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Tumor Lysis Syndrome (TLS) in Pediatric Populations

Developed by Stephanie Unrau and Marc Beaudin with Dr. Bev Wilson for PedsCases.com.
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Introduction:

Hello! My name is Marc Beaudin -- and my name is Stephanie Unrau. We are fourth year medical students from the University of Alberta, in Edmonton, Canada. This podcast was developed with Dr. Bev Wilson, medical director of the Northern Alberta Children's Cancer Program at the Stollery Children's Hospital. Today, we will discuss the topic of tumor lysis syndrome (TLS) in pediatric populations, as it is a common preventable life-threatening emergency in children with cancer[1].

This podcast will cover the following objectives:

Objectives:

1. Discuss the underlying pathophysiology of TLS, including reviewing key physiologic processes relating to electrolyte homeostasis
2. Describe the clinical presentation and diagnostic criteria for TLS
3. Stratify the risk factors for TLS
4. Identify interventions for patients at risk for or who have TLS.

Let's begin by reviewing some key physiology!

In order to function and survive, cells must maintain an intracellular environment distinct from the extracellular environment, which pertains to the concentration of specific proteins, electrolytes, and other small molecules. For example, through sensitive internal regulatory mechanisms, neurons maintain the potassium, sodium, and calcium gradients necessary for cell signalling. When this balance is perturbed, the body has certain mechanisms to help it revert back to the norm in a process called homeostasis.

In contrast with extracellular fluid, intracellular fluid is high in potassium, phosphate, nucleic acids, amino acids, polypeptides, and magnesium, and it is low in sodium, chloride, calcium, bicarbonate, and glucose[1]. The kidneys play a major role in maintaining the homeostasis of certain electrolytes such as sodium, potassium, calcium, phosphorus, and uric acid[1]. Typically, electrolytes are excreted at the glomerulus of the kidney, and are selectively reabsorbed throughout the nephron as per the body's requirements. Kidneys are pretty great,

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but they do have limits. Sometimes, electrolytic disturbances can be significant enough to overwhelm the kidneys, especially if there is a pre-existing renal pathology[1]. This can occur in TLS, a problem that occurs in patients with cancer.

Perturbation in tumor lysis syndrome, relation to cancer.

Cancer is a disease caused by uncontrolled division of abnormal cells, often characterized by rapid growth. Cancer cells are prone to dying due to their high turnover rate, common replication errors incompatible with cellular life, and being targeted in cancer therapy. Unlike apoptosis, which is a normal cellular mechanism that allows cells to degrade in a controlled and pre-programmed manner, cancer cells often lyse upon dying, thereby releasing intracellular content into systemic circulation. This can cause electrolyte abnormalities, which we rely mainly on the kidneys to correct.

In TLS, the death of cancer cells causes the massive release of intracellular components into systemic circulation, such that the kidneys are overwhelmed and cannot maintain homeostasis[1,2,4]. This brings us to the laboratory and clinical definitions of TLS. Since TLS is characterized by hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, the laboratory criteria for TLS are met when 2 or more of these electrolytic abnormalities are measured together within a 24 hour period AND they are present between 3 days before to 7 days after initiating chemotherapy. To meet criteria for clinical TLS, both the laboratory criteria AND at least one of the following clinical signs that can be caused by them are needed: increased creatinine level (meaning acute kidney injury/ AKI), seizures, neuromuscular instability, cardiac arrhythmia, or death![1] Although they are not part of the diagnostic criteria, lactic acidosis and very rarely, laryngospasm are also both associated with TLS and important for which to look out[1,4]. As you can see, TLS can be an acute and life-threatening problem.

Let's begin with a case. Your first patient of your pediatric oncology elective is Habib, an 8 year old boy who immigrated from Africa this year and was unfortunately diagnosed with Burkitt's lymphoma soon after. He is about to receive his first chemotherapy, and your preceptor asks you: should we be worried about Tumor Lysis Syndrome in this patient?

Etiology and risk factors of Tumor Lysis Syndrome

In children, TLS primarily occurs due to cancer treatment such as chemotherapy[1,4] and radiotherapy[4]. It can also occur spontaneously, although more commonly in adults with numerous co-morbidities; spontaneous TLS is extremely rare in children. In general, you can think of the risk of TLS being higher in anyone with bulky disease or high WBC counts, meaning cancers with high tumor burden that would release considerable intracellular contents all at once if lysis of these cells were to be provoked. Fortunately, we have qualified oncologists who prevent TLS during cancer treatment as part of their routine care. These require both more monitoring as well as strict prophylactic protocols to make sure they can be treated safely from a TLS perspective[1,2]. Risk is increased with certain cancer types, advanced staging, renal involvement, and elevated pre-treatment potassium, phosphate, uric acid, lactate dehydrogenase (LDH), and WBC[1,2,4]. A clinical pearl is that LDH is a particularly useful indicator in pediatric oncology and TLS as to who will likely need intervention! Typically, the risk of TLS is highest in the first 3 days of cancer therapy, but may begin as late as 7 days after therapy initiation[1]. Particularly, cancer types that are higher risk include acute leukemias, as well as Burkitt lymphoma and other advanced-stage non-Hodgkin lymphoma[1,2,4].

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So as we've said, TLS is more common with a great tumor mass and a high proliferation rate- this typically occurs in hematological malignancies[1,4]. An example of one such malignancy is Burkitt lymphoma (like in our case), a form of non-Hodgkin's B-cell lymphoma that is approximately 50x more common in Africa than the United States[9], particularly in children. The natural history for this disease without proper management would be that even in children, it can have such a high proliferation rate that it outgrows its metabolic supply, which results in spontaneous tumor lysis[1,4]. This can largely be prevented with careful management .Solid tumors, Hodgkin lymphoma, and early stage non-Hodgkin lymphoma are typically considered lower risk[1,2,4]. However, the risk may be elevated for these low-risk tumors in treatment that causes rapid cell lysis in the context of chemosensitive tumors, new and effective targeted therapies (e.g. biological therapies)[1,2,4], or impaired renal clearance[1,4]. Remember, the kidneys are crucial for clearing potentially lethal cell contents! And again, a clinician's best tool for prevention and management of TLS is a high index of suspicion.

Clinical assessment of Tumor Lysis Syndrome

So, you want to be on the lookout for TLS in your pediatric oncology patients! In addition to the symptoms required for clinical TLS diagnosis, TLS can present with systemic symptoms like lethargy; GI symptoms such as nausea, vomiting, diarrhea, anorexia; and GU or renal symptoms like hematuria. Much, much more rare presentations in urban centers are MSK symptoms like muscle cramps, and tetany; neurological symptoms like seizures; and critically, cardiac symptoms like heart failure, cardiac dysrhythmias, syncope, and possible sudden death[4]. It's a pretty hefty list, but the majority of the symptoms are related to acute kidney injury and the underlying metabolic derangements of hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and lactic acidosis.

Let's go through each of the clinically relevant substances released in TLS.

Potassium

Potassium plays an important role in maintaining membrane potential, homeostasis of volume, and transmission of action potentials. Excitable cells such as neurons and muscles are among the first to be affected by potassium dysregulation, as their function depends on depolarization. In hyperkalemia, the resting membrane potential is partially depolarized, causing the inactivation sodium channels that are vital to the action potential. This can result in paresthesias, muscle pain, muscle weakness, tiredness, palpitations, bradycardia, and numbness[1].
In extreme cases of hyperkalemia, this can result in life-threatening arrhythmias, such as ventricular tachyarrhythmias, and even sudden death[1,7].

Phosphate

Phosphate is necessary for regulation of cellular energetics and as a backbone for DNA and RNA. Although hyperphosphatemia is usually asymptomatic in and of itself, it is relevant because calcium phosphate is insoluble in water[1]. Spontaneous precipitation of calcium phosphate is prevented by keeping the calcium-rich extracellular environment from the phosphate-rich intracellular environment. While controlled precipitation of calcium phosphate is desired in bone formation, the uncontrolled deposition of calcium phosphate crystals in other tissues is problematic, particularly in the kidney parenchyma as it may cause acute kidney injury (AKI)[1,4]. The AKI further exacerbates the effects of TLS, as the pathophysiology of TLS stems from the kidney's inability to clear the electrolyte derangement[1].

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Calcium

Calcium plays a vital role in muscle contraction, neurotransmission, protein binding, and signalling. In neuromuscular physiology, calcium blocks sodium channels and inhibits depolarization, which sets the threshold for depolarization. Consequently, hypocalcemia reduces the threshold for depolarization, which is responsible for increased responsiveness in muscles and nerves, causing seizures. Further, as calcium binds proteins important in the coagulation cascade, hypocalcemia can impair coagulation.

The hypocalcemia in TLS is directly caused by the precipitation of calcium phosphate crystals previously described. Thus, high levels of phosphate can cause dangerous low levels of calcium[1]. Other manifestations of hypocalcemia include neuromuscular hyperactivity (e.g. spasms, convulsions, arrhythmias, numbness, and tetany), as well as impairment of the coagulation cascade (e.g. petechial rash or purpura)[1]. Life threatening conditions include laryngospasm and cardiac arrhythmias, particularly in the context of hyperkalemia and calcium phosphate deposition in the cardiac conduction system[1].

A clinical pearl is that electrocardiogram (ECG) is a particularly useful tool to determine whether the patient is experiencing arrhythmias, and gives useful clues whether the patient has hyperkalemia or hypocalcemia. In a patient with hyperkalemia, ECG findings may show narrow peaked T waves[1,7], prolonged PR interval[7], or widening of the QRS complex[1,7]. In a patient with hypocalcemia, ECG findings include a prolonged QT interval[7].

Nucleic acids

Nucleic acids are important components of DNA and RNA found in nucleated cells, and can be classified as purines or pyrimidines based on their molecular structure. Purines include adenine and guanine, while pyrimidines include thymine and cytosine. When found in the bloodstream, for example after cell lysis, purines are degraded into uric acid via the purine degradation pathway and excreted by the kidneys in the urine[1,4,7].

Purines are converted to xanthine, then uric acid via the enzyme xanthine oxidase[1,4]. As uric acid is poorly soluble in water, it is prone to precipitate as monosodium urate crystals, particularly in the acidic environment of renal tubules, which may lead to acute uric acid nephropathy[1,4]. While gout and uric acid kidney stones are common complications of hyperuricemia, they are not presenting features of TLS[1,4].

Lactic acidosis

Lactic acid is a normal by-product of anaerobic metabolism; however, the pathophysiology of lactic acidosis in association with TLS has not yet been elucidated[6]. Lactic acidosis, a high anion gap metabolic acidosis, is certainly an issue in TLS, as it can exacerbate the previously described derangements. It hinders intracellular uptake of potassium via proton-potassium exchangers, precipitates monosodium urate by decreasing uric acid solubility, and further promotes hyperphosphatemia via an extracellular shift of phosphate.

You respond to your preceptor that Habib's cancer is known to have a higher tumor cell mass, and consequently he is at a higher risk of TLS. You also suggest that before initiating chemotherapy, it is important to make sure he is well hydrated and has no signs of kidney impairment that could increase his risk. Very satisfied with your answer,

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your preceptor shows you his workup from last month, revealing healthy kidneys and normal lab-work at that time.
Three days later, you go to check on Habib's labs- these are being ordered every 8 hours, given his disease risk factors and that TLS is most likely to develop in the first 3 days after chemo. You notice with some concern that his LDH has become acutely elevated, as well as his blood urea and creatinine. You alert your preceptor, who motions you to follow her into Habib's room. Together, you do a focused history and physical. Habib has had some nausea but no vomiting, no muscle cramps or stiffness, but has been urinating less frequently and less volume despite continued normal PO intake. His physical exam is all normal and ECG lacks any narrow, spiked T waves or a prolonged QT interval.
Is this TLS?

Diagnosis of Tumor Lysis syndrome

One thing you may find if you do any pediatric oncology electives, is that TLS is rarely diagnosed using the full criteria- rather, indicators such as LDH and blood urea are acted upon quickly before any other of the criteria can be met. However, it is useful to understand the full criteria in order to understand the pathophysiology of TLS, as well as in conducting research so as to be certainly comparing the same condition across studies.

Remember how we mentioned the laboratory and clinical diagnostic criteria for TLS before? Well, these are derived from the Cairo-Bishop definition of TLS, modified by Howard in 2011[1,4]. There are actually a few more details for these criteria to consider:

In laboratory TLS, two or more metabolic abnormalities must be present in a 24-hour period, and must occur between 3 days before or up to 7 days after initiation of therapy. These metabolic abnormalities include Uric acid > age-corrected ULN; Potassium >6.0 mmol/L; Phosphorus >2.1 mmol/L (6.5 mg/dL); Corrected calcium <1.75 mmol/L (7.0 mg/dL)][1,2].

Clinical TLS technically requires the diagnosis of laboratory TLS plus a clinical criteria that is assumed to be a direct consequence of abnormalities confirmed in the laboratory. The clinical criteria include seizures, cardiac dysrhythmia, death, or increased creatinine level (increase, 1.5x over age-corrected ULN, or oliguria)[1,2].

Management of Tumor Lysis Syndrome

Back to our Case:
Thankfully, with modern protocols, Habib's TLS has gotten nowhere near the point of meeting full diagnostic criteria of clinical TLS. However, with our high index of suspicion it appears as though he may be developing TLS as he has elevated LDH, urea, and decreased kidney function despite ongoing hyperhydration.
You review his prophylaxis and see that he is already on allopurinol. Given that this appears not to be sufficient management at this time, how can you step up his management?

Any pediatric patient presenting with a potential malignancy should be evaluated for impaired kidney function (by measuring creatinine), hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia[1]. During cancer treatment, these tests should be repeated serially at intervals depending on the child's risk of developing TLS. Tests should be repeated periodically

depending on the risk of disease: Every 4-8 hours for high risk, every 8-12 hours for intermediate risk, and every 12-24 hours for low risk[1]. Don't forget that different malignancies become higher or lower risk depending on their white blood cell count and lactate dehydrogenase level[1].

Kidney function

One of the most important parts of TLS prevention is hyperhydration. Hyperhydration is used to prevent and manage TLS in malignancies at intermediate and high risk, aiming to optimize kidney function and decrease acidosis. Pediatric patients should be given empiric fluids IV at 1.5-2 times maintenance fluid levels in order to maintain a urine output of 3-5 mL/kg/h[1], until tumor burden is largely resolved, there is no evidence of TLS, and the patient is drinking and urinating adequately[5]. If the child weighs less than 10 kg, the target urine output is 4-6 mL/kg/h[5]. D5NS or D5 1/4NS is recommended, depending on the patient's natremic state[5]. Note that the fluids should not contain potassium or calcium because hyperkalemia and hyperphosphatemia are presenting features of TLS that we are also trying to avoid[1,5]. Monitor for fluid overload and third spacing[1,5]. Conversely, if hydration alone is insufficient, it is possible to administer loop diuretics[1], such as furosemide[5], as long as the patient does not have hypovolemia or obstructive uropathy[5]. Loop diuretics are helpfully potassium-WASTING and will also aid in preventing or managing hyperkalemia. For this same reason, it is important not to use potassium-sparing diuretics[1]. If hydration and loop diuretics are insufficient at rectifying oliguria, a pediatric nephrology consult is recommended[1].

Hyperkalemia

Hyperkalemia management mostly occurs through prevention. Stop all potassium supplementation until the resolution of TLS risks[1], and review medications that may cause hyperkalemia[1]. **Can you think of any medications that might cause hyperkalemia? (pause)** Think about how the renin-angiotensin-aldosterone axis gets rid of potassium in the urine, so any inhibitors of this axis, including ACE inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics, cause hyperkalemia by reducing renal potassium excretion[1]. The main med to think of stopping are NSAIDs! Other things to keep in mind but that wouldn't likely need to be stopped unless the TLS is presenting more severely than is typically seen in urban centers are calcineurin inhibitors (which also reduce the action of aldosterone[1]), and calcium-channel blockers and beta-blockers (which cause an extracellular potassium shift[1]). It therefore makes sense that in a pinch where there is life-threatening hyperkalemia, some of these same mechanisms can be reversed to push potassium back IN to cells, with beta-adrenergic agonists like insulin!

In the very unlikely scenario where TLS progresses to life-threatening cardiac complications from hyperkalemia, it is important to know what to do if it develops. This can happen in the context of untreated TLS. Rapid access to intensive care[5] is recommended if the patient develops severe muscle weakness[1,3], ECG findings of peaked T or wide QRS waves[1,3], or potassium >6 mmol/L[1,3]. In life-threatening hyperkalemia, the key is stabilize the heart, and to get as much potassium out of systemic circulation as possible, both acutely and long-term[1,3]. You can immediately decrease cardiac muscle excitability by giving calcium gluconate[3]. This buys you some time to address the acute hyperkalemia. You can use insulin as we mentioned before, plus glucose, as well beta-2 agonists like nebulized albuterol and sodium bicarbonate (remember, beta blockers were on the list of medications that can cause hyperkalemia)[3]. The duration of onset varies between 10-30 minutes depending on the medication, after which period an additional dose can be given[3]. Note: do not give sodium bicarbonate in the same line

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as calcium due to risk of precipitation[3]. Long-term, you can remove potassium from the body on a non-transient basis, either via renal excretion using loop diuretics[3], or via enteric excretion using sodium polystyrene[3], both having a 1-2 hour duration of onset[3]. If the child is unresponsive to diuretics or sodium polystyrene, or has severe renal dysfunction, consider hemodialysis as a last resort[1,3].

Hyperphosphatemia

Prevention and conservative management of hyperphosphatemia is also achieved via hyperhydration[1] by targeting 3-5 mL/kg/day of urine output as before, dietary restriction of phosphorus[1], and phosphate binders such as calcium acetate or sevelamer[1]. If it cannot be managed conservatively, furosemide is indicated to increase urine output[1].

Hypocalcemia

Hypocalcemia is defined as total serum calcium < 1.75 mmol/L or ionized calcium 0.8 mmol/L.

If symptomatic and hypocalcemic, we should give calcium gluconate 50-100 mg/kg by slow IV perfusion with close ECG monitoring. Do not administer calcium when a patient is in a hyperphosphatemic state as it may cause precipitation of calcium phosphate crystals[1]. If asymptomatic, no therapy is indicated.

Hyperuricemia

In the context of TLS, hyperuricemia can mean uric acid 8 mg/dL (>475 µmol/L), a >25% increase in uric acid levels, or inadequate response to hyperhydration and allopurinol[1]. To prevent hyperuricemia, the first line of prophylactic therapy is allopurinol[1,5], with adjustments for renal impairment[5]. Allopurinol is a xanthine oxidase inhibitor, and works by preventing the conversion of hypoxanthine and xanthine to uric acid. However, allopurinol is ineffective if uric acid levels are already elevated because it only intervenes in uric acid FORMATION by blocking xanthine oxidase[1,4,5].

Instead of allopurinol[4,5], patients with hyperuricemia or considered high-risk should receive a single dose of rasburicase[1,4,5], a urate oxidase that breaks down preformed uric acid. Note that rasburicase can cause hypoxemia due to methemoglobinemia[1,4] and hemolysis[5] in patients with G6PD deficiency.

Habib's management

In Habib's case, he should be receiving serial electrolytes and continued monitoring of kidney function every 4 hours. Because he has some mild hyperuricemia on his allopurinol, and he will need one dose of rasburicase because he is considered high-risk for TLS because of Burkitt leukemia.

You suggest this management to your preceptor and Habib experiences a full recovery! He is monitored for TLS until he is seven days post-therapy initiation and prophylaxis is weaned as appropriate.

Well done managing this case! Let's review the big take-home points we hope that you will remember from this podcast:

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TAKE-HOME POINTS

1. The kidney is an organ responsible for maintaining homeostasis of electrolytes, but can be overwhelmed in TLS. In rare but severe cases, TLS can be a life-threatening emergency in kids with cancer, when tumors release large quantities of intracellular material.
2. TLS is typically caused by cancer treatment, and is typically characterized by hyperuricemia, creatinine elevation, and lactic acidosis. Additionally, you need to watch for hyperkalemia, hyperphosphatemia, and hypocalcemia.
3. When initiating cancer treatment, it is important to give the necessary prophylaxis to prevent development of TLS, and consider TLS as part of the differential diagnosis for electrolyte abnormalities and acute kidney injury. The risk of developing TLS can be assessed by considering cancer type, staging, renal function, electrolytes, lactate dehydrogenase, and white blood cell count.
4. Severe TLS can present with neuromuscular symptoms, cardiac arrhythmias, and acute kidney injury. It can be formally diagnosed using the Cairo-Bishop laboratory and clinical diagnostic criteria, but clinicians should not wait until these features are present to act!
5. Management of TLS is largely through prevention and prophylactic treatment: hyperhydration protects and optimizes kidney function in higher risk patients, reviewing medications helps prevent electrolytic derangements, allopurinol and rasburicase can be used to prevent hyperuricemia, and close monitoring with serial lab tests are necessary for up to 7 days after receiving cancer treatment to watch out for laboratory signs of TLS.

Thanks for listening!

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