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Briefly Legal: Delayed Blood Transfusion Leads to Loss of Kidneys for Two Children

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Case 1

The patient is a 34-year-old G3P1 admitted at 34 5/7 with mild vaginal bleeding and regular uterine contractions. Her prenatal course had been uneventful, except for a positive Group B Streptococcus culture. A fetal ultrasound showed an anterior low-lying placenta. On admission, steroids, tocolysis with Mg sulfate, and antibiotics (ampicillin) were started. Six days after admission, an emergency cesarean section was performed because of persistent vaginal bleeding. During the procedure, the placenta was incised with the immediate onset of profuse bleeding. There was no mention of the urgency or maneuvers during the procedure. The time from incision to delivery was 20 minutes.

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The 2500 gram AGA male baby was limp and extremely pale at delivery. He was breathing spontaneously and was given blow-by oxygen. Apgar scores were 4 and 5. at 1 and 5-minutes, respectively. The estimated blood loss was 1000 ml. Neither cord gases nor the placenta was sent for evaluation.

At 14 minutes of life, the baby was admitted to the Newborn Intensive Care Unit, where the heart rate (HR) was 90 beats per minute (bpm), with shallow respirations, weak pulses, poor perfusion, and blood pressure (BP) of 37/20 (mean 26 mmHg). He was intubated for apnea and placed on a low ventilator setting with inspired oxygen of 30%. An umbilical arterial catheter (UAC) was inserted, but the attempts to insert an umbilical venous catheter failed. An arterial blood gas drawn at one hour of life revealed a pH of 7.06, a pC02 of 17 mmHg, a p02 of 303 mmHg, and a base deficit of 24.

The baby continued to be pale, with weak pulses poor perfusion with diastolic pressures in the teens. A complete blood count (CBC) revealed a WBC of 16,700 x10^3/uL, hemoglobin of 6 gm/dL, and a platelet count of 236 10^3/mL. At one hour and 3 hours after birth, 21 ml of normal saline (NS) was given over 10 minutes. Three hours after delivery, the BP continued to drop to profoundly low levels. Urinary output was poor. At 3 hours of life, he received a transfusion of packed red blood cells over the next 90 minutes. A second transfusion was initiated at 15 hours of age, by which time the baby was anuric. He developed disseminated intravascular coagulopathy with renal failure over the next two days [peak creatinine was 4.1 mg/dL]. He was referred to a center for renal replacement therapy and dialysis. The child has profound cognitive delays and is awaiting a kidney transplant on follow-up.

While the neonatologist and the Hospital (Nurses) were sued, the obstetrician performing the delivery was not sued.

The allegations against the neonatologist included:

1. Failure to timely recognize and respond to signs of neonatal hypovolemia secondary to the perinatal hemorrhage.
2. Failure to timely provide emergency blood transfusion beginning immediately after birth.
3. Failure to properly maintain the baby's blood volume while waiting for emergency blood transfusion. Normal saline should have been provided with continuous blood pressure monitoring

The allegations against the Nurses included:

1. Failure to timely recognize and respond to signs of neonatal hypovolemia secondary to the perinatal hemorrhage.
2. Failure to insist on earlier volume replacement; they should have used their chain of command if the physician was resistant to early volume replacement
3. Cord gases should have been sent

The plaintiff neonatologist and nurses were critical of the nurses and physician for not responding to the obvious hypovolemic situation. Pressors were not appropriate, but emergency uncrossed, untyped blood was needed. Notwithstanding the obvious obstetrical source of the problem, the treating physician responded in her deposition that she was evaluating the newborn for a metabolic and infectious problem.

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Case 2

A 35-year old G2P1 at 32 weeks gestation was admitted for possible preterm labor. Based on an ultrasound three months earlier, she was known to be carrying dichorionic/diamniotic twins and a velamentous insertion of the umbilical cord. Upon admission, the cervix was found to be 90% effaced, 4 cm dilated, with the vertex of the presenting twin at -1 station. Magnesium sulfate for tocolysis and antenatal steroids for lung maturation was administered. Intermittent fetal monitoring showed many variable and late decelerations in twin B. After two weeks of observation, preterm, premature labor ensued. Because of slow progress, labor was

augmented with Pitocin, and epidural anesthesia was provided. Artificial rupture of the membranes occurred 4.5 hours prior to the vaginal delivery. Twin A, a female weighing 2571 grams, was delivered by forceps and received positive pressure ventilation for 20 seconds. Apgar Scores were 8 and 9 at 1 and 5-minutes, respectively, and she pursued an uneventful neonatal course and is normal on follow-up evaluations. Following the delivery of Twin A, there was copious bleeding from the uterus. Nevertheless, it took 20 minutes to deliver Twin B with vacuum assistance. The blood loss was estimated to be >1000 ml. At delivery, Twin B, a male, weighing 2051-grams. He was pale, flaccid, lethargic, had poor perfusion and a weak cry. Suctioning of his nose and oropharynx in the delivery room produced moderate, thick, cloudy blood-tinged secretions. Positive pressure ventilation was provided for 20 seconds, followed by continuous positive airway pressure (CPAP) for 5 minutes. Apgar Scores (assisted) were 6, 8, and 7 at 1, 5, and 10 minutes respectively. Neither cord gases nor the placenta was sent for evaluation.

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On admission to the Newborn Intensive Care Unit (NICU), his heart rate was 156 beats per minute (bpm), his respiratory rate was 55 breaths per minute (BPM), his BP was 49/31 (mean 43 mmHg). Femoral pulses were strong. He was placed on continuous positive airway pressure (CPAP) with 40% inspired oxygen. Umbilical lines were inserted. Within 1 hour, his BP dropped to 21/11 (mean 18mmHg) and remained at that level over the next 24 hours. At 3.5 hours after birth, pressors and 20 ml of normal saline infusion per hour were initiated.

The first hematocrit was 34% but was 24% at 6 hours. The WBC was 8.7 10^3/uL; the platelet count was 144 10^3/uL. The first arterial blood gas at 2 hours showed a pH of 7.15, a pC02 of 12mmHg, a p02 of 130 mmHg, and a base excess of -22.5. At 5 hours, the baby was intubated for apnea. At 6 hours, an arterial gas showed a pH of 6.8, a pC02 of 12mmHg, a p02 of 158mmHg, and a base excess of -28.5. At 6.5 hours, he received 4 meq of bicarbonate. At 7 1/2 hours, 30 ml of packed red blood cells were given over 3 hours. After the transfusion, the BP was 35/24 (mean 27mmHg). At 14 hours, his creatinine was 1.8 mg/dL; his SGOT was 3200 u/L and SGPT 412 u/L. He developed disseminated intravascular coagulopathy, treated with fresh frozen plasma and another transfusion of packed red blood cells. His creatinine continued to increase and peaked at 4.6 mg/dL. An epinephrine drip was added to his other pressors for BP support. He became anuric and was transferred to another facility for renal replacement therapy and dialysis. He received a gastric tube because of feeding and aspiration issues. He was sent home at 48 days for home dialysis and received a cadaveric renal transplant at 16 months.

Allegations

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In both cases, the neonatologist and the Hospital were sued and settled. The obstetrician was not sued.

Discussion

Introduction

Acute kidney injury (AKI) is common in neonates who require admission to the neonatal intensive care unit (NICU). Compared to older infants, the newborn has specific physiological characteristics that increase AKI risk, including the kidney's high susceptibility to hypo-perfusion, high vascular resistance, elevated plasma renin activity, and decreased sodium reabsorption in the proximal tubules. Adding to the vulnerability of the neonatal kidney is the functional and developmental immaturity that affects glomerular filtration and tubular function (e.g., concentrating ability), hemodynamic changes that occur at delivery, as well as the various potential complications that may befall the fetus during the birthing process. The newly born has a number of potential clinical problems that increase the risk of AKI, namely perinatal asphyxia, hemorrhage during birth, prematurity, infection, congenital cardiac disease, and issues requiring abdominal and thoracic surgical intervention as well as extracorporeal membrane oxygenation. Nephrotoxic medications commonly used on NICU patients are also associated with AKI (Table 1). The 2 cases presented here are unusual because of the problems created by fetal hemorrhage and hypoxia prior to delivery leading to prolonged and profound hypotension after birth resulting in hypoxic brain injury and irreversible renal damage.

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In both cases, massive hemorrhage at birth from the incised placenta or torn umbilical cord resulted in significant hypovolemia. Because their depleted intravascular volumes were not timely replaced, profound hypotension and irreversible kidney damage ensued. More typically, AKI occurs in babies who have sustained hypoxic-ischemic insults during the intrapartum period because of fetal intolerance of labor secondary to placental insufficiency or

Prenatal	Intrapartum	Postnatal
Factors that increase risk of prematurity	Delivery complications resulting in hypoxia and/or ischemia	Conditions causing hypotension and/or hypoxia
Renal anomalies	Exposure to maternal nephrotoxic medications	Prematurity
		Exposure to nephrotoxic medications
		Congenital cardiac disease
		Abdominal and thoracic surgery
		Sepsis
		Extracorporeal membrane oxygenation
		Inborn errors of metabolism

Table 1 Risk Factors Associated with AKI

Stage	Serum Creatinine (SCr) mg/dL	Urine Output
0	No change in SCr or rise <0.3	≥0.5 mL/kg/h
1	Increase in SCr ≥0.3 within 48 h or rise in SCr ≥1.5-1.9 x times the reference SCr level within 7 d	<0.5 mL/kg/h for 6-12 h
2	Rise in SCr ≥2-2.9 times the reference SCr level with 7 d	<0.5 mL/kg/h for ≥12 h
3	SCr level ≥3 times the reference SCr level or SC level >2.5 or receipt of renal replacement therapy	<0.3 mL/kg per h for ≥24 h or anuria for ≥12 h

Table 2 Neonatal AKI KDIGO Classification

repeated cord compressions or difficult deliveries. In these situations, babies initially have normal or reduced urine output and a modest and transient rise in creatinine. AKI in these types of situations is secondary to myocardial dysfunction with resultant impaired perfusion to the kidneys. Generally, renal function in these babies is restored by discharge, but long-term issues remain possible.

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Definition of AKI

AKI, formerly called acute renal failure, is defined as an acute reduction in kidney function that results in a decline in glomerular filtration rate (GFR). It has traditionally been defined by an increase in serum creatinine (SCr), leading to retention of urea and other nitrogenous waste products and loss of fluid, electrolytes, and acid-base regulation. Various definitions of neonatal AKI have been used in research studies to understand the disease better and predict the outcome. The neonatal modified Kidney Disease Improving Global Outcome (KDIGO) definition is used in clinical practice and most epidemiological studies (Table 2). KDIGO is a nonprofit organization developing and implementing evidence-based clinical guidelines in kidney disease by translating global scientific evidence into practical recommendations for clinicians and patients. Clinicians most commonly define AKI as SCr >1.5mg/dL or an increase of at least 0.2-0.3 mg/dL per day. This definition underestimates the prevalence of AKI because during early AKI, a reduction in GFR has only a modest effect on creatinine excretion, and the level may remain unchanged. At birth, the SCr value reflects the maternal SCr, which is usually low during pregnancy.

"The exposure of neonates to nephrotoxic medications in the NICU also contributes to AKI. The primary medications include aminoglycosides, vancomycin, amphotericin B, acyclovir, and nonsteroidal antiinflammatory drugs (NSAID). NSAID treatment of patent ductus arteriosus (PDA) adds risk for mild AKI,"

Incidence of AKI

The incidence of neonatal AKI is dependent on the definition used, the characteristics of the study population (e.g., preterm versus term), the severity of illness, and whether surveillance of kidney function was performed proactively. Observational studies from the United States report an incidence that ranges from 20-40% for infants cared for in NICUs, with the risk of AKI being inversely proportional to gestational age and higher in the more severe illnesses. The reported incidence of AKI for very low birth weight neonates ranges between 16% and 40%, while the incidence of AKI in neonates born at ≥36 weeks and admitted to a NICU is 37%. There is a positive correlation between AKI and the severity of hypoxic-ischemic encephalopathy (HIE) with the incidence of

Location and incidence of AKI	Pathogenesis
Prerenal 85%	**Reduction of effective circulation**
	Impaired cardiac output secondary to perinatal asphyxia
	Prematurity with cardiovascular instability
	Critical cardiac heart defects
	Complete heart blockage
	Sepsis
	Third spacing
	Hypovolemia
	Bleeding
	Diarrhea
	Increased evaporative fluid loss (radiant warmer, thin skin of premature babies, abdominal wall defects, phototherapy)
Intrinsic Renal disease 11%	**Tubular and/or interstitial injury Acute tubular necrosis (ATN)**
	Ischemic injury if hypoperfusion is prolonged direct tubular endothelial and epithelial cell injury from ischemia and inflammation.
	Perinatal asphyxia, if it is severe, results in tubular damage and dysfunction with impaired reabsorption of Na+ and water decreased GFR.
	Prematurity with cardiovascular instability
	Nephrotoxic exposures
	aminoglycosides, indomethacin, vancomycin, amphotericin B
	Sepsis
	direct tubular injury (as well as prerenal hypoperfusion injury)
	Renal vasculature disease
	renal artery thrombosis
	renal vein thrombosis
	Glomerular and cystic renal disease
	polycystic kidney
	congenital nephrotic syndrome
Postrenal disease 3%	**Anatomic bladder obstruction**
	posterior urethral valves
	bilateral anomalies of renal pelvis or ureter
	Nephrocalcinosis
	premature baby

Table 3 Location, Incidence, and Pathogenesis of AKI

AKI. 7.4% 70% with HIE stages II and III respectively. AKI occurs in 30% to 50% of patients undergoing surgery for congenital heart disease and in almost 75% of babies undergoing extracorporeal membrane oxygenation ECMO). almost 60% of infants with surgically managed necrotizing enterocolitis (NEC) had severe AKI.

The exposure of neonates to nephrotoxic medications in the NICU also contributes to AKI. The primary medications include aminoglycosides, vancomycin, amphotericin B, acyclovir, and nonsteroidal antiinflammatory drugs (NSAID). NSAID treatment of patent ductus arteriosus (PDA) adds risk for mild AKI, while the risk of severe AKI diminished when NSAID treatment was effective.

Pathogenesis of AKI

The causes of neonatal AKI can be divided into pathophysiologic categories based on the anatomical locus of the initial injury (Table 3). The most common cause of AKI is prerenal, accounting for about 85% of cases. In term babies, t is most commonly secondary to impaired cardiac output from perinatal asphyxia, and in premature babies, it usually results from cardiovascular instability. Overlap exists for the various categories. For example, premature babies are vulnerable to prerenal, intrinsic, and postrenal AKI.

Prevention of AKI

The prevention of AKI in newborn infants requires maintaining an adequate circulatory volume, careful fluid and electrolyte man-

agement, and prompt diagnosis and treatment of hemodynamic or respiratory abnormalities. Nephrotoxic medications should be avoided in neonates at high risk for AKI. In babies with perinatal asphyxia, therapeutic hypothermia (TH) reduces the incidence of neonatal AKI compared to those untreated. Aminophylline has shown promise as rescue therapy in neonates with AKI treated with therapeutic hypothermia. Two studies revealed that AKI occurred less frequently in VLBW infants and preterm infants <33 weeks' GA who received caffeine within the first week of life. Based on these data, the number that needed to treat with caffeine to prevent 1 episode of AKI was 4.3.

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Asphyxia, Hemorrhage, and AKI

Renal impairment occurs in 23-70% of asphyxiated infants. Poor renal perfusion can be secondary to hypovolemia of the fetus or neonate because of perinatal hemorrhage at the time of birth or from diminished fetal cardiac output secondary to the adverse effect of hypoxia on the fetal myocardium. Causes of perinatal hemorrhage include umbilical cord rupture, placental abruption, vasa previa, velamentous insertion of the cord, feto-maternal or twin-to-twin transfusion, internal organ bleeding, or incision (trauma to) the placenta. Causes of fetal hypoxia during labor include placental insufficiency, multiple cord compressions, tachysystole, prolonged labor, and difficult delivery.

Prematurity, Birth Weight, and Nephron Number

In critically ill neonates, early gestational age and low birth weight are significantly associated with an increased risk of AKI. The earlier the gestational age and/or the lower the birth weight, the lower is the number of nephrons, and the less mature their function. Low birth weight (<2.5 kg at birth) increases by 70% the risk of developing chronic kidney disease. Low birth weight, in turn, may be the result of intrauterine growth restriction (IUGR) and/or preterm birth (<37 weeks' gestation). IUGR is multifactorial and generally results from restricted blood flow with inadequate delivery of oxygen and nutrients to the developing fetus. In developed countries, placental insufficiency is the primary cause of IUGR in the third trimester. Nephrogenesis begins at the fifth week of gestation and continues until 34-36 weeks' gestation, with a direct linear relationship between human birth weight and nephron number with linear regression predicting an additional 250,000 nephrons for each 1-kg increase in birth weight. The fetus has reached its adult complement of 2.0 to 2.7 million nephrons at term. However, because 60% of nephron formation occurs during the third trimester, nephrogenesis may be limited and/or disrupted by preterm birth while nephrogenesis is still ongoing. Of particular concern are infants born very (28 to 32 weeks gestation) or extremely premature (<28 weeks' gestation) because their kidneys are vulnerable and face stormy neonatal courses.

In addition to reduced nephron endowment, preterm infants experience other prerenal causes of AKI such as hypotension, hypoxia, and sepsis. Postrenal complications secondary to nephrocalcinosis also may contribute to AKI in preterm babies. Deposition of calcium phosphate and/or calcium oxalate within the tubulointerstitial regions of the kidney is common. Factors such as a high intake of calcium, phosphorous, and ascorbic acid; a low urinary citrate/calcium ratio; a high urinary calcium/creatinine ratio; and medications to prevent or treat chronic lung disease (with hypercalciuric side effects) are associated with the high incidence of nephrocalcinosis. The reported prevalence of nephrocalcinosis differs widely among populations (ranging from 7% to 41% or more) depending upon differences in the study populations, ultrasound equipment, and study criteria.

Premature babies have a low GFR at birth, which increases with gestational and postnatal age. The cause of the glomerular abnormalities associated with preterm birth is currently unknown. The abnormal glomeruli are found only in the outer cortex, suggesting that only the most recently formed glomeruli are at risk. Indeed, the extrauterine environment must be considered an abnormal environment for nephrogenesis. It may be that the changes in oxygen levels and/or hemodynamics that occur at the time of birth lead to persistent abnormalities. In contrast to the in utero environment (with low oxygen levels, high renal resistance, and low renal blood flow), preterm birth has been shown to accelerate renal maturation but with several structural glomeruli abnormalities.

Nephrotoxicity

Nephrotoxic-medication exposure is common in neonates and is increasingly recognized as the potentially most avoidable cause of AKI in this population. Nephrotoxic medications can cause AKI in a variety of ways, including decreased renal perfusion (nonsteroidal antiinflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors), direct tubular injury (aminoglycosides, amphotericin B, vancomycin nonsteroidal antiinflammatory drugs), or tubular obstruction (acyclovir). Prostaglandins maintain the patency of the fetal ductus arteriosus through its relaxant effect. After birth, when it is desirable to constrict the patent ductus in a preterm baby, a nonsteroidal antiinflammatory drug (NSAID) such as **indomethacin** is used to oppose the effect of prostaglandin E2 and cause the ductus to constrict. Simultaneously, however, these drugs cause afferent renal arteriole vasoconstriction, reducing the kidney's ability to regulate (increase) glomerular blood flow. While indomethacin can cause acute AKI, it is usually reversible.

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Maternal exposure to NSAID drugs also predisposes neonates to decreased renal perfusion and AKI. Interestingly, Guillet et al. have suggested that the PDA's underlying physiology is more important than management strategy in determining the likelihood of AKI in neonates <1500 grams. **Aminoglycosides** (gentamicin, amikacin, and tobramycin) are frequently used for neonates and are well known to potentially cause AKI, primarily by causing proximal tubular damage and intrarenal vasoconstriction. There is

a gradual rise in SCr levels with toxicity, and babies may become oliguric. Additionally, in animal studies, aminoglycosides have been shown to interfere with nephrogenesis.

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Intravenous contrast is associated with intrarenal vasoconstriction, tubular injury, and direct tubular injury. SCr rises 24-48 hours after exposure, and it usually presents as a non-oliguric AKI. Adequate intravascular volume must be maintained before exposure to this agent.

Acyclovir nephrotoxicity is classically attributed to tubular obstruction secondary to drug crystallization, but direct tubular toxicity from acyclovir metabolites may also contribute. Again, adequate hydration and slow infusion rates can prevent AKI.

Captopril is an angiotensin-converting enzyme (ACE) inhibitor used for treating high blood pressure and heart failure. The renin-angiotensin system is critical to fetal renal development, and interference with this delicate balance of intrarenal vasoconstrictor and vasodilator forces carries risk. ACE inhibitors decrease angiotensin II production leading to a reduction in GFR via decreased efferent arteriolar vasoconstriction. The risk is increased with volume depletion, renal ischemia, and reduced renal blood flow. Given the potential deleterious impact on postnatal renal development, it may be appropriate to avoid using ACE inhibitors in neonates < 32 weeks of age.

The role of **vancomycin** as a nephrotoxin remains controversial, particularly in the context of monotherapy with appropriate medication levels. Risk factors for AKI in neonates who receive vancomycin include higher troughs, concomitant nephrotoxins and/or diuretics, and severe illness. The possible cause of tubular injury is related to a generation of reactive oxygen species.

Renal blood flow

The conversion from fetal to postnatal circulations at birth substantially increases renal blood flow (RBF) as renal vascular resistance decreases and systemic blood pressure increases. By one week of age, as a proportion of cardiac output, RBF increases from 2 to 4% in the fetus to approximately 10% (the normal adult value is approximately 20%). After birth, the blood flow transitions from deeper, more mature glomeruli to superficial cortical glomeruli. The GFR normally improves slightly during the first several weeks of life. The urinary concentrating ability is low at birth and does not reach adult levels until one year.

Autoregulation accommodates changes in GFR and RBF. As a result of autoregulation, small changes in systemic BP produce parallel changes in afferent renal vascular resistance. A constant RBF and GFR are maintained over a range of systemic BPs and are set at a lower range of BP for infants compared with adults. If GFR is too low, metabolic wastes will not get filtered into the renal tubules from the blood. If GFR is too high, the renal tubules' absorptive capacity of salt and water becomes overwhelmed. Interference with this transition occurs with perinatal asphyxia and other perinatal stressors. The impaired autoregulation of the premature and critically ill newborn predisposes to AKI during periods of hypotension because the mechanisms to compensate for significant hemodynamic changes are overwhelmed. Although hypoperfusion usually results in prerenal AKI, prolonged hypoperfusion causes direct tubular endothelial and epithelial cell injury from ischemia and inflammation. Severe asphyxia results in diffuse tubular damage and dysfunction with impaired sodium and water reabsorption and decreased GFR. For infants with milder asphyxia, the impairment may only be a loss of renal concentrating ability. Renal tubules are particularly susceptible to ischemic injury after a mild and short-term insult and are further complicated with nephrotoxic medications.

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Serum Creatinine and Urine Output

Normally in term infants, SCr declines rapidly in the first two weeks to a nadir of 0.2-0.4mg/dL. In preterm infants, the decline is slower, and nadir values are reached over 1-2 months. In extremely preterm (<28 weeks) and very preterm infants (28-31 weeks), SCr may increase after birth, most likely due to low GFR and impaired tubular reabsorption of creatinine, followed by a slower decline over two months with the SCr values inversely related to decreasing gestational age.

The time of first void and urine volume is variable, but at least 50% of newborns void by 8 hours and nearly all before 24 hours. Urine output is not affected by gestational or postnatal age during the first week of life, averaging 3 to 4 mL/kg per hour.

Neonatal AKI may be oliguric (urine volume <1mL/kg/hour) or non-oliguric, depending upon the severity of the reduction in GFR and the degree of tubular reabsorption. Urinary concentration is limited in the newborn. Sodium reabsorption is lower in neonates compared with older individuals and is affected by gestational and postnatal age. Neonates have a lower threshold for proximal bicarbonate reabsorption than older children and adults. The net acid excretion by the distal nephron is limited in newborn infants,

especially preterm infants. It is important to also keep in mind that the first void may reflect urine in the fetal bladder before any in-utero hypoxic-ischemic insult occurs.

Biomarkers for AKI

Because of the diversity of gestational ages and the etiologies of AKI in neonates, a single biomarker is not a reliable predictor of AKI. SCr reflects kidney function, not injury, and is a delayed marker. A rise in SCr level indicates a loss of kidney function, reflecting injury up to 48 72 hours before.

Cystatin C (CysC) is a protease inhibitor that is freely filtered by glomeruli and reabsorbed in the proximal tubule. A rise in **serum** CysC level reflects a change in kidney function, whereas an elevated **urinary** CysC level is considered reflective of tubular injury. An increase in serum CysC level is thought to reflect a change in GFR, whereas an elevated urinary CysC is considered reflective of tubular injury. CysC has been shown to help in predicting a rise in SCr level 24 to 96 hours later in neonates post-surgery or after perinatal asphyxia.

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Neutrophil gelatinase-associated lipocalin (NGAL) is a protein-bound to neutrophil granules, filtered by the glomerulus and reabsorbed by the proximal tubules. NGAL is highly sensitive and specific for AKI in neonates with perinatal asphyxia.

AKI – Clinical Presentation

The signs in neonatal AKI are due to alterations of renal function and include edema secondary to progressive fluid accumulation, decreased or no urine output, and/or hypertension. Edema may result from fluid overload or other comorbidities, such as a capillary leak, heart failure, or hypoalbuminemia. The presence of normal urine output does not rule out AKI since some infants are nonoliguric. Hypertension is occasionally found in AKI. Abnormal laboratory findings may be the first clue to the problem; most commonly, the diagnosis of neonatal AKI is identified by routine testing of kidney function using SCr for at-risk patients in the NICU. Other laboratory findings that emerge in AKI include: a) hyponatremia because of an inability of the kidneys to excrete free water, b) hyperkalemia secondary to reduced GFR, decreased tubular secretion of potassium, tissue breakdown with the release of intracellular potassium, and metabolic acidosis resulting in transcellular movement of potassium, c) metabolic acidosis because of the injured kidneys' inability to regulate acid-base status d) hyperphosphatemia because the kidneys play a significant role in phosphate excretion e) hypocalcemia because of the hyperphosphatemia.

Chronic kidney disease (CKD)

The presentations of AKI and CKD are similar at birth, but in AKI, the kidney recovers over days and weeks; kidney dysfunction that persists for months to years is classified as CKD. The distinction between acute and chronic kidney disease at birth is difficult, as presentations are similar. Identifying the underlying cause is important since it provides information on the probability of the ultimate recovery of kidney function. The presence of dysmorphic features on physical examination, congenital anomalies, genetic disorders, and congenital nephrotic syndrome increases CKD's likelihood.

Late-onset AKI

Late-onset neonatal AKI occurs in infants older than seven days of age. These infants often have had an earlier episode of AKI and had comorbidities, including congenital heart disease, kidney anomalies, and necrotizing enterocolitis.

Medical Management

In the case of established oliguric AKI, a urinary catheter should be placed to exclude lower urinary tract obstruction. After bladder drainage is accomplished and no urine output is established, a 10-20 mL/kg fluid challenge should be administered over 1-2 hours to exclude prerenal AKI. The administration of a vasopressor will help to ensure adequate mean arterial pressure and sufficient renal perfusion. After assurance of the absence of lower urinary blockage and no response to a fluid challenge, management turns to fluid resuscitation and adequate mean arterial pressure maintenance. The goal is to provide supportive care until renal function is restored. During this period, fluid intake should be restricted to insensible losses, urine output, and other measured losses, e.g., through nasogastric or chest tubes. Twice daily weights and careful measurement of intake and output are essential to follow volume status. Nephrotoxic drugs should be discontinued. Medication should be adjusted by dose and interval. Metabolic acidosis may require treatment with sodium bicarbonate. Loop diuretics may be helpful, but if no response occurs or in the case of anuria, they should not be employed.

Renal replacement therapy should be considered if maximum medical management fails to maintain acceptable fluid and electrolyte levels. Indications include hyperkalemia, hyponatremia with symptomatic volume overload, acidosis, hypocalcemia, hyperphosphatemia, uremic symptoms, and an inability to provide adequate nutrition because of the need for fluid restriction in the face of oliguria. The two purposes of renal replacement therapy are ultrafiltration to remove water and dialysis to remove solutes. Generally, only neonates >1.5 kg may be considered for renal replacement therapies. Continuous renal replacement therapy is being used more frequently in neonates with AKI. For this procedure, the baby's blood is continuously circulated through a pump-driven extracorporeal circuit

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Outcome

AKI is not just a marker of severity of illness in neonates but is also independently associated with poor outcomes. In the past, AKI was felt to be completely reversible in neonates, with the idea that kidney function returning to baseline indicated no further renal risk. However, studies have demonstrated high rates of CKD in survivors of neonatal AKI and increased risks of bronchopulmonary dysplasia, intraventricular hemorrhage, hypertension, and poor long-term neurocognitive impairments. The term "crosstalk" was introduced in 2013, whereby AKI creates dysfunction in other organs and vice-versa, probably secondary to an inflammatory process. All neonates with an identified episode of AKI should be referred to nephrology for outpatient follow-up, especially with AKI stages 2 and 3, significant prematurity, IUGR, or underlying renal anomalies. Early identification of CKD allows implementation of strategies to slow the loss of kidney function

Obstetrical Considerations

Finally, it is necessary to comment on the obstetrical contribution to the above problems. In case #1, the placenta was in the path of the cesarean section incision. Ultrasound mapping of the placenta may permit avoiding it. When it cannot be avoided, there must be the understanding that **fetal** blood loss through the placenta may be rapid with devastating consequences. Under such circumstances, experienced neonatal providers and emergency blood replacement must be available at delivery. For the operating surgeon, when the placenta is cut, or the umbilical cord disrupted (in case #2), from the vulnerable attachment of the cord, either the fetus must be delivered with haste, or the amniotic cavity entered and the umbilical cord clamped with the fingers of the operating surgeon. In both cases, these potential problems were known before the delivery. There can be no justification for disregarding these potentially devastating complications.

"In both cases, these potential problems were known before the delivery. There can be no justification for disregarding these potentially devastating complications."

Suggested reading

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