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APPROACH TO PEDIATRIC ACUTE KIDNEY INJURY

Developed by Aspen Lillywhite, Aisha Farooq, and Dr. Emma Ulrich for PedsCases.com.
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Introduction:

Hi everyone, my name is Aspen Lillywhite, and I am a medical student at the University of Alberta. This podcast was created with the help of Dr. Emma Ulrich, a pediatric nephrologist at Stollery Children's Hospital, Edmonton Alberta. This podcast was also written by Aisha Farooq, who is also a medical student at the University of Alberta.

The aim of this PedsCases podcast is to develop an approach to acute kidney injury (AKI) in pediatric patients. This includes understanding the pathophysiology of AKI, developing a differential diagnosis, and initial work-up and management.

Objectives:

By the end of this podcast, the listener will be able to

1. Define acute kidney injury in pediatric patients.
2. Categorize AKI as functional (pre-renal), structural (renal) or post-renal based on the mechanism of injury.
3. Identify key components of the history and physical exam for children presenting with AKI.
4. Describe the initial workup and management of AKI with special attention to hypovolemia and functional AKI.

In order to fulfill our objectives, we will be working through a clinical case as we go along. Let's get to it!

Case:

You are a clinical clerk on your pediatric rotation. You are called to the ER to admit Sarah, a previously healthy 5-year-old female, for dehydration. The ER physician's report states that Sarah has had poor oral intake with vomiting and diarrhea for 3 days. She has been intermittently febrile with a maximum temperature of 38.1C, which her mom treated with Advil. Her vitals are as follows: HR 130, BP 89/50, RR 22, O2 saturation 97% on RA, and T38.2C (axillary). From the door, you see that Sarah is alert and in no immediate distress. She cries occasionally and clings to her mom. Before you enter, Sarah's nurse informs you that labs are back, and the creatinine is elevated.

What else do you want to know on history? What are your next steps?

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How do we define AKI in children?

Acute kidney injury (AKI) is defined as an acute decrease in glomerular filtration rate (GFR) which represents the amount of blood filtered each minute by the kidneys. GFR is most commonly estimated using serum creatinine, which is a breakdown product of muscle. Creatinine is freely filtered with very little reabsorption at the level of the nephron. Children are born with immature kidneys that are unable to fully concentrate urine. As children grow, renal function progressively increases until a mature glomerular filtration rate is reached around age 2. Normal serum creatinine values differ by age and for more information on that, please see the supplementary material.

AKI definition and severity is defined using international consensus guidelines published by Kidney Disease Improving Global Outcomes (KDIGO). KDIGO defines AKI as stage 1, 2 or 3 based on elevated serum creatinine or decreased urine output criteria (whichever is more severe). By serum creatinine, stage 1 is sCR >1.5x baseline, stage 2 is >2x baseline, and stage 3 is >3x baseline or requiring kidney replacement therapy. The complete KDIGO definition of AKI can be found in the supplementary materials. Although using creatinine to define AKI is simple and quick, creatinine measurement has several limitations: (1) creatinine is a delayed marker of kidney injury, rising up to 48 hours after renal insult; (2) creatinine is not routinely monitored in healthy children, so baseline creatinine is often unknown; (3) creatinine level is affected by muscle mass, fluid overload, and age.

Why is AKI important?

Most importantly, preventing, recognizing, and taking action when AKI is in its early stages can prevent later sequelae of AKI, including more severe kidney damage. Morbidity and mortality of AKI increases with increasing severity defined by KDIGO stage of AKI. This has been shown in large multicentre prospective cohort studies of pediatric AKI. In adults, AKI is also associated with CKD and hypertension; evidence of long-term kidney dysfunction has also been shown in pediatric observational studies.

Who is at risk of AKI?

Non-modifiable risk factors for AKI include younger age, acute illness severity, and underlying cardiac or liver disease. Modifiable risk factors include nephrotoxin exposure, such as NSAIDs or vancomycin.

How do we approach AKI?

AKI has a broad differential diagnosis. It can be useful to divide into 3 broad categories that consider the mechanism of injury: functional, structural and post-renal AKI. Let's go through each one separately.

Functional AKI

Functional AKI, previously known as pre-renal AKI, is the most common form of AKI. Functional AKI is caused by reduced renal perfusion due to 1) hypovolemia, 2) reduction in effective circulating volume, or 3) increased resistance to renal blood flow. Common causes of hypovolemia are dehydration due to poor oral intake or excess GI or urinary losses or bleeding.

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Reduced effective circulating volume can be caused by distributive shock (i.e., sepsis or anaphylaxis), heart failure, liver failure, or nephrotic syndrome. Finally, increased resistance to renal blood flow can be caused by renal artery stenosis or abdominal compartment syndrome.

In response to reduced blood flow, the kidneys employ several compensatory mechanisms. Prostaglandin release and renin-angiotensin system activation results in afferent arteriole vasodilation and efferent arteriole vasoconstriction to maintain GFR. To increase intravascular volume, the renin-angiotensin system stimulates increased tubular sodium and water reabsorption and antidiuretic hormone increases free water reabsorption.

Structural AKI

Moving on, the next category is intrinsic or structural AKI, previously known as intrarenal, which is due to renal dysfunction. Structural AKI can be further characterized into glomerular, tubular, interstitial or vascular causes.

Diving in, the most common cause of structural AKI is acute tubular necrosis (ATN), which occurs due to prolonged hypoperfusion leading to cellular damage and death. Regions of the kidney that have the highest energy requirements, such as the proximal tubule and medullary segment of the ascending limb of the loop of Henle, are typically the most affected. As cells die, debris builds up in the tubules and blocks forward tubular flow. This debris is often seen as brown or muddy granular casts in the urine.

Glomerular causes of structural AKI is a broad category. The most common cause of glomerular disease is acute glomerulonephritis (or nephritic syndrome) which occurs due to inflammation and damage of the glomeruli. Glomerulonephritis generally manifests with hypertension, hematuria, proteinuria, and edema.

Vascular causes of structural AKI include thrombosis (venous or arterial), vasculitis, and other hematologic causes such as hemolytic uremic syndrome, which presents with anemia, thrombocytopenia, and elevation in creatinine.

Interstitial causes of structural AKI involve injury to the renal interstitium. The most common cause is acute interstitial nephritis (AIN), which often occurs following infection or a new medication, and is almost like an allergic reaction that manifests in the kidney. Common offending drugs include NSAIDs, aminoglycoside antibiotics (ex: gentamicin), and proton pump inhibitors (PPIs), but any drug could cause AIN. Therefore, it is very important to inquire about new medications when seeing a patient with AKI. Signs of AIN often develop 3-5 days after taking the drug and the treatment is cessation of the medication and/or steroids.

Post-Renal AKI

The final category is postrenal AKI, which occurs due to obstruction in the urinary tract. These usually cause AKI when they are at or below the level of the bladder. Blockages above the bladder usually have to be bilateral to cause AKI, but they can be unilateral in a child with a single kidney (or post-kidney transplant). Important causes are urinary retention, kidney stones, or clots. Due to an obstruction of urinary flow, pressure backs up into the kidneys and results in hydronephrosis or swollen kidneys, resulting in a reduced GFR. Children with postrenal AKI are

at risk of ischemia, infection and sepsis. All children in whom there is a suspicion of post-renal AKI should have a renal ultrasound.

Once the obstruction is relieved, children with post-renal AKI are also at risk of severe polyuria, dehydration, and electrolyte disturbances due to ATN and should be monitored closely for these complications.

History:

Now that we have some background, let's go back and consider our case. You enter the room, introduce yourself to Sarah and her mom and start to take a history. When evaluating a child, it is always important to complete a full pediatric history. Additionally, as our differential diagnosis for AKI is quite broad, a systematic and focused approach is essential. The following are key aspects to ask on history:

- Urine output: children still in diapers should be asked about the number of wet diapers per day as a good proxy. Specifically, anuria is defined as no urine output, oliguria is defined as urine output <1 mL/kg/hour in infants and <0.5 mL/kg/hour for greater than 6 hours in children and polyuria is defined as urine output >3 mL/kg/hour.
- Urine colour and in particular whether there was any visible blood noted in the urine. Dark brown ("cola-like" or "tea-coloured") urine points to gross hematuria. If present, this is suggestive of nephritic syndrome or acute glomerulonephritis
- Other urinary symptoms are important to inquire about, including dysuria (which would be suggestive of urinary tract infection), nocturia (in older children), urgency, and frequency
- Fluid and dietary intake: it is very important to get an idea of regular fluid intake, as well as recent fluid intake during the acute illness. Children are high risk for dehydration due to their small size and this is one of the most common reasons for admission to hospital in pediatrics. It is also important to inquire about dietary intake (i.e., formula, quantity, and frequency of feeds) in all children to screen for nutritional deficiencies
- Fever: onset, duration and medications used to help control it
- Recent infection and infectious symptoms (i.e., sore throat, cough, coryza, vomiting, diarrhea, or rashes). GI losses can also be an important cause of dehydration
- Recent trauma or bleeding
- Swelling around eyes, ankles, legs, or abdomen. Edema is an important symptom of nephrotic syndrome. The edema is gravity dependent, so children often awaken with swollen / puffy eyes, which can be very alarming, but tends to improve during the day
- Swollen or painful joints
- Medications, particularly common nephrotoxins such as ibuprofen, and any new medications, vitamins, or herbal supplements
- A complete past medical history. In newborns, a good prenatal history that includes asking about any abnormalities on fetal ultrasound is important as this could point to congenital anomalies of the genitourinary system. When concerned about renal function, it is also important to ask about a history of urinary tract infections

Back to the case:

Going back to our case, Sarah's mom reports that she had a healthy pregnancy and Sarah was born vaginally at term with no complications. In fact, besides the usual seasonal viral infections that all children are prone to getting, Sarah has been completely healthy and is up to date with her vaccinations. On travel history, the family returned from a cruise about 4 days ago and about a day after that, Sarah developed clear, non-bilious vomiting and non-bloody diarrhea. Sarah's mom has not particularly noticed if Sarah is going to the bathroom to pee less often. She has barely been eating or drinking despite her mom's best efforts.

Physical Examination:

Paying particular attention to the hydration or volume status in patients with concern for AKI, a focused physical exam includes the following:

- Assess the child's general appearance to ascertain whether they are appropriately alert, responsive, and not in immediate distress. Young children are often irritable with new people, but can usually be soothed by the parent
- Vital signs are essential to determine whether the child is stable and if they have any findings pointing to a specific etiology. For example: fever may point to a current infection; tachycardia and orthostatic hypotension suggest volume depletion and hypertension suggests nephritic syndrome or acute glomerulonephritis
- Volume status exam is essential for any child with renal disease. This includes assessing fontanelle in infants, mucous membranes, skin turgor, and capillary refill. Delayed capillary refill (greater than 2 seconds) suggests volume depletion. Check for pitting edema by pressing firmly on the anterior aspect of the distal tibia for several seconds.
- Cardiorespiratory exam is important to detect signs of fluid overload, which may be indicated by adventitious breath sounds or a new murmur on auscultation. In older children, assessment of JVP can be an important sign related to fluid overload.
- Abdominal exam to check for pain, distension or enlarged, palpable kidneys or ascites.
- Skin exam to check for any rashes which may indicate vasculitis (non-blanching, petechial or purpuric rash) or impetigo (red sores or honey crusted rash).

Back to the case:

Let's go back to our patient, Sarah.

On exam, vitals are HR 130, BP 89/50, RR 22, O2 saturation 97% on RA, and T38.2C (axillary). Sarah is miserable, but alert and responds to her mother's suggestions and your attempts to engage her. Her peripheral capillary refill time is 3 seconds and mucous membranes appear dry. Her respiratory and cardiac exams are normal. She has no rashes on her face, arms, trunk or legs. Her abdomen is soft, non-distended and non-tender. She has no periorbital or peripheral edema.

Sarah's physical exam findings reassure you that she is stable, but likely suffering from mild-moderate dehydration due to GI losses combined with limited oral intake.

Investigations

Moving on to investigations, urinalysis and microscopy is an essential first step when evaluating any child with acute kidney injury. It measures specific gravity as a marker of urine concentration, protein, glucose, ketones, blood and nitrites and leukocyte esterase (markers for infection) in the urine. A dipstick quantifies substances found in the urine from negative to 4+, with a higher number indicating higher quantities. On urine microscopy, we can see white blood cells, red blood cells bacteria, epithelial cells, casts and crystals. If indicated, urinary sodium can be measured to calculate the fractional excretion of sodium (FENa), which is a test that calculates renal handling of sodium. A FENa below 1% suggests functional AKI as most of the filtered sodium is being reabsorbed to maintain intravascular volume. A FENa above 2% suggests ATN as there is tubular dysfunction. A level between 1 and 2% is non-specific. A FENa is less reliable if the child has received IV fluids or diuretics.

On bloodwork, it is important to assess renal function with a serum creatinine, urea, electrolytes including sodium, potassium, chloride, and total CO2. As mentioned earlier, an elevated serum creatinine or a significant rise from baseline is diagnostic for AKI. Measuring electrolytes is essential to ensure that the child is not developing life threatening electrolyte abnormalities such as hyperkalemia due to reduced renal function.

Other bloodwork is guided by findings on history and physical exam, as well as the level of concern for renal dysfunction. For example, a CBC and peripheral blood smear would be helpful to elucidate anemia or thrombocytopenia if suspecting vasculitis or hemolytic uremic syndrome.

Other electrolytes, including calcium, phosphorus, and magnesium, are measured in children with chronic kidney disease or tubular disorders. A blood gas is done to assess acid-base status and lactate, which measures perfusion status. If we suspect an autoimmune condition, we will do more specific tests. For example, if suspecting post-streptococcal glomerulonephritis, it is important to measure complements; if suspecting lupus, it is important to measure complements and autoantibodies. A sterile urine culture is ordered in children with suspected UTI. This should be collected by catheterization, rather than a bagged specimen, in children that are not toilet trained, and by mid-stream in older children.

In terms of imaging, a renal ultrasound should be done for children <2 years after their first febrile UTI in order to detect congenital anomalies of the genitourinary tract. It should also be done for any child where there is suspicion of post-renal causes of AKI. Invasive investigations, such as renal biopsy, are indicated for diagnostic and prognostic purposes under the direction of a pediatric nephrologist.

Back to the case:

Going back to our case, Sarah's urinalysis results show no blood, protein or casts, but a high specific gravity of 1.020. The urine is negative for nitrites and leukocyte esterase. Urinary sodium is low and FENa is <1%. From previous bloodwork, Sarah's baseline creatinine appears to be around 32 µmol/L and today her creatinine is elevated at 88 µmol/L. Her electrolytes and CBC are normal, except for an elevated hematocrit. A venous blood gas shows mild acidemia with pH 7.33 and bicarbonate 18 mmol/L. Lactate is slightly elevated at 1.9 mmol/L.

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You realize that her history, physical exam and lab findings are all pointing to hypovolemia induced, functional AKI. As her creatinine is elevated at about 2.75 times baseline, Sarah meets criteria for stage 2 AKI.

Management

The management for pediatric patients with AKI is guided by the presenting etiology. Fluid management will be guided by the patient's fluid status on presentation. For example, a hypovolemic child with AKI due to gastroenteritis will need fluid resuscitation in order to prevent progression to acute tubular necrosis. This is typically done by giving a normal saline bolus of 20 mL/kg, followed by maintenance fluids calculated with the 4-2-1 rule, taking previous deficit and ongoing losses into account. However, in children with abnormal renal function or polyuria, the 4-2-1 rule may over- or under-calculate fluid requirements and should not be used. If the child is hypervolemic (ex: heart failure, edema), then it may be necessary to restrict fluids and initiate a short-term loop diuretic such as furosemide.

In terms of medication management, nephrotoxic drugs such as NSAIDs, diuretics, ACE inhibitors, and antibiotics, especially aminoglycosides or vancomycin, should be avoided or renally dosed with close monitoring of drug levels.

Electrolyte disturbances can be prevented by restricting sodium to less than 2-3 mEq/kg/day to prevent fluid retention and not supplementing fluids with potassium or phosphorous in children with oliguric or anuric AKI unless they have hypokalemia or hypophosphatemia. Furthermore, electrolytes need to be monitored regularly in order to detect and treat any abnormalities quickly. If hyperkalemia is detected, an ECG should be done to check for peaked T waves or other rhythm abnormalities. Treatment should be initiated based on the severity of hyperkalemia and ECG results. Options include furosemide, to help eliminate potassium, and kayexalate can be used to bind potassium. Also, insulin or bicarbonate temporarily treat hyperkalemia by driving potassium into cells. Insulin must be given with glucose to prevent hypoglycemia. Severe or refractory hyperkalemia is an indication for dialysis.

Hypertension can be managed with short-acting antihypertensives (i.e., nifedipine). Hypertension with edema can be managed with diuretics. If hypertension is severe or refractory, consider consultation with a pediatric nephrologist.

Renal replacement therapy such as hemodialysis, peritoneal dialysis or continuous renal replacement may be needed if the child develops life threatening fluid overload, hyperkalemia/acidosis refractory to treatment, significant uremia, or inability to attain adequate nutrition. A pediatric nephrologist would decide the timing and modality for renal replacement therapy.

Back to the case:

Going back to our case, your preceptor discusses with you that Sarah is likely suffering from acute viral gastroenteritis, likely as a result of a pathogen such as norovirus. Prolonged vomiting and diarrhea along with little intake have caused her to develop moderate dehydration, causing hypovolemia. She further states it is essential we recognize and correct functional AKI before it has a chance to progress to ATN. Sarah is admitted and given a normal saline bolus at 20 mL/kg and started on intravenous fluids. Furthermore, we instruct Sarah's mom to stop

ibuprofen and instead switch to acetaminophen in order to avoid any further renal injury. Over the next day, her urine output stabilizes at about 1.0 mL/kg/hour. Her vomiting and diarrhea become infrequent until they stop altogether and she starts drinking and eating again. Her creatinine also normalizes on repeat measurement prior to discharge.

Take Home Messages

- AKI is defined by an acute elevation in serum creatinine and/or drop in urine output from baseline. The KDIGO definition is used to define AKI and its severity in children and adults.
- AKI has a broad differential diagnosis that can be divided into 3 categories: functional, structural (glomerular, tubular, interstitial or vascular) and postrenal causes.
- A systemic and focused history and physical exam focusing on genitourinary symptoms, urine output, and volume status are essential to help elucidate the cause of AKI and manage it appropriately.
- Investigations are guided by history and examination, but often include urinalysis with microscopy, electrolytes, serum creatinine, and urea.
- Management should focus on fluids and electrolytes along with treatment of the underlying cause
- Children with AKI or other renal dysfunction are referred to a pediatric nephrologist for management and, in severe cases, consideration for renal replacement therapy.

Now that we've come to the end of this podcast, we hope you are able to

1. Define acute kidney injury in pediatric patients
2. Categorize AKI as functional, structural or post-renal based on the mechanism of injury
3. Identify key components of the history and physical exam for children presenting with AKI
4. Describe the initial workup and management of AKI with special attention to hypovolemia and functional AKI

I hope this helped you develop a systematic and organized approach to the very large topic of AKI in pediatrics. Thank you so much for listening!

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Supplementary Materials:

Normal Creatinine Values by Age:

- Newborn (0-28 days): 0.3 - 1 mg/dL (27 to 88 micromol/L)
- Infant (1 mo-1 year): 0.2 - 0.4 mg/dL (18 to 35 micromol/L)
- Child (1-12 years): 0.3 - 0.7 mg/dL (27 to 62 micromol/L)
- Adolescent: 0.5 - 1 mg/dL (44 to 88 micromol/L)

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Criteria for the Kidney Disease Improving Global Outcomes (KDIGO) acute kidney injury for children

Stage	Serum creatinine (SCr)	Urine output
1	Increase to 1.5 to 1.9 times baseline, OR increase of ≥0.3 mg/dL (≥26.5 mcmol/L)	<0.5 mL/kg per hour for 6 to 12 h
2	Increase to 2 to 2.9 times baseline	<0.5 mL/kg per hour for ≥12 h
3	Increase greater than 3 times baseline, OR SCr ≥4 mg/dL (≥353.6 mcmol/L), OR Initiation of renal replacement therapy, OR eGFR <35 mL/min per 1.73 m^2 (<18 years)	<0.3 mL/kg per hour for ≥24 h, OR Anuria for ≥12 h

The time frames for the increases in serum creatinine are:

- Increase of SCr ≥0.3 mg/dL (≥26.5 mcmol/L) within 48 hours
- Increase in SCr >1.5 times the baseline within the prior seven days

eGFR: estimated glomerular filtration rate; h: hours.