypercalcemia. Hypophosphatemia is frequently seen in preterm neonates as a consequence of poor intake. Low phosphate levels stimulate PTH secretion which in turn increases intestinal calcium absorption and calcium resorption from the skeleton. Children on Extracorporeal Membrane Oxygenation (ECMO) experience hypercalcemia up to 30 % of patients, probably due to aberrant vitamin D-PTH regulation [68].

Rare congenital conditions must be considered in the presence of neonatal hypercalcemia. The calcium-sensing receptor (CASR) is expressed in the PTH producing chief cells of the parathyroid gland and the cells lining the kidney tubule. Inherited abnormalities of the CASR gene can cause either hypercalcemia or hypocalcemia. This autosomal recessive condition affects neonates and induces neonatal severe hyperparathyroidism (NSHPT) [69]. Hypercalcemia is usually severe and can be life-threatening. Typically, PTH levels are normal to high and calcium urinary excretion is low.

Subcutaneous fat necrosis (SFN) can be the consequence of a difficult delivery and is characterized by necrosis of fat and a local macrophagic reaction to the necrotic fat. Hypercalcemia derives from the excess of calcitriol produced by macrophages and is associated with a 15 % mortality rate [70]. Of interest, SFN with hypercalcemia has been recently associated with neonatal therapeutic hypothermia [71, 72]. Given the growing use of this therapy, blood calcium levels should be monitored in children undergoing therapeutic hypothermia.

Initial treatment of severe hypercalcemia in critical infants relies on hydration and loop diuretics. Calciuria can rapidly increase, which can worsen renal function and/or nephrocalcinosis. Withdrawal of hypercalcemic agents such as calcium supplements or vitamin D supplements is mandatory. Treatment of neonatal hyperparathyroidism is an urgent requirement. Steroids and biphosphonates have been used with success [73]. More recently, calcimimetic agent cinacalcet has been used successfully in neonatal hyperparathyroidism in combined treatment with biphosphonates [74].

Acute Kidney Injury (AKI) in Neonates

Definition and Epidemiology

Previously referred to as acute renal failure, acute kidney injury (AKI) is characterized by a sudden impairment in kidney function, which results in retention of nitrogenous waste products (urea for example) and altered regulation of extracellular fluid volume, electrolytes and acid-base homeostasis. The term “acute kidney injury” has replaced “acute renal failure” by most critical

care and nephrology societies primarily to highlight the importance of recognition of this process at the time of "injury" as opposed to waiting until "failure" has occurred [75].

Despite its limitations (as outlined above and in Chap. 46), SCr is the most commonly used measure to evaluate glomerular filtration in the clinical setting and is more specific than blood urea nitrogen (BUN). BUN is an insensitive measure of glomerular filtration rate (GFR) because it can be increased out of proportion to changes in GFR secondary to high dietary protein intake, gastrointestinal bleed, use of steroids and hypercatabolic states. If the BUN:SCr ratio exceeds 20, increased urea production or increased renal urea reabsorption that occurs in pre-renal azotemia should be suspected [76].

Historically the most common SCr cutpoint used to define neonatal AKI was set at an arbitrary cutoff of 1.5 mg/dL or greater, independent of day of life and regardless of the rate of urine output [77]. In 2009, we first used a categorical definition based on a rise in SCr to diagnose and define different stages of AKI [77]. Since then, we and others have used AKI definitions similar to those published by the 2007 AKIN and 2012 KDIGO guidelines [78–88]. A neonatal AKI definition has been adapted from the KDIGO definition (Table 48.3). The following modifications have been made to account for specific neonatal issues:

- Because SCr normally declines over the first week of life [13], each SCr is compared to lowest previous value.
- As SCr of 2.5 mg/dl represents glomerular filtration rate <10 ml/min/1.73 m^2 in neonates, this cutoff is used to define Stage 3 AKI (as opposed to 4.0 mg/dl in adults).
- UOP criteria have been adapted to levels obtained over 24 h.

Table 48.4 shows the incidence and outcomes of neonatal AKI in different neonatal populations using category AKI definitions similar to that presented here. However, more research is needed to develop, and validate this definition against hard clinical endpoints.

Risk Factors and Etiology

AKI is a common clinical condition in the NICU [85, 89–91]. Premature infants, sick near-term or term infants, and infants who undergo cardiopulmonary bypass or ECMO are at particular risk. Within each of these populations, the etiology and risk factors associated with the development of AKI vary. Also, since there is a wide variation in the incidence of AKI according to the AKI definition used and the number of SCr values measured, a uniform understanding of the risk factors for AKI is difficult to ascertain [89–95].

Table 48.3 Neonatal AKI definition

Stage	SCr criteria	Urine output (UOP criteria)
0	No change or rise <0.3 mg/dl	UOP >1 cc/kg/h (over previous 24 h)
1	↑ SCr of ≥0.3 mg/dl or ↑ SCr to 150–199 % × baseline	UOP >0.5 cc/kg/h and ≤1 cc/kg/h (over previous 24 h)
2	↑ SCr to 200–299 % × baseline	UOP >0.1 cc/kg/h and ≤0.5 cc/kg/h (over previous 24 h)
3	↑ SCr to ≥300 % × baseline or SCr ≥2.5 mg/dl or Receipt of dialysis	UOP ≤0.1 cc/kg/h (over previous 24 h)

Baseline SCr will be defined as the lowest previous SCr value

Table 48.4 Incidence and outcomes of neonates with AKI

Population	Incidence (%)	Mortality AKI v no AKI	Ref.
VLBW[a]	18	55 % vs. 5 %	[82]
ELBW[b]	12.5	70 % vs. 22 %	[89]
Sick near-term/term	18	22 % vs. 0 %	[78]
Sepsis	26	70 % vs 25 %	[90]
Asphyxiated Newborn	38	14 % vs. 2 %	[91]
ECMO[c]	71	72.7 % vs. 20 %[d]	[92]

[a]Very low birth weight (VLBW) infants <1500 g
[b]Extremely low birth weight (ELBS) infants <1000 g
[c]Extra Corporeal Membrane Oxygenation (ECMO)
[d]In group with highest stage of AKI

Table 48.5 Risk factors for AKI in neonates

Risk factors
Low birthweight
Prematurity
Perinatal asphyxia
5 min Apgar score ≤6
Hypotension
Respiratory distress syndrome
Heart failure
Urological anomalies
Dehydration
Sepsis
Nephrotoxic drugs
Umbelical artery catheters
Assisted ventilation
Inotropic support

The cause of AKI in neonates is multifactorial, and usually one or more perinatal contributing conditions coexist (Table 48.5). These conditions are important in identifying neonates at risk for development of AKI and because some of them are potentially preventable [96, 97]. The causes of AKI in newborns are typically divided into three groups: pre-renal failure, intrinsic renal failure and post-renal failure. Pre-renal and intrinsic renal failure both include congenital and acquired causes of AKI (Table 48.6) [89–94]. The most common form of AKI in neonates is pre-renal failure which accounts for more than 80 % of cases.

In numerous studies, *perinatal asphyxia and sepsis* are the most frequent associated conditions [90–92, 95, 97–99]. Asphyxia causes renal

Table 48.6 Causes of neonatal acute kidney injury

Prerenal	**Congenital malformations/antenatal damage**
Perinatal asphyxia/respiratory distress syndrome Hypovolemia/dehydration Hypotension Perinatal hemorrhage Necrotizing enterocolitis Sepsis Heart failure Congenital heart disease/cardiopulmonary bypass Nephrotoxic drugs: prostaglandin inhibitors, angiotensin –converting enzyme inhibitors, vasodilators	Maternal treatment: nonsteroidal anti-inflammatory drugs, converting enzyme inhibitors Intrauterine infections Congenital heart disease Congenital nephrotic syndrome Polycystic kidney disease Renal dysplasia/hypoplasia Congenital bilateral obstructive uropathies Neurogenic bladder
Intrinsic renal	**Acquired postnatal renal disease**
Acute tubular necrosis Cortico-medullary necrosis Congenital nephrotic syndrome Polycystic kidney disease Renal dysplasia/hypoplasia Vascular thrombosis (vein/artery) Disseminated intravascular coagulation Hemolytic uremic syndrome Isoimmune haemolytic disease with massive hemoglobinuria Acute pyelonephritis Infections/intrauterine infections Nephrotoxic drugs: aminoglycosides, amphotericin B, contrast media	Perinatal asphyxia/respiratory distress syndrome Hypovolemia/dehydratation Hypotension Perinatal hemorrhage Necrotizing enterocolitis Sepsis Heart failure Cardiac surgery/cardiopulmonary bypass Acute tubular necrosis Cortico-medullary necrosis Vascular thrombosis (vein/artery) Disseminated intravascular coagulation Hemolytic uremic syndrome Isoimmune haemolytic disease with massive hemoglobinuria Acute Pyelonephritis Nephrotoxic drugs: prostaglandin inhibitors, angiotensin –converting enzyme inhibitors, vasodilators, aminoglycosides, amphotericin B, contrast media
Postrenal	
Congenital bilateral obstructive uropathies Neurogenic bladder	

dysfunction secondary to redistribution of blood flow to more vital organs such as heart and brain at the expense of the others, especially kidneys and gut. The reported incidence of renal failure in asphyxiated neonates varies between 50 and 70 % [100–104]. In asphyxiated newborns, renal outcome correlates with oliguria but also with clinical markers of severity of asphyxia. In particular, Apgar score at 5 min <6 and hypoxic ischemic encephalopathy were much better predictors of adverse outcome than renal functional tests [102, 103].

Among the neonatal population, *premature infants* are particularly sensitive to asphyxia and hypoperfusion [82, 95]. Very low birth weight (VLBW) and extremely low birth weight (ELBW) children are at increased risk for AKI because of prenatal fetal distress secondary to intrauterine growth retardation and placental insufficiency and a postnatal course frequently complicated by hypotension and hypoxia and the need for cardio-pulmonary support. In the last 2 years, some studies focused their attention on AKI in VLBW/ELBW and reported an incidence of 12.5 % and 18 %, respectively [82, 95]. VLBW infants with AKI were more likely to have low birth weight, low gestational age and low Apgar scores and they frequently required umbilical arterial catheters, assisted ventilation and inotropic support. Conversely, Viswanathan et al. failed to demonstrate significant differences in demographic characteristics between patients with and without AKI. Nevertheless, infants with AKI had a higher mean airway pressure, a lower mean arterial blood pressure and higher exposure to cefotaxime than non-AKI controls [95].

Given the high vulnerability of the neonatal kidney to the effects of hypoperfusion, *acute tubular necrosis* (ATN) commonly occurs. Pre-renal failure is due to renal hypoperfusion or ischemia in the presence of a normal kidney. Hence, irrespective of whether pre-renal failure is caused by total body volume depletion or decreased effective blood volume, renal function quickly returns to normal if perfusion is rapidly restored. Conversely, if the insult is severe and prolonged, acute tubular necrosis can occur [89]. During renal hypoperfusion many compensatory mechanisms are activated; in particular intrarenal vasodilatory prostaglandins are released. In order to help differentiate pre-renal failure from ATN, urinary indices have been proposed, in particular urine sodium concentration and the fractional excretion of sodium (FENa) [105] (Table 48.7). The assumption is that renal tubules work properly in pre-renal failure and are able to reabsorb solute and water while they are damaged and do not adequately conserve sodium in ATN [2]. The urine samples for measuring indices must be obtained prior to a fluid and diuretic challenge. This could be difficult in oliguric neonates. Urine sodium less than 20 mEq/L and more than 50 mEq/L is suggestive of prerenal and intrinsic renal failure, respectively. FENa is calculated as urine sodium factored by serum sodium divided by urine creatinine factored by serum creatinine:

$$\text{FENa} = \text{urine sodium} \times \text{serum creatinine} / \text{serum sodium} \times \text{urine creatinine}$$

In term infants, a FENa above 3 % indicates intrinsic renal failure. Preterm babies physiologically lose more sodium than term infants and a FENa of more than 6 % can be used to define intrinsic AKI in infants between 29 and 32 weeks of gestation [92, 105].

Sepsis is the second most common condition associated with AKI after perinatal asphyxia [97]. AKI develops in 22–28 % of neonates with sepsis [91, 97, 99]. In a series of 200 neonates with sepsis, 52 (26 %) had AKI. Shock and low birth weight were good predictors of AKI in septic neonates. The latent period for the development of AKI in neonatal sepsis was short and AKI was oliguric only in 15 % of cases. Shock was also a significant predictor of fatality in these

Table 48.7 Urine indices to differentiate prerenal and intrinsic renal failure

Indices	Pre renal	Intrinsic renal
Urine sodium (mEq/L)	≤20–30	>40–50
Fractional excretion of sodium (FENa) (%)	<3	>3
FENa in term infants (%)	<1	>1

patients, being present in 97 % of those who died [99]. In developing country with limited resources, sepsis is more common than in developed countries [106] and is the most common cause of AKI in neonates, occurring in 31 % of newborns with a mortality rate of 65 % [98]. The pathogenesis of AKI in sepsis is multifactorial, including shock, disseminated intravascular coagulation, haemorrhage, cardiac failure, nephrotoxic drugs. All these conditions determine hypoperfusion.

Administration of *nonsteroidal anti-inflammatory drugs* (NSAID) (for instance, indomethacin for patent ductus arteriosus closure) can inhibit this compensatory mechanism and precipitate AKI during renal hypoperfusion. In a multicenter Italian Study, ibuprofen treatment of the neonate was identified as a risk factor correlated with impaired renal function and, interestingly, maternal consumption of NSAID during pregnancy negatively influence neonatal renal function as well [107]. *Antimicrobial agents* are another major class of drugs associated with the development of AKI in preterm infants. Nephrotoxic acute renal failure has been reported in association with aminoglycosides, acyclovir and amphotericin B [89]. In particular, aminoglycosides are widely used in pediatric patients. They accumulate in renal tubular cortical cells and exert nephrotoxicity causing damage of the epithelial cells of the proximal tubules secondary to lysosomal dysfunction [89, 108, 109]. Several studies have been performed to better understand the risk of nephrotoxicity associated with aminoglycoside therapy, A metanalysis analyzing 16 trials involving 823 neonates compared one dose per day to multiple doses per day of aminoglycoside and reported equal nephrotoxicity between the two regimens [110]. Similarly, in a recent Cochrane analysis considering 11 studies and 574 neonates once daily dosing did not lead to more nephrotoxicity than a twice-daily dosing regimen, and showed comparable efficacy [111].

In a study that included 81 consecutive cases of AKI in preterm infants in NICU, multivariate logistic regression analysis showed that ceftazidime administration was associated with a greater risk of AKI compared to the other variables selected from univariate analysis including ampicillin, ibuprofen and furosemide [107]. Cephalosporin antibiotics have also been implicated in a case-control study involving 46 matched pairs of infants with and without AKI. Infants who developed AKI had a significantly higher prior exposure to cefotaxime, benzodiazepines, diuretics, and dopamine/dobutamine [95].

Conservative Management of Neonatal AKI

Neonatal AKI is associated with a high morbidity and mortality. Unfortunately, very few trials designed to test interventions have been performed in the neonatal population. Management of AKI in newborns is therefore basically supportive and based on treatment of complications [85, 92, 112–114]. The first approach should be to precisely define the cause of AKI and to exclude pre-renal AKI [92, 113].

When, how much and how to implement a fluid challenge continues to be an area of controversy and active investigation. In the resuscitative phase, hypovolemia can be initially corrected by the administration of a *fluid challenge* of 20 ml/kg of normal saline in bolus. The Surviving Sepsis guideline recommends active fluid resuscitation to improve outcomes. However, a recent randomized trial of intravenous boluses in dehydrated African Children with severe infection did not show any benefit, and in fact showed improved survival in those randomized to care without an IV bolus [115]. After active resuscitation has occurred, the goals of therapy should be to limit the degree of fluid overload, meanwhile providing adequate nutrition and medications necessary to promote recovery. To prevent fluid overload, daily fluid input should not exceed insensible water losses (30 ml/Kg/day) plus urinary losses. To guarantee adequate energy and nutrient intake while maintaining restricted fluid intake, concentrated solutions should be used. The volume required to apply drugs should be minimized by administration of pure or highly concentrated infusion volumes [114]. Body

weight should be checked twice daily and the estimated fluid overload should be carefully assessed and tracked.

In order to maintain fluid balance and allow nutrition and drug infusions, *diuretics* are commonly used in patients with AKI. Studies in adult patients have not provided any evidence that diuretics improve survival or modify the course of AKI [116]. In young infants with AKI, furosemide use even was an independent predictor of poor renal outcome [117]. Nevertheless, diuretic use may facilitate clinical management by converting oliguric into non-oliguric AKI [116]. Although controlled study evidence is lacking, furosemide has been used in neonates with AKI to prevent progression to established renal damage. Intravenous furosemide boluses (1 mg/kg) have been adopted for the treatment of oliguria in this setting [118]. Studies in infants undergoing cardiac surgery suggest that continuous furosemide infusion is superior to intermittent bolus administration in improving urine output and spares cumulative dose of diuretic [119]. Recently, Bumetanide, a potent loop diuretic with similar pharmacologic characteristics as furosemide, was employed to increase urine output in preterm infants with oliguric AKI; while effectively increasing urine output the drug also caused a transient increase in serum creatinine levels, highlighting the nephrotoxic potential of loop diuretics in this vulnerable population [120, 121].

In order to improve urine output in critically ill term and preterm neonates, low dose *dopamine* has also been utilized [113]. Dopamine is an endogenous catecholamine that influences different catecholamine receptors in a dose-dependent manner, and, in particular, it has been claimed to induce a selective renal vasodilation at low dose [122]. In oliguric, non-hypotensive neonates, GFR and urine output increased significantly with dopamine infused at a rate of 2.5 μg/kg per min [123]. Moreover, dopamine induced renal and mesenteric vasodilation without an effect on cerebral blood flow when started precociously in preterm neonates treated with indomethacin for the presence of a patent ductus arteriosus [124]. However, an assessment of dopamine use in 19 NICUs and PICUs together with a literature review failed to demonstrate an improvement in renal function and urine output in neonates and pediatric intensive care patients [125]. Moreover, evidence emerged that dopamine may have detrimental effects by worsening renal perfusion in critically ill patients with AKI [126]. More recently, *Fenoldopam*, a selective dopamine A1 receptor agonist that decreases vascular resistance and increases renal blood flow, improved urine output in neonates requiring cardiac surgery with positive fluid balance despite diuretics [127]. However, in 40 infants undergoing cardiac surgery with cardiopulmonary bypass, Ricci et al. evaluated the effect of Fenoldopam infused at a low dose (0.1 μg/Kg/min) for 72 h starting soon after anesthesia. Fenoldopam did not produce effects on urine output, fluid balance and AKI incidence [128]. More recently, the same authors treated 40 infants undergoing cardiac surgery with a higher dose of Fenoldopam (1 μg/Kg/min) during cardiopulmonary bypass. They observed decreased urinary NGAL and cystatin C levels, but no difference in plasma creatinine and urine output between subjects receiving fenoldopam and placebo [129].

Perinatal asphyxia is the primary cause of AKI in neonates. During hypoxia and ischemia, adenosine is released and acts as a vasoconstrictive agent in the kidney contributing to a fall in glomerular filtration rate. In this setting, methylxanthines such as aminophylline and theophylline (non-specific *adenosine receptor antagonists*) can inhibit the vasoconstriction induced by adenosine [130, 131]. Three independent randomized trials in severe asphyxiated infants have shown that a single dose of theophylline, given early after birth, was associated with decrease in serum creatinine and improved urine output [130, 132–134]. Based on these findings, the KDIGO guidelines recommend a single dose of aminophylline for asphyxiated infants at risk for AKI. However, because theophylline has some potentially harmful neurologic effects and because therapeutic hypothermia is now standard of care in these infants, further comparative trials

are needed to determine whether these agents improve short-term and long-term renal and neurodevelopmental outcomes [135].

Few other studies have specifically addressed therapies for AKI in neonates. In a recent retrospective study of seven infants with hyperuricemia secondary to AKI treated with intravenous *rasburicase* administration of a single bolus determined a significant decrease of uric acid and creatinine and an increase of urine output within 24 h [136].

Drugs are common causes of AKI in neonates [107–109, 137]. In the setting of AKI, *evaluation of all medications* should be assessed to eliminate the potential use of nephrotoxic mediations, and to determine the proper dose of other medications in context of reduced renal function/drug clearance. Moreover, whenever possible, blood levels should be measured in order to maintain the levels in the therapeutic range and reduce the risk of nephrotoxicity [113, 114].

Electrolyte disorders and acidosis are common in neonates with AKI and may complicate the clinical course after AKI. For the management of electrolyte disorders we refer to the above sections of this chapter.

The degree of fluid overload is an independent predictor of mortality [138–141]. In a prospective study conducted on 58 neonates, those with AKI had more marked fluid overload and higher mortality rates over the first few days of life [142]. In a study of 154 newborns with AKI, fluid overload in excess of 7 % was independently associated with a 13-fold mortality risk [143].

Finally, efforts should be made to provide adequate *nutrition* in NICU patients with AKI [92, 112–114]. Trials in neonates are lacking but extrapolating data from critically ill children, underfeeding is common in AKI and it is important to ensure adequate caloric and protein intake in order to prevent catabolism [144]. This goal could be a challenge in oligo/anuric neonates and the risk of fluid overload should be carefully weighed against the risk of malnutrition. If nutrition cannot be provided due to risk of further fluid accumulation, initiation of renal replacement therapy should be considered.

Dialysis in Newborns

Over the past decades, technological advances and increased expertise have made it possible to support very small infants with dialysis. Nowadays, infants with AKI can receive all available dialysis modalities [142, 145, 146]. The choice of which form of renal support is used is dependent on institutional expertise, patient characteristics, and goals of therapy. Peritoneal dialysis (PD) has been extensively used in infants given its simplicity, ability to perform without sophisticated machines, and its slow, continuous action. It is usually well tolerated in small infants [147]. Hemodialysis (HD) can be performed in infants with good results, although poor vascular tolerance and the large extra-corporeal volume provide additional challenges [146]. In recent years, Continuous Renal Replacement Therapy (CRRT) has become the most popular form of treatment for children with AKI in the US, replacing in a large proportion the use of PD and HD [148]. By contrast, in a recent survey involving 34 European Pediatric Nephrology Centers PD was more commonly used in children with AKI than CRRT and HD (43 % vs 31 % and 26.5 %, respectively). Notably, the choice of PD relied mainly on clinical advantages and the simplicity of the method rather than on logistic or economic reasons (unpublished data).

The *indications* for the different renal support therapies for infants generally resemble those in older children, with some exceptions. General indications for therapy include severe hyperkalemia, intractable acidosis, uremia, fluid overload, prevention of fluid overload, inability to provide adequate nutrition due to concerns of fluid accumulation, and neonatal metabolic crisis from *neonatal hyperammonemia or leucinosis*.

Hyperammonemia is a severe clinical condition characterized by high ammonium levels, excess glutamine accumulation in astrocytes inducing cell swelling and brain edema. In most cases, it presents in full-term neonates with anorexia, seizures, lethargy, coma and death. Most frequently, it is caused by urea cycle defects (UCD) and organic acidurias (OA). The initial management of an undiagnosed hyperammonemia

includes stopping protein intake, intravenous glucose, and initiation of first-line medications including L-arginine, nitrogen scavengers, carbamylglutamate, carnitine, vitamin B12, and biotin. When conservative treatment fails and whenever there is severe symptomatic hyperammonemia, dialysis has to be rapidly established in order to avoid permanent neurological sequelae or death [149]. In leucinosis (maple syrup urine disease; MSUD), deficiency in branched chain ketoacid dehydrogenase leads to the accumulation of branched chains aminoacids (BCAA) leucine, isoleucine, and valine in cells and body fluids. Given the poor renal clearance of BCAA, their accumulation can cause neurologic damage. Medical treatment consists in incorporation of BCAA into protein synthesis with nutritional support but, like in hyperammonemia, it may not be successful and dialysis must be started to clear excess BCAA [150]. In both cases, extracorporeal dialysis provides higher clearances than PD [149, 151]. HD provides highest ammonium clearance [149] and it has been recommended as gold standard of therapy [152], although high volume CRRT (initially at 8 L/h/1.73 m^2) has been proposed as an alternative [149, 151, 153]. The practical application of CRRT in neonatal metabolic decompensation differs from that of AKI since it has been demonstrated in vitro that the clearance of ammonium and leucine achieved with CVVHD depend on dialysate flow rate, being substantially higher with increasing flow rates [151]. However, as in the case of AKI, there is no definite demonstrated association between a specific dialysis modality or of dialysis efficiency with survival. In the study of Schaefer et al. [151], out of nine patients the five with fastest depuration survived with no or mild neurological impairment while the other four died or survived with severe sequelae. By contrast, in the study of Pela et al. [154], four out of seven neonates with organic acidurias treated with PD survived with no or mild neurological impairment. Very likely, in these patients dialysis has to be regarded as a part of the overall treatment setting which includes the variable efficacy of pharmacological support and the timing of initiation of medical treatment and dialysis in the course of disease with a major modifying influence of the type of underlying metabolic defect on the final outcome.

The *choice of dialysis modality* in critical infants relies on the clinical goals, patient characteristics, and local expertise. Acute dialysis in infants with AKI is usually performed in NICU. Local expertise and facilities are determinant in addressing the dialysis modality choice. Dialysis in infants meets a number of difficulties. The most significant obstacle is represented by the *dialysis access*, both for PD and for extracorporeal dialysis.

Peritoneal dialysis (*PD*) is performed after placement of straight or "curled" infant catheters. This can happen by percutaneous placement or by surgery. Surgery usually provides better placement and less leakage problems [155], although PD catheter failure is highest in children below 6 months of age [156]. The fragility of the neonatal peritoneum requires operator experience. After catheter placement, leakage from catheter entrance, peritonitis, catheter obstruction, bleeding at catheter insertion, exit site infection and bowel perforation account for up to 50 % of all PD complications [145]. PD prescription in critical neonates is based on frequent, continuous exchanges, with low volumes of dialysate. Regardless whether the catheter is placed percutaneously or surgically, initial loads should be in a low range of 10–20 ml/kg of body weight. Larger loads may cause dialysate leakage and diaphragm lifting with respiratory complications [145]. Even with these small load volumes adequate ultrafiltration can be achieved [157]. Dwell times are usually short, down to 30–40 min in neonates. When large volumes of ultrafiltration are obtained, excessive sodium loss in the ultrafiltrate may occur. This loss is related to patient size and is most marked in neonates [158]. Oral, intravenous or intraperitoneal sodium supplementation may be needed. Starting with a standard glucose concentration (1.5 g/dl) is recommended to avoid initial hyperglycemia. Subsequently ultrafiltration rate must be monitored and dialysate glucose concentration adapted according to ultrafiltration needs.

Among the known advantages and disadvantages of each technique, some aspects peculiar to infants need to be stressed. With PD, good ultrafiltration rates can be achieved together with high small solute removal [159]. Hyperglycemia may sometimes complicate PD in neonates. The neonatal peritoneal membrane is particularly permeable and glucose in PD solutions diffuses into the mesenteric circulation more rapidly than in older patients [160, 161]. Deriving hyperglycemia may complicate PD in up to almost 50 % of cases [145] and it has been associated to mortality in infants and children after cardiosurgery [162]. Careful control of plasma glucose levels is therefore required in neonates on PD.

Before the advent and subsequent diffusion of extracorporeal continuous techniques, PD was the most utilized modality for dialysis treatment in infants [92]. Although to date it is not clear if a specific dialysis modality can influence the outcome, recently encouraging new data about PD outcomes in critical infants have been published. In 146 infants who underwent cardiopulmonary bypass surgery, Bojan et al. found a significant better survival at 30 and 90 days with "early" PD (started at the end of surgery or day after surgery) as compared with controls starting PD after the second day after surgery. Unfortunately, no assessment of fluid overload was recorded [163]. The impact of fluid overload on outcome in cardiosurgery infants was analyzed in the prospective trial of Sasser et al. [164], which sequentially evaluated two procedures: In the first study period, infants had only passive drainage of peritoneal fluid through a PD catheter placed at the time of surgery. In the second patient series PD was initiated at a mean of 2 h after arrival at the cardiac ICU. The infants receiving active PD had significantly more negative net fluid balance, lower mean inotrope score, lower serum cytokine concentrations and earlier sternal closure compared to the infants who had only their peritoneal fluid drained. Further analysis of these and other studies in infants who undergo cardiopulmonary bypass surgery suggest that attainment of a negative fluid balance is associated with improved survival and other clinical outcomes (Table 48.8). Taken together, early start of dialysis, avoidance of fluid overload and its consequent correction appear to favor a good outcome in critical infants and may be more important than the choice of treatment modality.

Vascular access for extracorporeal dialysis is often troublesome in infants and particularly neonates due to the mismatch between small vessel and the large diameter of the catheters required to obtain adequate blood flow. In a single center experience, of 174 children treated with CRRT,

Table 48.8 Time to dialysis start, percentage of patients reaching a negative fluid balance and survival rate of infants treated with PD after cardiopulmonary bypass surgery

Reference	n	Time to PD start	Patients with negative fluid balance (%)	Survivors (%)
Lowrie [226]	17	NA	35	24
Fleming [227]	21	2.5 days (1–6) after surgery	36	38
Golej [228]	116	NA, but 43 % of pts started on PD when CVP >10 mmHg	53	47
Werner [229]	23	2.6 ± 0.6 days	100	53
Dittrich [230]	27	In the OR or first hrs in ICU	100	73
Santos [231]	23	4.8 ± 16.8 h	100	57
Sorof [232]	20	22 h	100	80
Chien [233]	7	1.2 ± 0.4 days after AKI onset	NA	57

Data of the literature. Only in studies showing 100 % of patients reaching negative fluid balance with PD, survivor's percentage was 50 % or more

13 (7.4%) presented problems of venous catheterization; this complication was significantly more common in children under 12 months of age and in those weighing less than 10 kg [165]. In the largest available series of venous catheterizations in children and infants from the ppCRRT Registry, 5-French catheters showed the poorest survival, none of them lasting more than 20 h. Catheterization of the internal jugular vein and the use of CVVHD was found to be associated with best catheter survival [166]. The most commonly used CRRT catheters in neonates are dual-lumen, low resistance catheters. 6.5–7 F caliber and 7.5 cm length appears a good compromise between catheter diameter, vessel size, inner resistance and adequate blood flow. As an alternative, El Masri et al. recently demonstrated the successful use of two single-lumen 4 or 5 Fr catheters [167].

Blood flow is mainly dependent on vascular access performance. It is usually prescribed as 5–10 ml/kg body weight; in patients with need for a high clearance rate (e.g., hyperammonemic crisis) the maximally achievable flow rate should be used and will be rate limiting for the efficacy of purification.

There are few reports on the use of *intermittent hemodialysis* (*HD*) in neonates with AKI. HD is mainly used in metabolic crisis and intoxications, when urgent toxic compound removal is needed (see indications paragraph). In 1994, Sadowski described 33 acute infants weighing less than 5 kg [146] treated with intermittent HD. A high rate of hypotensive episodes was reported (64%), as well as a survival rate (52%) not different from that of subsequent studies utilizing CRRT [168]. This indicates that HD in neonates is probably tolerated less well than PD and CRRT while confirming that survival is mostly affected by the underlying disease rather than by dialysis characteristics.

Continuous Renal Replacement Therapy (*CRRT*) allows to accomplish metabolic and fluid control throughout 24 h, as opposed to the transient correction achieved by intermittent HD. Due to precision of monitoring and to the high clearance obtained in very small patients, CRRT has become most popular in critical infants [148]. In infants, the adaptation of CRRT monitors originally conceived for adults with the introduction of pediatric software and miniaturized circuits yielded a substantial improvement in dialysis treatment of infants [169]. Still, problems of accuracy for tiny volumes and, mainly, of blood priming remain. In particular, smallest circuits have blood priming volumes around 100 ml, largely exceeding the recommended 10% of blood volume of the infant [169]. This poses problems in the phase of preparation and a blood transfusion is needed in smallest patients to pre-prime the circuit. The large ECV also causes a dilution effect of platelets and coagulation factors which predispose the patient to bleeding. Similarly, blood restitution at the end of the session needs to be closely controlled and circuit blood is partially wasted or simply lost. In Tables 48.9 and 48.10 a list of currently available filters and monitors for neonates is provided.

Convective transport (achieved by *continuous venovenous hemofiltration*, *CVVH*) is theoretically indicated when the main target is the removal of large solutes. Among these, inflammation mediators are of particular importance in sepsis and SIRS. In this regard, it is of interest that most mediators are removed by adsorption and acrylonitril membranes provide

Table 48.9 Commercially available filters for neonatal CRRT

Filter	Manufacturer	Surface (m^2)	Membrane	Priming (ml)
Miniflow 10	Gambro-Lundia	0.045	AN69	3.5
Minifilter	Minntech	0.07	Polysulfone	6
Carpediem 1	Bellco	0.075	Polysulfone	27.2 (circuit)
Carpediem 3	Bellco	0.245	Polysulfone	41.5 (circuit)
HF20	Gambro-Lundia	0.20	AN69	60 (circuit)

Main characteristics

Table 48.10 Main commercially available monitors for pediatric and neonatal CRRT. Main characteristics

Monitor	Manufacturer	Pediatric lines	Neonatal lines	Blood pump range (ml/min)	Blood flow step-by[a]step increase (ml/min)	Fluid management range (ml/h)
Prismaflex[a]	Gambro-Lundia	yes	–	20–100	2	50–2500
Multifiltrate	Fresenius	yes	–	10–100	2	10–7000
Aquarius	Baxter	yes	–	10–200	2	50–11,000
Plasauto Sigma	Asahi	yes	yes	1–400	1	10–12,000
Carpediem	Bellco	–	yes	2–50	1	10–300

[a]Prismaflex equipped with HF20 circuit

highest removal [170]. Acrylonitril membranes have been recently made available for infant circuits [169].

Pre-filter administration of the replacement fluid (pre-dilution) is preferred in infants, given the low blood flow rate predisposing to hemoconcentration and filter clotting. At steady blood flow, the exchanged volume represents dialysis efficiency in CVVH. Diffusive solute transport (achieved by *continuous venovenous hemodialysis*, *CVVHD*) is indicated when aiming for rapid small solute removal. Diffusion and convection may be combined to exploit the advantages of both modalities (CVVHDF) and when removal of middle-sized molecules (which can be removed by convection but not diffusion) is needed.

No official recommendations for *depuration efficiency* in critical infants exist. In the ppCRRT Registry, no difference in survival was found between CRRT modalities, and between children receiving either less or more than 2 L/h/1.73 m^2 clearance [140]. In adults, high-flow rates in CRRT have been associated with hypophosphatemia [171]. Moreover, drug removal by CRRT is dependent on purification efficiency and often unpredictable, due to different prescription regimens, down time and mode of administration [172]. Given the inverse relationship between CRRT efficiency and patient volume and the lack of a clear association between CRRT dose and outcome in adults [171, 173] and children [140], in infants with AKI the search for a high dialysis dose is secondary to maintenance of fluid balance, nutrition adequacy, vascular stability and, above all, appropriate levels of essential drugs, like antimicrobials. A filtration rate of 2000 ml/h/1.73 m^2 seems appropriate in neonates with AKI.

Differently from HD, most commercially available monitors for CRRT are lacking a heating system or are equipped with heaters unsuitable for accurate heat preservation [174]. Heat loss with CRRT has been described in adults and was not found associated with major problems [175]. Given the immaturity of neonatal thermoregulation, CRRT induced heat loss could hamper the thermal protection adopted in NICU, especially in low birth weight neonates, with unpredictable consequences on vascular stability and survival [176].

Recently, a specific CRRT machine dedicated to newborns and small infants in the weight range of 2.0–9.9 kg has been realized (CARPEDIEM®, Bellco). This machine provides extraordinary accuracy in blood pump and fluid balance with a blood priming volume ranging 27–42 ml, according to three presently available circuits [181]. In 2014, Coulthard et al. showed the ability of a syringe-driven machine, the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS), to provide better clearance and more accurate ultrafiltration than peritoneal dialysis [177]. The device withdraws 5–12.5 ml aliquots of blood from a single-lumen central venous line, runs it across a dialysis filter and returns it back through a syringe pump. Askenazi et al. have adapted the Aquadex ultrafiltration system to provide CVVH to neonates (unpublished). These new promising approaches open new perspectives to the extracoporeal treatment of neonates with AKI [178].

Neonates are at an intrinsically high risk of hemorrhage, and extracorporeal treatment modalities are clearly fraught with an increased risk of hemorrhage in children and neonates with AKI if compared with PD [179]. Surprisingly little published information is available concerning *anticoagulation* for extracorporeal dialysis in neonates. In the ppCRRT registry, small children <10 kg were more likely to receive heparin anticoagulation compared to citrate regional anticoagulation [142].

Both heparin and low-molecular weight heparin (LMWH) are recommended [180]. Unfractioned heparin is used at 5–25 IU/kg/h both for hemodialysis and CRRT [180]. The increased bleeding risk in neonates on extracorporeal treatment mandates a most accurate control of coagulation with frequent activated clotting time (ACT) or activated partial thromboplastin time (aPTT) measurement at the bedside and consequent adjustments of heparin dose. As in older children, ACT has to be kept between 150 and 200 s. and aPTT between 40 and 65 s. In neonates with thromboembolic disease, low molecular weight heparin (LMWH) compounds reportedly need to be administered at higher doses in neonates than in older patients to obtain adequate therapeutic anti-Xa levels [180, 181]. Pre-term children need LMWH doses as high as 200 IU/kg every 12 h.

Experience with citrate anticoagulation in neonates is still limited but deserves further investigation given the high risk of bleeding in these patients. In older children citrate does not provide longer circuit lifespan than the heparin but clearly reduces bleeding complications [182]. The use of citrate regional anticoagulation in smaller children can be more challenging for several reasons. First, because traditional CRRT machines require a minimum blood flow, the amount of blood flow/kg is significantly higher in small compared to bigger children. Because the citrate dose is dependent on blood flow, the amount of citrate used in small children is therefore also higher, and may require higher clearance rates to achieve target levels. Furthermore, premature infants are born with immature liver function. Soltisiak et al. recently showed that in critically ill children with a low body weight, regional citrate anticoagulation using Prismocitrate (18/0) appeared to be safe and easy to use with less circuit clotting compared to heparin anticoagulation [183].

Outcomes of Neonatal AKI

AKI is associated with significant mortality in critically ill children [184, 185] and adults [186–190], even after controlling for medical co-morbidities, severity of illness scores, and patient demographics. Over the past few years, epidemiological studies in a several high-risk groups of neonates have been performed, including very low birth weight infants, near term/term infants with perinatal depression, neonates with severe asphyxia undergoing hypothermia, neonates receiving extra-corporeal membrane oxygenation and infants with cardiopulmonary bypass – associated AKI. Using contemporary, categorical AKI frameworks such as modifications of the AKIN [77] and RIFLE classification systems [184, 186] that allow for improved diagnosis and staging of AKI by severity, these studies have provided some evidence that AKI is independently associated with mortality in neonates and young infants even when controlling for potentially confounding demographics, co-morbidities, and interventions.

Very Low Birth Weight (VLBW) Infants

Koralkar et al. [82] published a prospective study in 229 VLBW infants (500–1500 g). Using a neonatal AKI definition similar to Table 48.3, they found that 41/229 (18 %) of the cohort developed AKI (Stage 1 = 10, stage 2 = 10; stage 3 = 21). Infants with AKI were more likely to have lower birth weight, gestational age, and Apgar scores, as well as higher rates of assisted ventilation and inotropic support. In the AKI group, 42 % died, compared with 5 % children in without AKI. The association of AKI with mortality was largely confirmed when controlling for multiple confounders [adjusted HR = 2.3 (95 % CI = 0.9, 5.8); $P = 0.06$]. Viswanathan et al. [98]

performed a retrospective analysis on 472 extremely low birth weight infants (<1000 g). Using SCr ≥1.5 mg/dl as a cutoff to define AKI, the incidence of AKI was 12.5 %. When matching AKI and non-AKI children for time period, birth weight and gestational age in a case-control design, mortality in the AKI cases was 33/46 (70 %) compared to 10/46 (22 %) in the controls (p < 0.001).

Sick Near Term/Term Infants

Askenazi et al. recently reported on 58 neonates with birth weight >2000 g and 5-min Apgar score ≤7 admitted to level 2/3 NICU [80]. AKI (defined according to Table 48.3) occurred in 16 %. All infants without AKI survived while 2/9 (22 %) of those with AKI died (p value < 0.001).

Infants with Perinatal Asphyxia Treated with Hypothermia

Selewski et al. retrospectively analyzed 96 infants who received therapeutic hypothermia [81]. Using the AKIN definition for AKI, they found that 38 % of the infants developed AKI. Only 1/58 (2 %) infants without AKI died, as compared to 5/36 (14 %) with AKI. The children who developed AKI required longer duration of mechanical ventilation and had a longer NICU and hospital stay.

Infants Who Receive Extra-Corporeal Membrane Oxygenation (ECMO)

In a large retrospective cohort study using data from the Extracorporeal Life Support Organization (ELSO) registry, Askenazi et al. evaluated the impact of AKI and renal support therapy (RST) in infants who received ECMO for non-cardiac reasons [77]. AKI was defined as SCr ≥1.5 at any time point during the hospital stay. Among 7941 neonates, 27.4 % died. Non-survivors had higher rates of AKI (19 % vs. 3.9 %) and renal support therapy (RST) than survivors (39.7 % vs. 16 %). After adjusting for numerous confounding variables, both AKI (odds ratio 3.2; $P < 0.0001$) and RST (odds ratio 1.9; $P < .0001$) remained significant risk factors for death. Two smaller studies also had similar findings. In a retrospective chart review of infants with congenital diaphragmatic hernia requiring ECMO, Gadepalli et al. found 48/68 patients (71 %) had AKI by the RIFLE classification [99]. Patients with AKI "failure" (300 % rise in SCr) had increased time on ECMO, decreased ventilator free days, and decreased survival (27.3 % with "failure" vs. 80 % without AKI, $P = 0.001$). Shuhaiber et al. also found higher rates of AKI in non-survivors vs. survivors (80 % vs. 40 %, $P = 0.03$) among 20 patients (75 % neonates) requiring more than one ECMO run after congenital heart surgery [100].

Infants Who Undergo Cardiopulmonary Bypass (CPB) Surgery

Outcomes after AKI in infants undergoing CPB have been recently reported in three studies. Blinder et al. conducted a retrospective chart review of 430 infants (<90 days, median age 7 days) with CPB 101). Using a modified AKIN definition (which included urine output criteria) they documented AKI in 52 % of the infants (stage 1 = 133, stage 2 = 60, stage 3 = 30). Post-operative AKI of all stages was associated with longer ICU stay; AKI stages 2 and 3 were associated with increased risk of prolonged mechanical ventilation and need for post-operative inotropic therapy. The mortality rate in those with AKI was higher than in those without [12 % vs. 3 %, $P < 0.001$]. Moreover, risk of death increased with AKI severity [Stage 2 OR 5.1; Stage 3 OR 9.5]. Krawczeski et al. evaluated 374 patients (including 35 neonates) undergoing CPB surgery [102]. They defined AKI as an absolute increase in SCr ≥0.3 mg/dL from baseline within 48 h of surgery and found that 8 of the 35 neonates (23 %) had AKI by median 1 day after CPB. No differences in mortality were seen between neonates with and without AKI in this small neonatal subset. Alabbas et al. retrospectively analyzed 122 infants who received cardiopulmonary bypass surgery [103]. Using the AKIN definition, the incidence of AKI was 76 / 122 (62 %) (AKI stage 1 = 22; stage 2 = 19; stage 3 = 33). Severe stage 3 AKI was associated with mortality (OR 6.7) and longer ICU stay (HR = 9.1).

Outcomes of Neonates Treated with Renal Support Therapy for AKI

The interpretation of outcome of infants treated with dialysis is hampered by several problems. In retrospective studies, the main problem is the lack of a univocal AKI definition. More than 30 AKI definitions have been proposed and this weakens our ability to compare studies [109]. Secondly, treatment choices are usually made according to local availability and expertise rather than medical criteria. Thirdly, modality changes and modality assignment according to severity of illness are, more or less intentionally, common practice. Finally, major challenges for prospective studies are the paucity of patients, ethical issues regarding randomized designs, and frequently the logistic and organizational difficulties of performing clinical research in the ICU setting.

While there are no controlled studies on this issue, the outcomes of critical neonates treated with dialysis are generally unfavorable [159, 161, 172] and the in-hospital stay is complicated [173]. A recent survey in the US showed that in 10,322 hospitalized children the in-hospital mortality and length of stay were higher in children ≤1 month of age and in patients needing dialysis [172]. The most important outcomes information in infants with AKI treated with dialysis comes from the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry. In this registry, the cohort of children <10 kg (n = 84) had lower survival rates than children >10 kg (n = 166) (43 % vs 64 %). Not differently from older children, fluid overload (FO), high PRISM2 score and urine output at dialysis initiation were found to be associated with mortality. In particular, patients with FO >20 % at the time of CRRT initiation had an almost five times higher odds ratio of death than those who initiated CRRT with <10 % FO. In regard to dialysis treatment, significantly better survival was found in patients able to achieve dry weight during CRRT. Briefly, these data indicate that an established fluid overload predisposes to a poor outcome but its correction may reverse this association and, therefore, should be further studied [161].

Long-Term Effects of Prematurity and AKI on CKD

Chronic kidney disease (CKD) affects 26 million adult Americans and likely has its origins in early life, as links between prematurity/low birth weight and chronic kidney disease in adulthood become increasingly apparent [191]. Pre-term delivery disrupts nephrogenesis, which is usually not complete until around 34–36 weeks gestation. A small number of autopsy studies have suggested that nephrogenesis continues for only a short time after birth [9, 192, 193]. The remaining nephrons hypertrophy to compensate for decreased nephron mass and, according to Brenner's hypothesis, the resultant "hyperfiltration" eventually becomes deleterious and leads to glomerulosclerosis with sodium retention, systemic hypertension, proteinuria and progressive chronic kidney disease [194]. Thus, premature birth may 'prime' infants for kidney injury and chronic kidney disease. Indeed, premature infants with a birthweight less than 2500 g have nearly twice the odds of having low glomerular filtration rate, microalbuminuria, end-stage renal disease and hypertension than their term counterparts [195].

Moreover, the impact of additional AKI events in the NICU on long-term kidney and health outcomes is not yet known. Previously, it was assumed that subjects who survive an episode of AKI would recover kidney function without long-term sequelae; however, recent data from animals [196], critically ill children [197, 198] and adults [199–211] suggest that AKI survivors are indeed at risk for development of CKD. In a recent meta-analysis, adults with AKI had an almost ninefold risk to develop incident CKD, a threefold risk to progress to end-stage kidney disease and a doubled mortality risk compared to patients without AKI [212].

The role that AKI plays in the development of CKD in the infant population is still unknown. Several case reports document that CKD can develop in infants who had AKI; however, these studies are small single center retrospective reports [89, 213]. Human autopsy and animal studies suggest that AKI affects post-natal nephron development. Premature

infants who suffer AKI were shown to have fewer layers of nephrons and abnormally configured glomeruli compared to term neonates [9, 193]. Large prospective cohort studies designed to determine risk factors for long-term CKD are urgently needed to define the most appropriate surveillance protocols and identify the subjects at greatest risk.

Future Directions in Neonatal AKI

Over the last few years, our understanding of neonatal AKI has improved and we now have clear epidemiological evidence that suggest that AKI is common and associated with mortality in this age group. New AKI definitions based on SCr, urine output, Cystatin C and emergent urinary biomarkers promise to improve our ability to reliably define neonatal AKI. Studies in VLBW neonates [214, 215], infants undergoing cardiopulmonary bypass surgery [216–224], and other sick NICU patients suggest that these biomarkers can predict a subsequent rise in SCr (Fig. 48.3) as well as mortality [80]. However, large comparative studies will be required to determine which functional and kidney injury biomarkers can best predict hard clinical outcomes. Importantly, the normal ranges of urine biomarkers in premature neonates will require careful validation since excretion varies by gestational age, probably due tubular immaturity [214]. With better definitions and earlier indicators of AKI, we will be able to better understand the risk factors, develop preventive strategies, and timely apply appropriate management to improve the outcomes in those at risk for AKI.

Another emerging breakthrough regards the provision of extracorporeal treatments for neonates. Thanks to major technological advances, dialysis machines miniaturized for the specific needs of neonates have recently been developed and are currently undergoing clinical testing [177, 225]. Maximizing the efficiency and safety of renal support therapies with these devices will change our approach to the neonate with AKI. One day soon, any infant who could benefit from renal support therapy will no longer be left without an appropriate and safe treatment option.

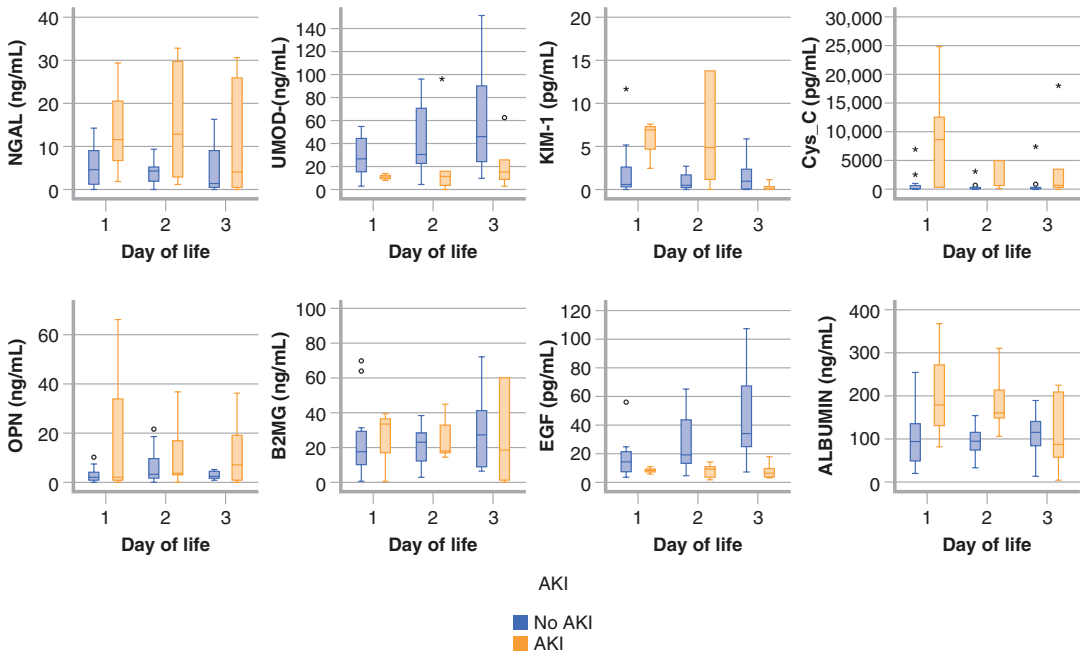

Fig. 48.3 Urine biomarkers differ in sick pre-term/term neonates (>2500 g) with vs. without acute kidney injury (Used with permission from Elsevier from Askenazi et al. [80])

References

1. Rudolph AH, Teramo M, et al. Studies on the circulation of the previable fetus. Pediatr Res. 1971;5: 452–65.
2. Jose PA, Fildes RD, Gomez RA, Chevalier RL, Robillard JE. Neonatal renal function and physiology. Curr Opin Pediatr. 1994;6(2):172–7.
3. Yao LP, Jose PA. Developmental renal hemodynamics. Pediatr Nephrol. 1995;9(5):632–7.
4. Paton JB, Fisher DE, DeLannoy CW, Behrman RE. Umbilical blood flow, cardiac output, and organ blood flow in the immature baboon fetus. Am J Obstet Gynecol. 1973;117(4):560–6.
5. Gruskin AB, Edelmann Jr CM, Yuan S. Maturational changes in renal blood flow in piglets. Pediatr Res. 1970;4(1):7–13.
6. Evan Jr AP, Stoeckel JA, Loemker V, Baker JT. Development of the intrarenal vascular system of the puppy kidney. Anat Rec. 1979;194(2):187–99.
7. Chikkannaiah P, Roy M, Kangle R, Patil PV. Glomerulogenesis: can it predict the gestational age? A study of 176 fetuses. Indian J Pathol Microbiol. 2012;55(3):303–7.
8. Abrahamson DR. Glomerulogenesis in the developing kidney. Semin Nephrol. 1991;11(4):375–89.
9. Rodriguez MM, Gomez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. Pediatr Dev Pathol. 2004;7(1): 17–25.
10. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth S. Formulas to estimate GFR in children with chronic kidney disease. J Am Soc Nephrol. 2009;20(3):629–37.
11. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol (Berlin, Germany). 2007; 22(11):1839–48.
12. Brion LP, Fleischman AR, McCarton C, Schwartz GJ. A simple estimate of glomerular filtration rate in low birth weight infants during the first year of life: noninvasive assessment of body composition and growth. J Pediatr. 1986;109(4):698–707.
13. Gallini F, Maggio L, Romagnoli C, Marrocco G, Tortorolo G. Progression of renal function in preterm neonates with gestational age < or = 32 weeks. Pediatr Nephrol (Berlin, Germany). 2000;15(1–2):119–24.
14. Lolekha PH, Jaruthunyaluck S, Srisawasdi P. Deproteinization of serum: another best approach to eliminate all forms of bilirubin interference on serum creatinine by the kinetic Jaffe reaction. J Clin Lab Anal. 2001;15(3):116–21.
15. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatr. 1984;104(6): 849–54.
16. Demirel G, Celik IH, Canpolat FE, Erdeve O, Biyikli Z, Dilmen U. Reference values of serum cystatin C in very low-birthweight premature infants. Acta Paediatr. 2013;102(1):e4–7.
17. Kandasamy Y, Smith R, Wright IM. Measuring cystatin C to determine renal function in neonates. Pediatr Care Med: J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2013;14(3):318–22.
18. Sulyock E. Neonates. In: WE BTAEH, editor. Pediatric nephrology: Lippincott, Williams and Wilkins; Philadelphia, PA 1999.
19. Guignard J. Renal morphogenesis and development of renal function. In: Taeusch HE, Ballard RA, Gleason CA, editors. Avery's diseases of the newborn. 8th ed. Philadelphia: Elsevier Saunders; 2005. p. 1257–66.
20. Goldstein L. Renal ammonia and acid excretion in infant rats. Am J Physiol. 1970;218(5):1394–8.
21. Quigley R, Baum M. Neonatal acid base balance and disturbances. Semin Perinatol. 2004;28(2):97–102.
22. Day R, Franklin J. Renal carbonic anhydrase in premature and mature infants. Pediatrics. 1951;7(2): 182–5.
23. Linder N, Hammel N, Hernandez A, Fridman E, Dlugy E, Herscovici T, et al. Intestinal perforation in very-low-birth-weight infants with necrotizing enterocolitis. J Pediatr Surg. 2013;48(3):562–7.
24. Merlob P, Litwin A, Mor N. Possible association between acetazolamide administration during pregnancy and metabolic disorders in the newborn. Eur J Obstet Gynecol Reprod Biol. 1990;35(1):85–8.
25. Taeusch HE, Ballard RA, Gleason CA, editors. Avery's diseases of the newborn. 8th ed. Philadelphia: Elsevier Saunders; 2005.
26. Ozand PT, Gascon GG. Organic acidurias: a review. Part 2. J Child Neurol. 1991;6(4):288–303.
27. Yurdakok M. What next in necrotizing enterocolitis? Turk J Pediatr. 2008;50(1):1–11.
28. Johnson PJ. Sodium bicarbonate use in the treatment of acute neonatal lactic acidosis: benefit or harm? Neonatal Netw: NN. 2011;30(3):199–205.
29. Lokesh L, Kumar P, Murki S, Narang A. A randomized controlled trial of sodium bicarbonate in neonatal resuscitation-effect on immediate outcome. Resuscitation. 2004;60(2):219–23.
30. Kette F, Weil MH, Gazmuri RJ. Buffer solutions may compromise cardiac resuscitation by reducing coronary perfusion pressure. JAMA. 1991;266(15): 2121–6.
31. Papile LA, Burstein J, Burstein R, Koffler H, Koops B. Relationship of intravenous sodium bicarbonate infusions and cerebral intraventricular hemorrhage. J Pediatr. 1978;93(5):834–6.
32. Parker MJ, Parshuram CS. Sodium bicarbonate use in shock and cardiac arrest: attitudes of pediatric acute care physicians. Crit Care Med. 2013;41(9):2188–95.
33. Niermeyer S, Kattwinkel J, Van Reempts P, Nadkarni V, Phillips B, Zideman D, et al. International guidelines for neonatal resuscitation: an excerpt from the guidelines 2000 for cardiopulmonary resuscitation

and emergency cardiovascular care: international consensus on science. Contributors and reviewers for the neonatal resuscitation guidelines. Pediatrics. 2000;106(3):E29.
34. van Thiel RJ, Koopman SR, Takkenberg JJ, Ten Harkel AD, Bogers AJ. Metabolic alkalosis after pediatric cardiac surgery. Eur J Cardiothorac Surg. 2005;28(2):229–33.
35. Wong HR, Chundu KR. Metabolic alkalosis in children undergoing cardiac surgery. Crit Care Med. 1993;21(6):884–7.
36. Tutay GJ, Capraro G, Spirko B, Garb J, Smithline H. Electrolyte profile of pediatric patients with hypertrophic pyloric stenosis. Pediatr Emerg Care. 2013;29(4):465–8.
37. Kundak AA, Dilli D, Karagol B, Karadag N, Zenciroglu A, Okumus N, et al. Non benign neonatal arrhythmias observed in a tertiary neonatal intensive care unit. Indian J Pediatr. 2013;80(7):555–9.
38. Gruskay J, Costarino AT, Polin RA, Baumgart S. Nonoliguric hyperkalemia in the premature infant weighing less than 1000 grams. J Pediatr. 1988;113(2):381–6.
39. Jeffery J, Sharma A, Ayling RM. Detection of haemolysis and reporting of potassium results in samples from neonates. Ann Clin Biochem. 2009;46(Pt 3):222–5.
40. Masilamani K, van der Voort J. The management of acute hyperkalaemia in neonates and children. Arch Dis Child. 2012;97(4):376–80.
41. Greenough A, Emery EF, Brooker R, Gamsu HR. Salbutamol infusion to treat neonatal hyperkalaemia. J Perinat Med. 1992;20(6):437–41.
42. Gruy-Kapral C, Emmett M, Santa Ana CA, Porter JL, Fordtran JS, Fine KD. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. J Am Soc Nephrol. 1998;9(10):1924–30.
43. Ohlsson A, Hosking M. Complications following oral administration of exchange resins in extremely low-birth-weight infants. Eur J Pediatr. 1987;146(6):571–4.
44. Malone TA. Glucose and insulin versus cation-exchange resin for the treatment of hyperkalemia in very low birth weight infants. J Pediatr. 1991; 118(1):121–3.
45. Vemgal P, Ohlsson A. Interventions for non-oliguric hyperkalaemia in preterm neonates. Cochrane Database Syst Rev. 2012;(5):CD005257.
46. Australian Resuscitation C, New Zealand Resuscitation C. Medications and fluids in paediatric advanced life support. ARC and NZRC guideline 2010. Emerg Med Australas: EMA. 2011;23(4):405–8.
47. Chevalier RL. The moth and the aspen tree: sodium in early postnatal development. Kidney Int. 2001;59(5):1617–25.
48. Hartnoll G, Betremieux P, Modi N. Randomised controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants. Arch Dis Child Fetal Neonatal Ed. 2000;82(1):F24–8.
49. Modi N. Sodium intake and preterm babies. Arch Dis Child. 1993;69(1 Spec No):87–91.
50. Baraton L, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Roze JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. Pediatrics. 2009;124(4): e655–61.
51. Ertl T, Hadzsiev K, Vincze O, Pytel J, Szabo I, Sulyok E. Hyponatremia and sensorineural hearing loss in preterm infants. Biol Neonate. 2001;79(2): 109–12.
52. Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol (Berlin, Germany). 2005;20(12):1687–700.
53. Prempunpong C, Efanov I, Sant'anna G. The effect of the implementation of therapeutic hypothermia on fluid balance and incidence of hyponatremia in neonates with moderate or severe hypoxic-ischaemic encephalopathy. Acta Paediatr. 2013;102(11):e507–13.
54. Segar JL. Neonatal diuretic therapy: furosemide, thiazides, and spironolactone. Clin Perinatol. 2012; 39(1):209–20.
55. Hoch M, Netz H. Heart failure in pediatric patients. Thorac Cardiovasc Surg. 2005;53 Suppl 2:S129–34.
56. Edjo Nkilly G, Michelet D, Hilly J, Diallo T, Greff B, Mangalsuren N, et al. Postoperative decrease in plasma sodium concentration after infusion of hypotonic intravenous solutions in neonatal surgery. Br J Anaesth. 2014;112(3):540–5.
57. Sumpelmann R, Mader T, Dennhardt N, Witt L, Eich C, Osthaus WA. A novel isotonic balanced electrolyte solution with 1 % glucose for intraoperative fluid therapy in neonates: results of a prospective multicentre observational postauthorisation safety study (PASS). Paediatr Anaesth. 2011;21(11):1114–8.
58. von Rosenstiel N, von Rosenstiel I, Adam D. Management of sepsis and septic shock in infants and children. Paediatr Drugs. 2001;3(1):9–27.
59. Hsu SC, Levine MA. Perinatal calcium metabolism: physiology and pathophysiology. Semin Neonatol: SN. 2004;9(1):23–36.
60. Saggese G, Baroncelli GI, Bertelloni S, Cipolloni C. Intact parathyroid hormone levels during pregnancy, in healthy term neonates and in hypocalcemic preterm infants. Acta Paediatr Scand. 1991;80(1):36–41.
61. Karlen J, Aperia A, Zetterstrom R. Renal excretion of calcium and phosphate in preterm and term infants. J Pediatr. 1985;106(5):814–9.
62. Barnes-Powell LL. Infants of diabetic mothers: the effects of hyperglycemia on the fetus and neonate. Neonatal Netw : NN. 2007;26(5):283–90.
63. Borkenhagen JF, Connor EL, Stafstrom CE. Neonatal hypocalcemic seizures due to excessive maternal calcium ingestion. Pediatr Neurol. 2013;48(6):469–71.

64. Stevens CA, Carey JC, Shigeoka AO. Di George anomaly and velocardiofacial syndrome. Pediatrics. 1990;85(4):526–30.
65. Chiruvolu A, Engle WD, Sendelbach D, Manning MD, Jackson GL. Serum calcium values in term and late-preterm neonates receiving gentamicin. Pediatr Nephrol (Berlin, Germany). 2008;23(4):569–74.
66. Friis B, Sardemann H. Neonatal hypocalcaemia after intrauterine exposure to anticonvulsant drugs. Arch Dis Child. 1977;52(3):239–41.
67. Cote CJ, Drop LJ, Daniels AL, Hoaglin DC. Calcium chloride versus calcium gluconate: comparison of ionization and cardiovascular effects in children and dogs. Anesthesiology. 1987;66(4):465–70.
68. Hak EB, Crill CM, Bugnitz MC, Mouser JF, Chesney RW. Increased parathyroid hormone and decreased calcitriol during neonatal extracorporeal membrane oxygenation. Intensive Care Med. 2005;31(2): 264–70.
69. Pacifici GM. Clinical pharmacology of the loop diuretics furosemide and bumetanide in neonates and infants. Paediatr Drugs. 2012;14(4):233–46.
70. Marx SJ, Attie MF, Spiegel AM, Levine MA, Lasker RD, Fox M. An association between neonatal severe primary hyperparathyroidism and familial hypocalciuric hypercalcemia in three kindreds. N Engl J Med. 1982;306(5):257–64.
71. Akcay A, Akar M, Oncel MY, Kizilelma A, Erdeve O, Oguz SS, et al. Hypercalcemia due to subcutaneous fat necrosis in a newborn after total body cooling. Pediatr Dermatol. 2013;30(1):120–3.
72. Strohm B, Hobson A, Brocklehurst P, Edwards AD, Azzopardi D, Register UTC. Subcutaneous fat necrosis after moderate therapeutic hypothermia in neonates. Pediatrics. 2011;128(2):e450–2.
73. Allgrove J. Use of bisphosphonates in children and adolescents. J Pediatr Endocrinol Metab. 2002;15 Suppl 3:921–8.
74. Wilhelm-Bals A, Parvex P, Magdelaine C, Girardin E. Successful use of bisphosphonate and calcimimetic in neonatal severe primary hyperparathyroidism. Pediatrics. 2012;129(3):e812–6.
75. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
76. Feld LG, Springate JE, Fildes RD. Acute renal failure. I. Pathophysiology and diagnosis. J Pediatr. 1986;109(3):401–8.
77. Askenazi DJ, Griffin R, McGwin G, Carlo W, Ambalavanan N. Acute kidney injury is independently associated with mortality in very low birthweight infants: a matched case-control analysis. Pediatr Nephrol (Berlin, Germany). 2009;24(5):991–7.
78. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol (Berlin, Germany). 2013;28(4):661–6.
79. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr. 2013;162(4):725–29.e1.
80. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Parwar P, Sonjara S, et al. Urine biomarkers predict acute kidney injury in newborns. J Pediatr. 2012;161(2):270–5 e1.
81. Askenazi DJ, Montesanti A, Hunley H, Koralkar R, Pawar P, Shuaib F, et al. Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants. J Pediatr. 2011;159(6):907–12 e1.
82. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. Pediatr Res. 2011;69(4):354–8.
83. Phelps CM, Eshelman J, Cruz ED, Pan Z, Kaufman J. Acute kidney injury after cardiac surgery in infants and children: evaluation of the role of angiotensin-converting enzyme inhibitors. Pediatr Cardiol. 2012;33(1):1–7.
84. Aydin SI, Seiden HS, Blaufox AD, Parnell VA, Choudhury T, Punnoose A, et al. Acute kidney injury after surgery for congenital heart disease. Ann Thorac Surg. 2012;94(5):1589–95.
85. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr. 2012;24(2):191–6.
86. Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Crit Care Med. 2011;39(6):1493–9.
87. Bagga A, Bakkaloglu A, Devarajan P, Mehta RL, Kellum JA, Shah SV, et al. Improving outcomes from acute kidney injury: report of an initiative. Pediatr Nephrol (Berlin, Germany). 2007;22(10): 1655–8.
88. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):179–84.
89. Andreoli SP. Acute renal failure in the newborn. Semin Perinatol. 2004;28(2):112–23.
90. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? Pediatr Nephrol (Berlin, Germany). 2009;24(2):265–74.
91. Agras PI, Tarcan A, Baskin E, Cengiz N, Gurakan B, Saatci U. Acute renal failure in the neonatal period. Ren Fail. 2004;26(3):305–9.
92. Gouyon JB, Guignard JP. Management of acute renal failure in newborns. Pediatr Nephrol (Berlin, Germany). 2000;14(10–11):1037–44.
93. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. J Thorac Cardiovasc Surg. 2012;143(2):368–74.

94. Drukker A, Guignard JP. Renal aspects of the term and preterm infant: a selective update. Curr Opin Pediatr. 2002;14(2):175–82.
95. Viswanathan S, Manyam B, Azhibekov T, Mhanna MJ. Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. Pediatr Nephrol (Berlin, Germany). 2012;27(2): 303–11.
96. Walker MW, Clark RH, Spitzer AR. Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk. J Perinatol. 2011;31(3):199–205.
97. Mortazavi F, Hosseinpour Sakha S, Nejati N. Acute kidney failure in neonatal period. Iran J Kidney Dis. 2009;3(3):136–40.
98. Vachvanichsanong P, McNeil E, Dissaneevate S, Dissaneewate P, Chanvitan P, Janjindamai W. Neonatal acute kidney injury in a tertiary center in a developing country. Nephrol Dial Transplant. 2012;27(3):973–7.
99. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006;73(6):499–502.
100. Karlowicz MG, Adelman RD. Nonoliguric and oliguric acute renal failure in asphyxiated term neonates. Pediatr Nephrol (Berlin, Germany). 1995;9(6):718–22.
101. Gupta BD, Sharma P, Bagla J, Parakh M, Soni JP. Renal failure in asphyxiated neonates. Indian Pediatr. 2005;42(9):928–34.
102. Durkan AM, Alexander RT. Acute kidney injury post neonatal asphyxia. J Pediatr. 2011;158(2 Suppl):e29–33.
103. Aggarwal A, Kumar P, Chowdhary G, Majumdar S, Narang A. Evaluation of renal functions in asphyxiated newborns. J Trop Pediatr. 2005;51(5):295–9.
104. Kaur S, Jain S, Saha A, Chawla D, Parmar VR, Basu S, et al. Evaluation of glomerular and tubular renal function in neonates with birth asphyxia. Ann Trop Paediatr. 2011;31(2):129–34.
105. Subramanian S, Agarwal R, Deorari AK, Paul VK, Bagga A. Acute renal failure in neonates. Indian J Pediatr. 2008;75(4):385–91.
106. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375(9730):1969–87.
107. Cuzzolin L, Fanos V, Pinna B, di Marzio M, Perin M, Tramontozzi P, et al. Postnatal renal function in preterm newborns: a role of diseases, drugs and therapeutic interventions. Pediatr Nephrol (Berlin, Germany). 2006;21(7):931–8.
108. Twombley K, Baum M, Gattineni J. Accidental and iatrogenic causes of acute kidney injury. Curr Opin Pediatr. 2011;23(2):208–14.
109. Taber SS, Mueller BA. Drug-associated renal dysfunction. Crit Care Clin. 2006;22(2):357–74, viii.
110. Nestaas E, Bangstad HJ, Sandvik L, Wathne KO. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2005;90(4): F294–300.
111. Rao SC, Srinivasjois R, Hagan R, Ahmed M. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2011;(11):CD005091.
112. Kumar G, Vasudevan A. Management of acute kidney injury. Indian J Pediatr. 2012;79(8):1069–75.
113. Sweetman DU, Riordan M, Molloy EJ. Management of renal dysfunction following term perinatal hypoxia-ischaemia. Acta Paediatr. 2013;102(3):233–41.
114. Moghal NE, Embleton ND. Management of acute renal failure in the newborn. Semin Fetal Neonatal Med. 2006;11(3):207–13.
115. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364(26):2483–95.
116. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL. High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Am J Kidney Dis. 2004;44(3):402–9.
117. Chiravuri SD, Riegger LQ, Christensen R, Butler RR, Malviya S, Tait AR, et al. Factors associated with acute kidney injury or failure in children undergoing cardiopulmonary bypass: a case-controlled study. Paediatr Anaesth. 2011;21(8):880–6.
118. Moghal NE, Shenoy M. Furosemide and acute kidney injury in neonates. Arch Dis Child Fetal Neonatal Ed. 2008;93(4):F313–6.
119. Luciani GB, Nichani S, Chang AC, Wells WJ, Newth CJ, Starnes VA. Continuous versus intermittent furosemide infusion in critically ill infants after open heart operations. Ann Thorac Surg. 1997;64(4):1133–9.
120. Oliveros M, Pham JT, John E, Resheidat A, Bhat R. The use of bumetanide for oliguric acute renal failure in preterm infants. Pediatr Care Med: J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2011;12(2):210–4.
121. Cotton R, Suarez S, Reese J. Unexpected extra-renal effects of loop diuretics in the preterm neonate. Acta Paediatr. 2012;101(8):835–45.
122. Seri I, Abbasi S, Wood DC, Gerdes JS. Regional hemodynamic effects of dopamine in the sick preterm neonate. J Pediatr. 1998;133(6):728–34.
123. Lynch SK, Lemley KV, Polak MJ. The effect of dopamine on glomerular filtration rate in normotensive, oliguric premature neonates. Pediatr Nephrol. 2003;18(7):649–52.
124. Seri I, Abbasi S, Wood DC, Gerdes JS. Regional hemodynamic effects of dopamine in the indomethacin-treated preterm infant. J Perinatol. 2002;22(4):300–5.
125. Prins I, Plotz FB, Uiterwaal CS, van Vught HJ. Low-dose dopamine in neonatal and pediatric intensive care: a systematic review. Intensive Care Med. 2001;27(1):206–10.

126. Lauschke A, Teichgraber UK, Frei U, Eckardt KU. 'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure. Kidney Int. 2006;69(9):1669–74.
127. Costello JM, Thiagarajan RR, Dionne RE, Allan CK, Booth KL, Burmester M, et al. Initial experience with fenoldopam after cardiac surgery in neonates with an insufficient response to conventional diuretics. Pediatr Care Med: J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2006;7(1):28–33.
128. Ricci Z, Stazi GV, Di Chiara L, Morelli S, Vitale V, Giorni C, et al. Fenoldopam in newborn patients undergoing cardiopulmonary bypass: controlled clinical trial. Interact Cardiovasc Thorac Surg. 2008;7(6):1049–53.
129. Ricci Z, Luciano R, Favia I, Garisto C, Muraca M, Morelli S, et al. High-dose fenoldopam reduces postoperative neutrophil gelatinase-associated lipocaline and cystatin C levels in pediatric cardiac surgery. Crit Care. 2011;15(3):R160.
130. Jenik AG, Ceriani Cernadas JM, Gorenstein A, Ramirez JA, Vain N, Armadans M, et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics. 2000;105(4):E45.
131. Lynch BA, Gal P, Ransom JL, Carlos RQ, Dimaguila MA, Smith MS, et al. Low-dose aminophylline for the treatment of neonatal non-oliguric renal failure-case series and review of the literature. J Pediatr Pharmacol Ther: JPPT: Off J PPAG. 2008;13(2):80–7.
132. Bakr AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia – a study in a developing country. Pediatr Nephrol. 2005;20(9):1249–52.
133. Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: a randomized, placebo-controlled trial. J Pediatr. 2006;149(2):180–4.
134. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis. 2009;3(4):222–6.
135. Tsai HM. The kidney in thrombotic thrombocytopenic purpura. Minerva Med. 2007;98(6):731–47.
136. Hobbs DJ, Steinke JM, Chung JY, Barletta GM, Bunchman TE. Rasburicase improves hyperuricemia in infants with acute kidney injury. Pediatr Nephrol. 2010;25(2):305–9.
137. Cataldi L, Leone R, Moretti U, De Mitri B, Fanos V, Ruggeri L, et al. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. Arch Dis Child Fetal Neonatal Ed. 2005;90(6):F514–9.
138. Gillespie RS, Seidel K, Symons JM. Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. Pediatr Nephrol (Berlin, Germany). 2004;19(12):1394–9.
139. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med. 2004;32(8):1771–6.
140. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int. 2005;67(2):653–8.
141. Sutherland SM, Zappitelli M, Alexander SR, Chua AN, Brophy PD, Bunchman TE, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis: Off J Natl Kidney Found. 2010;55(2):316–25.
142. Askenazi DJ, Goldstein SL, Koralkar R, Fortenberry J, Baum M, Hackbarth R, et al. Continuous renal replacement therapy for children </=10 kg: a report from the prospective pediatric continuous renal replacement therapy registry. J Pediatr. 2013;162(3):587–92 e3.
143. Duzova A, Bakkaloglu A, Kalyoncu M, Poyrazoglu H, Delibas A, Ozkaya O, et al. Etiology and outcome of acute kidney injury in children. Pediatr Nephrol (Berlin, Germany). 2010;25(8):1453–61.
144. Kyle UG, Akcan-Arikan A, Orellana RA, Coss-Bu JA. Nutrition support among critically ill children with AKI. Clin J Am Soc Nephrol. 2013;8(4):568–74.
145. Hakan N, Aydin M, Zenciroglu A, Aydog O, Erdogan D, Karagol BS, et al. Acute peritoneal dialysis in the newborn period: a 7-year single-center experience at tertiary neonatal intensive care unit in Turkey. Am J Perinatol. 2014;31(4):335–8.
146. Sadowski RH, Harmon WE, Jabs K. Acute hemodialysis of infants weighing less than five kilograms. Kidney Int. 1994;45(3):903–6.
147. Barratt TM. Renal failure in the first year of life. Br Med Bull. 1971;27(2):115–21.
148. Warady BA, Bunchman T. Dialysis therapy for children with acute renal failure: survey results. Pediatr Nephrol (Berlin, Germany). 2000;15(1–2):11–3.
149. Picca S, Dionisi-Vici C, Abeni D, Pastore A, Rizzo C, Orzalesi M, et al. Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators. Pediatr Nephrol. 2001;16(11):862–7.
150. Jouvet P, Jugie M, Rabier D, Desgres J, Hubert P, Saudubray JM, et al. Combined nutritional support and continuous extracorporeal removal therapy in the severe acute phase of maple syrup urine disease. Intensive Care Med. 2001;27(11):1798–806.
151. Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Dialysis in neonates with inborn errors of metabolism. Nephrol Dial Transplant. 1999;14(4):910–8.

152. Summar M. Current strategies for the management of neonatal urea cycle disorders. J Pediatr. 2001;138(1 Suppl):S30–9.
153. Haberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis. 2012;7:32.
154. Pela I, Seracini D, Donati MA, Lavoratti G, Pasquini E, Materassi M. Peritoneal dialysis in neonates with inborn errors of metabolism: is it really out of date? Pediatr Nephrol. 2008;23(1):163–8.
155. Chadha V, Warady BA, Blowey DL, Simckes AM, Alon US. Tenckhoff catheters prove superior to cook catheters in pediatric acute peritoneal dialysis. Am J Kidney Dis. 2000;35(6):1111–6.
156. Stone ML, LaPar DJ, Barcia JP, Norwood VF, Mulloy DP, McGahren ED, et al. Surgical outcomes analysis of pediatric peritoneal dialysis catheter function in a rural region. J Pediatr Surg. 2013;48(7): 1520–7.
157. Golej J, Kitzmueller E, Hermon M, Boigner H, Burda G, Trittenwein G. Low-volume peritoneal dialysis in 116 neonatal and paediatric critical care patients. Eur J Pediatr. 2002;161(7):385–9.
158. Paulson WD, Bock GH, Nelson AP, Moxey-Mims MM, Crim LM. Hyponatremia in the very young chronic peritoneal dialysis patient. Am J Kidney Dis. 1989;14(3):196–9.
159. Ricci Z, Morelli S, Ronco C, Polito A, Stazi GV, Giorni C, et al. Inotropic support and peritoneal dialysis adequacy in neonates after cardiac surgery. Interact Cardiovasc Thorac Surg. 2008;7(1): 116–20.
160. Fischbach M. Peritoneal dialysis prescription for neonates. Perit Dial Int. 1996;16 Suppl 1:S512–4.
161. Warady BA, Alexander SR, Hossli S, Vonesh E, Geary D, Watkins S, et al. Peritoneal membrane transport function in children receiving long-term dialysis. J Am Soc Nephrol. 1996;7(11):2385–91.
162. Egi M, Morimatsu H, Toda Y, Matsusaki T, Suzuki S, Shimizu K, et al. Hyperglycemia and the outcome of pediatric cardiac surgery patients requiring peritoneal dialysis. Int J Artif Organs. 2008;31(4):309–16.
163. Bojan M, Gioanni S, Vouhe PR, Journois D, Pouard P. Early initiation of peritoneal dialysis in neonates and infants with acute kidney injury following cardiac surgery is associated with a significant decrease in mortality. Kidney Int. 2012;82(4):474–81.
164. Sasser WC, Dabal RJ, Askenazi DJ, Borasino S, Moellinger AB, Kirklin JK, et al. Prophylactic peritoneal dialysis following cardiopulmonary bypass in children is associated with decreased inflammation and improved clinical outcomes. Congenit Heart Dis. 2014;9(2):106–15.
165. Santiago MJ, Lopez-Herce J, Urbano J, Solana MJ, del Castillo J, Ballestero Y, et al. Complications of continuous renal replacement therapy in critically ill children: a prospective observational evaluation study. Crit Care. 2009;13(6):R184.
166. Hackbarth R, Bunchman TE, Chua AN, Somers MJ, Baum M, Symons JM, et al. The effect of vascular access location and size on circuit survival in pediatric continuous renal replacement therapy: a report from the PPCRRT registry. Int J Artif Organs. 2007;30(12):1116–21.
167. El Masri K, Jackson K, Borasino S, Law M, Askenazi D, Alten J. Successful continuous renal replacement therapy using two single-lumen catheters in neonates and infants with cardiac disease. Pediatr Nephrol (Berlin, Germany). 2013;28(12): 2383–7.
168. Symons JM, Chua AN, Somers MJ, Baum MA, Bunchman TE, Benfield MR, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol: CJASN. 2007; 2(4):732–8.
169. Rodl S, Marschitz I, Mache CJ, Koestenberger M, Madler G, Zobel G. Continuous renal replacement therapy with Prismaflex HF20 disposable set in children from 4 to 15 kg. Asaio J. 2011;57(5):451–5.
170. Bouman CS, van Olden RW, Stoutenbeek CP. Cytokine filtration and adsorption during pre- and postdilution hemofiltration in four different membranes. Blood Purif. 1998;16(5):261–8.
171. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361(17):1627–38.
172. Thompson AJ. Drug dosing during continuous renal replacement therapies. J Pediatr Pharmacol Ther: JPPT: Off J PPAG. 2008;13(2):99–113.
173. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359(1):7–20.
174. Hothi DK, St George-Hyslop C, Geary D, Bohn D, Harvey E. Continuous renal replacement therapy (CRRT) in children using the AQUARIUS. Nephrol Dial Transplant. 2006;21(8):2296–300.
175. Yagi N, Leblanc M, Sakai K, Wright EJ, Paganini EP. Cooling effect of continuous renal replacement therapy in critically ill patients. Am J Kidney Dis. 1998;32(6):1023–30.
176. Thermal protection of the newborn: a practical guide. Geneva: World Health Organization, 1997 WHO/RHT/MSM/97.2
177. Coulthard MG, Crosier J, Griffiths C, Smith J, Drinnan M, Whitaker M, et al. Haemodialysing babies weighing <8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): comparison with peritoneal and conventional haemodialysis. Pediatr Nephrol (Berlin, Germany). 2014;29(10): 1873–81.
178. Ronco C, Garzotto F, Ricci Z. CA.R.PE.DI.E.M. (Cardio-Renal Pediatric Dialysis Emergency Machine): evolution of continuous renal replace-

ment therapies in infants. A personal journey. Pediatr Nephrol. 2012;27(8):1203–11.
179. Kreuzer M, Ehrich JH, Pape L. Haemorrhagic complications in paediatric dialysis-dependent acute kidney injury: incidence and impact on outcome. Nephrol Dial Transplant. 2010;25(4):1140–6.
180. Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e737S–801.
181. Chander A, Nagel K, Wiernikowski J, Paes B, Chan AK. Evaluation of the use of low-molecular-weight heparin in neonates: a retrospective, single-center study. Clin Appl Thromb Hemost: Off J Int Acad Clin Appl Thromb/Hemost. 2013;19(5):488–93.
182. Brophy PD, Somers MJ, Baum MA, Symons JM, McAfee N, Fortenberry JD, et al. Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant. 2005;20(7):1416–21.
183. Soltysiak J, Warzywoda A, Kocinski B, Ostalska-Nowicka D, Benedyk A, Silska-Dittmar M, et al. Citrate anticoagulation for continuous renal replacement therapy in small children. Pediatr Nephrol (Berlin, Germany). 2014;29(3):469–75.
184. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028–35.
185. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and epidemiology of acute kidney injury varies with definition interpretation. Clin J Am Soc Nephrol: CJASN. 2008;3(4):948–54.
186. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int. 2008;73(5):538–46.
187. Cuhaci B. More data on epidemiology and outcome of acute kidney injury with AKIN criteria: benefits of standardized definitions, AKIN and RIFLE classifications. Crit Care Med. 2009;37(9):2659–61.
188. Uchino S. Outcome prediction for patients with acute kidney injury. Nephron Clin Pract. 2008;109(4):c217–23.
189. Macedo E, Castro I, Yu L, Abdulkader RR, Vieira Jr JM. Impact of mild acute kidney injury (AKI) on outcome after open repair of aortic aneurysms. Ren Fail. 2008;30(3):287–96.
190. Bagshaw SM, George C, Bellomo R. Changes in the incidence and outcome for early acute kidney injury in a cohort of Australian intensive care units. Crit Care. 2007;11(3):R68.
191. Carmody JB, Charlton JR. Short-term gestation, long-term risk: prematurity and chronic kidney disease. Pediatrics. 2013;131(6):1168–79.
192. Faa G, Gerosa C, Fanni D, Nemolato S, Locci A, Cabras T, et al. Marked interindividual variability in renal maturation of preterm infants: lessons from autopsy. J Matern Fetal Neonatal Med. 2010;23 Suppl 3:129–33.
193. Sutherland MR, Gubhaju L, Moore L, Kent AL, Dahlstrom JE, Horne RS, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. J Am Soc Nephrol. 2011;22(7):1365–74.
194. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens. 1988;1(4 Pt 1):335–47.
195. White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. Am J Kidney Dis: Off J Natl Kidney Found. 2009;54(2):248–61.
196. Basile DP. The endothelial cell in ischemic acute kidney injury: implications for acute and chronic function. Kidney Int. 2007;72(2):151–6.
197. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3–5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006;69(1):184–9.
198. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis: Off J Natl Kidney Found. 2012;59(4):523–30.
199. Weiss AS, Sandmaier BM, Storer B, Storb R, McSweeney PA, Parikh CR. Chronic kidney disease following non-myeloablative hematopoietic cell transplantation. Am J Transplant. 2006;6(1):89–94.
200. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA. 2009;302(11):1179–85.
201. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med. 2008;168(6):609–16.
202. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76(8):893–9.
203. Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. Nephrol Dial Transplant. 2010;25(7):2203–9.
204. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376(9758):2096–103.
205. James MT, Ghali WA, Tonelli M, Faris P, Knudtson ML, Pannu N, et al. Acute kidney injury following

coronary angiography is associated with a long-term decline in kidney function. Kidney Int. 2010;78(8):803–9.
206. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223–8.
207. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med. 2011;171(3): 226–33.
208. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, Go AS. Nonrecovery of kidney function and death after acute on chronic renal failure. Clin J Am Soc Nephrol. 2009;4(5):891–8.
209. Choi AI, Li Y, Parikh C, Volberding PA, Shlipak MG. Long-term clinical consequences of acute kidney injury in the HIV-infected. Kidney Int. 2010;78(5):478–85.
210. Ando M, Ohashi K, Akiyama H, Sakamaki H, Morito T, Tsuchiya K, et al. Chronic kidney disease in long-term survivors of myeloablative allogeneic haematopoietic cell transplantation: prevalence and risk factors. Nephrol Dial Transplant. 2010;25(1):278–82.
211. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int. 2009;76(10):1089–97.
212. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5): 442–8.
213. Abitbol CL, Bauer CR, Montane B, Chandar J, Duara S, Zilleruelo G. Long-term follow-up of extremely low birth weight infants with neonatal renal failure. Pediatr Nephrol (Berlin, Germany). 2003;18(9):887–93.
214. Askenazi D, Koralkar R, Levitan EB, Goldstein SL, Devarajan P, Khandrika S, Mehta R, Ambalavanan N. Baseline values of candidate urine Acute Kidney Injury (AKI) biomarkers vary by gestational age in premature infants. Pediatr Res. 2011;70(3):302–6.
215. Lavery AP, Meinzen-Derr JK, Anderson E, Ma Q, Bennett MR, Devarajan P, et al. Urinary NGAL in premature infants. Pediatr Res. 2008;64(4):423–8.
216. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol: CJASN. 2008;3(3):665–73.
217. Devarajan P, Krawczeski CD, Nguyen MT, Kathman T, Wang Z, Parikh CR. Proteomic identification of early biomarkers of acute kidney injury after cardiac surgery in children. Am J Kidney Dis: Off J Natl Kidney Found. 2010;56(4):632–42.
218. Koyner JL, Garg AX, Shlipak MG, Patel UD, Sint K, Hong K, et al. Urinary cystatin C and acute kidney injury after cardiac surgery. Am J Kidney Dis: Off J Natl Kidney Found. 2013;61(5):730–8.
219. Krawczeski CD, Goldstein SL, Woo JG, Wang Y, Piyaphanee N, Ma Q, et al. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass. J Am Coll Cardiol. 2011;58(22):2301–9.
220. Krawczeski CD, Woo JG, Wang Y, Bennett MR, Ma Q, Devarajan P. Neutrophil gelatinase-associated lipocalin concentrations predict development of acute kidney injury in neonates and children after cardiopulmonary bypass. J Pediatr. 2011;158(6): 1009–15 e1.
221. Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, et al. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers. 2009;14(6):423–31.
222. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365(9466): 1231–8.
223. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, et al. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2006;70(1):199–203.
224. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol: CJASN. 2010;5(3):395–401.
225. Ronco C, Davenport A, Gura V. The future of the artificial kidney: moving towards wearable and miniaturized devices. Nefrol: Publicacion Oficial Soc Esp Nefrol. 2011;31(1):9–16.
226. Lowrie LH. Renal replacement therapies in pediatric multiorgan dysfunction syndrome. Pediatr Nephrol. 2000;14(1):6–12. PMID: 10654321.
227. Fleming F, Bohn D, Edwards H, Cox P, Geary D, McCrindle BW, et al. Renal replacement therapy after repair of congenital heart disease in children. A comparison of hemofiltration and peritoneal dialysis. J Thorac Cardiovasc Surg. 1995;109(2):322–31. PMID: 7853885.
228. Golej J, Kitzmueller E, Hermon M, Boigner H, Burda G, Trittenwein G. Low-volume peritoneal dialysis in 116 neonatal and paediatric critical care patients. Eur J Pediatr. 2002;161(7):385–9. Epub 2002 May 9. PMID: 12111191.
229. Werner HA, Wensley DF, Lirenman DS, LeBlanc JG. Peritoneal dialysis in children after cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1997;113(1):64–8; discussion 68–70. PMID: 9011703.
230. Dittrich S, Dähnert I, Vogel M, Stiller B, Haas NA, Alexi-Meskishvili V, et al. Peritoneal dialysis after infant open heart surgery: observations in 27 patients. Ann Thorac Surg. 1999;68(1):160–3. PMID: 10421133.

231. Santos CR, Branco PQ, Gaspar A, Bruges M, Anjos R, Gonçalves MS, et al. Use of peritoneal dialysis after surgery for congenital heart disease in children. Perit Dial Int. 2012;32(3):273–9. doi: 10.3747/pdi.2009.00239. Epub 2011 May 31. PMID: 21632441; PMCID: PMC3525423.
232. Sorof JM, Stromberg D, Brewer ED, Feltes TF, Fraser CD Jr. Early initiation of peritoneal dialysis after surgical repair of congenital heart disease. Pediatr Nephrol. 1999;13(8):641–5. PMID: 10502118.
233. Chien CC, Wang HY, Chien TW, Kan WC, Su SB, Lin CY. A reference equation for objectively adjusting dwell volume to obtain more ultrafiltration in daily practice of peritoneal dialysis. Ren Fail. 2010;32(2):185–91. doi: 10.3109/08860220903541127. PMID: 20199180.