LUCAS PARKER'S 2018 E. COLI O157:H7 ILLNESS CAUSED BY ROMAINE LETTUCE



Lucas before illness

Lucas Parker is a 3½ year old little boy who lives in Richmond, British Columbia, Canada, with his dad Nathan, mom Karla, brother Alexander now two years old, and new baby brother Seth now nine months old. Lucas was just 2 years old at the time he was exposed to contaminated romaine lettuce when he consumed food purchased from Gino's Pizza in Pismo Beach, California on October 11, 2018. His family had no way to detect that the food was contaminated by the deadly bacterium *E. coli* O157:H7.



Parker family before Lucas' illness

Background medical history

Lucas Parker was born at Surrey Memorial Hospital in British Columbia, Canada on March 30, 2016. Karla's pregnancy was normal, with the exception of gestational diabetes that was well managed with regular prenatal care and ultrasound monitoring. Lucas weighed in at almost 8.5 pounds and was born vigorous and healthy, with Apgar scores of 8 and 9 at one and five minutes. Lucas' first two years were not without the usual things that worry parents, and he visited the ER a number of times for upper respiratory infections, and in March 2017 he was diagnosed with post-viral reactive airway disease (asthma). He suffered one minor head injury in July 2017 after tumbling a short distance off the edge of a sofa at 16 months of age. When Lucas was 2½ years old, his pediatrician Dr. Singh referred him with a "communication disorder," when his speech seemed delayed. Kuppuchipalayam Kaliappan Ramesh, MD evaluated Lucas and diagnosed him with ASD ("autism spectrum disorder"). Lucas was otherwise healthy, thriving, and meeting all other growth and developmental milestones. In June 2018, Molecular Cytogenetics Lab reported a "microarray analysis" that did not identify any "gain or loss of chromosomal material."



Lucas enjoying playground fun



Lucas and Karla having fun



More fun at the park

Road trip to Disneyland

Lucas and his family were on a road trip along the West Coast down to Disneyland, accompanied by Karla's mom and Nathan's son Matthew, who was about to turn 8 on October 17, 2018. The family wanted this to be a leisure trip. They rented a car and wanted to see the sights as they traveled the scenic highway south, including some beach areas as they got further south. Karla's mom recalls that the family had planned to stop in Pismo Beach. on the 11th of October, about 3 hours north of Los Angeles. On October 11, 2018, they arrived late in the evening and were so tired they did not feel up to stopping at a grocery store for supplies. Because it was so late and their hotel room did not have a kitchen, they decided to order takeout, choosing a pizza and antipasto salads.



Nathan recalls that Lucas wanted to share his salad, and so he did:

The antipasto salad came, it was bedded on romaine lettuce.. and Lucas, being attached to my hip the way he was, "... wanted to eat what daddy was eating... what are you eating daddy? I want some!"

By the time the family arrived at Disneyland on October 17, 2018, Lucas was acting "off" and was finicky and crying in the car as they arrived at the park. Nathan recalls, "... something was just not right." Lucas had had an "off diaper" at the hotel – "it was 'off' and smelled foul..." Nevertheless, Lucas appeared to be physically fine the rest of that day at Disneyland.



In the car upon arrival at Disneyland

Despite his discomfort in the car on the way to Disneyland, Lucas settled down and the family went into the park to celebrate Matthew's birthday. Lucas seemed to be physically fine and had a good time with the family.



Legoland at Disneyland

Symptom onset

The following day, October 18, 2018, Lucas had his first bloody diarrhea.

Nathan recalls: "I knew something was wrong."

Grandma: "We had to go home, he was sick. (grandma) – as we started to drive, he got sicker and sicker – all I remember was hearing him in the back... 'mommy-tummy – owie owie – mommy tummy...' – just having diarrhea all the time... -- There was no way anyone could imaging just how sick he was. We didn't know the signs of E. coli –I'd never seen anyone with E. coli -- we had no idea how sick he was.

Karla: "he had diarrhea and then would start vomiting – he was puking and puking and puking – we're in the United States, we aren't in Canada, we don't know what to do – we just wanted to get back as fast as we can, because we felt like his health was deteriorating.

En route, Lucas was so sick, they decided to stop so Lucas could get medical attention.



Heading north from SoCal to Olympia

Providence St. Peter Hospital



Providence St. Peter ER – Olympia, WA

On Friday, October 19, 2018, at 5:44 PM, the family arrived at Providence St. Peter Hospital in Olympia, Washington, where Ian Strand DO evaluated Lucas in the emergency department for "Blood in Stool; Diarrhea (Peds); Fatigue; Emesis; and Abdominal Pain." In triage, Nathan explained that the family was from British Columbia and were on their way back to Canada from California, where they had visited Disneyland. Nathan stated that Lucas had become acutely ill, so the family was trying to get back to Canada.

Nathan described to the triage nurse how Lucas had so far experienced approximately 36 hours of abdominal pain, nausea, vomiting, diarrhea, and bloody stools. The little boy had awakened early the previous morning with abdominal pain, and shortly after that he vomited. Later that morning he had his first bout of soft stool. The soft stool progressed throughout the day and, by last evening, he had his first episode of "bloody mucoid stool." Lucas had had 5 diapers just

that day full of bloody, mucousy diarrhea. Nathan stated that he and his wife had tried to give Lucas some children's liquid Tylenol, but he promptly vomited it up. They were finally able to break up a single dose into 2 smaller doses later in the day, which Lucas was able to hold down, but he had been unable to eat any food. Lucas had been acting very sleepy throughout the day, but he stopped running fevers, according to his dad.

Responding to questions about Lucas' exposure history, Nathan indicated that the whole family had a bunch of new food exposures on the trip. No one else had become sick, although Karla did have a single episode of loose stool. Nathan explained that Lucas had been a healthy child before the trip, and he had no chronic medical conditions or prior hospitalizations. He also had no known allergies to medications or foods. Dr. Strand noted that Lucas' only significant history was a diagnosis of "pre-autism," which had been diagnosed because of a significant speech delay. Despite this, he was developing normally and was a healthy, active toddler.

On exam, Dr. Strand found Lucas with a high-normal temperature of 99.7°F. His blood pressure was slightly elevated for his age (107/72), he was tachycardic with a pulse in the 130s to 140s, and he was mildly tachypneic with a respiratory rate of 20. Dr. Strand observed that Lucas was "well-developed and well-nourished." He was active and did not seem to be in any distress. He did exhibit signs of dehydration, with dry and tacky mucous membranes, but his HEENT exam was otherwise unremarkable. His heart and lungs sounded normal, and he was oxygenating well on room air. His main abnormal finding was abdominal tenderness, which Dr. Strand described as "mildly uncomfortable" when he applied pressure on exam. A KUB¹ x-ray showed no abnormalities. An IV was started and blood sent to the lab for analysis.

While under observation in the ER, Lucas was given intravenous fluids to rehydrate him, and he was given sublingual Zofran for nausea. A CBC was significant for an elevated white count of 31.1. His platelets were 424K, BUN 19, and serum creatinine 0.31. His hemoglobin and hematocrit were elevated at 14.9 and 44.6%.²

Dr. Strand was specifically interested in checking Lucas for hemolytic uremic syndrome, given his bloody diarrhea, nausea, and vomiting. Dr. Strand explained that the elevated white count was likely from Lucas' acute diarrheal illness, and he considered the other lab results reassuring ("normal platelet count, normal renal function, and no anemia"). After the IV fluids and a few hours of observation, he commented:

He is looking much better. He is moving around the bed interacting with parents. He has tolerated 3 cold apple juice containers here in the emergency department. His family is from Canada and has a family physician that can [reassess] him in the next 24 hours.

ER diagnosis "infectious diarrhea illness and dehydration"

Dr. Strand discussed the results of Lucas' workup with Nathan and Karla and discharged

¹ KUB = Kidney-ureters-bladder

² Reference ranges for this US Laboratory: WBC 6.0-15.5K, hemoglobin 11.5-33.5 g/dL, hematocrit 34-40%, platelets 250-550K, BUN 8-25 mg/dL, creatinine 0.7-1.3 mg/dL

Lucas from the ER so the family could continue their trek northward back to Canada. Dr. Strand documented his discharge diagnosis:

Given his current clinical presentation and diagnostic findings I believe that the most likely diagnosis is consistent with infectious diarrheal illness and dehydration. At this point I believe that he is at low risk for an emergent etiology of his symptoms requiring further intervention at this time and consider discharge a reasonable course of action at this time.

Dr. Strand specifically discussed the symptoms that would be most concerning and necessitate emergent re-evaluation by a hospital ER (e.g. fever, bloody vomit or bowel movements, inability to hold down food or water, worsening pain, passing out, and weakness). Lucas was discharged to the care of his mom and dad just before 9 PM.



Olympia to Vancouver BC

Finally home...

Nathan and Karla arrived home with the kids sometime after midnight on Saturday, October 19, 2018. Hoping the worst was behind them, they tucked Lucas into bed. Their relief at being home was short-lived. Although they planned to contact their pediatrician in the morning anyway, they could not wait that long when Lucas awakened very ill.

British Columbia Ambulance Service

Just before 7 AM on Saturday, October 20, 2018, the BC Ambulance Service was summoned to the Parker family home after Lucas woke up with more vomiting, this time

containing blood. Alarmed, the family called for EMS transport to the local hospital. When the medics arrived, they observed that Lucas was tracking their movements but was otherwise lethargic and had glassy eyes. He seemed overly warm to touch. Lucas would or could not respond verbally to their queries, so the medics relied on his parents to describe his symptoms. Assessing Lucas prior to transport, he was notably tachycardic with a heart rate of 168, his blood pressure was elevated at 121/80, but he was not having any trouble breathing and had good blood oxygen concentration (96%). After completing their assessment, the medics transferred Lucas to a gurney, and then to the ambulance. They arrived at Richmond Hospital at 7:39 AM.



Ambulance ride to Richmond Hospital

Richmond Hospital – Emergency Department

Upon arrival at Richmond Hospital on Saturday, October 20, 2018, Lucas was admitted for observation to the emergency department under the care of Steven Fedder, MD. Upon arrival at the hospital, Lucas was quickly taken to triage, where Nathan and Karla filled in the staff about his condition. Lucas was currently having multiple, frequent diarrhea stools with episodic mucous and blood, occurring every 30-60 minutes. Dr. Fedder was in to see Lucas at 8 AM and learned that the family had been traveling up the coast from Disneyland when the toddler became acutely ill, stopping at an emergency room in Olympia the day before. Dr. Fedder thought Lucas looked very lethargic and dehydrated and ordered an IV fluid bolus and careful rehydration with continuous fluids after that. Blood cultures were drawn and a CBC and metabolic panel sent to the lab. Lucas was given Tylenol around 10 AM for a fever of 100.4°F.

Dr. Fedder reviewed the details of Lucas' illness, with recurrent vomiting and diarrhea for the 4 days before coming to the Richmond ER. He found it notable that the vomitus had been occurring on a frequent basis but did not contain blood at first. On the morning prior to the ER assessment, Lucas had vomited up blood at home that was said to a large quantity (described as "half cup" by Nathan). Nathan had not seen any black/maroon stools (melena). Dr. Fedder observed that Lucas was having abdominal pain, but the toddler was minimally verbal and unable to localize it for the doctor. He was not in respiratory distress. Per his parents, Lucas was progressively more lethargic over the 48 hours before coming to the ER, and his urinary output had decreased.

Lethargic, tachypneic, tachycardic...

On examination, Dr. Fedder observed that Lucas was alert to voice but noticeably lethargic. His respirations were rapid at 30 breaths per minute, and he appeared quite pale. His capillary refill was prolonged at approximately 3 sec. Dr. Fedder described Lucas' heart rate of 160-170 as sinus tachycardia, with normal blood pressure for age, and no fever at present. Lucas was clearly dehydrated, with dry and tacky mucous membranes. His abdomen did not seem to be tender, and his neurologic exam revealed motor function in all extremities. His pupils were equal and reactive to light, and he had normal extraocular eye movements. Lucas appeared to be responsive to his parents.

Leukocytosis, initially normal platelets and renal function, but LDH elevated...

When Lucas' lab results were reported, they were significant for an elevated white blood cell count of 37.9, and hemoglobin 151. His initial platelet count was in normal range at 278K. His BUN and creatinine were measured in normal range at 7.2 and 46 (*note Canadian reference ranges below*).³ His liver function tests were normal, but his LDH⁴ was elevated at 428.

Mild fever, administration of antibiotics (ceftriaxone), clinically improved...

Dr. Balbinder Singh Gill came in to see Lucas and gave him a dose of Tylenol for a fever of 100.4°F. Lucas was given 750 mg of ceftriaxone for his fever and elevated white count. During his first three hours in the ER, Lucas appeared clinically improved, with more active interaction with his parents and his pulse rate normalized into the 140 range. He was even observed to be watching videos on his dad's cell phone. The doctors thought that Lucas' most likely diagnosis was significant dehydration secondary to gastroenteritis, "… possibly a bacterial enteritis." He did not appear to have any renal impairment and no signs of severe sepsis, and no clear surgical etiology for his symptoms.

Richmond Hospital Day 1 – Admitted for observation of dehydration and gastroenteritis

Dr. Fedder conferred with the pediatric Balbinder Gill, MD, who agreed to admit Lucas to the hospital from the ER for further observation and management. In an addendum to his ER summary, Dr. Fedder commented that a gentle digital rectal exam while Lucas was still in the ER revealed no melena and no blood. He opined that the blood observed in Lucas' vomitus was likely related to a Mallory-Weiss tear⁵ and not related to any significant hepatic or intestinal abnormality, particularly as his hemoglobin was stable.

Lucas was admitted under Pediatrics but stayed in the emergency department during the entirety of his admission. His blood work was repeated that evening at 7 PM, showing a decrease in his hemoglobin to 133, and his platelets dropped to 93K. His creatinine increased to 82, and his

³ NOTE CANADIAN VALUES: Normal reference ranges for this lab: WBC 5.0-16.0K, hemoglobin 105-147 g/L, hematocrit 0.33-0.40, platelets 180-490K, INR 1.1, albumin 34-50 g/L, urea (BUN) 2.0-8.2 mmol/L, creatinine 10-50 µmol/L, LDH 140-280 U/L, CRP < 3.1 mg/L

⁴ In HUS, lactate dehydrogenase (LDH) level is commonly elevated. Serial measurements of LDH help track the approximate level of hemolytic activity. Bitzan, Martin, and Anne-Laure Lapeyraque. "Postinfectious Hemolytic Uremic Syndrome." *Pediatric Kidney Disease*, 2016, pp. 653–731., doi:10.1007/978-3-662-52972-0_26.

⁵ Mallory-Weiss Syndrome: Hemorrhage from the upper gastrointestinal tract due to a tear in the mucosa of the esophagus or gastroesophageal junction. Violent retching usually precedes the bleeding. Venes, Donald. Taber's Cyclopedic Medical Dictionary (Taber's Cyclopedic Medical Dictionary (Thumb Index Version)) (Page 1449). F.A. Davis Company. Kindle Edition.

BUN decreased to 6.4. His liver enzymes began to increase and his LDH spiked to 2795. A CRP⁶ was drawn and was elevated at 154.



Waiting in misery to be transferred

At 8 PM that same day, nursing notes reflect that Lucas continued to be febrile despite dosing with Tylenol; his rectum appeared irritated and was seeping a small amount of frank red blood. Lucas was reportedly very irritable and difficult to examine: "Becomes agitated and attempts to crawl away from writer w/ rectal temp. Cries slightly. Comforted by father."

Richmond Hospital Day 2 – Worsening labs, schistocytes – likely HUS – awaiting transfer

During the night, Lucas expelled bloody, mucousy diarrhea about every 30-60 minutes. His emesis continued and sometimes contained blood. Lucas' morning blood draw on October 21, 2018 revealed a number of worsening values, including a further decline in his platelets to 36K. A peripheral blood smear revealed occasional schistocytes.⁷



Pediatrician Balbinder Gill, MD was summoned to the ER to evaluate Lucas, and he

⁶ Increased blood levels of CRP are present in many infectious and inflammatory diseases (including in patients with coronary artery disease, in whom it is sometimes employed as a risk factor). CRP levels are sometimes monitored serially to determine if infectious or inflammatory diseases have been effectively treated. Venes, *Ibid* Note 100 at 1926.

⁷ The hallmark of hemolytic uremic syndrome in the peripheral smear is the presence of schistocytes. These consist of fragmented, deformed, irregular, or helmet-shaped RBCs. They reflect the partial destruction of red blood cells (RBCs) that occurs as they traverse vessels partially occluded by platelet and hyaline microthrombi. The peripheral smear may also contain giant platelets. This is due to the reduced platelet survival time resulting from the peripheral consumption/destruction. A consumptive coagulopathy is typically not present. Nayer, Ali, and Luis M. Ortega. "Journal of Nephropathology." *Journal of nephropathology* 3.1 (2014).

observed that the toddler's urinary output had decreased overnight. He opined that Lucas was developing hemolytic uremic syndrome and contacted British Columbia Children's Hospital to arrange a transfer, but at 11:00 AM there were no beds available. Finally, in the early afternoon, a bed opened up. Locum tenens Vicki Chow, MD documented the consult and transfer of care:

Lucas was discussed with the PICU team and the CTU team at BC Children's regarding his evolving HUS. He will be transferred under the care of Dr. Humphreys (nephrology) at BCCH. Prior to transfer, his electrolytes showed a potassium 5.5 and sodium 147. He was transitioned to IV D5½NS with no potassium, which equates to his insensible losses. He was allowed to drink the volume of his urine output. He was placed on a low potassium and low phosphate diet. He was also given 1 dose of Lasix to facilitate urine output and the elevated potassium. Lucas was also initially started on IV ceftriaxone, he has been afebrile for over 12 hours and in light of the likely E. coli infection, this was discontinued. A stool sample has been sent for culture and sensitivity as well as Shiga toxin.



Ambulance ride north to BCCH

British Columbia Children's Hospital – Hospital Day 1



British Columbia Children's Hospital

On Sunday, October 21, 2018, the ambulance carrying Lucas arrived at British Columbia Children's Hospital arrived shortly after 2 PM. Lucas' was directly admitted to the "CTU Violet" ward, where he was admitted by pediatrics and pediatric nephrology (per scribe for Drs. Amy Dmytryshyn and Rob Humphreys).

The doctors reviewed Lucas' history of illness that began while on a trip to Disneyland in southern California. Lucas arrived with his records from Richmond Hospital, in which Dr. Gill had raised the suspicion of a Mallory-Weiss tear as the cause for upper GI bleeding.

Of immediate concern upon his arrival at BCCH, the doctors identified that Lucas had decreased urine output ("little noted in diapers"), increasing lethargy, dehydration, and jaundice, and his abdomen was diffusely tender with edema around his umbilicus as well as in his lower extremities. They reviewed his current labs, showing a WBC 26.1, hemoglobin 115, hematocrit 0.36, decreasing platelets, LDH 10,438, total bilirubin 4.0, and peripheral blood smear with evidence of schistocytes—a stool culture for *E. coli* and Shiga toxins was pending. The doctors found it notable that Lucas had been treated with antibiotics while at Richmond Hospital (ceftriaxone IV).

Nephrology Consultation – Diagnosis D+HUS, acute renal failure, oligo/anuria

Lucas' was admitted to the pediatric nephrology service with the diagnoses: 1) D+ HUS – "prognosis severe given increased WBC increased LDH," "ARF – "last urine output 2:30 – oliguric, possible anuric given small volume less than 10 mL." Nephrology resident Kristen Favel, MD consulted around 3-4 PM and commented that Lucas' clinical presentation was consistent with "D+ HUS,"⁸ with oliguria,⁹ thrombocytopenia, acute kidney injury, and anemia. His urinary output on Saturday was estimated to be 449 mL, and on Sunday so far it had diminished to 78 mL. At the same time, Lucas was retaining fluid with a weight gain of 1.2 kg since it was first measured at Richmond Hospital. Dr. Favel changed his IV fluid to $\frac{1}{2}$ normal saline, and she placed restrictions on his intake of potassium and phosphorus. She ordered a one-time dose of Lasix, hoping to stimulate the production of urine and treat his volume overload. Lucas had no response to the Lasix, with no increase in his urinary output.

Lucas did not currently have a fever. His blood pressure was 108/78 (high for age), his heart rate was 140 beats per minutes, and his respirations 26 per minute. He was oxygenating well with a SpO2¹⁰ at 98% on room air. Dr. Favel ordered amlodipine to treat Lucas for hypertension.

⁸ HUS is classified in 2 subgroups: HUS associated with a foodborne infection with Shiga toxin-producing *Escherichia coli* (STEC+) and atypical HUS (aHUS), or STEC- HUS. McCoy, Nicole, and Donald J Weaver. "Hemolytic Uremic Syndrome with Simultaneous Shiga Toxin Producing *Escherichia Coli* and Complement Abnormalities." *BMC Pediatrics* 14 (2014): 278. *PMC*. Web. 31 Jan. 2017.

https://www.medscape.org/viewarticle/751917

⁹ Oliguria is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children, and less than 400 mL daily in adults. It is one of the clinical hallmarks of renal failure and has been used as a criterion for diagnosing and staging acute kidney injury (AKI), previously referred to as acute renal failure. https://emedicine.medscape.com/article/983156-overview

¹⁰ Pulse oximetry devices measure SpO2 (peripheral capillary oxygen saturation). They work by emitting and

His labs were scheduled to be repeated every 8 hours and he was monitored via telemetry. Dr. Favel considered Lucas' anemia significant and added MAHA¹¹ to his diagnoses, although he had no obvious active bleeding or symptoms of heart failure. No blood transfusions were ordered for the time being, pending serial lab results.

Nephrology Attending - continued oligo/anuria - dialysis imminent

At 6:15 PM, nephrology attending Rob Humphreys, MD came in to check on Lucas, observing that there had been no increase in his urinary output with the Lasix, he was showing signs of fluid retention, and his blood pressure was still elevated for a toddler (greater than the 95th percentile). Lucas also exhibited hyperkalemia (high potassium). Dr. Humphreys ordered that bicarbonate be added to Lucas' IV fluids. If his potassium continued to increase, Dr. Humphreys indicated that Lucas would need to be started on peritoneal dialysis. He conferred with Lucas' parents that their son was likely going to be in the hospital at least a week, possibly even a month, and may require chronic hemodialysis or peritoneal dialysis because of the damage being caused to his kidneys.

BCCH Day 2 – sudden neurologic deterioration – decreased LOC – possible seizures

On October 22, 2018, resident V. Masson was summoned to Lucas' bedside at 6:15 AM at the request of the nursing staff to assess him for decreased level of consciousness. His dad Nathan reported that when Lucas awakened about 20 minutes earlier, he was less responsive and only opened his eyes to loud voices or touch. He was no longer tracking with his eyes and was totally nonverbal. On examination, Dr. Masson found Lucas' with "cycling movements" of his lower extremities, upper extremity tremors that were suppressible, and without purposeful movement of any of his extremities, which were intermittently rigid and exhibited spasticity. No clonus¹² was present, but his reflexes were brisk at "3+" in all extremities. Neither the doctor nor Lucas' dad could get him to walk when brought to a standing position. Lucas' blood pressures were elevated in the 120/80 range, and he was tachycardic with a heart rate in the 160's to 170's. His respiratory status was stable with a patent airway.

According to the nursing staff, Lucas had been alert and interactive at 10 PM the night before, and his dad had not heard him crying or screaming before he woke up around 5:30 AM. Dr. Masson alerted nephrology, who expressed concern that Lucas might have experienced an

then absorbing a light wave passing through blood vessels (or capillaries) in the fingertip. Aung, KoKo. "Guideline: Panel Recommends Maintaining SpO2 at No Higher than 96% in Most Acutely Ill Hospitalized Patients." Annals of Internal Medicine, American College of Physicians, 19 Mar. 2019

¹¹ "Microangiopathic hemolytic anemia (MAHA)" is now used to designate any hemolytic anemia related to RBC fragmentation, occurring in association with small vessel disease. In DIC, RBC fragmentation is thought to result from the deposition of fibrin or platelets within the microvasculature. The term "thrombotic microangiopathy (TMA)" is also used to describe syndromes characterized by MAHA, thrombocytopenia, and thrombotic lesions in small blood vessels. The most prominent diagnoses associated with TMA are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). George, James N, and Roseleen S Charania. "Evaluation of Patients with Microangiopathic Hemolytic Anemia and Thrombocytopenia." *Seminars in Thrombosis and Hemostasis*, U.S. National Library of Medicine, Mar. 2013, www.ncbi.nlm.nih.gov/pubmed/23390027/.

¹² *Clonus*: Spasmodic alternation of muscular contractions between antagonistic muscle groups caused by a hyperactive stretch reflex from an upper motor neuron lesion. Sustained pressure or stretch of one of the muscles usually inhibits the reflex. Venes, *Ibid* Note 100 at 503.

"intracranial bleed vs. thrombotic event vs. encephalopathy" and stated they were en route to see him. Kristen Favel, MD arrived for nephrology at 6:30 AM, finding Lucas facing but not focusing/fixing on his dad, and he was shivering/shaking. Lucas did not have a fever, but he remained tachycardic (HR 145) with a blood pressure of 119/76.

Observation of abnormal (decorticate) posturing...

Lucas was difficult to examine, as he was crying and became even more upset when moved. Dr. Favel observed that Lucas was clenching and holding his hands to his chest [*decorticate posturing*] and was kicking his legs in a cycling manner, increasing these movements with stimulation.



Decorticate vs. decerebrate posturing¹³

When not being touched, Lucas would momentarily settle before resuming repetitive movements. Radiology was called for neuroimaging, given Lucas' change in level of consciousness. Lucas was given nifedipine to bring his blood pressure down—the doctors were concerned about possible hypertensive encephalopathy—followed by a dose of midazolam (Versed).¹⁴ The pediatric intensive care (PICU) resident was called to help treat Lucas for possible seizure activity, as well as an increase in Lucas' tachycardia to the 200's. The PICU physician gave Lucas a second dose of midazolam emergently ("IV push").

Respiratory therapy summoned for seizure activity...

Respiratory therapy arrived on the scene shortly, responding to an urgent call to assist with a possible neurologic and/or respiratory emergency. She arrived to find Lucas' having an apparent

¹³*Posturing*: Three types of abnormal posturing are *decorticate* posturing, with the arms flexed over the chest; *decerebrate* posturing, with the arms extended at the sides; and *opisthotonos*, in which the head and back are arched backward. Decorticate posturing indicates that there may be damage to areas including the cerebral hemispheres, the internal capsule, and the thalamus. *While an ominous sign of severe brain damage, the damage of which decorticate posturing is indicative is not as serious as that indicated by decerebrate posturing*. Classically, decerebrate posturing implies brainstem involvement from a compressive or destructive process, while decorticate posturing implies a more rostral (frontal brain) and potentially less dire insult. The *Glasgow Coma Scale* reflects these differences, with a lower (worse) score given for decerebrate posturing. Michelson, David, et al. "Evaluation of Stupor and Coma in Children." *Up-To-Date*, Wolters Kluwer Health, 4 Jan. 2018.

¹⁴ *Midazolam* is used emergently to treat status epilepticus (seizures) It is marketed under the trade name Versed, among others, and is a benzodiazepine medication also used for anesthesia, procedural sedation, trouble sleeping, and severe agitation. It works by inducing sleepiness, decreasing anxiety, and causing a loss of ability to create new memories. <u>https://www.mayoclinic.org/drugs-supplements/midazolam-injection-route/description/drg-20064813</u>

seizure, with hypertonic musculature and posturing ("bilateral decorticate movement") and not responding to voice or pain. However, Lucas was spontaneously breathing on his own and was not on supplemental oxygen, with a rapid respiratory rate of 45-50 per minute. Once Lucas' seizure episode was under control with medication, the care team prepared to move him to the pediatric intensive care unit (PICU) after a stat head CT was done.

CT scan suggestive of ischemia or edema

Lucas was transported to radiology for a head CT around 8 AM to rule out "PRES¹⁵ vs. CNS bleed vs. clot." Radiologist Brendon Graeber, MD performed the scan for the clinical indications of: "2 yo male with [hemolytic uremic syndrome], platelets 20... Change in neuro status now with decreased level of consciousness... not tracking, no focal findings, rule out [intracranial hemorrhage], appears encephalopathic." Dr. Graeber's assessment was limited by motion artifact degrading the images, but he observed:

There is symmetric hypoattenuation in the white matter adjacent to the frontal horns of the lateral ventricles. The gray-white matter differentiation is otherwise normal.¹⁶ No intracranial mass or hemorrhage is identified. There is no mass effect or midline shift. The ventricles are normal in size. Posterior fossa structures and extra-axial CSF spaces are normal. There is no osseous abnormality. The right maxillary sinus is opacified. The mastoid air cells are well-aerated.

With reference to the "symmetrical hypoattenuation" in the frontal lobe white matter. Dr. Graeber termed this finding "nonspecific" and stated that it could represent areas of ischemia or edema. Follow-up imaging with an MRI was planned.



Lucas' 10/22/18 CT scan – ventricles visible in horizontal section on right

¹⁵ SEE NOTE 112.

¹⁶ *Grey-white differentiation* refers to the appearance of the interface between cerebral and cerebellar white matter and grey matter on brain CT and MRI. The term is most often used when trying to differentiate cytotoxic from vasogenic edema. In cytotoxic edema, there is a loss of grey-white differentiation (i.e. inability to distinguish white matter from grey matter which is typical for infarction and hypoxic-ischemic encephalopathy). In vasogenic edema, there is an accentuation of grey-white differentiation (which is typical for a tumor or abscess). Hacking, Craig. "Grey-White Differentiation: Radiology Reference Article." *Radiopaedia Blog RSS*, https://radiopaedia.org/articles/grey-white-differentiation?lang=us

Admitted to PICU – PICU Day 1 – "Acute renal failure secondary to HUS" – platelets 20K

Shortly after the CT scan, Elizabeth Hankinson, MD admitted Lucas to the pediatric intensive care unit (PICU) for neurologic monitoring and further stabilization. She wrote orders for Lucas to have a nasogastric tube inserted and have his neuro status documented every 2 hours.

Pediatric nephrology resident Kristen Favel, MD arrived in the PICU, noting Lucas' current working diagnosis as "acute renal failure secondary to HUS." She observed that he was fluid overloaded (weight increased greater than 1 kg), hypertensive, oliguric/anuric, but had stable electrolytes at that time. Lucas still had bloody diarrhea, transaminitis, and an elevated amylase level. Lucas' platelets dropped down to 20K that morning, and his hemoglobin was low at 85. Hematology cautioned the surgical team that Lucas needed to have a platelet transfusion if he was going to have any procedures that day. Dr. Favel advised against hemodialysis, favoring peritoneal dialysis, because of the risk of blood lost to the HD circuit with platelets as low as his were.

Pediatric Neurology Consultation - decerebrate (extensor) posturing

Dr. Connolly and neurology resident Jonathan Smith, MD evaluated Lucas at 8:45 AM for the neurology service at the request of pediatrician Dr. Dmytryshyn. Dr. Connolly reviewed what the care team reported about Lucas' clinically-observed seizure activity:

He was found at 6:30 this morning to have altered LOC by the CTU team. He was observed to be having BL extensor posturing¹⁷ with spontaneous eye opening and shivering. He did not respond to verbal stimuli but has persistently responded to noxious stimuli¹⁸ with withdrawal. This state has been somewhat fluctuant, in that he sometimes appears to calm down and will have some normalization of tone and decreased shivering, though does not have increased responsiveness. He has received 3 doses of midazolam, 2 buccal and 1 IV in the context of arranging transport and his CT this morning and it was noted that his tone did improve, though his level of consciousness did not.



Extensor (decerebrate) posturing

¹⁷ Decerebrate rigidity (DR) in humans results from a midbrain lesion and is manifested by an exaggerated extensor posture of all extremities. Davis, R A, and L Davis. "Decerebrate Rigidity in Humans." *Neurosurgery*, U.S. National Library of Medicine, May 1982, <u>https://www.ncbi.nlm.nih.gov/pubmed/7099417/</u>. See NOTE 110.

¹⁸ Assessing the patient's response to noxious stimuli (i.e., sternal rub, deep nail bed pressure, etc.) is a technique commonly employed to determine a patient's level of consciousness. Even a semi-conscious patient will usually respond by withdrawing from a painful stimulus. Cervero, Fernando, MD. "What is a noxious stimulus?" *What is a noxious stimulus*? N.p., 1996. Web. 31 Jan. 2017.

When he was found this morning with altered level of consciousness, an urgent CT head was arranged and transferred to ICU. The CT head did not show any acute bleed and no evidence of significant edema or compression or herniation. There was note made of bilateral frontal periventricular hypodensities of uncertain etiology, query ischemia versus edema.

Dr. Connolly examined Lucas, observing continued extensor posturing that was somewhat more pronounced on the left than the right. He did appear to have occasional semi-volitional movement of his right hand, although she noted significant rigidity throughout his left arm and his legs. He was shivering and his jaw was clenched. Lucas' eyes were spontaneously open and he looked straight ahead. His blood pressure was elevated at 115/80, and he was tachycardic with a heart rate of 200. Lucas was oxygenating normally on room air. He was afebrile (temp 37.9C) and exhibited spontaneous eye opening, but no response to verbal stimuli or withdrawal to painful stimuli. Lucas' left pupil was half a millimeter larger than the right but both were equally reactive to light. His facial movements appeared symmetric, and his tongue was midline. Notably, Lucas exhibited no gag reflex. Dr. Connolly noted significant neck stiffening, or "meningismus."¹⁹ She attempted to test Lucas for "Dolls eye sign"²⁰ and observed an intact horizontal gaze, but "vertical gaze" could not be stimulated because of his posturing. On motor examination, Lucas' deep tendon reflexes were 2+ throughout, with "upgoing toe on the right side and fixed flexed toe on the left."²¹



Babinski sign (fanning of toes) -- abnormal after age 2

¹⁹ Neck stiffness, or *meningismus*, is irritation of the brain and spinal cord with symptoms simulating meningitis, but without actual inflammation. It is an important subset of neck stiffness that defines neck stiffness in association with meningeal irritation. With meningismus, the child typically has fever, restriction of neck movement (of neck flexion in particular), and pain. Conditions presenting with meningismus require emergency evaluation and management. Causes include meningitis and infection of adjacent structures such as spinal epidural abscesses. Venes, *Ibid* Note 100 at 1489.

²⁰ *Dolls eye* sign refers to the deviation of a person's eyes to the opposite side when the head is rapidly rotated. This is a normal finding in neonates but is otherwise indicative of coma. Venes, *Ibid* Note 87 at 2005.

²¹ The *plantar reflex* is a nociceptive segmental spinal reflex that serves the purpose of protecting the sole of the foot. The clinical significance lies in the fact that the abnormal response (Babinski sign) reliably indicates metabolic or structural abnormality in the corticospinal system upstream from the segmental reflex. Thus the extensor reflex has been observed in structural lesions such as hemorrhage, brain and spinal cord tumors, and multiple sclerosis, and in abnormal metabolic states such as hypoglycemia, hypoxia, and anesthesia. Walker HK. The Plantar Reflex. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 73. Available from: https://www.ncbi.nlm.nih.gov/books/NBK397/

Dr. Connolly was unable to test Lucas' strength. He exhibited withdrawal in all 4 extremities that was more pronounced in his right upper arm. There were no petechiae or bruising. There was one small café au lait spot²² on his right upper thorax that measured 1.5 cm in greatest diameter. Dr. Connolly was very concerned about the sudden change in Lucas' neurologic status overnight, and she documented her thoughts about possible causes:

Regarding the differential for his altered mental status and tone changes, bleeding as well as clotting are of significant concern. Additionally, his changes in blood pressure and renal function are very possibly contributory. Could consider causes of increased [intracranial pressure] and meningeal irritation such as venous sinus thrombosis, cerebral edema, PRES, as well as other possible diffuse cerebral processes, such as multiple micro infarctions. Uremic encephalopathy may be contributory, though there were not dramatic changes in his blood work from a time when he was neurologically well. Additionally, there is no clinical myoclonus, but this is worth considering. Additionally the clinical picture could be complicated by superimposed seizure secondary to whatever the underlying neurologic insult is.

Dr. Connolly requested that an MRI be done urgently, as well as an EEG. The plan was to sedate Lucas and intubate him, as he would otherwise be unable to tolerate these procedures.

Elective Endotracheal Intubation

Shortly after Dr. Connolly's assessment, Lucas was sedated and ventilated with a bag and mask, after which he was paralyzed with rocuronium and ketamine, intubated, and placed on mechanical ventilation. An orogastric tube was also inserted. After intubation, his sedation was continued with morphine and midazolam. Lucas was currently tachycardic at 190 bpm and tachypneic with a respiratory rate of 30. He did not require supplemental oxygen on the vent.



Bag and mask ventilations prior to intubation

²² Ruling out *neurofibromatosis*: Café au lait macules are observed in 95% of patients with neurofibromatosis type 1 (NF1), which is the most frequently occurring neurocutaneous syndrome. These spots may also be observed in patients without NF1. "Cafe Au Lait Spots." *Background, Pathophysiology, Etiology*, 12 Nov. 2019, https://emedicine.medscape.com/article/911900-overview.



Continued extensor posturing (accounts for 2 points on Glasgow Coma Scale)

Dr. Hankinson resumed Lucas' care after he was intubated while he awaited the MRI exam. She noted that he alternated between hyper- and hypotonia of his legs, with pointed toes, extensor posturing of both arms, and "shivering" in both arms. ("stops when you hold the arm"). Dr. Hankinson observed that Lucas was edematous in his extremities and scrotum. She noted that Lucas had his eyes closed, withdrew to pain, and made no sounds. She assigned him a Glasgow Coma Scale²³ of 6-8.

	1	2	3	4	5	6
Eye (E)	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal (V)	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused / disoriented	Oriented, converses normally	N/A
Motor (M)	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Glasgow Coma Scale (example - not included in medical records) - note different scores for posturing

Nephrology Attending – Lucas anuric overnight

At 9:30 AM, Dr. Humphreys checked in on Lucas and reviewed the events that had occurred since the night before, noting his severe neurologic deterioration. He opined that Lucas' "seizure" was secondary to hemolytic uremic syndrome CNS (central nervous system) irritability rather than a clinical convulsive episode, although he was admittedly at risk with such a low platelet count. Dr. Humphrey's observed that Lucas was intermittently "posturing," especially

²³ The *Glasgow Coma Scale* was first published in 1974 at the University of Glasgow by neurosurgery professors Graham Teasdale and Bryan Jennett. The Glasgow Coma Scale (GCS) is used to objectively describe the extent of impaired consciousness in all types of acute medical and trauma patients. The scale assesses patients according to three aspects of responsiveness: eye-opening, motor, and verbal responses. Reporting each of these separately provides a clear, communicable picture of a patient's state. Jain S, Teasdale GM, Iverson LM. Glasgow Coma Scale. [Updated 2019 Mar 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-Available from: https://www.ncbi.nlm.nih.gov/books/NBK513298/

during physical examination. Dr. Humphreys reviewed Lucas' labs and observed that Lucas had not produced any urine overnight ("~10 mL past 24° despite Lasix challenge"). He requested a urology consultation for peritoneal dialysis placement ("PD preferred to HD due to decreased platelets decreased hemoglobin and challenged with further blood loss/transfusions. Will potentially start PD tomorrow pending renal function.")

Dr. Humphreys was interested in the results of the MRI to assess for posterior reversible encephalopathy syndrome²⁴ (PRES) or thrombotic microangiopathy (TMA) changes. He thought that PRES was most likely since Lucas' blood pressures were in the hypertensive range for his age. If there were TMA changes on the MRI, Dr. Humphreys thought they should consider giving Lucas eculizumab (Soliris). He agreed with Lucas' placement in the PICU for closer monitoring of his neurologic status. He discussed his plan with Lucas' parents and planned to keep an eye on his blood pressures in the morning, "... due to PRES risk."

Urology Consultation – recommendation for peritoneal dialysis (PD)

Kristen Favel, MD and John Masterson, MD came in for urology to consult about the placement of a peritoneal catheter later that day for urgent dialysis. Dr. Favel examined Lucas, finding him now intubated and sedated. He still had an elevated blood pressure of 122/94 and tachycardia of 180 beats a minute. Since Lucas had such a low platelet count, Dr. Masterson agreed with hematology that Lucas should have a platelet transfusion perioperatively.

MRI shows cerebral ischemia, small vessel thrombotic microangiopathy; no hemorrhage

On October 22, 2018 at 11:30 AM, neuroradiologist Michael Sargent, MD took Lucas for an urgent MRI to "Query CSVT²⁵ [cerebral sinus venous thrombosis]." Dr. Sargent identified bilateral asymmetrical T2 and FLAIR hyperintensities²⁶ in the periventricular and subcortical

Posterior reversible encephalopathy syndrome [PRES (also known as reversible posterior leukoencephalopathy syndrome)] presents with rapid onset of symptoms including headache, seizures, altered consciousness, and visual disturbance. It is often—but by no means always—associated with acute hypertension. If promptly recognized and treated, the clinical syndrome usually resolves within a week, and the changes seen in magnetic resonance imaging (MRI) resolve over days to weeks. Chronic kidney disease and acute kidney injury are both commonly present in patients with PRES, and PRES is strongly associated with conditions that co-exist in patients with renal disease, such as hypertension, vascular and autoimmune diseases, exposure to immunosuppressive drugs, and organ transplantation. It is therefore important to consider PRES in the differential diagnosis of patients with renal disease and rapidly progressive neurologic symptoms. Posterior reversible encephalopathy syndrome is an increasingly recognized disorder, with a wide clinical spectrum of both symptoms and triggers, and yet it remains poorly understood. Hobson, Esther V et al. "Posterior reversible encephalopathy syndrome: a truly treatable neurologic illness." *Peritoneal dialysis international: journal of the International Society for Peritoneal Dialysis* vol. 32,6 (2012): 590-4. doi:10.3747/pdi.2012.00152

²⁵ *Cerebral sinus venous thrombosis* (CSVT) is a rare form of venous thromboembolism (VTE). This disease can affect the cerebral venous drainage and related anatomical structure. The symptoms may be related to increased intracranial pressure imitating a pseudotumor. Alvis-Miranda, Hernando Raphael et al. "Cerebral sinus venous thrombosis." *Journal of neurosciences in rural practice* vol. 4,4 (2013): 427-38. doi:10.4103/0976-3147.120236

²⁶ White matter hyperintensities (WMH) are a manifestation of small vessel disease. They may be caused by small subcortical infarcts but more often are related to a process called "incomplete infarction," reflecting chronically reduced blood flow in deep areas of the brain. Such reduced blood flow leads to hypoxia, alters mechanisms of cerebral autoregulation, and promotes transcription of inflammatory genes, breakdown of the blood brain barrier, and entry of proinflammatory proteins into vessel walls and the brain parenchyma. Even in the absence

white matter and body of the corpus callosum and fornix. There was an area of T2 hyperintensity in the right posteromedian thalamus. There were also signal changes in the bilateral lentiform nuclei²⁷ and external capsule. Dr. Sargent observed "scattered innumerable foci of diffusion restriction" within the white matter regions of signal abnormality with more confluent diffusion restriction seen adjacent to the frontal horns and in the genu of the corpus callosum." Notably, there was sparing of the cerebral cortex.

Dr. Sargent found no evidence of venous sinus thrombosis or hemorrhage. His findings were "consistent with presumed small vessel ischemia of thrombotic microangiopathy (HUS/TMA²⁸) without hemorrhage.



Lucas' MRI 10/22/18 – lateral view

Lucas' MRI 10/22/18- horizontal cross section view

of frank infarction, these processes lead to demyelination, axonal loss, reduced glial density, vacuolation, and atrophy of the overlying cortex, the traditional pathologic hallmarks of late-stage WMH. *White Matter Hyperintensities on Magnetic Resonance Imaging: What's a Clinician to Do?*

https://www.mayoclinicproceedings.org/article/S0025-6196(19)30075-8/fulltext

²⁷ The *lentiform nucleus* is a collective name given to the putamen and globus pallidus, both of which are nuclei in the basal ganglia. The basal ganglia are involved in a variety of cognitive, emotional, and movement-related functions. <u>https://www.neuroscientificallychallenged.com/blog/what-are-basal-ganglia</u>

HUS/TMA: Thrombotic microangiopathies are a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia and microthrombi leading to ischemic tissue injury. Microangiopathic hemolytic anemia (MAHA) is the hallmark of thrombotic microangiopathy. It is a process of red blood cell destruction within the microvasculature accompanied by thrombocytopenia due to platelet activation and consumption. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are primary forms of thrombotic microangiopathies. Arnold, Donald M et al. "Thrombotic microangiopathies: a general approach to diagnosis and management." *CMAJ* : *Canadian Medical Association journal = journal de l'Association medicale canadienne* vol. 189,4 (2017): E153-E159. doi:10.1503/cmaj.160142



Electroencephalogram (EEG)

An EEG was performed and showed slowing but no subclinical seizures. Cyrus Boelman, MD read the EEG and dictated his findings:

This EEG, recorded in sedated stupor, is severely abnormal. The background is dysrhythmic and suppressed. This EEG is suggestive of moderate-severe encephalopathy, and focal cerebral dysfunction, particularly over the left posterior head region. Further neuro imaging correlation is recommended.

Dr. Connolly and Dr. Smith met with the PICU team and Dr. Humphrey's nephrologist and reviewed the MRI and EEG findings. They ordered the initiation of Keppra²⁹ at that time, because the doctors felt that Lucas was at high risk of seizures. They also suggested that immunotherapy might be considered in light of the neurological and MRI findings. The neurologists advised that

²⁹ Levetiracetam (brand name Keppra) is used in the treatment of seizures; epilepsy; bipolar disorder; neuralgia; new daily persistent headache and belongs to the drug class pyrrolidine anticonvulsants. "LEV 500 Pill levetiracetam 500 mg." *LEV 500 Pill - levetiracetam 500 mg*. Drugs.com, n.d. Web. 31 Jan. 2017.

the EEG electrodes be left in place and the EEG repeated on the 23rd or sooner depending on Lucas' clinical course. Lucas was soon to go to the operating room, so continuous EEG monitoring could not be implemented.



Lucas deathly ill

Surgical implantation of PD catheter – Antibiotic preload and platelets transfused

At 4:30 PM on October 22, 2018, Dr. Masterson took Lucas to the operating room, where he inserted a peritoneal dialysis catheter with Lucas under general anesthesia. Lucas was placed on antibiotic therapy for the procedure (one dose of cefazolin IV) and he was transfused with platelets intraoperatively. After the catheter was in place and sutured in position, the catheter was tested with 250 mL of normal saline infused into Lucas' abdomen and then removed. The catheter flushed easily. Prior to moving Lucas back to the PICU, the doctors also took the opportunity to insert a central line, performed by the anesthesia team.

BCCH Day 3 – PICU Day 2 – continued anuria/oliguria – obtunded off sedation

On October 23, 2018, Kristen Favel, MD and Rob Humphreys, MD consulted for pediatric nephrology at 8:20 AM. They observed that Lucas, despite the discontinuation of sedating drugs postoperatively, he remained obtunded.³⁰ He remained on mechanical ventilation. His blood pressure had normalized on antihypertensive medications (currently 80/66), and his heart rate was closer to normal range at 109. The doctors observed that 500 mL of fluid had been successfully instilled and drained during the insertion of the peritoneal dialysis catheter in the OR. Lucas remained anuric/oliguric with a 24-hour urinary output of 42 mL.

A chest x-ray identified a right sided pleural effusion, which the doctors thought should

³⁰ People who are obtunded have a more depressed level of consciousness and cannot be fully aroused. Lethargy and obtundation also describe the drowsy state. Venes, *Ibid* Note 100 at 551.

improve after peritoneal dialysis was started. Lucas' hemoglobin had fallen from 82 to 78 overnight, and his platelets went up to 200 with the transfusion but were down to 168 that morning. In addition, schistocytes were observed on his peripheral blood smear, and his LDH was still greater than 10,000. Lucas no longer had diarrhea. The doctors ordered peritoneal dialysis to be started that morning "in light of electrolyte abnormalities to make room for nutrition." They planned to start feeding Lucas once fluid removal was initiated, with Novasource[®] Renal.³¹

Peritoneal dialysis³² – CCPD Day 1 (cycles 1-19)

On October 23, 2018 at 10:45 AM, continuous cyclic peritoneal dialysis (CCPD) was initiated, with Dianeal³³ 1.5% dialysis solution with 500 U/L heparin, 60 minutes per cycle. Cycles 1-15 were to run consecutively throughout the day, with cycles 16-19 continuing overnight.



Example PD catheter placement (NOT Lucas)

Confirmation of positive Shiga toxin 2 – STEC HUS

At 5:50 PM that afternoon, Dr. Humphreys wrote an addendum to his earlier note that the lab reported a positive result from Lucas' stool studies, showing positive for Shiga toxin 2 ("STEC 2") and that two samples had been sent to the CDC. He stated: "Initial [stool sample] *E. coli* negative/STEC 1&2 negative, but second sample positive." Dr. Humphreys noted that an order for eculizumab had been approved by the hospital pharmacy, and the medication had been procured.

³¹ NOVASOURCE[®] RENAL is a calorically dense, complete nutritional formula that provides protein, vitamins and minerals specifically to meet the needs of people with chronic kidney disease (CKD) on dialysis, acute kidney injury (AKI), fluid restrictions due to CKD or AKI, or electrolyte restrictions. https://www.nestlehealthscience.us/brands/novasource/novasource-renal

³² Peritoneal dialysis was the first RRT modality used for the management of AKI in children of all ages and remains the preferred method in younger children. CCPD = continuous cycling peritoneal dialysis. Also known as automated peritoneal dialysis (APD), CCPD uses a machine (automated cycler) that performs multiple exchanges over several hours, often during sleep. The cycler automatically fills the abdomen with dialysate, allows it to dwell there and then drains it to a sterile bag that is later emptied. Cullis, Brett, et al. "Peritoneal Dialysis for Acute Kidney Injury." *Peritoneal Dialysis International*, vol. 34, no. 5, 1 July 2014, pp. 494–517., doi:10.3747/pdi.2013.00222.

³³ DIANEAL is a hypertonic peritoneal dialysis solution containing dextrose, a monosaccharide, as the primary osmotic agent. An osmotic gradient must be created between the peritoneal membrane and the dialysis solution in order for ultrafiltration to occur. The hypertonic concentration of glucose in DIANEAL exerts an osmotic pressure across the peritoneal membrane resulting in transcapillary ultrafiltration. Like other peritoneal dialysis solutions, DIANEAL contains electrolytes to facilitate the correction of electrolyte abnormalities. <u>https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020183s024lbl.pdf</u>

Continuous EEG monitoring begun

At 1:58 PM, neurologist Peter Wong, MD initiated continuous EEG monitoring for the purpose of detecting ictal episodes (seizures). Initially, Dr. Wong observed that Lucas was in a stuporous state and the background was markedly suppressed, except for high voltage delta³⁴ activity in the bilateral anterior quadrants (right greater than left); however, there was no obvious epileptiform activity. Dr. Wong continued Lucas on Keppra for seizure prophylaxis.

Eculizumab dose No. 1

At 8 PM on October 23, 2018, Lucas was administered eculizumab 600 mg IV over four hours.³⁵ EEG monitoring was resumed and would remain continuous for the next two days.



Karla comforting Lucas

BCCH Day 4 - PICU Day 3 - CCPD Day 2 (cycles 20-42) - transfusion pRBCs

³⁵ *Eculizumab* (Soliris): Severe complications due to Shigatoxin-associated hemolytic uremic syndrome (STEC-HUS) currently present a serious challenge since no specific treatment for this condition is available. Eculizumab, a terminal complement inhibitor, has been used especially in STEC-HUS patients with severe neurological involvement, but the efficacy remains undetermined. Keenswijk, Werner, et al. "Is Eculizumab Efficacious in Shigatoxin-Associated Hemolytic Uremic Syndrome? A Narrative Review of Current Evidence." *European Journal of Pediatrics*, vol. 177, no. 3, 2017, pp. 311–318., doi:10.1007/s00431-017-3077-7.

³⁴ EEG waveforms are generally classified according to their frequency, amplitude, and shape, as well as the sites on the scalp at which they are recorded. The most familiar classification uses EEG waveform frequency (e.g., alpha, beta, theta, and delta). Delta waves, like other brain waves, are recorded with an electroencephalogram (EEG) and are usually associated with the deep stage 3 of NREM sleep, also known as slow-wave sleep (SWS), and aid in characterizing the depth of sleep. Blume WT, Kaibara M. *Atlas of Pediatric Electroencephalography*. 2nd ed. Philadelphia: Lippincott-Raven; 1999.

On October 24, 2018 at 2:30 AM, the nephrology team changed Lucas' peritoneal dialysate to 2.5% dextrose solution and 500 U/L heparin. Lucas had standing orders to receive chloral hydrate³⁶ as often as every 4 hours for agitation. Liz Hankinson, MD evaluated Lucas for pediatric intensive care and observed that the toddler remained unresponsive, but the EEG overnight confirmed no subclinical seizures, and there was slightly improved slowing. Lucas continued to exhibit increased tone in his extremities and had 3+ beats of ankle clonus. Dr. Hankinson noted other clinical concerns included bilateral pleural effusions and hypoglycemia—hence the change in his dialysate to a higher dextrose concentration. Lucas continued on Novasource feeds via his nasogastric tube; he was tolerating this, so Dr. Hankinson stopped IV fluids and increased the Novasource rate to make up his fluid needs.

Improving chest x-ray and labs

At 6:39 AM, radiologist John Mawson, MD reviewed a portable chest x-ray and compared it to the imaging done on October 23 that showed a right-sided pleural effusion. He observed that, during the preceding 24 hours, the aeration in Lucas' left chest had improved and the amount of a previously-observed anterior herniation of his right lung had decreased. There was some reduction in the volume of his pleural effusions. At 9:30 AM, the nephrology team arrived, noting that Lucas' serum creatinine had gone from 366 down to 335 since starting CCPD. The doctors ordered another transfusion of packed red blood cells pRBCs later that day for a low hemoglobin.

Social Work Consultation

Later that day, Rhonda Kotick, MSW visited Nathan and Karla to provide support, noting that Lucas' younger brother Alexander was also present. Nathan and Karla stated that they were holding up reasonably well. "They are positive people and are trying to keep their thoughts and energy positive around Lucas." A number of extended family members were reportedly present periodically. Karla requested additional support from the Indigenous Patient Liaison.

Continuous EEG Monitoring – PLED³⁷ suspected on EEG

Dr. Wong oversaw Lucas' continuous EEG monitoring overnight (cEEG) October 24 and through the morning on October 25, 2018, which demonstrated a gradual emergence of more

³⁶ *Chloral hydrate* was once the preferred sedative agent for diagnostic imaging in infants and children younger than three years of age and is efficacious for that purpose. The use of chloral hydrate as the primary sedation agent has declined across the nation after commercial production of the liquid formulation ceased. Although alternative sedatives have gained popularity, some pharmacies have continued to provide oral chloral hydrate by compounding it from raw ingredients. Farr, K. M., Moffett, B. S., Jones, J. L., Rogers, A. P., & Chumpitazi, C. E. (2019). Chloral Hydrate Sedation in a Dexmedetomidine Era. *Hospital Pharmacy*. https://doi.org/10.1177/0018578719836639

³⁷ *Periodic lateralized epileptiform discharges* (PLED) are associated with acute or subacute structural injury of the cerebral cortex, either diffuse or focal; however, PLEDs may also be seen in patients with a chronic static cerebral lesion or chronic epilepsy. There is substantial controversy over whether PLEDs and related discharges represent an epileptic phenomenon meriting aggressive treatment, or alternatively are simply a marker of severe brain injury of little or no specificity. Téllez Zenteno JFPillai SNHill MDPillay N Chronic PLEDs with transitional rhythmic discharges (PLEDs-plus) in remote stroke. *Epileptic Disord* 2007;9 (2) 164-169

activity in bilateral posterior quadrants with the appearance of some theta³⁸ activity throughout. That morning, the EEG background had become less suppressed. Dr. Wong noted the first appearance of what looked like broad sharp waves with PLED-like behavior in the bilateral frontal polar areas occurred at approximately 8 PM that evening. There was no evolution or clinical accompaniment. These bursts of PLED-like activity lasted 1-2 minutes and appeared on seven occasions during the next 11 hours.



FIGURE 17.1 (A) Periodic discharges, (B) rhythmic delta activity, and (C) spike-wave.

Example of PLED-like activity on EEG

BCCH Day 5, PICU Day 4 - CCPD Day 3 (cycles 43-66) - Possible seizures

At 4 AM on October 25, 2018, pediatric intensivist Prakash Krishnan, MD was summoned to Lucas' bedside for two episodes of apparent seizure activity in the preceding hour. The first episode lasted a minute and 15 seconds (3 AM), during which Lucas was observed to have rhythmic blinking and tongue thrusting and an increased heart rate. His pupils were equal and reactive during the episode. Half an hour later (3:31 AM), Lucas experienced a recurrence lasting one minute, in which his eyes were deviated to the upper left, with rhythmic blinking and variable heart rate. Dr. Krishnan arrived and reviewed the EEG tracing with Dr. Andrew, who planned to review the tracing with the Neurology Team in the morning. Meanwhile, Lucas continued to exhibit spontaneous eye opening, with minimal response to noxious stimuli ("trap squeeze³⁹").



³⁸ *Theta rhythms* are commonly encountered in the frontocentral regions and are usually related to drowsiness or heightened emotional states. In the past, theta rhythms were associated with a variety of clinical conditions, including epilepsy, but their common occurrence is now better appreciated as a normal variant. Blume, *Ibid* Note 129.

³⁹ Clinical tests, such as loss of verbal contact, eyelash reflex, corneal reflex, and jaw relaxation, are used to assess the depth of anesthesia. "Trapezius squeeze test" (TST) is one such clinical test. It is a simple test to perform in which 1–2 inches of trapezius muscle is held and squeezed in full thickness and response is evaluated in the form of toe/body movement. Hooda, Sarla et al. "Trapezius squeeze test as an indicator for depth of anesthesia for laryngeal mask airway insertion in children." *Journal of anaesthesiology, clinical pharmacology* vol. 28,1 (2012): 28-31. doi:10.4103/0970-9185.92430

Trap squeeze test

This produced some motor movement, but otherwise Lucas had no response. Now 48 hours off sedation, and three days since his MRI, Lucas continued to have increased tone in all extremities, with one beat of ankle clonus, consistent with hyperreflexia. He exhibited no purposeful, spontaneous movement at that time. After receiving a unit of pRBCs the day before, Lucas' labs revealed a hemoglobin of 98, platelets 21K, and LDH 10,000. His creatinine was 340 and urea 28.6 (up from 335 and 25). His abdomen was notably distended, but he was currently producing no stool.

Pediatric Neurology - More PLED-like activity on EEG

Dr. Ha consulted for neurology at 11 AM and reviewed the cEEG and video EEG from 3 AM, which had recorded no overt seizures but did reveal diffuse slowing. Lucas was continued on Keppra prophylaxis. Dr. Ha commented: "The team will decide when to image brain." Dr. Wong commented about Lucas' EEG changes: "These bursts of PLED-like activity lasted 1-2 minutes and appeared on seven occasions, the last one occurring on October 25 at 06:55. Monitoring was discontinued on October 25 at approximately 09:00. The Neurology Team was kept aware of the EEG findings throughout the period of monitoring."

BCCH Day 6, PICU Day 5 - CCPD Day 4 (cycles 67-93) - signs of sepsis

Overnight on October 25-26, 2018, Lucas experienced episodes of hypotension with drops in his blood pressure down to the 80/30 range. He was provided with 20 mL/kg fluid bolus, with some improvement in his blood pressure. Lucas' labile blood pressures, coupled with an increase in his white blood cell count to 42.5 and recurrent hyperglycemia requiring multiple insulin adjustments, concerned the doctors that Lucas was becoming septic. He remained on mechanical ventilation, although he continued to initiate his own breaths ("riding the vent"). Lucas' heart rhythm was observed to be irregular during the times he did that, so the doctors consulted cardiology.

Antibiotics begun (vancomycin and cefotaxime) – continued anuria

The PICU team started Lucas on broad spectrum IV antibiotics (vancomycin and cefotaxime). Lucas was not suspected of having peritonitis, because his abdomen was soft and the peritoneal fluid return from dialysis was clear. His antibiotics were renally-dosed and planned to continue for at least 48 hours, or until the blood cultures were resulted. Pharmacy was requested to check vancomycin levels every 12 hours. Lucas' insulin was restarted and his antihypertensive medication (amlodipine) was discontinued. New blood cultures were re-sent before the antibiotics were started, and Lucas remained on Keppra for seizure prevention. Lucas was slated to receive his second dose of eculizumab seven days after his first dose, which was on the 23rd.

Lucas' CCPD continued uninterrupted, and nephrologist Pritichi Kadam, MD agreed with the management plan by the PICU team. Lucas current creatinine was 320 and his LDH had come

down to 6963. Dr. Kadam wanted Lucas' to begin EPO⁴⁰ dosing the following week as it appeared his renal failure was going to be prolonged. Lucas remained entirely anuric at this point.

Possible neurologic improvement...

Dr. Ha visited Lucas at 9:30 AM on October 26, 2018, and Nathan told him that Lucas had grabbed/squeezed his hand. He stated that his son was also opening his eyes more spontaneously and seemed to be more responsive to his voice, as well as to tactile stimulation. After an examination, Dr. Ha commented: "Doll's eye movement present though not robust." Dr. Ha also noted Lucas continued to have brisk reflexes but no clonus. He thought that these findings represented an improvement over Lucas' previous exam. Without any clear seizure activity on the cEEG, Dr. Ha saw no reason to order additional imaging at this time.

Later in the afternoon, Dr. Ha discussed Lucas' neurologic condition with Dr. Schrader, who wondered whether Lucas might have underlying metabolic/genetic conditions that could predispose him to neurologic sequelae. "In the context of previous history of autism, chromosomal microarray [CMA]⁴¹ might also be helpful elucidating the etiology of any genetic predisposition or developmental condition that could contribute to the current neurological sequelae. Therefore, we recommend TIDE⁴² workup and CMA investigation."

BCCH Day 7, PICU Day 6 - CCPD Day 5 (cycles 94-117) - Continued antibiotics

On Saturday, October 27, 2018, Lucas remained on IV antibiotic therapy. However, nephrology resident Dr. Hankinson wrote orders to discontinue Lucas' cefotaxime/vancomycin at 48 hours if his blood cultures failed to grow any bacteria. The frequency of his lab tests was set for ABG's every 6 hours, and other labs every 24 hours. Lucas continued to receive enteral doses (via NG or NJ tube) chloral hydrate for episodes of irritability. For his ongoing hemolytic anemia, he was started on weekly subcutaneous erythropoietin (EPO). Lucas required another transfusion of pRBCs on October 27 when his hemoglobin dropped to 65.

Neurologist Anita Datta, MD observed that Lucas had experienced "decreased seizures treated by Keppra," perhaps in reference to clinically-observed seizure-type activity, as his EEG tracing was read as "unrevealing for subdural seizures/status [epilepticus]." Nevertheless, Lucas exhibited episodic "posturing" and vital sign changes, according to nursing staff.

⁴⁰ Erythropoietin (also known as EPO) is a growth factor that stimulates the production of red blood cells. Most of the cells in the blood are red blood cells, whose main function is to carry oxygen throughout the body. <u>https://www.themmrf.org/multiple-myeloma-knowledge-center/myeloma-treatments-guide/growth-factors/erythropeietin/</u>

⁴¹ Chromosomal microarray (CMA) is increasingly utilized for genetic testing of individuals with unexplained developmental delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), or multiple congenital anomalies (MCA). Miller, David T et al. "Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies." *American journal of human genetics* vol. 86,5 (2010): 749-64. doi: 10.1016/j.ajhg.2010.04.006

⁴² The TIDE (Treatable Intellectual Disability Endeavor) Protocol is a two-tiered evidence-based approach used to screen children for treatable genetic conditions (inborn errors of metabolism) causing intellectual disability. BCMJ, vol. 57, No. 9, November 2015, Pages 387-393 Clinical Articles. <u>https://www.bcmj.org/articles/introduction-</u> tide-protocol-screen-children-treatable-intellectual-disability-first

Lucas remained on mechanical ventilation and regularly initiated breaths over his ventilator settings. On exam at 9:30 AM, Dr. Datta found Lucas responsive to noxious stimuli by briskly opening his eyes, as well as to voice. His pupils were reactive. He did not make eye contact, track, or "blink to threat." Overall, Dr. Datta thought that Lucas appeared neurologically "brighter," and more responsive and no changes were made to his Keppra seizure prophylaxis.

BCCH Day 8, PICU Day 7 - CCPD Day 6 (cycles 118-141) - antibiotics discontinued

On Sunday, October 28, 2018, Kayla Flood, MD consulted for pediatric nephrology at 8:45 AM and noted that Lucas continued to require chloral hydrate as well as lorazepam for agitation overnight. Lucas continued to retain fluid and still had intermittent bloody diarrhea. He was not producing any measurable urine. His peritoneal dialysis fluid looked pink but not cloudy—Dr. Flood requested that the fluid be cultured if it became cloudy or if Lucas started running a fever. He ran a fever of 101.5°F during his most recent blood transfusion, and new blood cultures were drawn. She noted that Lucas' blood pressure was still labile and they should consider restarting his amlodipine because he was still at increased risk for PRES. Lucas remained on mechanical ventilation and required supplemental oxygen to keep his SpO2 in the 90th percentile since the posturing episodes began. In addition, Lucas had increased edema in his hands, legs, and scrotum. His creatinine that day was 336 and urea 32.4. His blood cultures were showing no growth at 48 hours, so his antibiotics were discontinued. He continued with Novasource feeds.

Worsening neurologically... pattern of white matter brain injury – possible seizures

Pediatric ICU resident Kate Maki, MD looked in on Lucas at 11:30 AM. Dr. Maki observed that Lucas had begun having increasing "abnormal movements" overnight: "... decerebrate arm posturing associated with dilated pupils, increased blood pressure, increased heart rate." These occurred spontaneously as well as with stimulation. There were no observed clonic movements, and the episodes improved with lorazepam. Lucas exhibited more eye opening, but he had an inconsistent gag/cough reflex and was minimally responsive to noxious stimuli. Neurology was consulted and recommended a repeat EEG to rule out seizures.



Lucas exhibiting extensor "posturing"

At 2:30 PM, Dr. Maki was summoned urgently to the PICU when Lucas suddenly worsened, exhibiting "posturing," eyes open without gaze deviation, and increased tone in all extremities. His heart rate increased into the 170's and his blood pressure was elevated, during episodes that were brief in duration (10-30 seconds). There were three witnessed episodes, all similar and provoked by stimulus. Neurology was again consulted, who felt that these movements reflected a pattern of white matter brain injury, consistent with what was seen on Lucas' MRI. They explained that his brain injury was likely becoming more clinically evident "the more he woke up." Plans were underway for repeat imaging the following week. Meanwhile, neurology advised the use of Ativan (lorazepam) for prolonged posturing episodes and planned to discuss other treatment options at a family meeting the next day.

BCCH Day 9, PICU Day 8 - CCPD Day 7 (cycles 142-165) - trial of Precedex

On Monday, October 29, 2018, Dr. Datta arrived for neurology at 7:50 AM and reviewed the weekend events. On exam, the doctor found that she was able to elicit the same abnormal movements noticed by staff over the weekend (increased HR/BP, pupil dilation, extensor posturing, muscular rigidity) by the use of noxious stimuli or other motor stimulation. Dr. Datta ordered a repeat EEG to rule out seizures related to the posturing. She suspected that the abnormal movements might be "sympathetically driven⁴³."

Dr. Datta thought Lucas might benefit from the use of prophylactic Precedex⁴⁴ and/or clonidine, which could help sort out the root cause of Lucas' anomalous posturing and neurologic symptoms. She planned to repeat an EEG later in the day to rule out an ictal (seizure) correlate. Dr. Datta continued his Keppra without any change in dosage for seizure prophylaxis. She commented: "Seems to be improving slowly."

Dr. Hankinson evaluated Lucas for pediatric critical care, reviewing his current acute problems of hyperglycemia on insulin infusion, as well as his most current episodes of posturing with increased heart rate and blood pressure. His heart rate was 110-200, responsive with stimulation into the tachycardic range. His blood pressure was in normal range, but he was hypertensive when posturing. He was afebrile except for during periods of agitation, when his temperature rose as high as 101°F.

Started on Precedex for presumed "sympathetic drive agitation"

⁴³ The sympathetic nervous system (SNS) is one of the two divisions of the autonomic nervous system (ANS), the other being the parasympathetic nervous system (PNS), These systems largely work unconsciously in opposite ways to regulate many functions and parts of the body. Colloquially, the SNS governs the "fight or flight" response while the PNS controls the "rest and digest" response. The main overall end effect of the SNS is to prepare the body for physical activity, a whole-body response affecting many organ systems throughout the body to redirect oxygen-rich blood to areas of the body needed during intense physical demand. Alshak MN, M Das J. Neuroanatomy, Sympathetic Nervous System. [Updated 2019 May 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542195/

⁴⁴ Precedex (dexmedetomidine) is a new generation highly selective α2-adrenergic receptor (α2-AR) agonist that is associated with sedative and analgesic sparing effects, reduced delirium and agitation, perioperative sympatholysis, cardiovascular stabilizing effects, and preservation of respiratory function. Kaur, Manpreet, and P M Singh. "Current role of dexmedetomidine in clinical anesthesia and intensive care." *Anesthesia, essays and researches* vol. 5,2 (2011): 128-33. doi:10.4103/0259-1162.94750

Dr. Hankinson agreed that Lucas seemed to be more alert and responsive to touch, intermittently withdrawing from stimuli. She observed that Lucas' abnormal movement episodes involved posturing in extension, with his head flexed to the left, pupils dilated, and occurred largely in response to stimulus. Lucas still did not track, make eye contact, or interact with others. He was difficult to settle despite receiving four doses of lorazepam and several doses of chloral hydrate overnight. She agreed with Dr. Datta's recommendation for the use of Precedex and ordered the implementation of an infusion of that drug, "... as these events most likely due to sympathetic drive agitation."

It was Dr. Hankinson's opinion that Lucas was not ready for extubation from mechanical ventilation quite yet, but if his reflexes improved further, she thought he might be ready in the next few days. Lucas still had an unreliable gag reflex, but Dr. Hankinson ordered a trial of avoiding nasogastric suctioning to see how he handled his secretions on his own. Lucas was still anuric and had 2+ pitting edema in his legs, as well as mild scrotal edema. His HUS labs were beginning to improve, with a downtrending LDH and rising platelets. He was scheduled for his second dose of eculizumab the following day. Dr. Hankinson requested the involvement of physical therapy and occupational therapy for splinting of his developing upper extremity contractures, as well as movement therapy.

Insertion of right cephalic vein PICC line – another transfusion pRBCs

At 1:51 PM, radiologist Gordon Culham, MD placed a right basilic vein peripherally inserted central catheter (PICC) line under ultrasound guidance. He confirmed placement in the right superior vena cava/right atrium with a chest x-ray.



While confirming proper placement, Dr. Culham compared the imaging to the last chest x-ray done on the 27th, observing a new right upper lobe partial lung collapse. Dr. Culham also noted that Lucas' nasojejunal tube had retracted into the pylorus (stomach). Lucas required another transfusion of pRBCs that afternoon for a hemoglobin down to 71.

Electroencephalogram (EEG) - severely abnormal, but no seizures

Dr. Datta performed and reviewed a repeat EEG at 5 PM, during which she saw no well-

formed "posterior dominant rhythm."⁴⁵ She observed suppression of the left hemisphere, especially "posterior quadrant predominant bifrontal." She also identified a pattern that demonstrated a "sometimes more prominent right hemisphere compared to left." Dr. Datta's impression was that the EEG was severely abnormal but was not diagnostic of seizure activity. She was able to capture one of Lucas' "events" during the EEG:

During this EEG, Lucas had a typical event of increased heart rate, dilated pupils and extension in all four limbs. This event was caused by stimulation by the nurse and lasted about 2 minutes. No EEG change was correlated.

This EEG, recorded in a stuporous state, is severely abnormal. The background is slow and suppressed in left hemisphere. This EEG is compatible with functional or structural abnormality in left hemisphere, due to suppression. Generalized slowing consistent with moderate encephalopathy of nonspecific etiology. Event captured not consistent with seizure.

BCCH Day 10, PICU Day 9 - CCPD Day 8 (cycles 166-189) - 2nd dose eculizumab

On October 30, 2018, nephrologist Dr. Kadam arrived during morning rounds and noted that Lucas' morning labs reflected an increase in his hemoglobin to 97 and platelets to 144. His LDH was down to 1701. Lucas remained sedated on mechanical ventilation, with the settings on low. His peritoneal dialysis (CCPD) continued uninterrupted without any recent changes to his dialysate. Dr. Kadam planned to administer Lucas' second dose of eculizumab later that day.

Precedex discontinued secondary to hypotension

Dr. Datta saw Lucas at 10 AM and reviewed the results of the EEG with his parents, explaining that although "paroxysms were captured on EEG" the day before, there was no "ictal/electrographic correlate" to suggest they were seizures. Dr. Datta observed that Lucas had continued to have episodes of abnormal movement despite being on Precedex, but the drug had had to be discontinued in any event because it caused Lucas' blood pressure to drop. The PICU team was in the process of changing him over to a midazolam infusion instead.

Continued posturing and abnormal reflexes

On exam, Lucas had "more robust triple flexion" in his legs, which was more prominent on the left. The nursing staff reported that they had witnessed episodes of posturing, extension, eye gaze, dilatation of pupils, and hypertonia, all of which occurred with either stimulation or pain. Dr. Datta noticed that Lucas' eyes were roving and he did not "blink to threat" or make eye contact. Although he opened his eyes to stimulation, Dr. Datta did not find a "convincing" response to

⁴⁵ A posterior dominant rhythm is normal. When the patient is relaxed with eyes closed, the background is usually characterized by the posteriorly dominant alpha rhythm, also known simply as the posterior dominant rhythm. Britton JW, Frey LC, Hopp JLet al., authors; St. Louis EK, Frey LC, editors. Electroencephalography (EEG): An Introductory Text and Atlas of Normal and Abnormal Findings in Adults, Children, and Infants [Internet]. Chicago: American Epilepsy Society; 2016. The Normal EEG. Available from: https://www.ncbi.nlm.nih.gov/books/NBK390343/

voice or command. Lucas did not move to command. He had a "flexor response⁴⁶" in his upper extremities that was "more convincing than yesterday."

Suspicion for paroxysmal sympathetic hyperactivity

Dr. Datta thought that Lucas continued to show signs of recovery on "coma exam," but she was still not clear about what was causing the episodes of posturing. She continued to be suspicious for paroxysmal sympathetic hyperactivity,⁴⁷ with underlying pain vs. stimulation as the "driver." Dr. Datta continued to opine that Lucas' episodes were not attributable to seizures. She researched the treatment of this disorder and printed out two different papers on pharmacologic management that she attached to Lucas' chart. Lucas continued to receive morphine and midazolam for pain and anxiety. Dr. Datta considered the use of beta blockers could be considered (clonidine, propranolol), "but hypotension may be observed." She also thought that gabapentin could be considered, but renal dysfunction might be a concern. Meanwhile, she wanted to watch Lucas clinically before making any changes in his care plan.

Prolonged episodes of hypertension when posturing - still anuric

Dr. Hankinson noted that Lucas' had an increase in "episodes" overnight, including agitation with periods of increased blood pressure and heart rate, dilated pupils, posturing, as well as hypotension following a dose of Precedex. The PICU team responded with an infusion of albumin and a transfusion of pRBCs, and they discontinued orders for any further doses of Precedex. For persistent agitation, Lucas required two doses of chloral hydrate and four doses of lorazepam, which were only minimally effective and did not reduce the number of his "episodes." Lucas remained on Keppra for seizure prophylaxis. The PICU team was hoping that the addition of morphine and midazolam infusions might help calm things down, which were titrated to avoid buildup in the setting of Lucas' renal failure. If ineffective, they planned to try using hydromorphone (Dilaudid). Lucas' blood pressures went as high as 200 systolic when posturing, but they did not want to use antihypertensives at this time because of the risk for more hypotensive episodes. This would leave PICU team unable to fully control Lucas' blood pressure, which was labile secondary to his severe neurologic irritability.

⁴⁶ *Hoffmann reflex* (Hoffmann sign, sometimes simply "Hoffmann's", also finger flexor reflex) is a neurological examination finding elicited by a reflex test which can help verify the presence or absence of issues arising from the corticospinal tract. Gottlieb, G L, and G C Agarwal. "Effects of Initial Conditions on the Hoffman Reflex." *Journal of Neurology, Neurosurgery, and Psychiatry*, U.S. National Library of Medicine, June 1971, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1083456/.

⁴⁷ Paroxysmal sympathetic hyperactivity: A substantial minority of patients who survive an acquired brain injury develop a state of sympathetic hyperactivity that can persist for weeks or months, consisting of periodic episodes of increased heart rate and blood pressure, sweating, hyperthermia, and motor posturing, often in response to external stimuli. The unifying term for the syndrome—paroxysmal sympathetic hyperactivity (PSH)—and clear diagnostic criteria defined by expert consensus were only recently established. PSH has predominantly been described after traumatic brain injury (TBI), in which it is associated with worse outcomes. The pathophysiology of the condition is not completely understood, although most researchers consider it to be a disconnection syndrome with paroxysmal driven by a loss of inhibitory control over excitatory autonomic centres Meyfroidt, Geert, et al. "Paroxysmal Sympathetic Hyperactivity: The Storm after Acute Brain Injury." *The Lancet. Neurology*, U.S. National Library of Medicine, Sept. 2017, https://www.ncbi.nlm.nih.gov/pubmed/28816118



Periorbital edema (example, not Lucas)

Pitting edema

As for his nutritional needs, Dr. Hankinson observed that Lucas' electrolytes had stabilized on Novasource, so they planned to transition him to 100% Nutren Jr. the following day. He still exhibited signs of fluid overload, with 2+ pitting edema up to his shins.

Lucas remained anuric, and ultrafiltration was successfully removing small amounts of fluid during CCPD. Lucas' blood sugars were improving enough to halve his insulin requirements. His differential diagnosis included pancreatic dysfunction and the doctors wanted to recheck his lipase with his next blood draw. A family meeting was planned for Friday to discuss Lucas' progress.



Lucas with fluid overload, facial edema, periorbital edema

BCCH Day 11, PICU Day 10 - CCPD Day 9 (cycles 190-213) - frankly bloody stools

October 31, 2018 at 2:50 AM, the PICU nursing staff paged PICU physician Kate Maki, MD when Lucas began expelling mixed tarry and deep red stools. There were at least two episodes

that appeared to contain about 50 mL of blood each time. A pantoprazole (Pantoloc⁴⁸) infusion was started per order after the first episode of bleeding, and a transfusion of pRBCs was initiated at the same time. Lucas' current labs showed a hemoglobin of 69, platelets 177K, fibrinogen 4, and a coagulation panel (PT and INR) was pending. Dr. Maki conferred with the gastroenterologist on call after the second episode and requested a bedside consultation for the suspicion of an upper GI bleed.

Pediatric Gastroenterology Consult – Diagnosis stress gastritis – multiple bleeding points

Pediatric gastroenterologist Vishal Avinashi, MD examined Lucas in the PICU, finding that he had been put on nothing by mouth (NPO) after the first bloody stool was noted. Since the bloody stools, Lucas had also exhibited possible bloody sputum when his orojejunal (OJ) tube aspirate looked "rusty colored." Dr. Avinashi reviewed Lucas' labs and did an exam and considered the possibilities of stress gastritis with diffuse bleeding, stress ulcer with localized bleeding, or a worsening of his HUS. He thought it most likely that Lucas had gastritis secondary to "stress in the ICU," with multiple bleeding points that did not require a procedural treatment. He agreed with the dosing with the PPI.

Stress induced gastritis

- It is usually associated with severe trauma, hypotension, sepsis, major burns renal or respiratory failure.
- Lesions due to intracranial trauma are usually deeper than other causes.
- Acute stress lesions begin minutes or hours after the trauma in the areas of mucosal pallor.
- Shallow erosions occur in the fundus.



Dr. Avinashi thought it unlikely that Lucas' current rectal bleeding and bloody OJ aspirate represented a worsening of his HUS, as his platelets and coagulation profile were stable. He recommended 24 hours of Pantoloc infusion and, if there was no improvement, he would examine Lucas via endoscopy (upper GI and colonoscopy). He approved pantoprazole boluses if needed, given there were multiple infusions going through his line. Dr. Avinashi wanted Lucas to be kept NPO and recommended that consideration be given to switching him to parenteral (intravenous) nutrition.

BCCH Day 12, PICU Day 11 - CCPD Day 10 (cycles 214-237) - hypotension, ST changes

During the night and early morning hours of Saturday, November 1, 2018, Lucas experienced a number of bradycardic episodes, with a heart rate dropping down to 60-70 beats per

⁴⁸ Pantoprazole belongs to the family of medications called proton pump inhibitors (PPIs). Proton pump inhibitors are used to treat conditions such as stomach ulcers, intestinal ulcers, and gastroesophageal reflux disease (GERD, reflux esophagitis) by reducing the amount of acid the stomach produces. https://chealth.canoe.com/drug/getdrug/pantoloc
minute. His blood pressure remained stable. There were ST changes⁴⁹ noted intermittently on an electrocardiogram, which the PICU team indicated were also captured on an ECG two days before. Lucas' troponin (cardiac enzyme) was normal, as was a BNP⁵⁰ level measured at 34. The PICU team continued to monitor Lucas but did not think he had myocardial/pericardial issues. Dr. Hankinson checked in on Lucas early in the morning and reviewed the overnight issues. Lucas was afebrile and it was thought that his temperature fluctuations noted during his dystonic episodes were related to autonomic instability and not infection. Nevertheless, blood samples and a tracheal aspirate ⁵¹ were cultured and were pending results. Lucas remained stable on mechanical ventilation. He was no longer hyperglycemic and did not require any further insulin. Lucas' morning labs showed improving HUS labs, with rising platelets to 173-189K, and his hemoglobin was stable at 86-96. Dr. Hankinson noted that Lucas had received his second dose of eculizumab the night before and that the PICU team was planning to extubate him as soon as possible.

Gastroenterology re-visit - continued PPI therapy for stress gastritis bleeding

Dr. Avinashi stopped in to see Lucas for gastroenterology in the morning. He observed that there had been no further blood in his stool or melena since 5:30 PM the day before. On exam, Dr. Avinashi identified dried blood surrounding the perianal area. He continued to diagnose likely stress gastritis with multiple small bleeding points. He advised a month of PPI therapy and approved the slow introduction of enteral feeds, so Lucas was not going to need TPN. Dr. Avinashi planned to follow Lucas for the next few days to ensure he had resolution of the active bleeding.

Dr. Ha rounded for neurology at 9:20 AM. On exam, Lucas continued to exhibit spontaneous eye opening ("eyes roaming") and still did not blink to threat. There were no apparent purposeful extraocular movements, and he had a brisk corneal reflex bilaterally. He had a cough reflex, but no gag. Lucas continued to display extensor posturing, but his ankles could not be examined as PT/OT had placed soft AFO braces for prevention of contractures. Lucas was not moving to command. He withdrew to painful stimulus of all four extremities.

Neurology Consultation - CNS microangiopathy - CT planned after family meeting

Attending neurologist Linda Huh, MD visited Lucas in the afternoon and reviewed his history and did her own exam. She observed that Lucas probably had central nervous system microangiopathy with encephalopathy (as noted on MRI), in addition to a movement disorder (dystonia). She concurred that there were slow improvements in Lucas' responsiveness, as well as

⁴⁹ The ST segment is the flat, isoelectric section of the ECG between the end of the S wave (the J point) and the beginning of the T wave. The ST Segment represents the interval between ventricular depolarization and repolarization. The most important cause of ST segment abnormality (elevation or depression) is myocardial ischemia or infarction. Other processes may be associated with ST elevation such as hyperkalemia, pulmonary embolism. Hanna, Elias B., et al. "ST-Segment Elevation: Differential Diagnosis, Caveats." *Cleveland Clinic Journal of Medicine*, 7 June 2018, https://www.mdedge.com/ccjm/article/99933/cardiology/st-segment-elevationdifferential-diagnosis-caveats.

⁵⁰ *B-type natriuretic peptide* (BNP) is a hormone secreted by the left or right ventricle of the heart Concentration of this peptide in the bloodstream rises during episodes of decompensated heart failure. Venes, *Ibid* Note 100 at 1769.

⁵¹ The tracheal aspirate culture preliminary report was printed on 11/1/18 and was positive for 3+ *Pseudomonas koreensis*, 1+ Staphylococcus aureus, and 2+ normal oropharyngeal flora. Antibiotic susceptibility results were to follow but were not found in the medical records, final report not found.

in his rigidity and dystonic posturing. However, Dr. Huh thought he might be more lethargic from the midazolam, so she ordered his dose decreased. On exam, Dr. Huh observed blurring of Lucas' left optical disc but did not see a retinal hemorrhage—she was unable to evaluate the right. His eyes exhibited a downward and deviated gaze ("sunsetting"), and Dr. Huh observed decreased extraocular movements to lateral gaze, with doll's eyes. She thought that it would help to get a CT scan to rule out a worsening brain hemorrhage, but she deferred writing that order until after a staff and family meeting could be held.

Social Work Meeting with Family

Rhonda Kotick, MSW had been meeting with Lucas' family daily, and she met with them again that afternoon with the PICU team and neurologists. The doctors had a frank discussion with Nathan and Karla about Lucas' diagnoses and prognosis, assuring them that they would continue to treat Lucas despite not knowing what his long-term prognosis was at that time. The neurologists discussed their findings and their desire to proceed with a CT scan that afternoon. Nathan and Karla expressed that they remained hopeful and felt that staying positive was the best way to help their son get better. They agreed to the scan.

CT Head – increasing white matter abnormality

On November 1, 2018 at 4:00 PM, radiologist Brendon Graeber, MD did an unenhanced CT scan of Lucas' head, comparing it to the previous imaging from October 22, 2018. Dr. Graeber documented his observations:

There is much more extensive white matter attenuation abnormality compared to the prior CT. Extent of white matter abnormality also appears greater than on MRI, with decreased attenuation now seen diffusely throughout the cerebral hemispheres from the ependyma to the gray-white junction. There is also significantly decreased heterogeneous attenuation in the basal ganglia, worst in the lentiform nuclei. There is no large intra axial or extra axial hemorrhage. New punctate foci of increased attenuation in the forniceal columns anteriorly and left basal ganglia may represent foci of parenchymal microhemorrhage. Lateral ventricles are increased in size. Third ventricle is slightly more prominent. Cerebral aqueduct appears patent with normal size and configuration of the fourth ventricle. Sulci and basal cisterns are preserved.



Dr. Graeber attributed the ventricular enlargement to parenchymal volume loss from white matter disease, and not hydrocephalus. He saw no evidence of a "large" hemorrhage, but he observed likely focal microhemorrhages in the fornix and left lentiform nuclei. He discussed his findings with Dr. Huh at 4:45 PM.



Lucas' CT scan 11/1/18 – corpus callosum visible on left and lateral ventricles on both views



Family meeting after CT scan – continued supportive care

Neurology resident Dr. Chin met with Nathan and Karla along with Dr. Huh and Dr. Bennett at 5:45 PM. They explained that there was no sign of a large hemorrhage; however, there was lateral ventriculomegaly (enlargement), which appeared to be related to volume loss from the brain's parenchyma⁵² related to white matter disease. There appeared to be a significant increase in the extent of white matter abnormality. The doctors discussed that Lucas had a guarded prognosis with potentially irreversible injury to his brain ("detrimental effect on cognition/development/language/motor skills/vision are possible"), but they would not know the extent of injury until after time and rehabilitation. Finally, the doctors reassured the family that they intended to continue with supportive care to prevent any further injury.

BCCH Day 13, PICU Day 12 - CCPD Day 11 (cycles 238-261) - continued anuria

November 2, 2018 at 8:30 AM, Dr. Kadam evaluated Lucas for nephrology, finding him still entirely anuric. His peritoneal dialysis continued uninterrupted. Lucas' morning labs showed that Lucas had recovered a platelet count of 232K. His LDH was down to 1367. His hemoglobin was stable at 86. Dr. Kadam noted that Lucas continued to exhibit volume overload, but CCPD had successfully removed 330 mL of fluid via ultrafiltration. He was currently on an insulin drip, which had to be restarted after discontinuing it the day before. Dr. Kadam thought it likely that Lucas was absorbing some glucose from the dialysate during CCPD. He was receiving Novasource Renal tube feeds at 16 mL/hour. Lucas continued to have red/bloody stools. Dr. Kadam continued him on weekly EPO dosing for hemolytic anemia.

Pediatric critical care physician Dr. Hankinson reviewed the results of Lucas' CT scan the day before. Lucas remained intubated and ventilated, and Dr. Hankinson found him less responsive that morning. He was medicated with midazolam and gabapentin to reduce his agitation. He had increased tone in all four extremities, and the doctor noted sunsetting eyes and possible papilledema,⁵³ which had also been noted by Dr. Huh in the preceding days. Dr. Hankinson made no changes to Lucas' current care plan but commented that the care team would need to start involving Canuck Place Children's Hospice ⁵⁴ and Sunny Hill ⁵⁵ for long-term support and planning, deferring to neurology as to when that should start.

Pediatric Neuroradiology Consultation with Mark Halvorson, MD

⁵² *Parenchyma* refers to the essential parts of an organ that are concerned with its function in contradistinction to its framework (stroma). Venes, *Ibid* Note 100 at 1744.

⁵³ *Papilledema* refers to swelling of the optic disk with dilated veins, blurred optic disc margins, flame-shaped hemorrhages in the nerve fiber layer adjacent to the disk, and an enlarged blind spot on the visual field. It is caused by increased intracranial pressure, often due to a tumor of the brain pressing on the optic nerve. Venes, *Ibid* Note 100 at 1732.

⁵⁴ *Canuck Place Children's Hospice* is a pediatric palliative care provider with mobile clinical programs and two hospice locations: Vancouver and Abbotsford. Services include clinical respite and family support, pain and symptom management, 24-hour phone consultation support and in-house clinical care, art and education, recreation therapy, grief and loss counselling, and end-of-life care. <u>https://www.canuckplace.org/</u>

⁵⁵ British Columbia Children's Hospital also operates the *Sunny Hill Health Centre for Children*, which provides specialized services to children and youth with developmental disabilities aged birth to 19. http://www.bcchildrens.ca/our-services/sunny-hill-health-centre

Neurology attending Linda Huh, MD visited Lucas at 2:40 PM and discussed the CT scan from the day before with Mark Halvorson, MD, pediatric neuroradiologist. They discussed that Lucas' scan was more in keeping with "... progression of disease, as opposed to evolution of previous disease." Dr. Huh pointed out that the timeline was difficult to pinpoint, as the two CT scans were ten days apart. She commented in her chart notes:

In view of progression despite therapy with Eculizumab (2 doses), feel it would be of possible benefit to treat with steroids. The potential side effects and the potential for no benefit were discussed with parents who would like to trial steroids in view of the grave prognosis. MRI head and spine for Monday. Family meeting thereafter.

Methylprednisolone – Steroid Pulse Dosing

Dr. Huh started Lucas on steroid pulse dosing (methylprednisolone IV 100 mg/day) on November 2, 2018 for his "neurologic complications related to ischemia." Medication ordered for five-day course. Lucas' blood glucose increased with the steroids and he was kept on an insulin infusion. He continued uninterrupted on peritoneal dialysis. His dialysate was changed back to 1.5% to 2.5% combination Dianeal given impaired clearance with hyperglycemia. Lucas experienced an episode of oxygen desaturation overnight, but a stat chest x-ray showed nothing acute. He remained intubated and sedated on mechanical ventilation, and his tube feeds were restarted after being discontinued briefly. He was currently not having any diarrhea or frank rectal bleeding.

BCCH Day 14, PICU Day 13 - CCPD Day 12 (cycles 262-286) - continued steroid pulse

On Saturday, November 3, 2018, Jennifer Retallack, MD evaluated Lucas for pediatric critical care and noted that Lucas was on day number two of steroid pulse dosing with IV methylprednisolone. He had periodic fever spikes up to 100.8°F, but these were not considered "true" fevers as they were associated with episodic agitation. Dr. Retallack commented that Lucas was overall stable but would need close management of his dialysis and blood glucose over the five-day steroid pulse. She was most concerned about Lucas' CNS status. He was currently "settled" but on midazolam. Dr. Retallack discussed Canuck Place with Lucas' parents. The care team currently planned a trial of extubation soon after Lucas had an MRI on Monday. Therefore, they would attempt to wean him off midazolam and Dr. Retallack decreased Lucas' ventilator rate to see if he tolerated it.

Dr. Leonid looked in on Lucas for neurology and talked to the nursing staff about his CNS status, and they reported no change. He examined Lucas, finding him sedated and unresponsive on mechanical ventilation. His eyes were open with a fixed, disconjugate gaze⁵⁶ and dilated pupils. Lucas exhibited extensor posturing to stimulation and had brisk reflexes of 3+.

⁵⁶ A disconjugate gaze is a failure of the eyes to turn together in the same direction. Uncoupling of eye movements may occur in many diseases and conditions, including injuries to the oculomotor nerves; fractures of the orbit; strokes affecting the brainstem, frontal lobes, or cerebrum; multiple sclerosis; some nutritional deficiencies. Venes, *Ibid* Note 100 at 1001.



Disconjugate gaze (illustration, NOT Lucas)

Dr. Leonid concurred with the continuation of IV methylprednisolone and the plan for an MRI of his head on Monday. Dr. Leonid observed that Lucas required minimal ventilator support and agreed with the plan for extubation post MRI when possible after the MRI. A family meeting was planned for after the imaging was done.

BCCH Day 15, PICU Day 14 - CCPD Day 13 (cycles 287-310) - first urine since PD

Dr. Hankinson rounded for pediatric critical care early in the morning on Sunday, November 4, 2018 and observed that Lucas had begun producing urine. He was now on day 3 of a 5-day steroid pulse, intended to address the inflammatory process going on in his brain. She noted that he had also completed 2 doses of eculizumab. Lucas' CNS symptomatology had not changed, and he continued to exhibit intermittent extensor posturing to stimulus with pupil dilation, and his reflexes remained brisk at 3+. Dr. Hankinson wrote orders to increase Lucas' dose of gabapentin to 160 mg/day to control sympathetic irritability and posturing, while decreasing his midazolam so he would be weaned by the time of his MRI the next day. She opined that Lucas' prognosis was poor given his CT findings, and the care team was in the process of getting Canuck Place and Sunny Hill involved in Lucas' care.

Dr. Favel evaluated Lucas for nephrology that morning and was less impressed with the amount of urine Lucas had produced: "Question of VERY SMALL AMOUNT OF URINE IN DIAPER TODAY. Otherwise remains anuric." (*capitalization emphasis by physician*) She made no changes to his peritoneal dialysis.

Palliative Care Consultation

Later in the afternoon at 4:36 PM, Amy J. Mable, MD came in with her resident James Harris, MD to consult with the care team and Lucas' family about supportive care planning for Lucas. They documented their interaction with the family:

We had a chance to meet with Lucas' father, Nathan, his mother, Carla, and his grandmother, Carmen. Their understanding of his current physical status is quite accurate. They understand that he has had a devastating neurologic injury and the prognosis is unclear with respect to his possible recovery.

They do however remain hopeful that he will improve. They appreciate that he is ventilator dependent at this point in time and will require a trial extubation to understand about whether or not he can ventilate and protect his airway independently. They have been in numerous conversations with the neurology service and anticipate a meeting early next week for discussion prognostication, having initiated the steroid trial. From a renal a point of view, he has tolerated his peritoneal dialysis well, and they have seen small gains including the initiation of a scant amount of urine output over the last day or so.

From a physical point of view, the family believe they are seeing incremental improvements. They see him as being more aware than he was previously. They attribute improvements in the opening of his eyes, the movement of his hands, and his reactivity to their voice. The clinical accuracy of this is not clear at this time to me whether these clinical gains are agreed upon by the ICU and neurology service.

From a social perspective, the family have been close by Lucas' side throughout his stay. The family makeup includes his mother and father, Nathan, and Carla, as well as the paternal grandmother, Carmen. There is a half-sibling, Matthew who is 8 years old and a 14-month-old sibling, Alexander. The whole family has been with Lucas during his time in the ICU.



A mother's quiet vigil

The parents currently reside in Richmond and Grandma lives in Surrey. The parents have been together for 4 years. Mom is First Nations (with her band in New Brunswick) having grown up in Winnipeg and Vancouver. The parents have known each other for 10 years but have been together for 4. They described meeting during "rougher times." There seems to be a past history for prior substance use. Dad identifies personal and spiritual gains through recovery. He sees this as having allowed him a perspective and provided him with a perspective on his own life as well as that of Lucas'. The home is full of animals and Lucas loves pets. They have a rabbit and cats as well as 2 geckos at home.

From an emotional point of view, Lucas is described as a sweet child. His parents see him as a blessing and are grateful for every day they have been with him. They described his tendencies which were suspicious for autism spectrum disorder and have expressed how grateful they are for being able to learn from him each and every day. His First Nations name means "calmer of storms" and they describe this as being very much his personality. He loves playing with cars, playing with Lego, and also enjoys "smudging." They see him as a kind and gentle soul. They believe at this time that he is aware and present with them during his time in the ICU.

The doctors stressed that it remained unclear at that time what the exact trajectory of Lucas' health was going to be. "Certainly, the family is aware of the gravity of the situation." They discussed the next steps, including assessing the possibility of success with an extubation and the possibility of a required re-intubation. They did not yet discuss what to do in the event of extubation failure. The family described their understanding of brain plasticity as a source of hope, and they were optimistic with respect to his renal trajectory on the basis of having begun to produce urine. Dr. Mable summarized:

At this time, [Lucas' parents] describe knowing that there is a long road ahead and being prepared to take that route. They are hoping to engage with the rehabilitative services to begin to understand what Lucas' future might look like. They know there will be ongoing conversations regarding prognostication and that that may, in some capacity, shape their particular Goals of care.

BCCH Day 16, PICU Day 15 - CCPD Day 14 (cycles 311-332) - Day 4/5 steroids - Anuric

On Monday, November 5, 2018, neurologist Anita Datta, MD checked in with Lucas and his family at 9 AM, observing that the toddler was on the 4th day of a 5-day steroid pulse with IV methylprednisolone. He was still on sedation with midazolam, as the PICU team had been unable to lower his dose over the weekend, despite increasing his gabapentin. Dr. Datta noted that Lucas continued to open his eyes spontaneously, as well as with noxious stimuli, but he did not respond to voice or command. His pupils were sluggishly reactive and he did not respond with blink to threat. Lucas' gaze was downward and to the left. His cough/gag was not assessed, but the nurses reported it was inconsistent. Dr. Datta did not think there had been any clinical neurologic changes on the IVMP pulse. She discussed the MRI planned for that day to help with prognostication, and they would try to wean Lucas off his sedation ahead of the imaging. The PICU team hoped they could extubate Lucas the next day. Dr. Datta cautioned that Lucas' progress remained "guarded" at that time.

Dr. Kadam visited Lucas for nephrology and made no changes to his peritoneal dialysis. Lucas had not produced any more urine since the scant amount the day before. PD ultrafiltration had removed 450 mL of fluid in the preceding 24 hours, and his electrolytes were stable.

New MRI confirms worsening brain injury

At 1:30 PM on November 5, 2018, radiologists David Healey, MD and Brendon Graeber, MD performed an unenhanced MRI of Lucas' head and spine for his history of "atypical [*sic*] HUS

and multi-system involvement including significant CNS history." The radiologists were asked to address whether there had been progression of disease or involvement of new areas, and to give an opinion on the extent of disease and irreversibility of injury. For comparison, the doctors looked at the imaging from October 22 and November 1, 2018. The doctors summarized their impression:

- 1. Significant progression of extensive cerebral disease.
- 2. Interval development of confluent cerebral white matter edema.
- 3. Innumerable hemorrhagic foci throughout the cerebral white matter, at the site of prior diffusion restriction likely reflecting micro-hemorrhagic foci within prior infarcts.
- 4. New basal ganglia diffusion restriction suggesting new regions of ischemia.
- 5. Bilateral lentiform nucleus hemorrhage.
- 6. Left frontal extra-axial focal Tl hyperintense / susceptibility abnormalities may reflect thrombosis of small superficial cortical veins, or less likely subarachnoid hemorrhage or focal cortical hemorrhagic infarction.
- 7. Notable interval volume loss.
- 8. Features of intrinsic renal disease. In summary, the reversible cases of cerebral injury related to thrombotic microangiopathy that have been described in the literature have had features of cytotoxic and interstitial edema but not hemorrhage. The extent of hemorrhagic abnormality visible here suggests that some of the cerebral injury will not be reversible; how much is difficult to say.



Images from Lucas' 11/5/18 MRI



The lentiform nucleus or lenticular nucleus comprises the putamen and the globus pallidus within the basal ganglia. With the caudate nucleus it forms the striatum. It is a large, lens-shaped mass of gray matter just lateral to the internal capsule.

Family Meeting about MRI

At 5:45 PM, Dr. Datta met with the family, the PICU team, nursing staff, social worker, and a representative from Canuck Place. She explained the new findings on the MRI, most significantly the volume loss and hemorrhage throughout the white matter of Lucas' brain. She discussed the significance of the diffuse signal change through the white matter, and the new diffusion restriction in the basal ganglia. Dr. Datta discussed Lucas' clinical decline in neurologic status and how it related to the worsened MRI, explaining that there was significant concern for motor and cognitive impairment, although the severity of this was not predictable.

Social Work Consultation

Ms. Kotick stayed behind with the family after the meeting to help them assimilate the new information they received from Dr. Datta. Nathan and Karla expressed that they were upset by the news, but they had been talking amongst themselves and "... were aware that this might indeed be the case." Nathan expressed his willingness to take Lucas home as long as he can breathe on his own. Both he and Karla stated that if Lucas was unable to breathe on his own, they knew they might need to make decisions about goals of care. A trial extubation was tentatively planned for the next morning. Karla and Nathan were doing their best to stay strong in order to provide Lucas with the strength and support he needed. Recognizing the struggle ahead, they requested support from the Psychology service. Ms. Kotick made the referral and also arranged for a dog to visit Lucas as he loved animals. Karla also asked for the chance to lie in bed with Lucas.



Karla lying in bed with Lucas

BCCH Day 17, PICU Day 16 - CCPD Day 15 (cycles 333-356) - Extubation - d/c planning

On Tuesday, November 6, 2018, Dr. Hankinson evaluated Lucas during morning rounds for pediatric critical care. This was his 5th and final day of the steroid pulse. Lucas was taken off midazolam in preparation for extubation. He continued to have episodes of extensor posturing, pupil dilation and occasional sunsetting with stimulation. He opened his eyes minimally that morning and had no purposeful movements. He remained on Keppra for seizure prophylaxis. The PICU team began Lucas' PSV⁵⁷ trial and temporarily discontinued his tube feeding.

Extubation – spontaneous breathing on room air

Dr. Datta looked in on Lucas at 9:40 AM to see how he was doing with the vent taper. His cough and gag reflexes remained inconsistent, but he coughed spontaneously with stimulation. Lucas was extubated at 9:55 AM and demonstrated spontaneous respirations on room air.

⁵⁷ Traditional methods of ventilator weaning include spontaneous breathing trials (SBTs), progressive decreases in the level of pressure support during pressure support ventilation (PSV), and progressive decreases in the number of ventilator-assisted breaths during intermittent mandatory ventilation (IMV). An SBT refers to a patient breathing through the endotracheal tube either without any ventilator support (eg, through a T-piece) or with minimal ventilator support (eg, a low level of pressure support, automatic tube compensation [ATC], or continuous positive airway pressure [CPAP]). Tobin MJ, Jubran A. Weaning from mechanical ventilation. In: Principles and Practice of Mechanical Ventilation, Jubran A, Tobin MJ (Eds), McGraw Hill, New York 2006. p.1185.



Sunny Hill Rehab Consultation – Discharge Planning

At 10:30 AM, Jill S. Hoube, MD visited Lucas and his family at BCCH to discuss acute rehab at Sunny Hill. Nathan and Karla described Lucas' baseline developmental level before he got sick with STEC HUS, which Dr. Hoube summarized:

- Eyesight and hearing prior to traumatic brain injury (TBI) tested normal.
- Was speaking prior to TBI (seeing speech therapist)
- Was attending daycare, playing with other children and being more emotionally regulated.
- Motor (fine and gross) were normal
- Speech delayed 4 word sentences at the time of TBI
- Made eye contact but not overly affectional child.
- Fixated on Legos and stacking objects but would break stacked objects to build new ones.

Dr. Hoube summarized Lucas' current function:

- Currently ventilated and intubated with his own driven respirations.
- Semi-volitional movements of right hand; dad describes "rotation of write [*sic*]" and "twitching of his fingers"
- Coughs with secretions
- No spontaneous eye opening, no response to verbal stim
- Withdraws to pain
- +Dystonia (decerebrate posturing)
- No seizures.

Lucas was in the process of being extubated at the time Dr. Hoube arrived for her assessment. She observed that, after extubation, Lucas still had a nasogastric tube for feeds, lines for fluids/meds, and a peritoneal dialysis catheter implanted in his abdomen. He had soft AFO braces on his feet to prevent contractures. Dr. Hoube examined Lucas and found his abdomen distended from peritoneal dialysis. Lucas was lying in an extended, decerebrate posture in bed. He responded to noxious stimuli by withdrawing, but he had no other response to touch or voice, and

his eyes were closed. Dr. Hoube examined Lucas' eyes with an ophthalmoscope and confirmed edema at the optic disc. There was no facial asymmetry. He had increased tone throughout his extremities, but no clonus. Dr. Hoube reviewed Lucas' last EEG from October 22, 2018.

Dr. Hoube outlined what Lucas would need when he was moved to Sunny Hill, which could happen as soon as he was medically stable. He had to be off peritoneal dialysis without the need for active medical intervention.

BCCH Day 18, PICU Day 17 - CCPD Day 16 (cycles 357-379) - stable on room air

On November 7, 2018, Dr. Hankinson evaluated Lucas early in the morning. He was oxygenating well on room air without any increased work of breathing (WOB). Auscultation of his lungs revealed coarse crackles bilaterally, but this was not a new finding. Dr. Hankinson thought that Lucas was stable post extubation. However, without a gag or cough reflex, she wondered if he had too much sedation from accumulating gabapentin, returning CO2, or changes to his neurologic status. She worried he might not be able to reliably protect his airway. Once it was determined he could do that, they planned to transition Lucas out of the PICU to a regular pediatric bed for ongoing peritoneal dialysis, rehab, and continue their plan to move him to Sunny Hill. Canuck Place, neurology, Sunny Hill, and the Psychiatry Service were all involved in discharge planning and support services for Lucas.

Plans to discontinue dialysis

Lucas continued with uninterrupted CCPD. His serum creatinine was currently 253, and his urea 35. Dr. Kadam came in for nephrology and recommended that Lucas continue with continuous cycling peritoneal dialysis at that time, but she decreased the number of cycles in 18 hours and adjusted his dialysate. Lucas still required dialysis for fluid removal, as he had not yet recovered adequate urinary output.

Stat call to neurology for prolonged posturing

At 6:20 PM, Dr. Krishnan was summoned urgently to the PICU when Lucas suddenly appeared to have worsened neurologically. He began moaning, had an increased heart and respiratory rate, and he exhibited prolonged, exaggerated posturing (about an hour). His oxygen saturation remained stable, however, and he did not have a fever. By the time Dr. Krishnan arrived, the episode appeared to be resolving; however, she called to confer with Dr. Retallack. Dr. Retallack did not think the episode represented new or clinical worsening of Lucas' condition. She thought the moaning was newly audible because he was no longer on the vent. She advised continued observation and monitoring.

BCCH Day 19, PICU Day 18 - CCPD Day 17 (cycles 380-400)

Dr. Kadam evaluated Lucas for nephrology at 8:45 AM on Thursday, November 8, 2018 and implemented a decrease in Lucas' peritoneal dialysis cycles, with 18 hours of CCPD followed by 6 hours with the PD catheter capped off. Lucas' serum creatinine was down to 211 and his urea was 30.4. His urinary output overnight increased to a total of 425 mL. Dr. Hankinson evaluated

Lucas for pediatric critical care and talked to the family about Lucas' recovering renal function and reduction in the CCPD cycles. Lucas continued with clusters of posturing episodes up to 15 minutes in length overnight, which resolved with midazolam. She changed his gabapentin to less frequent dosing, as his posturing was "generally controlled" during daytime hours. Lucas still did not have a consistent cough or gag reflex, and he had required some deep suctioning overnight; however, he only needed suctioning once during the day. She saw no signs of "silent aspiration." Dr. Hankinson ordered a trial of only superficial suctioning to see if Lucas might be stable enough to transfer to the pediatric ward.

BCCH Day 20, PICU Day 19 - CCPD discontinued - continued urinary production

On November 9, 2018, Dr. Kadam came in for nephrology at 9:30 and observed that Lucas continued to produce urine overnight. His current urinary output was estimated to be 1.5 mL/kg/day and he had no pitting edema in his lower extremities. He continued to have mild facial edema. Dr. Kadam questioned the possibility of a current active infection, as the nursing staff reported he had a number of loose stools overnight and was vomiting more than he usually did.



Vomiting and facial edema

Lucas did not have a fever, however. Stool, blood and urine cultures were sent to the lab as a precaution. Lucas was just finishing the 24-hour CCPD cycle that started at 6 AM on the 8th and ending at 10:45 AM on the 9th. Dr. Kadam wrote orders to stop peritoneal dialysis with Cycle No. 400.

Neurology deems Lucas stable enough to leave PICU – Keppra discontinued

Dr. Datta arrived at 9:55 AM and the family told her that Lucas appeared to be more responsive than he had been, and the nursing staff reported that he was opening his eyes to mild stimulation. On exam, Lucas' eyes were currently closed and he had no spontaneous movement or vocalization, but he opened his eyes to noxious stimulation. The nursing staff had been able to elicit a weak gag reflex overnight. Dr. Datta observed that Lucas exhibited brisk reflexes (3+) in all extremities and had spasticity of his "ankles and upper limbs, forearm pronators, and finger flexors." She ordered his Keppra seizure prophylaxis discontinued, as there had been no clinically observed true seizures or electrographic seizures to date. Dr. Datta signed off Lucas' case for the purposes of daily monitoring but planned to remain available as needed after he was transferred out of the PICU.

Discharged from PICU to regular pediatric bed

Dr. Hankinson evaluated Lucas for pediatric critical care and noted that he had exhibited grunting and nasal flaring when "upset" that morning. She auscultated decreased airway entry to his right lung base and his respiratory rate was rapid at 30 breaths per minute, but Lucas was oxygenating well on room air. His heart rate increased to 180 with the episode. This witnessed extra "work of breathing" improved afterward, and Dr. Hankinson suspected that Lucas had some aspiration with the vomiting episode but recovered from that with a return to normal respirations and heart rate. She considered the "3 loose stools" and single episode of mucoid emesis of minimal significance in terms of evaluating him for discharge from the PICU. She requested that a *C. difficile* test be added to the lab requests for the stool sent to the lab and added a peritoneal fluid culture to the list. Dr. Hankinson observed that Lucas had a normal blood glucose off insulin that morning, which had been successfully discontinued after the steroid pulse without any further hyperglycemia. After stabilizing Lucas with additional gabapentin, Dr. Hankinson approved Lucas for transfer out of the PICU.

At 12:40 PM, Lucas was moved out of the ICU. Upon discharge, his exam was significant for tachycardia (heart rate 175) and tachypnea (respiratory rate 40), but he was afebrile with a blood pressure 110/70. Many of his labs were still abnormal but improving. Lucas serum urea was 22.9 and creatinine 165, LDH 1077, GGT 30, neutrophils 22.56. His peritoneal fluid was clear and colorless. His urinalysis was significant for proteinuria, glucose, and blood, with a pending culture. His stool test for toxigenic *C. difficile* was negative, and a culture was pending. Blood culture results were pending.

Lucas' PICU exit physical exam included a Glasgow Coma Scale value of 5-8. His neuro exam was as listed previously. Lucas was considered high risk for aspiration because of his lack of a consistent gag/cough reflex. He was receiving Pedialyte only via his OJ tube while his loose stools persisted, and the doctors wrote orders to resume his regular formula feeds after it had resolved. Although Lucas had been taken off peritoneal dialysis, nephrology planned to continue monitoring him in the pediatric ward. Dr. Kadam wrote orders to flush the peritoneal dialysis catheter with heparin every seven days, and Dr. Hankinson continued Lucas' prescribed a PPI drug (omeprazole 15 mg/NG twice daily), neuropathy drug (gabapentin 120 mg/NJ twice daily), and an anemia drug (EPO 2000 units SQ weekly), with prn acetaminophen via his NG tube every 4 hours as needed (up to 5 doses) for fever or pain. Endocrinology advised subcutaneous insulin as needed for hyperglycemia.

Sunny Hill and Canuck Place were copied on the PICU discharge summary, and they requested that a G-tube be implanted before Lucas was transferred to Sunny Hill. Dr. Jennifer Smitten, MD accepted Lucas as a patient in the pediatric ward ("CTU Violet") just before 11 AM on November 9, 2018.

BCCH Day 21-22-23 - CTU Violet - settling in over the weekend

On Saturday, November 10, 2018, nephrologist Dr. Flood visited Lucas, continuing to follow him for his history of HUS and AKI Stage 3, now off peritoneal dialysis for one day. She observed that his renal function labs were stable (urea 16.4, creatinine 148), but his blood pressure continued to register high normal (95th percentile). She restarted him on amlodipine for blood

pressure control and observed that he had been transitioned to SQ insulin (Levemir 0.5 units qhs) the day before to keep his blood sugars in good control.

Canuck Place Children's Hospice Consultation

A representative from Canuck Place Children's Hospice met with Lucas' family at 3 PM that afternoon. Lucas was having a dystonic episode at the time of the visit (back arching, hands flexing, crying out, increased heart rate), but he settled down after changing his position. His doctors added lorazepam sublingually to his medication orders to help with further episodes. The family took this opportunity to get their questions answered about Sunny Hill Children's Centre, and so arrangements were made for them to get a visit to go over all their concerns.

Pediatric resident Dr. Mohammad cared for Lucas over the weekend and wrote a summary of both days on the 11th. Lucas' formula was changed to Novasource Renal and he was tolerating the change well. Lucas continued to increase his urinary output. His IV fluids were stopped except TKO ("to keep open") so venous access would remain available. Lucas was off all antibiotics and remained afebrile. Physiotherapy was slated to work with Lucas on a daily basis to mobilize his limbs and do some PT teaching for Nathan and Karla so they could participate at the maximum.

Continued hyperglycemia from steroids

Endocrinology resident Dr. Milton returned on Sunday, November 11, 2018, noting that Lucas' hyperglycemia had responded well to subcutaneous insulin. His continued hyperglycemia was thought to be related to the steroid dosing. Dr. Flood also returned on the 11th to check on Lucas' labs after he had been on Novasource Renal. She was satisfied that his electrolytes were stable, he was producing urine and was tolerating his feeds. She discussed Lucas' fluid balance with Dr. Smitten and told her that she was signing off daily renal management now that Lucas was off peritoneal dialysis, and she would leave its management to the CTU team. Dr. Flood added that the nephrology service planned to follow Lucas long-term in the renal clinic as an outpatient when the time came.

On Monday, November 12, 2018, pediatrician Dr. Latraus visited Lucas during morning rounds, finding him very unsettled, crying, and posturing. His heart rate was rapid at 280 [*sic*], but his blood oxygenation was stable without desaturations on room air. After receiving two doses of lorazepam, Lucas settled down. These episodes were very distressing to his family and the staff, and Dr. Latraus encouraged Lucas' parents to accept a trial of clonidine.

BCCH Day 24 – Surgical Consultation for PEG tube

On Tuesday afternoon, November 13, 2018, Nicole Jedrzejko, MD came in to see Lucas at the request of the care team for Lucas' diagnosis of "orogastric feed dependency post HUS encephalopathy." The surgery team was requested to assess Lucas for the insertion of a gastrostomy tube (PEG tube). Dr. Jedrzejko consulted with urologist Dr. Masterson about a plan to remove Lucas' peritoneal dialysis catheter at the same time as the surgery for the insertion of a gastrostomy tube. The family agreed with this plan and surgery was scheduled for the coming Friday.

Continued posturing episodes

At 5:45 PM, Dr. Mohammad visited Lucas for the pediatric service. Nathan told the doctor that Lucas had "burped, sneezed, and coughed" during the night. Dr. Mohammad could not elicit the same responses on exam. The nursing staff stated that Lucas and his parents had experienced a difficult night for three nights in a row, during which Nathan and Karla were up all night long trying to deal with Lucas' "dysautonomic episodes," which had changed little in character since he was in the PICU. Nathan held off on using the clonidine until 6 AM that morning, wanting to try environmental changes before resorting to medication. During the episodes, Lucas was tachycardic with heart rates up to 180, fixed dilated pupils. He had also started grinding his teeth. Dr. Mohammad saw no improvement in Lucas' Glasgow Coma Score. He talked to Nathan about trying the clonidine at midnight so Lucas could settle overnight, and he agreed to try it.

BCCH Day 25-26 – Medical Psychology Consultation

On November 14, 2018, Penny Snedden, PsyD and her resident Sara Anderson, MD consulted for the mental healthcare service and noted that this was the first time their team had met with the family since Lucas was transferred out of the PICU. Nathan and Karla reported that they had been keeping well and supporting each other and were able to successfully outline their needs to the medical team earlier in the week when Lucas was first transferred – both he and the family were getting little sleep because of the need to monitor Lucas so closely. Nathan and Karla felt that they had advocated well and were satisfied with Lucas' care. They anticipated Lucas' surgery to have his G-tube inserted and catheter removed on Friday would clear the way for Lucas to transfer to Sunny Hill the next Monday. "They noted very high expectation for Lucas' recovery (i.e., that he will return to pre-illness functioning). It will be important to monitor parents' expectations through Lucas' rehab."

Other than the clearly difficult time for the family through Lucas' prolonged hospitalization and current needs, Nathan expressed that the family's greatest concern at that time was his 8-yearold son Matthew (from a previous relationship). Evidently, Matthew lived in Sunny Hill with his grandma (Nathan's mom), his legal guardian. Nathan reported that Matthew had significant behavioral and developmental concerns and was struggling with visiting Lucas in the hospital, which caused him to become withdrawn or aggressive). Behavioral strategies were suggested for his next visit on Saturday, as well as suggestions to provide him with some child-centered time 1 on 1 with a parent. Further, it was suggested that child life become involved to help support parents explain Lucas' hospitalization to Matthew further. Child youth mental health was suggested to support Matthew and grandma w/ continued behavioral and emotional support. We will continue to check in this week to support parents.

Better night with clonidine

Dr. Mohammad checked in on Lucas in the afternoon and was happy to hear that Lucas had a better night with midnight clonidine. He was tolerating his gastric feeds very well without vomiting or diarrhea. His blood sugars were better controlled on minimal insulin. Lucas continued to produce urine at a rate of 1.9 mL/kg/hr (110 mL over preceding 24 hours). Dr. Mohammad

considered this an improvement and a sign of renal recovery. His blood pressures were still elevated (124/88) and he tended towards tachycardia. Dr. Kaden advised increasing his free water in his feeds. Dr. Mohammad thought Lucas' eye puffiness was decreasing.

On Thursday, November 15, 2018, Lucas renal function labs were improving (creatinine 79, urea 19.5) and he was clinically stable. He seemed to be responding to the clonidine and an increase in his gabapentin dose, with milder dystonic episodes, which were less frequent, and he was not screaming as loudly when they occurred. The doctors were preparing for Lucas' Friday surgery to remove the PD catheter and implant a gastrostomy tube, so he was kept NPO overnight.

BCCH Day 27-29 - to the OR for PD tube removal, PEG tube insertion

On Friday, November 16, 2018, Robert Baird, MD and Nicole Jedrzejko, MD took Lucas to the operating room for removal of his peritoneal dialysis catheter and insertion of the gastrostomy feeding tube. The procedures were done with Lucas under general anesthesia and implementation of laparoscopy. There were no complications, and at 3 PM Lucas was admitted to the postoperative care unit. The nursing staff noted that Lucas opened his eyes on his own and responded to his dad's voice.

The following day, the G-tube functioned well and Lucas initially tolerating his formula; however, shortly thereafter, he had ~ 15 minutes in which he vomited several times. The emesis was dark brown in color and tested positive for blood. The doctors ordered further feeds to be held until they could investigate further.



Example of PEG tube placement (NOT Lucas)

Postop Surgical Consultation

At 3:25 PM, on November 17, 2018, Dr. Ceston evaluated Lucas for general surgery along with Dr, Skargard. They determined that Lucas had been coughing before he vomited. They ordered a PPI infusion and to use only Pedialyte for the next "feeding" later that night. The doctors suspected that the blood was residual from the surgery itself and was not significant. Lucas had no further vomiting after he received Pedialyte overnight on the 18th. He continued with increasing urine production up to 700 mL in 24 hours, and his creatine dropped from 79 to 62. His blood pressure was still elevated in the 95th percentile of normal, so that was monitored rather than medications added.



Lucas with his G-tube

BCCH Day 29 – Preparation for transfer

On November 18, 2018, Datal Mohammad, MD and Brenden Hursh, MD addressed the fact that Lucas still required insulin, but his parents had not yet received formal diabetes education. Since they were not certain whether this would be an acute vs. chronic issue, they wanted Nathan and Karla to receive training by their team before leaving BCCH. After transfer to Sunny Hill, the endocrinology plan for Lucas was to continue his blood sugar checks every 8 hours and call BCCH Endocrinology for instructions if the levels warranted insulin dosing.

Pediatric attending Amie Dmytryshyn, MD also evaluated Lucas for transfer from BCCH to Sunny Hill. His discharge diagnoses included:

- 1. Traumatic brain injury secondary to hemolytic uremic syndrome.
- 2. Renal failure secondary to hemolytic uremic Syndrome (resolved)
- 3. Persistent hyperglycemia secondary lo hemolytic uremic syndrome.

Dr. Dmytryshyn summarized how Lucas had stabilized medically and no longer required peritoneal dialysis, and his blood sugars were stable on Levemir dosing. She noted that he had not had any further deterioration in his Glasgow Coma Scale. Additionally, Lucas' laboratory findings showed improving renal function as well as improving electrolytes. However, Dr. Dmytryshyn cautioned that Lucas was still adjusting to G-tube feeds after its insertion on November 16, 2018. She summarized his condition prior to discharge:

Neurologically, he remains below his pre-admission baseline; however, does show evidence of a swallow and gag reflex as well as some possible visual fixation on objects. He does remain quite neurologically irritable as he is still recovering from an extensive brain injury secondary to HUS.

At the time of transfer, Lucas is still bedbound and has a GCS consistently below 10. His pupils are asymmetric in response to light, and he does not formally fix or

follow objects consistently on examination. A gag reflex can be elicited on examination, which was not present in prior exams. Chest sounds clear with no evidence of aspiration and heart sounds are normal and is well perfused and pulses can be felt distally in all 4 limbs.

Abdominal exam does reveal a G-tube in situ with no evidence of infection or displacement. Abdomen is not distended and not tender to palpation and is soft with no masses present. Dermatologically, there is no rash or lesions present. Lucas is not yet fitted for a wheelchair but has spent some time sitting in bed with PT, but spends most of his time in a fixed, supine position. Finally, he is quite sensitive to light and noises and prefers a dimly lit room and visitors to speak in a more hushed volume.

DISCHARGE INSTRUCTIONS:

Lucas is being transferred co Sunny Hill Hospital where he will receive consultation with physiotherapy, occupational therapy, recreational therapy, and other specialists as needed for his rehabilitation. He would likely benefit from proper splinting when he gets to SHH. It has also been suggested that he be started on baclofen for muscle spasm as he starts PT. Currently, he is being G-tube fed and is withstanding formula feeds. However, his feeds will have to be adjusted as he grows and as his kidney function improves.



Sunny Hill Health Centre for Children – a brief stay ...

Sunny Hill Health Centre for Children

On November 19, 2018, Nancy Lanphear, MD received Lucas at Sunny Hill and performed his admission history and physical exam. Dr. Lanphear reviewed Lucas' records from BCCH, specifically focusing on the consultation done by Dr. Hoube from their facility before he was discharged. She summarized Lucas' problem list by system, followed by his diagnosis list:

1. NEUROLOGIC: He has not had seizures. Previous EEG showed no subclinical seizures. He has significant dystonia and has dysautonomia; this has been treated

with gabapentin and prn clonidine. He is not on anticonvulsants. He has an altered level of consciousness which has had some lightening as parents now report an occasional cough and that doctors have been able to elicit a gag response. The family believes that he periodically has shown some interest in their voice or in TV, but this is for short periods. He has significant irritability and has some sleep disruption.

- 2. NEPHROLOGY: He has not had peritoneal dialysis for at least 1 week, according to the mother. His peritoneal dialysis catheter was removed and 2018; this was placed without difficulty. He has had borderline hypertension. This is being monitored. He initially had fluid restriction and is no longer. His creatinines have been quickly improving, and the hope is that his renal function has fully returned to baseline. He has been placed on a reduced protein formula, and the recommendation is that he can be normalized to a regular formula soon as this would have been done at BCCH if he had remained there.
- 3. ENDOCRINOLOGY: He had hyperglycemia which was felt to be secondary to steroid use and HUS. He is followed by Endocrinology and is currently getting frequent glucose checks and has been typically getting long-acting insulin based on his BG per Endocrinology. He has a protocol for treating hypo and hyperglycemia. Hyperglycemia will be treated with rapid-acting insulin. checks are currently communicated to Endocrinology for advice on management of blood sugars.
- 4. GASTROENTEROLOGY: He has had a history of some emesis and diarrhea consistent with his HUS. He had emesis the day after G-tube placement had some coffee ground appearance. This was felt to be secondary to G-tube insertion. He is also prn PEG and stools have improved.
- 5. DIAGNOSES:
 - Hemolytic uremic syndrome with brain injury secondary to ischemia.
 - Previous history of concern with autism. He had been referred to the BC Autism Assessment Network prior to this episode.
 - Acute renal failure, improving.
 - Borderline hypertension.
 - Hyperglycemia, treated with insulin.
 - Dysautonomia and dystonia

After he was formally admitted, Dr. Lanphear wrote orders for him to begin OT, PT, and Speech Therapy. She also wanted to get Recreation therapy involved to help with the family over time with outings. The family voiced the hope that on weekends, once he was more stable, they could take Lucas home with them on pass. Dr. Lanphear prescribed Baclofen⁵⁸ for management of Lucas' hypertonicity, noting that he would also likely need other prn and baseline medications. She discussed this with Nathan and Karla, and they concurred. Dr. Lanphear started him out on three-times-daily dosing, as his tone was contributing to his irritability and intermittent vomiting

⁵⁸ Baclofen (Lioresal, Gablofen) Baclofen presynaptically inhibits the nerve terminal. It is centrally acting and can be administered intrathecally or orally. Baclofen is the preferred drug for spasticity related to spinal cord injury (SCI) or multiple sclerosis (MS) and is useful in cerebral palsy. Tolerance can occur. "Spasticity Medication: Skeletal Muscle Relaxants, Benzodiazepines, Alpha2-Adrenergic Agonists, Botulinum Toxins." *Spasticity Medication: Skeletal Muscle Relaxants, Benzodiazepines, Alpha2-Adrenergic Agonists, Botulinum Toxins*, 11 Nov. 2019, https://emedicine.medscape.com/article/2207448-medication. caused by extensor posturing. She also planned serial labs to check his renal function, blood glucose, etc.

Sunny Hills Day 2 – Respiratory distress during night, continues to worsen...

Unfortunately, when Lucas was administered his first doses of Baclofen, he was inadvertently given two doses within a 2-3 hour time frame. The overdose not immediately identified. During the early morning hours of November 20, 2018, his dad noticed that Lucas' respiratory rate had changed. Nathan observed that Lucas was having some periodic breathing changes, including alternating cycles of deep and shallow breathing. When brought to the attention of the nursing staff, it was noted that Lucas' lungs were clear and saturations "good." He was in his usual state of decreased consciousness. Lucas then received his morning and afternoon doses of Baclofen at the prescribed dose. As the day wore on, Lucas was noted to have a shift in respiratory effort with 2-3 breaths followed by an up to 10+ second pause. The nursing staff contacted the call physician, Dr. Armarnik, who in turn contacted Dr. Lanphear.

Ambulance transport to BCCH for baclofen overdose – HTN, bradycardia, bradypnea

On exam, Dr. Lanphear noted an alteration in Lucas' level of consciousness, with no response to painful stimuli compared to when she examined him on admission the day before. The decision was made to send Lucas to the BCCH ER for evaluation of increased intracranial pressure. Before transport, his blood pressure was elevated at 155/104, with an abnormally slow respiratory rate of 10-12, and bradycardia (pulse 58). He did not have a fever. The ambulance crew arrived at 8:38 PM. *S*

The ambulance left Sunny Hills at 9:23 PM, accompanied by a Sunny Hill nurse and the paramedic team, who started a peripheral IV and secured him for transfer. Lucas was monitored by ECG on the way to the ER. CTU attending at BCCH, Amie Dmytryshyn, was aware and agreed with the plan for Lucas to return for an evaluation in the ER and possible readmission to the hospital.

BCCH – Emergency Department – confirmation of baclofen overdose

At 9:42 PM on November 20, 2018, Diona Murray, MD and David Migneault, MD received Lucas in the ER and talked to Nathan about his observations of his son's respiratory changes overnight and during the following day. The double dose of Baclofen had been discovered by this time. Upon arrival in the ER, Lucas was asleep but soon woke up and had his eyes open and looking around. His blood pressure was down to 120/70 and he was tachycardic (130-160), but he was oxygenating well on room air. His respirations slowed to 12 per minute while asleep but returned to greater than 20 (normal) when awake. Lucas' white blood cell count was elevated at 22.8K. The doctors assigned Lucas a working diagnosis of "CNS/respiratory suppression 2° Baclofen." At 10:30 PM, Radiologists Jeffrey Hu, MD and Susan Gowdy, MD x-rayed Lucas' chest and compared it with the last one he had done on November 8, 2018. They observed "prominent pulmonary vasculature favored to be related to low lung volumes," but they could not identify aspiration pneumonia.

Pediatric Attending Consultation – concern for increased intracranial pressure

Pediatric resident Mark Cheng-Yu Tsai, MD and Amie Dmytryshyn, MD consulted for the ER doctors for "changes in his neurologic status as well as vital sign changes, including irregular respiration, bradycardia, and hypertension." Dr. Dmytryshyn reviewed Lucas' brief history of admission to Sunny Hill. Nathan told her that Lucas' neurologic function was improved ("according to the father was eyes opening spontaneously, and he was able to look around") but the Sunny Hill team informed her that this was not the case—he had spontaneous eye opening but no purposeful gaze. He would cry when he was upset, and he had some spontaneous arm movements, but it was unclear whether they were purposeful or not.



After being transferred to BCCH ER for "concerns of a Cushing triad⁵⁹" Dr. Dmytryshyn became less concerned for increased intracranial pressure as Lucas' presenting symptoms slowly resolved and Lucas had no localizing signs on his neurologic exam. However, Dr. Dmytryshyn remained concerned about the change in his neurologic status, especially with low tone and areflexia, as well as decreased level of alertness. She summarized her concerns regarding the Baclofen overdose:

He did get baclofen 15 mg about 28 hours ago, as well as another 7.5 mg dose of about 10 hours ago. The half-life of this medication is 3-4 hours when normally renally excreted. His renal function is reasonable at this time. His last dose of baclofen was at 2 PM on November 20, 2018; however, Dad describes a strong temporal relationship with starting baclofen and, as such, an overdose could pump could be possible. An overdose would present as increased secretions, areflexia, decreased tone, hypertension, as well as vomiting, which would all be consistent with his presentation. However, there is some question given how low the total dose he received was and how far out from the ingestion he was. We will need to closely monitor for potential toxicity effects, including further depression of CNS and respiratory status. We will do an ECG to monitor his QTc. He will continue to be monitored for seizures.

Because Lucas presented with an increase in his WBC count and neutrophils, Dr. Dmytryshyn ordered continued antibiotic therapy while they waited for results from his blood and urine cultures. She held his formula G-tube feeds, given his decreased level of consciousness and

⁵⁹ *Cushing response* is a reflex due to cerebral ischemia that causes an increase in systemic blood pressure. This maintains cerebral perfusion during increased intracranial pressure. Venes, *Ibid* Note 100 at 603.

increased risk of aspiration. "We will run him D5NS at 75% to run him slightly dry in order to mitigate the risk of syndrome of inappropriate antidiuretic hormone secretion as well as to manage his secretions better." She continued his EPO as his hemoglobin was still now. For Lucas' dysautonomia, she continued the gabapentin and clonidine; "... however, we will have ongoing vigilance with regard to central nervous system depressive effects."

BCCH Readmission - Day 1 (cumulative hospital day 30)

At 4 AM on November 21, 2018 Lucas was moved to a pediatric bed in "CTU Violet." Zoltan Gyorgyi, MD assessed Lucas for neurology at 12:30 PM and listed his admission diagnoses: "st. p. HUS, stroke, severe neuro deficit, dystonia, autonomic dysregulation." He noted Lucas' symptoms after overdose of Baclofen included bradycardia, hypertension, and irregular breathing. Since his arrival back a BCCH, Lucas had exhibited increased blood pressures and heart rate, but his breathing pattern gradually normalized. However, he continued to have sluggish eye movements. Dr. Gyorgyi discussed Lucas' neuro status with his parents, who thought that he was at his baseline ("or better"), with no meningeal signs.⁶⁰ Lucas was tachycardic (heart rate 159). BP 115/62 (post nifedipine) CRP 25, RR 15-20, sats 100% RA. Given the half-life of baclofen, Dr. Gyorgyi anticipated the sides effects would continue to decline, and he advised the use of clonidine in case of increasing hypertension and tachycardia in the meantime.

CT Head - interval worsening, white matter necrosis

On November 21, 2018 at 2:14 PM, radiologist Mark Rollo Halvorson, MD performed an unenhanced CT scan of Lucas' head, comparing it to prior imaging. Dr. Halvorson observed a mild decrease in the white matter hypoattenuation since the prior head CT three weeks earlier. Dr. Halvorson identified interval development of moderately extensive periventricular white matter cystic changes, suggesting necrosis. There was also visibly worsening ventricular enlargement, "... which may be ex vacuo⁶¹ in nature given white matter volume loss. Correlate with the patient's current clinical status." (*No images available for Lucas' 11/21 CT*)



Normal Anatomy

Ventriculomegaly

CTU Senior Consultation

Patrick McDonald, MD assessed Lucas for respiratory decompensation relative to the

⁶⁰ Kernig sign (reflex contraction and pain in the hamstring muscles, when attempting to extend the leg after flexing the hip), Brudzinski's sign (flexion of the hips when the neck is flexed from a supine position), and neck rigidity are used specifically to assess a patient's with suspected meningitis. Venes, *Ibid* Note 100 at 1327.

⁶¹ Hydrocephalus *ex vacuo* refers to the appearance on brain imaging of enlarged lateral ventricles, caused by atrophy of the brain. Venes, *Ibid* Note 100 at 1154.

baclofen overdose. Dr. McDonald did not think that Lucas' head CT reflected increased intracranial pressure—the ventricular enlargement appeared to be secondary to [white matter] volume loss and necrosis. He observed that Lucas' blood gases initially showed respiratory alkalosis, which resolved over time, and his chest x-ray was unchanged. The persistent hypertension was responsive to nifedipine, a calcium channel blocker antihypertensive drug.

Dr. McDonald's impression was that Lucas' deteriorating and changed respiration status reflected in central hypoventilation ("oxygenation not an issue and not currently hypercapneic") was likely related to his "evolving abnormal/injured brain." He opined that the symptoms of baclofen toxicity (especially with Lucas' "dysfunctional kidneys") only clouded his clinical presentation and should resolve. As to his persistent hypertension, he thought this was most likely from dysautonomia,⁶² for which he would need to remain on antihypertensive medication. He cautioned that continued monitoring for seizures and PRES was warranted. Dr. McDonald advised holding the baclofen for the time being and "discuss better dystonia management considering decreased renal clearance." He recommended close monitoring and treatment of Lucas' hypertension with nifedipine while the renal team advised further management. Lucas' feeds were held and his G-tube clamped pending further management plans by the CTU team.

PICU Consultation

At 8 PM, Jennifer Retallack, MD consulted for the PICU at the request of the care team. Dr. Retallack noted that Lucas had returned almost immediately from Sunny Hill after being transferred there to begin rehab. She reviewed his symptoms that were suggestive of a "relatively large baclofen dose (decreased [respiratory rate], tone, responsiveness, increased vomiting)." She observed that he now presented with irregular respiratory rate was 22 (normal), heart rate and intermittently increased blood pressure. Lucas' current respiratory rate was 22 (normal), heart rate 140 (tachycardic), and blood pressure 105/65 (normal). He was oxygenating well on room air. Dr. Retallack reviewed the CT results and agreed there were no signs of increased intracranial pressure on the imaging. Lucas exhibited intermittently increased muscle tone and cried out with any stimulation.

Dr. Retallack did not see any indication for admitting Lucas to the PICU at that time and recommended that his care team continued his clonidine and gabapentin medications, but not to give him any baclofen. "Do wonder if symptoms yesterday related to dose. Although CR normalizing, actual renal clearance might be abnormal with renal insult?" Dr. Retallack planned to discuss restarting baclofen with pharmacy at small dose. She did not think the baclofen had caused irreversible harm as the CT was consistent with evolution of Lucas' initial injury.

BCCH Readmission – Day 2 (cumulative Day 31)

⁶² *Dysautonomia* is an umbrella term for several different medical conditions that cause a malfunction of the Autonomic Nervous System. The ANS controls the "automatic" functions, such as heart rate, blood pressure, digestion, dilation and constriction of the pupils of the eye, kidney function, and temperature control. People living with various forms of dysautonomia have trouble regulating these systems, which can result in lightheadedness, fainting, unstable blood pressure, abnormal heart rates, malnutrition, and in severe cases, death. "What Is Dysautonomia?" *Dysautonomia International:* http://www.dysautonomiainternational.org/page.php?ID=34

On Thursday, November 22, 2018, Dr. Van Brummelen saw Lucas in the morning, noting that he had been stable overnight and tolerated Pedialyte. She observed that there appeared to be more respiratory secretions than "spit-up" of stomach contents. Lucas' morning labs showed a creatinine of 59 and urea 6.2. Lucas was afebrile, but his blood pressure were still elevated (135/103) and his heart rate variable. Lucas was given a baclofen dose that morning, with a plan to introduce the drug very slowly ("start at 2.5 mg tid, increase by 2.5 mg weekly and only to dose effective for him"). Dr. Van Brummelen commented that the team hoped to transfer Lucas back to Sunny Hill the following Monday.

Respiratory therapy came in to reposition and suction Lucas at 11 AM, noting a moderate amount of secretions with some blood from his nares. Physiotherapy worked with Lucas on range of motion and avoidance of worsening contractures.

Nephrology Consultation

At 4:47 PM on November 22, 2018, Kate Flood, MD consulted for nephrology and observed that Lucas' blood pressure continued to run hypertensive to 165/100, which was responsive to nifedipine. His irregular respirations improved overnight. His urinary output was increasing. Dr. Flood termed Lucas' musculature as "spastic quadriplegia with 3+ reflexes, 4+ in lower. Hands clenched bilaterally." Lucas' urinalysis exhibited proteinuria (5 grams) with some blood and glucose. Dr Flood listed differential diagnoses that included hypertensive encephalopathy given Lucas' decreased level of consciousness, baclofen overdose ("less likely to cause hypertension but CAN cause urinary retention which causes HTN"), autonomic instability secondary to neurologic injury, and increased intracranial pressure ("hypertension, sunsetting eyes, irregular respirations"). She opined that Lucas needed further investigation and workup prior to placing him on long-term antihypertensive medications, without knowing the underlying etiology; however, "... autonomic dysautonomia is most likely."

Dr. Flood outlined a list of lab tests she thought were essential (creatinine, urea, lytes, postvoid residual bladder scan with next BP > 130). She recommended an ophthalmology consultation as part of the "rule out" for increased intracranial pressure. Blood pressures were recommended to be taken manually only, and his clonidine increased to an enteral dose of 50 mcg twice daily. Dr. Flood advised that a beta blocker be considered as a first line antihypertensive. Finally, she requested a Palliative Care consultation for symptom management of secretions, dysautonomia, etc., from Canuck Place Children's Hospice.

BCCH Readmission – Day 3 (cumulative Day 32)

Dr. Flood returned to see Lucas on November 23, 2018 in the afternoon, noting that his blood pressures remained variable overnight from hypotensive to hypertensive (82/32 to 148/101). She thought this was related to his dysautonomia, combined with renal dysfunction. Dr. Flood observed that Lucas continued to have significant proteinuria, which she thought would best addressed with an ACE inhibitor when it came time to prescribe a long-term medication: "... may be best option as would provide nephron protection from proteinuria, though at this point wouldn't recommend at this time." Dr. Flood commented that baclofen had no recommended renal dose adjustment, "... yet it is renally excreted. I suggest a very SLOW dose increase and adjustment w/

extended half-life taken into consideration."

Sunny Hill Consultation

Dr. Laupher stopped in for Sunny Hill and expressed their hope that Lucas would return when stable. She stated she was very sorry about the medication error: "Parents voiced understanding of error of the need to start meds at lower dose than previously trialed. This so far has been successful. Parents voiced appreciation that I came by to discuss."

BCCH Readmission – Day 4-5 (cumulative Days 33-34)

On Saturday, November 24, 2018, Nathan became upset when Lucas' seemed overly sedated on the baclofen, requesting that the drug be stopped. Pediatric resident E. Van Brummelen, MD visited Lucas on Sunday and noticed that his blood sugars had been running very high ever since he was put on bolus feeds. It was quickly discovered that his formulate had formerly been diluted with water 50/50, so this change was implemented with improvement in his values. Lucas continued to have high blood pressures (126/93), along with variable tachycardia (HR 124-160). He did not require supplemental oxygen to keep his saturations in the 90th percentile.

Dr. Van Brummelen observed that Lucas' was in the process of adapting to his evolving brain injury sequelae, and he was beginning to settle into "... what seems to be his new baseline neurological status. Tone under control, glucose should be coming down now that feeds are diluted, and desats seem to be with increased tone – i.e., his new baseline." On exam, Lucas was awake and became upset when his arms were manipulated to check his muscle tone. An EEG was run that showed no seizures. Lucas' renal function labs showed an increase in his urea from 11.4 to 23.6, and his creatinine went from 60 to 65. Dr. Van Brummelen continued Lucas' baclofen with no increases at this point ("kidneys require slow increase"). Meanwhile, she recommended a Parkinson's drug (Trihexyphenidyl⁶³) as a backup as needed for increasing dysautonomia. Lucas received NPH insulin that afternoon and was to be administered Levemir again that night per endocrinology.

BCCH Readmission - Day 6-7 (cumulative Days 35-36)

On Monday, November 26, 2018, Dr. Van Brummelen evaluated Lucas in the early afternoon, observing that he had experienced desaturations of his blood oxygen during the night into the 80th percentile, which was associated with "bearing down, emesis." He was administered gabapentin to little effect, as his baclofen had been held over the weekend at his dad's request. Lucas continued to exhibit tachycardia (HR 104-163), but his blood pressure was in normal range at the time of Dr. Brummelen's assessment. She talked to Sunny Hill about other medication possibilities, and the recommendations were shared with Lucas' dad; the consensus opinion was to resume the baclofen that day. It appeared that the desaturations were accompanied by a "trigger," so the staff was advised to monitor for that.

⁶³ Artane (trihexyphenidyl) is an antispasmodic drug used to treat the stiffness, tremors, spasms, and poor muscle control of Parkinson's disease. Artane is also used to treat and prevent the same muscular conditions when they are caused by certain drugs. <u>https://www.rxlist.com/artane-side-effects-drug-center.htm</u>

Desaturations noted by nursing staff

During the night, the nursing staff observed desaturations of Lucas' blood oxygen down as low as the 70th percentile, with a gradual return to the 90th percentile over the next 15 seconds, requiring repositioning and stimulation to effect recovery.

On Tuesday, November 27, 2018, Dr. Flood came in for nephrology at 11 AM and observed that Lucas' blood pressures remained high, above the 95th percentile. She recommended clonidine for blood pressure control. She questioned whether seizures might be contributing to the spikes in Lucas' blood pressure.

CTU Senior

Dr. Van Brummelen came in after Dr. Flood and also questioned possible seizure activity, with desaturations of his oxygenation overnight. Nathan refused Lucas' midnight baclofen dose, as he requested it to be given earlier in the morning/evening so he could observe its effect. Lucas heart rate had decreased with a prior dose, hence the request. Dr. Brummelen thought Lucas' tone had decreased compared to the day before and decreased his gabapentin dose per Sunny Hill recommendations. She agreed to restart the baclofen on a schedule suitable to his dad. If he tolerated it well, he was scheduled for an increase in dose the following day. Dr. Van Brummelen requested a neurology consultation to assess Lucas for seizures.

Neurology Consultation

Anita Datta, MD consulted neurology for Lucas' new episodes of desaturations and apneic spells. She reviewed the events that led up to Lucas' return to BCCH and how he had done since being readmitted. She observed that the ER staff initially had concerns for Cushing's Triad ("secondary to increased ICP"), but imaging had not shown that to be the case. However, an admission to CTU was made for observation and further workup of the desaturations and vital signs changes. Lucas' dad reported he had seen no related eye movements or tonic limb movements with the apneic spells, which occurred when he was sleeping and resolved spontaneously.

Dr. Datta reviewed Lucas' most recent head CT from the 21st and, compared to the last one three weeks earlier, there was mildly decreased white matter hypoattenuation. However, there was new and moderately extensive periventricular white matter necrosis with cystic changes, as well as worsened ventricular enlargement. There were no ICP changes, and no intracranial hemorrhage.

Dr. Datta viewed the recent CT and clinical changes as suspicious for seizures, especially given his medical history, and hoped that EEG monitoring would help sort out whether these were seizures or not. She discussed restarting an antiepileptic drug (Keppra) but did not want to do that until and if the EEG showed evidence of seizure. Once stabilized, she also thought a sleep study would help.

On exam, Lucas was initially asleep but roused with touch. His eyes opened but did not fixate. He yawned and cried out but settled with his dad's touch. Lucas had his soft splints off in bed with his arms in fixed and flexed position, and his extremities exhibited increased tone. His

legs were flexed and he had 3 beats of clonus with upgoing plantars, and 4+ reflexes in all limbs. Dr. Datta identified a poorly defined optic discs with questionable hemorrhagic effect, but the vessels looked normal. She noted doll's eyes with nystagmus horizontally. His face was symmetrical without facial droop.

An EEG was in process that afternoon, and the preliminary report was abnormal with a slow and suppressed background in the left hemisphere, which was consistent with structural and function abnormality. Moderate encephalopathy was seen but no seizure activity was noted.

BCCH Readmission – Day 8 (cum #37) – overnight EEG reflects severe encephalopathy

On November 28, 2018, a continuous EEG tracing was completed that encompassed the prior 24 hours. The drowsy background showed poorly organized posterior dominant activity, which was not reactive to eye opening and closing. The background consisted of "unreactive low amplitude diffuse polymorphic delta activity with eye movement artifacts seen anteriorly. No epileptiform or electrical seizure activity was noted." The official EEG report stated:

This EEG, recorded in drowsiness, is severely abnormal. The background is dysrhythmic and suppressed. This EEG is suggestive of severe encephalopathy. This EEG has deteriorated as the suppression is now more bilaterally symmetric compared to the previous EEG, dated October 29, 2018.

Endocrinology changed Lucas from bolus feeds to continuous feeds via his G-tube to keep his blood sugars under better control, which required scheduled and prn insulin dosing.

BCCH Readmission – Day 9-10 (cumulative Days 38-39)

On Thursday, November 29, 2018, Dr. Van Brummelen evaluated Lucas for the CTU Violet team. Lucas remained afebrile, but his blood pressured continued to be elevated. His tone was about the same. His blood sugars fluctuated and endocrinology adjusted his insulin doses on continuous formula feeds. Lucas developed constipation, and so PEG⁶⁴ supplementation was started. The plan was to move Lucas back to Sunny Hill, but this would not be possible until his blood sugars were under control. P. Neuman, MD from Canuck Place Children's Hospice visited Lucas and his family on November 30, 2018. Dr. Neuman noted that overall Lucas was stable but having daytime irritability associated with significant tachycardia. This morning he was having difficulty with feed tolerance. He noted that PEG was started the day before. "Plan is for transfer back to Sunny Hill early next week. Dad very involved and supporting Lucas."

Dr. Van Brummelen came in and noted that Lucas had been having difficult with vomiting, which appeared to be associated with his constipation. His blood sugars were difficult to control and were slowly stabilizing as his emesis and stooling improved. Lucas had another bleeding episode from his mouth that morning, so Dr. Van Brummelen ordered coagulation studies with his next blood draw. He was still having trouble with constipation, so the doctor ordered PEG and

⁶⁴ Polyethylene glycol is an osmotic laxative. Polyethylene glycol works by retaining water in the stool, resulting in softer stools and more frequent bowel movements. MiraLAX is a form of PEG. https://www.miralax.com/

lactulose as needed. Dr. Van Brummelen planned to move Lucas back to Sunny Hill the following Monday once his blood sugars were stable.

BCCH Readmission – Day 11-17 (cumulative Days 40-46)

Over the weekend of December 1-2, 2018, Lucas' persistent hyperglycemia changed little on his current insulin regimen, so endocrinology continued to make adjustments. Although he remained afebrile, his heart rate continued to rise throughout the day, and Lucas appeared at baseline increased tone ("normal" for him). Endocrinology was waiting for the results of a test for autoimmune diabetes (GAD 65 antibodies⁶⁵). Lucas continued to have trouble with vomiting, usually in the morning. His exam was unchanged. His formula was Novasource Renal diluted 50/50 with Pediasure.

On Monday, December 3, 2018, the nursing staff noted that Lucas had repeated episodes of hypotension during the early morning hours. He continued to vomit and his doctors wondered about motility issues with the continuous feeds. His blood sugars were not in sufficient control to consider a move back to Sunny Hill. Endocrinology made changes in his feed rates and insulin dosing times in an attempt to remedy it. Over the next couple of days, Lucas' electrolytes were unstable (elevations in calcium, phosphate, magnesium) and his renal function labs were worsened (elevated urea and poor renal clearance). Nephrology resident Sophia Sweatman, MD was called in to consult about this and opined that his persistently elevated urea could be related to dehydration from all the vomiting. Lucas' was being slowly titrated up on his baclofen dose because the drug was renally excreted, and there were no standard renal adjustment recommendations available to follow. The renal dietician made adjustments to his feeds with a plan to switch Lucas to Suplena, and Zofran was added to his medication list to help with his vomiting.

On December 6, 2018, Dr. Brummelen evaluated Lucas for CTU Violet in the evening, finding his tone much improved over his morning exam. She observed that Lucas continued to have episodes of hypotension overnight (as low as 79/26) and began weaning his clonidine by eliminating the nighttime dose. Lucas appeared to be tolerating the slow incremental increases in baclofen. He was vomiting less with the use of Zofran.

On Friday, December 7, 2018, Lucas made the change to Suplena formula feeds, with no immediate difference in his persistently elevated blood sugars. Endocrinology continued his insulin as the previously prescribed doses. Dr. Sweatman observed that Lucas' urea level was improved on Suplena, which contained less protein than Novasource Renal. Lucas continued to be hypertensive when fussy (BP 157/113) but stabilized when he settled down. Dr. Van Brummelen continued to monitor his baclofen dosing.

BCCH Readmission - Day 18-21 (cumulative Days 47-50)

Over the weekend of December 8-9, 2018, Lucas vomiting more than usual and ran a lowgrade fever. The nursing staff administered Tylenol with good effect. He had been unable to wean

⁶⁵ GAD65 antibody is also the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes. <u>https://neurology.testcatalog.org/show/GD65S</u>

off clonidine and was kept on twice daily dosing for his fussy episodes with blood pressure spikes. His blood sugars were finally stabilizing on his new formula. He was no longer constipated but now tended towards lose stools, so adjustments were made to his lactulose dose and the PEG (MiraLAX) was discontinued. Lucas was especially irritable on Sunday night and had one hypotensive episode as low as 80/20, and the nursing staff was unable to take his pressure manually because of extreme stiffness of his arms. Nathan became upset that Lucas was awakened by repeated blood pressure attempts, and his feeds were paused until 4 AM while they determined that he was stabilizing his pressures.

On Monday, December 10, 2018, Dr. Van Brummelen observed that Lucas had a "rough weekend." He was often in pain/discomfort, but the clonidine decreased his blood pressure at the same time as helping him settle down—the attempt to wean him from the drug ended up worsening his sleep pattern. Dr. Van Brummelen changed Lucas' clonidine dose back to 12 mcg in the morning. She observed that "… vomiting seems to be Lucas' new baseline." She made arrangements to move Lucas to Sunny Hill in the next day or so. Endocrinology attending Ka Lo Carol Lam, MD agreed with that plan now that Lucas' blood glucose levels had stabilized within a target range of 4-10 mmol/L. Dr. Lam instructed the Sunny Hill team to work closely with the Endocrine team for any changes to Lucas' feeds and insulin dosing.

Discharged back to Sunny Hill

On Tuesday, December 11, 2018, Tammie Joanne Dewan, MD evaluated Lucas for discharge from BCCH and wrote his discharge summary, with an assessment and plan:

- 1. Dystonia. Continue with gabapentin and clonidine.
- 2. Diabetes management.
- 3. Vomiting. Improved but overall quite persistent. May be related to dystonia.
- 4. Nephrology/HTN. D/c nifedipine, monitor BP on clonidine. Repeat electrolytes in a week. Follow-up with general nephrology 3-4 months.
- 5. FEN Suplena.

<u>Sunny Hill Health Centre for Children – Readmit Week 1</u>

On Tuesday, December 11, 2018, Lucas was transferred by ambulance back to Sunny Hill Health Centre for Children. Esias Van Rensburg, MD formally admitted him a 1:45 PM and summarized his readmission status:

... Lucas has overall symptomatic complex of dystonia and dysautonomia secondary to the CNS acquired injury. In addition, he has hyperglycemia, anemia, and feeding difficulties with recurrent vomiting

Dr. Van Rensburg noted that Lucas was being readmitted to resume the rehabilitation activities that had been planned before his last admission was cut short by complications from the use of baclofen:

He is being admitted to Sunny Hill Health Centre for initiation of rehabilitation,

and ongoing supports in regard to tone management, insulin and feeding management, and eventual transition planning home.

From a functional perspective, Lucas will require support with mobility and equipment such as a wheelchair, a standing frame, and as he is recovering, consideration for a walker. In regard to high tone, he will require ankle-foot orthotics and resting splints for upper extremities.

Lucas will also require feeding via alternate feeding mode currently provided through gastric tube and will continue to require a specialized formula in light of the reduced renal function.

Lastly, Lucas will require respite options and additional block services as required, which will include physical therapy, occupational therapy, and aquatics, recreational therapy. As such, we will request that Lucas be considered for the At Home Program to support additional benefits in transition planning phase.

Sunny Hill – Physical Medicine & Rehab Consultation

On December 19, 2018 PM&R specialist Grace Tin-Yan Li, MD evaluated Lucas in consultation for tone management with respect to his brain injury. Dr. Li reviewed Lucas' past medical history, finding it notable for "prior suspicion of autism." In speaking with Lucas' parents, she understood that Lucas had been scheduled for an appointment at the Compass Centre for confirmation of his diagnosis. However, the appoint that had been set up for November 2018 was interrupted because of his hospitalization. Nathan stated that Lucas had otherwise been well prior to getting sick with STEC HUS. He had been walking and talking appropriately, although he had not yet been potty trained, per his dad.

Dr. Li observed that as a result of his E. coli O157:H7 infection, Lucas developed hemolytic uremic syndrome, decreased kidney function initially requiring dialysis, and diabetes relating to pancreas injury. Dr. Li reviewed Lucas' extensive medical records from both of his hospitalizations at BCCH, as well as at Sunny Hill. She saw that he had been trialed on wrist splints but could not tolerate them, as they rubbed into his face because his elbows were too flexed. Dr. Li documented her examination of Lucas:

He was somewhat irritable this morning, and so it was difficult to fully assess him. His father was present for this assessment. His father was able to fully straighten his fingers and extend his wrists on both sides. His elbows could be extended to 90 degrees maximally, although this was uncomfortable. His shoulders could be abducted to 90 degrees maximally. In terms of the legs, he did have knee extensor tone. His ankles were actually neutral and did not have significant clonus or tone here. We got him standing with his father supporting him by his armpits. He was able to bear weight through both legs, although he did require some head support for this. Otherwise, he was not able to follow commands. His father tells me he has had a few isolated words such as no mommy and why me. Dr. Li considered Lucas' current situation, involving almost two months in the hospital "... in relation to hemolytic uremic syndrome causing kidney injury, pancreas injury with diabetes, and diffuse ischemic injury to the brain. He has had significant tone to the upper more than lower extremities for the past at least 1 month." Given Lucas' difficulties with positioning, Dr. Li recommended that they proceed with botulinum toxin treatments to help relieve Lucas' severe muscle stiffness and contractures. She discussed what the treatment entailed with his dad. Nathan agreed to go ahead, and Dr. Li injected a total of 100 units of botulinum toxin. equally into both biceps in 2 spots. Lucas tolerated this well with no immediate complications. Dr. Li also addressed Lucas' baclofen administration, which had been difficult to manage because of his resolving kidney injury:

As it has been tricky to up-titrate his oral medications, this has been done cautiously. Given his resolving kidney injury, he has not tolerated medications well and he did have over-sedation with recent baclofen dose, and so up-titration is now slowed. I understand he has also had issues with benzodiazepines while in the hospital, and so they have been cautious to start on this. Another consideration could be for tizanidine. This injection will be done in conjunction with serial casting to try to straighten out the elbows.

BCCH Outpatient Neurology Consultation

On January 15, 2019, Anita Datta, MD evaluated Lucas in the pediatric neurology clinic, recalling him from his hospitalization at British Columbia Children's Hospital but remaking that much of his neurology care was managed by her colleagues. Dr. Datta noted that Lucas was currently a resident at Sunny Hill. She talked to Nathan about Lucas' progress, which had been minimal "... but heading in the right direction." Nathan's biggest concern was that Lucas' baclofen dose had been increased too quickly to his current dose of 2.5 mg per day. He described that Lucas had started having prolonged dystonia at night, predominantly involving his left hand and causing him discomfort all night. He also thought that Lucas was more sedated, and he was vomiting more than usual. He was not sure if some of these movements were seizure related. Nathan showed videos of some of the episodes to Dr. Datta, and she did not think they were. Nathan described that sometimes Lucas would stare straight ahead, or his eyes were deviated to one side, and sometimes he did lip smacking. Dr. Datta told Nathan that they could clarify this by doing some video EEG monitoring to either rule out or identify seizures, as this could affect his treatment. Dr. Datta noted that the gabapentin Lucas was taking was a seizure medicine, but it was quite weak and she would use something else for seizures. Dr. Datta summarized Lucas' condition based on his history and her exam:

Developmentally, he is quite limited. He will say 1 syllable, he smiles. Dad says only once he saw him stretch his arm backwards and was unsure if this was related to reflux or spontaneous. He sleeps well at nighttime. His respiratory rates are variable. Sometimes his heart rate will drop when he is sleeping, but it is known that he has autonomic dysfunction movement disorder.

He did have an MRI done in [November] 22, 2018. This showed wellcircumscribed focus of T2 hyperintensity in the posterior medial right thalamus, bilateral heterogeneous, lentiform nucleus hyperintensity, confluent with external capsule hyperintensity, abnormal signal in the tails of the caudate nuclei and the dorsal tegmental track, scattered innumerable foci of diffusion restriction within the white matter regions of signal abnormality, with more confluent restriction seen adjacent to the frontal horns and the genu of the corpus callosum. Focal diffusion restriction was also noted in the posterior medial right thalamus. His findings were consistent with presumed small-vessel ischemia or thrombotic microangiopathy without hemorrhage. There is incidental cyst-like focal abnormality in the posterior right superior frontal gyrus.

Dr. Datta recommended a repeat MRI in about 6 months, as well as a referral to her colleague, Dr. Gabriella Horvath, "... who is very good in managing movement disorders to see if she has any other opinions regarding managing these movements, as this seems to be one of the biggest concerns for the family." She planned to follow-up after Lucas had video EEG monitoring.

Sunny Hill Health Centre for Children

On January 23, 2019, Carey Matsuba, MD evaluated Lucas as part of the visual impairment program. Dr. Matsuba identified featured consistent with cortical visual impairment but was unable to rule out a component of injury related to his optic radiations. Lucas continued PT, OT, SLP, and Therapeutic Recreation rehabilitation. On February 6, 2019, an assessment of Lucas' level of consciousness was completed and a meeting of the various disciplines was held. The Rappaport Coma/Near Coma Scale was used to assess Lucas' level of consciousness. Of the eleven parameters on the scale ten were tested; the response to command was not included in the assessment as Lucas did not have the physical capabilities to respond to the command request.

Rappaport Coma/Near Coma Scale⁶⁶

On the Rappaport Coma/Near Coma Scale, Lucas' scaled score was 2.0 which placed him in the "Near Coma" level. Doug Herasymuik, OT explained the testing and results, describing that Lucas was consistently responsive to stimulation when presented to two sensory modalities or was inconsistently or partially responsive to simple commands. Prior to beginning the LOC [level of consciousness] assessment, a one-minute period of observation was completed. The following responses/behaviors were noted:

Lucas responded to the bell ringing; initially with a startle on the first bell ringing and he then responded by stilling his breathing and opening his eyes. With the flashlight; he avoided the light once by closing his eyes. In asking Lucas to look at me and track me; he picked me up left of mid-line and tracked me moving to his left/my right. He did not respond to the visual threat. Lucas was also tested visually

⁶⁶ Rappaport et al. are authors of two scales: Coma/Near-Coma Scale (CNC, 1992) and Disability Rating Scale (DRS, 1999). The Coma/Near Coma (CNC) scale was developed to measure small clinical changes in patients with severe brain injuries who function at very low levels characteristic of near-vegetative and vegetative states. The CNC essentially expands the levels of the DRS that incorporate the vegetative and extreme vegetative categories. The CNC has five levels, based on 11 items, that can be scored to indicate the severity of sensory, perceptual, and primitive response deficits. Opara, J A et al. "Clinimetric measurement in traumatic brain injuries." *Journal of medicine and life* vol. 7,2 (2014): 124-7.

with a pompom. He was able to pick the pompom up and tracked it from his peripheral vision to his left and followed it to mid-line. In moving through the assessment; Lucas had a partial response to the ammonia and to the shoulder tap. He had a clear quick response to the nasal swab on both nares - grimace. With the finger pinch Lucas had a delayed movement of his left thumb once; there was no response to the ear pull. Lucas was noted to make two vocalizations during the assessment.

No response to Botox

On February 8, 2019, neurologist spoke to Dr. O'Connor at Sunny Hill about Lucas' response to the Botox injections from the outpatient visit. There had been no effect at all from the injections, and Lucas had been unable to tolerate the usual doses of oral medications.

Acute Rehabilitation Program Interim Report

On February 21, 2019, Dr. Nancy Lanphear, Developmental Pediatrician at Sunny Hill, reported on Lucas' progress in their program. She outlined that Lucas had been receiving "Nursing and Medical Care, Physiotherapy, Occupational Therapy, Speech Therapy, Music Therapy and Social Work Services, while an inpatient at Sunny Hill Health Centre." Dr. Lanphear was impressed by the strong network of support from his parents, grandparents, and their social network. Dr. Lanphear outlined the areas the Sunny Hill teamwork working on with Lucas, including "Activity Tolerance and Self-Regulation," "Cognition," "Communication," "Eating and Drinking Skills," "Physiotherapy," and "Self-Care."

Notably, Lucas was observed to tolerate sessions up to 30 minutes in length. He was severely cognitively impaired, scoring 1.8 on the Rappaport Coma/Near Coma Scale. His communication was limited to vocalizations that were more in response to an activity or stimuli than to persons. Lucas remained NPO, receiving all of his nutrition and hydration via G-tube, making him unsafe for any other enteric (oral) intake, but he would suck on a flavored tongue depressor when brought to his lips. Although the range of motion of Lucas' jaw had been improving, Lucas was not yet opening his mouth (other than to yawn or to cry) in response to a tongue depressor. For Physiotherapy, Lucas was transported by wheelchair or carried by his dad, and PT was focusing on anti-gravity strength and control of Lucas' head, neck and trunk, through playing in different positions. He was building up tolerance for alternative positioning equipment. Lucas was not able to participate in self-care but tolerated oral and other hygiene. Dr. Lanphear made a referral for Lucas to participate in the Community Brain Injury Program for Children and Youth in BC.

BCCH – Pediatric Nephrology Clinic Outpatient

On February 22, 2019, Lucas was seen for his first post-discharge follow-up at the pediatric nephrology clinic, seeing resident Elizabeth Hankinson, MD along with attending Rob Humphreys, MD. Nathan brought Lucas to the visit. The doctors reviewed the details of Lucas' prolonged hospitalizations and progress at Sunny Hill, noting his history of severe hemolytic uremic syndrome requiring PICU admission, intubation, peritoneal dialysis, and two doses of

eculizumab from October 2018 to November 2018. They noted that because of the significant neurologic involvement with his HUS, Lucas was currently still admitted at Sunny Hill for ongoing rehabilitation. Dr. Humphreys summarized Lucas' current condition as reported by Nathan:

In talking to Nathan, it sounds like Lucas has generally stabilized during his past two months at Sunny Hill. From a neurologic point of view, he still struggles with significant dystonia, and has yet to develop purposeful movements. He is able to fix on objects, and occasionally vocalize, but not with meaningful words at this point. Most recent medication change was the addition of trihexyphenidyl for Lucas's movement disorder and dystonia, approximately 2 weeks ago.

From a renal point of view, Dr. Humphreys observed that there had not been any ongoing concerns. Lucas had no further edema. His PD catheter removal site was well-healed, and his blood work continued to show improvement with a continual downtrending (normalization) of his serum creatinine. His ureas had also normalized since his formula was changed to one with a lower protein content. Dr. Humphreys noted that Lucas was fed via his G-tube, now at four times a day. He did not require any electrolyte supplementation, diuretics, or fluid restriction. According to his Sunny Hill records, he had been gaining weight on this formula.



Nathan and Lucas, G-tube in situ

Dr. Humphreys noted that Lucas voided regularly into his diaper, with no concerns for hematuria or dysuria. He had no symptoms of bruising, bleeding, or pallor. He had rescue nifedipine on his medications list at for hypertension, but his dad did not think any had been given, as his blood pressures had normalized. "However, some of these are not manual readings, and some of them have been measured on his leg." Lucas stooled regularly, with PEG (MiraLAX) given as needed. There were no recent issues with constipation, and he had not had any seizures.

Dr. Humphreys examined Lucas, during which his eyes opened spontaneously, and he did not appear in any acute distress. He did have episodes of brief dystonia. He was hypertonic to all four extremities, with the upper extremities more so than lower. Lucas' pupils were equal and
reactive, and he could be seen to intermittently fix on objects close to his face. He was drooling, with no nasal congestion, and his respirations were easy. His cardiopulmonary exam was normal, as was his abdomen, and he had no peripheral edema. Notably, his abdomen was soft and nondistended and his G-tube site was clean.

Lucas' urine that day continued to exhibit significant proteinuria (2+ on dipstick), as well as blood. On laboratory urinalysis, there was 0.75 g/L of protein with a protein creatinine ratio of 93, and trace blood with 3-10 red blood cells per high power field. "This is a vast improvement from his previous urinalyses on system, which showed a protein to creatinine ratio of 981 on November 23, 2018, and persistent proteinuria of 1.5 g/L on November 28, 2018." Dr. Humphreys reviewed blood work from February 6, 2019, which showed a normal CBC with white blood cell count of 12.8, hemoglobin 131, and platelets 486. He had normal electrolytes with sodium 137, potassium 3.6, chloride 103, bicarb 25, magnesium 1.02, urea 4.1, and creatinine 48. His creatinine demonstrated a continuous downward trend from the 60s at the beginning of December, and his urea was down significantly from 15.5 on December 7, 2018, to 5.9 on December 10, 2018, coinciding with switching his formula to Suplena. It had since been in the normal range.

Dr. Humphreys discussed that Lucas' blood pressure recordings from Sunny Hill continued to be elevated for his height and age. He also discussed Lucas' persistent proteinuria and hematuria, with a quantified amount on protein to creatinine ratio continuing to fall. Dr. Humphreys discussed the use of ACE inhibitor therapy, as this would treat both Lucas' hypertension and his proteinuria, However, given Lucas's normal systolic blood pressure reading in clinic, he decided to hold off prescribing any medication that day. He advised continued blood pressure checks, preferably manually on his arm. If Lucas developed persistent hypertension with systolics above 110, Dr. Humphreys thought they should start the ACE inhibitor.

In terms of follow up and monitoring from a renal recovery point of view, Dr. Humphreys wanted to get a nuclear medicine renal scan/GFR⁶⁷ in December 2019, approximately 1 year post Lucas coming off peritoneal dialysis. He also wanted to do a renal ultrasound and recheck his labs at that time. He stated that Lucas did not need to see him in follow up before then, unless any other specific concerns were brought up from his other care team members. Finally, Dr. Humphreys agreed with stopping his EPO, as his hemoglobin was now within target range.

Sunny Hill Health Centre for Children – discharged

On March 1, 2019, Ram Mishaal, MD evaluated Lucas for discharge from Sunny Hill. His discharge diagnoses included:

- 1. Hemolytic uremic syndrome with acquired ischemic brain injury.
- 2. Previous history of concussion with autism. He has been referred to BC Autism Assessment Network prior to this episode.
- 3. Acute renal failure, requiring peritoneal dialysis, improving. Currently still

⁶⁷ Nuclear GFR Study estimates the glomerular filtration rate of the kidneys which determines how well the kidneys are filtering the blood. The test requires an injection of a small amount of radioactive substance ('tracer') into a vein. The tracer travels to the kidneys by the blood stream. <u>https://www.healthline.com/health/glomerular-filtration-rate</u>

demonstrates proteinuria.

- 4. Borderline hypertension, improved.
- 5. Hyperglycemia, treated with insulin, probably secondary to steroid treatment.
- 6. Cortical visual impairment.
- 7. Anemia, resolved.
- 8. Dysautonomia, resolved.
- 9. Dystonia.
- 10. G-tube feeding

Dr. Mishaal discharged Lucas that day from inpatient services, but he would continue to receive therapy as an outpatient at Sunny Hill Acute Rehabilitation Unit until community therapists could start working with him. In addition, he would continue to be seen by the neuromotor team at Sunny Hill, as well as by Endocrinology and Nephrology at BCCH.

Sunny Hill Hospital Outpatient Clinic

On March 13, 2019, Grace Tin-Yan Li, MD evaluated Lucas in the outpatient clinic, who was accompanied by his dad and the physiotherapist, for consideration of a repeat botulinum toxin injection. Lucas was sick that day with an ear infection, so the injection could not be done that day. Dr. Li described Lucas' focused examination:

We looked at his standing. His tone is quite variable at times while supine/sidelying. He is in the plantar flexed position and at times while sitting, he can be in the dorsiflexed position. While standing with the exercise ball in front of him, he can get to fully neutral, slightly worse on the right side. He attends to hyperextend on the right side. Despite this, he can get perhaps about 10 degrees beyond neutral on the left easily and just to neutral on the right. He seemed to weight bear more so out through the left leg while he was standing today. He has some head control, although this is limited. At times, he has some minimal ability to the extend or rotate his head. At most other times, his head rests on the ball.



Lucas in wheelchair at home

Dr. Li thought that the injection might help Lucas and scheduled him to return for

botulinum toxin injections to his biceps. She also wanted his dad to consider musculocutaneous nerve root blocks, which could be done in June 2019 at the spasticity clinic. With respect to his AFO bracing, Dr. Li suggested that Lucas wear resting AFOs only. "It seems that while standing he can maintain his ankle position well, however, can be more variable when he is asleep." Lucas returned to the clinic for the Botox injections on March 22, 2019, and Dr. O'Connor agreed to see him in June to trial the bilateral musculocutaneous nerve block. Lucas' family received accessibility recommendations from Dr. Van Rensburg and was provided with equipment, with others to be ordered.

BCCH – Pediatric Endocrinology Clinic Outpatient

Daniel Metzger, MD also saw Lucas on March 13, 2019 at the diabetes clinic. At this clinic visit, no laboratory investigations were performed. After a review of Lucas' recent blood sugar control, Dr. Metzger decided to stop Lucas' insulin completely. "It appears that his beta cells have recovered from whatever insult they were subjected to during his HUS episode, which did also involve high-dose glucocorticoids." Lucas had tested negative for GAD 65 antibodies. Dr. Metzger asked the family to recheck his blood sugars for another week or so and then only when he was ill. They were contact the clinic if his blood sugars were consistently above 8, at which point we might need to re-institute insulin, but this seemed unlikely to occur.

BCCH – Outpatient Biochemical Diseases

On April 5, 2019, Gabriella Horvath, MD evaluated Lucas at the request of the BCCH Pediatric Neurology Clinic, reporting her assessment to Dr. Datta in a letter of the same date. Dr. Horvath took a very thorough medical history, including of Karla's pregnancy and birth with Lucas. Dr. Horvath noted that it had been unremarkable, except that they found a small cyst in the left brain on fetal ultrasound, "... but that was considered to be nonspecific and no follow-up was needed." Lucas had demonstrated the normal developmental stages as documented by his pediatrician at regular intervals. Notably, Lucas' language development was slow to start, but by age 2 to $2\frac{1}{2}$ just before he got sick, he had about 200 words and was putting 5 words together in sentences:

He was a very smart boy according to his dad. Father said that he was reading to him at grade 7 level material and he was listening intently. The reason that they took him to have autism assessment was because he had some repetitive mannerism; he was stacking cans and he was lining up cars, but he was very engaged in daycare, he was very emotional with parents, he had no problems with touch or other sensory input, and he was given a possible diagnosis of autistic tendencies.

Dr. Horvath reviewed the course of the devastating illness that befell Lucas after the family had to cut short their family vacation to California. She reviewed all the records leading up to his severe brain injury:

His MRI is quite affected. He does have cortical white matter and basal ganglia involvement and he ended up in very severe dystonic posturing with autonomic

dysfunction. He had a prolonged rehabilitation at Sunny Hill and he slowly is improving. He is continuing to receive Botox treatment in the upper arms, which is helping somewhat, but unfortunately, he does have almost constant dystonic posturing whenever he is excited, afraid, startled, or uncomfortable, he is screaming and he is in a severe arching, opisthotonic posturing. He is shaking, he has spontaneous clonus bilaterally, and he is holding his arms in flexion close to his body with his palms flexed and his legs and feet extended, and his toes curled under his feet. He is getting relief only when he is sleeping. He is on medication and quite intense physiotherapy. Father is also looking into some massage therapy or music therapy.

Dr. Horvath reviewed Lucas' current medications list and did her own exam.

... He was sleeping initially, but [Nathan] placed him prone and he was drooling excessively. He woke up in a puddle of drool by the time I finished talking to Dad and wanted to examine him. As soon as he woke up, he was immediately in the severe dystonic posture as I described before. He was crying inconsolably, but Father knew some position tricks when he could break the tone; for example, the left side was improved when he placed him on his right side and we could bend his knees and his hips and his ankles, and when he turned him on the left side then we could move the right lower extremity. Then he settled and even his upper extremities were relaxed, and I did not notice or find any contractures, but this was short lived. He became soon again very tense and his arms were flexed close to his body. When [Nathan] put him in his chair he started screaming immediately and he looked very uncomfortable. He had whole body tremors, clonus bilaterally, and it was really hard to watch how he was suffering.

Dr. Horvath had a long discussion with Nathan about Lucas' prognosis and possible management of such severe dystonia. "He is still hoping that Lucas will recover, and, of course, there will be maybe some degree of recovery, but I would be very cautious in suggesting that he will walk or speak again, which is Father's expectation right now." Dr. Horvath made some adjustments to Lucas' medications, increasing his clonidine to more frequent dosing, and increasing his trihexyphenidyl gradually. They would know when to stop increasing it if Lucas had side effects like urinary retention or dry mouth, which she did not think would be a problem. She planned to call him in about 4 to 6 weeks to see if Lucas had any improvement his dystonia.

Dr. Horvath also requested the addition of a CK on Lucas' next blood work—if they continued to be elevated, she would add another drug (dantrolene – a muscle relaxer), "especially because he does have the history of renal involvement." Nathan also told Dr. Horvath about eye movements that she thought might be suggestive of oculogyric crises,⁶⁸ "… and together with the basal ganglia destruction, I think that if nothing works, we could give him a trial of levodopa

⁶⁸ Oculogyric crisis (OGC) is the name of a dystonic reaction to certain drugs or medical conditions characterized by a prolonged involuntary upward deviation of the eyes. The term "oculogyric" refers to the bilateral elevation of the visual gaze, but several other responses are associated with the crisis. Solberg, Marianne, and Jeanette Koht. "Oculogyric Crises." *Tremor and other hyperkinetic movements (New York, N.Y.)* vol. 7 491. 24 Jul. 2017, doi:10.7916/D85X2N2D

carbidopa.⁶⁹ Dopamine being produced in the basal ganglia this may be beneficial to him." Dr. Horvath also talked about other possible treatment that was being used in Calgary for children with cerebral palsy, "transcranial magnetic stimulation⁷⁰" and promised to talk to Dr. Datta about this. "Maybe we can ask the Calgary neurology team if they would consider treatment for Lucas."

Dr. Horvath went on:

We also talked about deep brain stimulation, but, of course, Lucas is still too young to have deep brain stimulation in Canada because the device by Medtronic is only approved for patients 7 years and older. Definitely there are centers where deep brain stimulation is done for children who are much younger; for example, in London, United Kingdom, or Montpellier, France, and there might be some research studies also in the United States who would take him, but I think that we should still try some other avenues. The father is very much aware of deep brain stimulation risks, especially the infection, but I think that he might have had some unrealistic expectations from the outcome. I told him that if it would help it would only help with the tone and it would not make him be verbal or if he has severe cognitive deficiency that it would not help with that. We can anytime talk more about this, but I do not think that he is ready to discuss this yet.

While Dr. Horvath was talking with Nathan, she noticed that Lucas exhibited lip-smacking episodes a couple of times, which lasted for about 30 seconds. During this time, he also displayed disconjugate eye movements. "Although his eye movements are not good even when he is not having the lip-smacking, I think that this was unusually abnormal and I will mention this to Dr. Datta, as she will be following up with the family and I think that she will request further EEG assessment." Dr. Horvath concluded the visit with a plan to talk with Nathan and the family in 4-6 weeks for further management plans.

<u> British Columbia Children's Hospital – ER visit</u>

On April 19, 2019, Lucas was brought to the ER at BCCH, where Dr. Judge evaluated him for vomiting during feeding. He was brought to the hospital by ambulance, and the paramedics reported that Lucas was breathing spontaneously by the time of their arrival. Evidently Lucas had already been in the ER the day before for a facial rash. On exam in the ER, Dr. Judge noted that Lucas was working harder than normal to breathe, and he had foamy saliva around his mouth. He had a raised rash on his left cheek and forearm. Pulmonary specialist Regan L. Ebbeson, MD was summoned to the ER to evaluate Lucas for difficulty breathing. He documented the episode as described by Nathan:

⁶⁹ Carbidopa and levodopa combination are used to treat Parkinson's disease, sometimes called shaking palsy or paralysis agitans. <u>https://www.mayoclinic.org/drugs-supplements/carbidopa-and-levodopa-oral-</u>route/description/drg-20095211

⁷⁰ Transcranial magnetic stimulation (TMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression. TMS is typically used when other depression treatments haven't been effective. This treatment for depression involves delivering repetitive magnetic pulses, so it's called repetitive TMS or rTMS. <u>https://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/about/pac-20384625</u>

Lucas presented to emergency department by ambulance after an acute event this morning at home. Lucas had a single episode of vomiting during his feed this morning. This was followed by what Dad interpreted as a dystonic reaction which resulted in significant neck extension and behavior concerning for possible choking. He was slightly blue around the lips and in the face for approximately 5 seconds, after which Dad picked him up, provided a few abdominal thrusts followed by a couple of chest compressions. Lucas began crying and turned more red in color. They called EMS during the event and when they arrived, his father, Nathan, commented that he felt that he was returning to his normal baseline. There were no abnormal movements during this event. Afterwards he was crying and somewhat irritated and had some dystonic movements, but then began settling. They felt the paramedic visit and ambulance ride were quite disruptive to him and further triggered some of his dystonia.

Lucas has otherwise been well without any infectious concerns. He was in the emergency department yesterday on April 18, 2019, for assessment of a cheek rash and rash on his left forearm, which progressed over the previous 3-4 days. They were prescribed Betaderm as well as hydrocortisone, which they started yesterday. He has otherwise been afebrile and tolerating his feeds. He does have episodes of emesis 1-2 times per week, but the uniqueness of today's visit was the significant episode of choking which followed.

Lucas remained in the ER for 8 hours under observation, where Dr. Jordan determined that Lucas had suffered an aspiration or chocking episode. There were initial concerns for low blood oxygen levels, but he was soon doing well on room air without a repeat episode. He had no further episodes and tolerated his feeds in the ER. Dr. Jordan discussed admitting Lucas to the hospital, but Nathan and Karla were comfortable taking him home because the hospital environment was very stressful for Lucas and a significant trigger for his dystonia. Given Lucas' improvement throughout the day, Dr. Jordan agreed to let him go home with his parents.

BCCH – Pediatric Outpatient Neurology

On April 25, 2019, Lucas was again seen in the pediatric neurology clinic by Dr. Datta to evaluate him for possible seizure like episodes, at the request of Dr. Horvath. Since Dr. Datta last saw Lucas in January, Nathan reported that he had been progressing well from a neurological perspective. Nathan did not express any concerns for seizure activity. "He has noticed very occasional episodes of lip-smacking, but these are never in coordination with any non-responsiveness, eye or head deviation."

Nathan indicated that most of Lucas' issues appeared to be secondary to his dystonia. Overall, he was happy that Lucas' dystonia was improved from what it had been, and particularly since left Sunny Hill. In coordination with Dr. Horvath, Lucas was receiving trihexyphenidyl to 0.8 mg 3 times a day which he felt had brought Lucas' dystonia into much better control. Lucas still had still episodes of "acute dystonic crisis" following excitement or changes in position.



Lucas' needs fully met at home by mom and dad

Nathan discussed Lucas' recent visit to the ER for an episode of emesis with choking and difficulty breathing as well as dystonia. He explained that Lucas was assessed in the emergency department and transferred back to home. Nathan stated that there had been no further choking episodes since then.

Dr. Datta noted that Lucas had not had a recent EEG or an MRI. The most recent MRI [*sic*] was done in November 2018, and she reviewed those results.



Nathan expressed to Dr. Datta some significant concerns he had about his at-home support as well as his coping as a caregiver:

He is worried because since his discharge home at the beginning of May 2019 from Sunny Hill he has been Lucas' primary caregiver and as of right now has no respite care. He has been linked in with the early childhood intervention team who have visited Lucas at home 3 times since he has been discharged to home, but he has not been assessed by speech language pathology or OT. The dad was asking about services through the At-Home Program. During our visit Dad became quite upset relating his perception of his interactions with the healthcare system as well as the demands of caring for Lucas and how that is affecting him.



Lucas able to stand only with total support



Grandma holding Lucas with mom looking on...

Dr. Datta reviewed Lucas' current condition:

Developmentally Lucas has not made significant progress since he was last seen in our clinic. He is not able to sit and control his neck without support. Dad says that he sometimes moves his arm or his left leg, but he is not sure if it is purposeful movement. Dad feels that Lucas will track him with his eyes. From a language perspective Lucas makes vocalizations and Dad feels that he vocalizes in response to questions Dad asks him but he [utters] no identifiable words. Lucas did have an auditory response test done on April 2, 2019; however, the report has been shown as technically unsatisfactory due to too much conflicting auditory data and that a repeat test with sedation was recommended. This has been passed along to Lucas' father.

Dr. Datta examined Lucas, noting that he had episodes of acute dystonia at rest, lasting "normally" 5-10 seconds when he became quite upset, but then he would relax between episodes. He became upset with physical exam. After examining Lucas and talking with Nathan, Dr. Datta thought it was unlikely that Lucas was having any significant seizure activity. "Because of this we are not planning to pursue an EEG for him right now and he is no longer on the epilepsy monitoring unit list." Dr. Datta answered Nathan's questions about transcranial magnetic stimulation therapy, and she promised to look into this therapy for Lucas. She was pleased that Nathan felt that Lucas' dystonia was improved with changes in his medication. He indicated a plant to follow-up with Dr. Horvath. Finally, Dr. Datta promised to look into programs for Nathan where he could be referred for help with at-home support regarding his concerns about caring for Lucas. Dr. Datta provided a letter to outlining Lucas' care needs for Nathan's use:

TO WHOM IT MAY CONCERN:

This letter is regarding Lucas Parker. I am Lucas's neurologist. As you know, Lucas is a 3-year-old male with a history of hemolytic uremic syndrome in October of 2018. His condition was severe and there were numerous complications in hospital, including renal failure and hypertension. He also had a serious brain injury. At the present time, he has cortical visual impairment, severe developmental delay, a movement disorder consisting of dystonic movements throughout the day. He did have a seizure disorder but this has resolved. He is currently tube-fed. He is very different from what his baseline was prior to the onset of the hemolytic uremic syndrome.

I strongly feel that Lucas requires additional supports in the community. At the present time, he is requiring full-time one-on-one care regarding most of the daily needs, including feeding, dressing, settling, sleeping, etc. I feel that with optimized care there could be some improvements in his development. He requires intensive speech language therapy. He will need physiotherapy and occupational therapy; I feel the family would benefit from respite as they are having to do full-time one-on-one care Please do not hesitate to call me if there are any further questions or concerns. I would be happy to provide further information. Sincerely, *Anita Datta*, *MD*

BCCH – Outpatient Biochemical Diseases

On May 17, 2019, Dr. Horvath had a phone meeting with Nathan and documented the call in a letter to Dr. Datta of the same date:

I had the opportunity to follow up with Lucas' father on May 21, 2019. This phone follow-up was arranged to see how he is doing after we made some changes in his dystonia medication in April 2019, when he came to clinic. We increased his trihexyphenidyl to 1 mg tid and also added a 3rd dose of clonidine during the day, and Lucas' dad is reporting that he is doing much better since these meds were

adjusted. His tone is improved. He probably has a few episodes when his tone is increased lasting for about an hour and half, maybe every day, but they did not have to give him prn clonidine, which is good.

He is coming off the renal formula and will start the Compleat formula. He is going to start alcohol and Botox injections in his arm by Dr. Grace Li in Sunny Hill. They saw Dr. Matsuba last week, and his vision has improved a little bit. He thought that his visual impairment is more due to cortical damage rather than local problem with optic nerve.

The father is trying to get services and therapy introduced in the home. He did have quite a few questions about the future and various options, and suggestions that we discussed last time in clinic, but right now I think that most important is that he is continuing his current therapy and physical therapy and rehabilitation, and see how much he can recover in function, and then if he is getting worse, then maybe we can talk about other options for treatment. At this time I do not think that there is any role in introducing other medications.

There is still some room to increase his trihexyphenidyl if the tone increases, especially that he does not display any side effects from it. He is followed closely by the tone management clinic at Sunny Hill, so I did not make any plans to actively follow Lucas in clinic, but I told Dad that if he has any questions in the future or would like to discuss other options for treatment, including surgical intervention, then he can just call our office, and then we will book him for a follow-up appointment.

Outpatient Spasticity Clinic

On June 10, 2019, Lucas was seen by Russell O'Connor, MD at the BCCH Outpatient Spasticity Clinic, referred by Dr. Grace Li for his significant spasticity and dystonia. Dr. O'Connor noted that Lucas had experienced some troubles with sedation and respiratory suppression with oral sedatives used around the time of his botulinum toxin injection, so he decided not to use any sedation with Lucas at all.

Before Dr. O'Connor implemented any injections, he discussed the possibilities and options with Nathan. The main issue was to see if they could do a semi-permanent block over Lucas' musculocutaneous nerve to try and decrease his elbow flexor tone. Dr. O'Connor noted that when Lucas was sitting or lying, his arm was tucked up underneath him, which was "... obviously going to lead to an elbow flexed position. He seemed to tolerate range of motion relatively well while here in clinic." Dr. O'Connor proceeded with treatment:

Excellent muscle stimulation was obtained with 1 Hz stimulation and 1 milliamp stimulation intensity. A total of 2.5 mL of 1% lidocaine was injected around the nerve in a donut technique. He tolerated this really quite well. The arm almost immediately decreased to 1+ and we could get to approximately 130 degrees still at maximum extension of the elbow, but clearly could not get past that 130 mark.

Based on this, we decided to proceed on with a left sided phenol injection to the musculocutaneous nerve. The left musculocutaneous nerve was a little bit more difficult to see and find, but with stimulation we were able to identify this with ultrasound guidance. A total of 1.5 mL of phenol was injected around the left musculocutaneous nerve. This was clearly much more uncomfortable for him than the right side was. His range did improve from 110 degrees, final range to about 130 here at clinic. They are going to continue to splint his wrist in an extended position and stretch him. If they get substantial improvement with phenol, we could repeat the right side phenol injection next clinic to the right musculocutaneous nerve. This will depend on results with this round of injections to see whether family and dad want to proceed on or not.

Lucas' was scheduled for follow-up through Dr. Grace Li, and he asked her to let him know if she wanted him to proceed with any further injections

Sunny Hill Hospital Outpatient Clinic

On July 5, 2019, Lucas returned to see Dr. Grace Li in the Sunny Hill outpatient clinic, in follow-up of his visit with Dr. O'Connor for a lidocaine block of his right musculocutaneous nerve and phenol block for the left muscular cutaneous nerve. Dr. Li noted that at the time they were able to improve the R2 range from 120 degrees to 130 degrees. In the interim, Nathan reported that they had not noticed much improvement, and Lucas' positioning continued to be a challenge. However, Lucas now was getting PT twice weekly, speech therapy twice weekly, and OT once weekly. They were also getting RMT, lymphatic drainage, and kinesiologist support. Dr. Li noted that Dr. Horvath had adjusted Lucas' medications and he was now on:

- 1. Baclofen 15 mg tid.
- 2. Clonidine increased dose to tid. He is now on 1.25 mL in the morning, 1 mm at mid-day, and 1.8 mL at night.
- 3. Trihexyphenidyl 2.4 mL tid. (0.4 mg/mL)
- 4. Gabapentin 100 mg tid.
- 5. Omeprazole 15 mg twice daily.

Overall, Nathan and Karla felt that Lucas was improving. He was less fussy unless he was hungry or wanted to be picked up. They felt that he was doing a lot more. He could now tolerate being in the wheelchair for 55 minutes. They felt that he had some voluntary movements such as nodding of the head, moving the tongue, and purposeful leg movements. He could grasp with his hands better on the right hand. Nathan assisted Dr. Li with Lucas' examination that day, and she observed that he had increased tone throughout in the lower extremities, increased tone through the knee extensors, and sustained ankle clonus, more significant on the left. He seemed to have some withdrawal response to stimulation of his toes. After much discussion, Nathan agreed for Dr. Li to proceed with a brachioradialis injection,

Dr. Li made the following changes to Lucas' care plan:

1. Medications: gradual gabapentin taper.

- 2. Adjunctive medications: discussed this with Dr. Horvath in the past and will follow up with Dr. Datta with respect to this. Considering trial of levodopa.
- 3. Focal injection: Unfortunately, even the focal lidocaine block did not provide us with significant relief in the elbow flexors. I suspect quite a degree of contracture underlying. Brachioradialis injection trial today. No further biceps injections. Referral to Dr. Pike to see if he may consider tendon release for the elbow flexors to help with positioning.
- 4. Therapies: receiving a variety of therapies through Jordan's Principle. No clear objective improvement in LOC. Re-evaluated at the 6-12 month interval

BCCH – Pediatric Outpatient Neurology

On August 13, 2019, Lucas returned to see Dr. Datta at the pediatric outpatient neurology clinic. She noted that since he was last seen in April 2019, Lucas had been connected with the Blind Beginnings program and cortical visual impairment. His visual acuity was measured by ophthalmology at 20/540. They noted that Lucas could fix on items but did not track reliably.

Nathan told Dr. Datta about Lucas' visits with Dr. Horvath and Dr. Li, as well as with Dr. O'Connor. The Botox injections had proved ineffective. Nathan stated that a decrease in Lucas' gabapentin dose seemed to make matters worse. He and Karla were interested in brachioradialis injections as well as a referral to Orthopedics for possible elbow flexor tendon release. Nathan stated that they had not yet heard from Orthopedics.

Dr. Datta observed that, overall, Lucas was making some small gains with his therapies. Nathan and Karla stated that Lucas had more control of his head and could nod yes or no, and he could move his eyes around to indicate some of his interests. They were also confident they had observed some semi-purposeful movements. PT was working with him twice a week and had done some treadmill training, as well as using an "Upsie" support device to help Lucas with some mimicked walking. Lucas still required total care, which Nathan provided. They had also just had a new baby, adding to their stress.

Lucas still exhibited episodic irritability, with associated dystonia and pain. Nathan reported that his secretions had improved without recurrent episodes of choking or aspiration. He and Karla wondered about advancing Lucas' diet with some textures by mouth, as he had been completely NPO since his first hospitalization.

Dr. Datta talked about getting Lucas reassessed for intake by the complex care clinic there were so many specialists and medications involved in Lucas' care, it was difficult for the family to coordinate them, let alone know who to contact when they had questions. Dr. Datta was concerned about caregiver burnout, since Lucas required a high level of care and respite had yet to be arranged.

For Lucas' dystonia, Dr. Datta requested that Dr. Horvath reassess whether the baclofen can be increased or if another agent would be more appropriate. She hoped Dr. Horvath could coordinate with Dr. Li, as this seemed to be Lucas' greatest issue and source of discomfort. A swallow assessment also seemed in order prior to considering any changes in Lucas' oral status. Finally, Dr. Datta discussed that CBD could be effective both for Lucas' traumatic brain injury and associated seizure risk, as well as dystonia management. Dr. Datta provided a letter of support for CBD use as well as a prescription titration plan to CanniMed. This required applying to be a patient so that Lucas could begin using CBD as part of his management.

Sunny Hill Hospital Outpatient Clinic

On August 20, 2019, the family "met" with Dr. Li for a telephone visit at Dr. Datta's request to talk about Lucas' medications. Lucas' dose for his baclofen was originally calculated for a weight of 28 pounds, and he now weighed closer to 40. Nathan described that Lucas had always liked to lie prone with his head facing the right side. However more recently, he was turning his head into midline and could not breathe well in this position. This had not been helped by the family dealing with viral illnesses recently, including Lucas. There had also been some change of routine after the birth of his new brother 9 or 10 days earlier. Nathan reported that Lucas had made some improvements with respect to speech. There was an episode recently where he was attempting to say "hey guys" with speech therapy. He also had recently demonstrated some capability to do visual tracking as well. Dr. Li summarized the phone visit and changes to Lucas' care plan:

- 1. Tone medications: change baclofen from 15 to 20 mg three times daily and resume prior dose of gabapentin (100 mg tid).
- 2. Botox: No further focal spasticity injections.
- 3. Contractures: Surgical consult
- 4. CBD oil: as per Dr. Datta. They are planning to pursue this.
- 5. Complex care clinic involvement.
- 6. Neuromotor program involvement.

<u>Sunny Hill Outpatient Rehab – Neuromotor Program – Tone Management Clinic</u>

On September 4, 2019, Ram Mishaal, MD evaluated Lucas at the tone management clinic at Sunny Hill Health Centre. Dr. Mishaal identified Lucas' working rehab diagnoses as "mixed spastic and dystonic quadriplegia and profound developmental impairment secondary to an acquired brain injury due to hemolytic uremic syndrome." Nathan and Karla described that Lucas had a difficult summer with viral infections and then episodes of choking after he vomited, which required direct action to clear his throat.

Nathan reported that Lucas' tone had improved with an increase of baclofen and initiation of CBD oil. Dressing was easier, and he was tolerating his clothing better. It was still sometimes difficult to dress him, as his elbows were flexed and he would stiffen when upset. There were no difficulties with positioning or changing diapers. Dr. Mishaal noted that, in her last report, Dr. Li had recommended surgical intervention for bilateral elbow contractions and had put in a referral for an Ortho consult.

After reviewing Lucas' history, current care, and doing his own examination, Dr. Mishaal made the following recommendations:

- 1. We recommend that he be seen by Orthopedics to assess his contractures and the need for surgical intervention.
- 2. We would like to increase the baclofen to 20 mg x 3 per day. We would like to use the tablets and not the suspension. Lucas has previously had systemic side effects with respiratory depression with initiation of baclofen, which was thought to be related to his renal dysfunction. This happened when he was admitted for acute rehabilitation. Since then, his renal function has improved, and he has been able to tolerate increasing doses of baclofen with no prominent side effects. Hence, we feel comfortable with a minor increase of his baclofen from 17.5 to 20 mg x 3 per day.
- 3. We are in agreement with the CBD oil increases.
- 4. We will increase the omeprazole to 25 mg twice per day to target signs of gastroesophageal reflux.
- 5. We would like Lucas to try PEG (MiraLAX) daily instead of using suppositories. We would start at 10 mg daily, aiming for a soft stool daily. The dose can be increased or decreased to achieve the desired result.
- 6. We recommend that the family ensure that the inner elbow area is patted dry after the hot tub and that they use a barrier cream such as Desitin or the dimethicone cream to the area a few times during the day.
- 7. We will do a phone follow-up call in 2 weeks' time and may at that time add some more gabapentin at bedtime to assist with sleep, if the changes to baclofen and omeprazole have not assisted with this.
- 8. We discussed the importance of sleep hygiene and routine to assist with sleep.
- 9. We have asked Lucas's father to pass on this information, and our clinic reports to his OT and SLP, to contact our nurse clinician Carolyn Chowne, regarding an oral stimulation program. He seems to be ready to try some oral stim.
- 10. We will see Lucas for follow-up in 6 months' time, unless earlier follow-up is required. At that time, we will consider trying to wean him off the clonidine.

BCCH – Nuclear Medicine Renal Imaging

On Tuesday, November 12, 2019, Lucas went for testing at BCCH to assess his kidneys. Moira Stilwell, MD performed NM Renal GFR testing utilizing dynamic monitoring for 30 minutes, noting prompt perfusion to both kidneys. Lucas' kidneys appeared symmetrical in size, shape, and position. There was symmetrical mild delayed peak accumulation and delayed transit and excretion, but no evidence of high-grade obstruction. Dr. Stilwell reported the results: "The current GFR measures 62.94 milliliters/minute per 1.73 sq meters body surface area. Differential function is 49.43% on the left and 50.57% on the right."

BCCH – ER

After the Nuclear Medicine scan on Tuesday, Lucas exhibited increased vomiting and increased tone. His parents brought him to the ER for evaluation, and the doctors did not think his emesis was related to the contrast medium from the scan. Their main concern was for dehydration from a likely viral syndrome, so Lucas was given IV fluids and observed for a short time before releasing him back home to the care of his parents with a diagnosis of early gastroenteritis.

MRI reveals evolution of the encephalopathic disease process...

On November 19, 2019, Lucas returned to BCCH for a repeat MRI of his head. Mark Halverson, MD performed the exam and found that, since the prior November 2018 study, there has been evolution of the extensive bilateral white matter abnormality, with increased cavitation⁷¹ and encephalomalacia⁷² and with progressive *ex vacuo* dilation of the lateral and third ventricles. Some of the extensive confluent white matter⁷³ T2/FLAIR hyperintense signal abnormality seen previously had decreased, but there remained periventricular T2 hyperintensity concerning for residual gliosis⁷⁴ related to the prior disease process.

Dr. Halverson explained:

Susceptibility weighted imaging demonstrates susceptibility effect suggesting hemosiderin⁷⁵ staining in the most prominent cavitary lesions. The extent of abnormal hemorrhage-related signal abnormality has decreased compared to the prior study. The hippocampi are smaller than expected with slight signal abnormality, also distorted by the temporal horn enlargement. There is moderate fluid in the right mastoid and middle ear. Paranasal sinuses remain aerated. No orbital lesion is visible. No gross abnormality of the intracranial vascular flow voids.

Dr. Halverson concluded:

Since the prior study one year ago, there has been expected evolution of the previously discovered extensive hemorrhagic cerebral white matter damage with encephalomalacia, gliosis, generalized white matter volume loss and ex vacuo ventricular dilation.

White and gray matter explained:

⁷¹ Cavitation: the formation of an empty space within a solid object or body. Also, the formation of bubbles in a liquid or less solid substance. Venes, *Ibid* Note 100 at 419.

⁷² Malacia = "softening." Encephalomalacia is the softening or loss of brain tissue after cerebral infarction, cerebral ischemia, infection, craniocerebral trauma, or other injury. Venes, *Ibid* Note 100 at 1446.

[•] Brain tissue is made up of cell bodies ("gray matter") and the filaments that extend from the cell bodies ("white matter").

[•] The density of cells (volume of gray matter) in a particular region of the brain appears to correlate positively with various abilities and skills.

[•] The density of cells is determined by both genes and environmental factors, such as experience.

[•] The speed with which we can process information is governed by the white matter.

The proliferation of astrocytes in the central nervous system after an injury to the brain or spinal cord. *Id.* Hemosiderin deposition in the brain is seen after bleeds from any source, including chronic subdural

hemorrhage, cerebral arteriovenous malformations, cavernous hemangiomata. *Id*.



Ventriculomegaly visible on Lucas' MRI on 11/19/19



Sunny Hill - Televisit

On November 27, 2019, Carolyn Chowne, RN spoke with Nate on the phone for a "Televisit." Nathan was interested in the use of a TENS machine for Lucas and wanted to know if they had any guidelines or protocols for that. He also wanted to know the results of Lucas' most recent MRI. The nurse deferred any discussion about the MRI to Dr. Datta and offered to set up an appointment for the family to meet with her for a discussion. Regarding the TENS unit, the nurse spoke with Dr. Grace Li on November 29th, who expressed no concerns about the therapy as long as it was used under the guidance of a therapist who was familiar with the treatment modality and to monitor Lucas closely for comfort, agitation, or any distress.

Carolyn Chowne, RN had another Televisit with Nate on December 2, 2019, this time about concerns he had with Lucas' having possible GI distress, as he appeared to wince and seemed

uncomfortable with burping and some small spit-ups with that. They discussed that it was possibly constipation and so Dr. Mishaal was consulted about increasing his lactulose dose. The nurse wrote an addendum to her chart note when Nate called her back to tell her that Lucas had vomited his entire morning feed and was continuing to have some emesis of stomach bile. She advised Pedialyte for the rest of the day, as well as Gravol (Canadian form of Dramamine), but advised Nate to take Lucas to the ER if he became more concerned.

Ambulance to the ER...

At 6:20 PM on December 2, 2019, the family summoned BC Emergency Health Services to send an ambulance after Lucas had vomited all his feeds for 24 hours, and he had had no bowel movements for 3-4 days. Lucas was brought to the BCCH ER, where an abdominal and chest x-ray showed no obstruction, although there was a moderate amount of retained fecal contents through the colon. The doctors reassured Lucas' parents and gave Lucas IV fluids and Clonidine, advising them to go slower on his feeds with less amount each time but spaced more closely together. Of note, the imaging revealed ongoing diffuse osteopenia (decreased bone mineral density).

<u>Sunny Hill – Televisit</u>

On December 4, 2019, Carolyn Chowne, RN had another Televisit with Nate in the morning to see how Lucas was doing, and Nate told her about the ER visit. He stated that Lucas' younger brother became ill the next day and then that morning Lucas spiked a fever up to 41°C, which came down to normal quickly after being given acetaminophen/paracetamol. Lucas was currently tolerating his feeds at half strength and Pedialyte/formula blend, and he had not had any more vomiting since leaving the ER. His brothers were seen in the clinic and diagnosed with croup. Nate indicated that Lucas did not have any respiratory difficulty or cold symptoms at that time.

Carolyn Chowne, RN spoke with Nate again on December 18, 2019, who told her that Lucas was now well after recovering from an upper respiratory viral infection, which also developed into an inner ear infection. However, these had cleared up and he was now happy and well. She documented the rest of the Televisit:

Dad states that Lucas has been handling his feeds well and his overall tone is good. He is comfortable in multiple positions and seems happy. They were to have had an appointment with nephrology but dad has delayed this until the spring to avoid being in BCCH during the cold and flu season. We reviewed that should any concerns arise over the holiday period that the family has a walk in clinic just down the road with whom they have developed a good working relationship and that if there are further concerns they can call sunny Hill and ask for the physician on call if there are more specific tone questions.



Dad caring for Lucas, ready for his next med...



The Parker Family – Christmas 2019



Out trying to be a normal family (Lucas on right)

MEDICAL CARE 2020

BCCH ER – hospitalized for "first episode unproved seizure"

On April 21, 2020, Lucas was transported from his home to the ER at British Columbia Children's Hospital for an observed seizure lasting 35 minutes. Lucas' father Nate wasted no time calling for an ambulance to transport him to the ER. The seizure had come about after a relatively poor night of sleep and minor infectious symptoms, including nasal congestion and "sniffing." On admission, Lucas was afebrile and the doctors noted that he had no known infectious contacts. Nate reported that the seizure involved shaking rhythmic jerking and shaking of Lucas' arms and legs with his arms extended, and his eyes were fixed and glazed. Lucas was reportedly unresponsive during the event. He exhibited post-ictal drowsiness but was quickly back to baseline, according to Nate.

Lucas was in the hospital for two additional days. He was diagnosed with a "first episode unprovoked seizure, remote symptomatic seizure secondary to acquired brain injury." Lucas was initiated on Keppra 10 mg/kg twice daily and did not require any rescue medication while in hospital, but at his dad's request, his "rescue medication" was switched from midazolam to Ativan. Nate was provided with additional seizure teaching prior to discharge. While admitted, Lucas was assigned a secondary diagnosis of "emesis with feed intolerance," which required additional IV fluids and temporary reduction of his gastric tube feed volumes. He experienced prolonged tachycardia during his admission, but his doctors thought this was secondary to dehydration from the reduction in his feeds. Since they did not think Lucas' management would be changed, they were able to avoid additional invasive imaging and EEG testing for the duration of his hospital stay.

In their discharge summary, pediatric resident Marabeth Kramer, MD and supervising physician James Hyun-Sup Lee, MD outlined Lucas' treatment course for the three days he was

hospitalized, commenting that no cardiac arrhythmias had been detected, other than sinus tachycardia related to dehydration. Blood and urine cultures failed to grow any bacteria to suggest an infectious cause for his seizure activity. Lucas had no further seizures in the hospital, and Keppra was added to his medication regimen for continuation after discharge, as well as Ativan (lorazepam) sublingual "rescue medication" were another seizure to occur. On April 23, 2020, Lucas was discharged in stable condition, with a plan for him to see Dr. Datta at the end of June.

BCCH Neurology Outpatient Televisit

On June 25, 2020, neurologist Anita Datta, MD conducted a neurology "televisit" in follow-up of Lucas' hospitalization for seizure. Nate reported that Lucas was overall doing well and was tolerating the Keppra dosing, and there had been no further seizures. Lucas' reportedly had diminished dystonia recently, although Nate observed that any anxiety caused him to arch or increase his leg movements. Lucas was given Ativan during these episodes, which seemed to help. Developmentally, Nate noted that Lucas was making eye contact, laughed occasionally, and had his own way of communicating. They were working very closely with Physio and Speech Language Pathology. Lucas was also on CanniMed (CBD), and Dr. Datta wrote a letter in support of the use of this medication.

BCCH Nephrology Outpatient Televisit – started on ACE inhibitor for proteinuria

Nephrologist Robert Humphreys, MD evaluated Lucas on September 4, 2020 for proteinuria via "Televisit." The doctor found it encouraging that Lucas was starting to tolerate some oral intake with sips of water and mashed fruit, and he was able to tolerate some yogurt. Nate wondered about a barium swallow sometime soon. Dr. Humphreys started Lucas on an ACE inhibitor (enalapril) for the proteinuria⁷⁶ and prescribed iron for anemia.⁷⁷

BCCH Oupatient Hip Surveillance – "coxa valga deformity"

On September 22, 2020, Stacey Miller, PT saw Lucas as an enrollee in the Child Health BC Hip Surveillance Program for Children with Cerebral Palsy, after hip/pelvis imaging was completed at the request of Dr. Ramesh on September 17. Imaging revealed increased left hip subluxation and lateral uncovering of the right femoral head, as well as "increased apparent coxa valga deformity.⁷⁸ It was recommended that Lucas be seen by a pediatric orthopedic surgeon, and he was scheduled to see Dr. Leveille in one month.

⁷⁶ The early antiproteinuric effect of ACE inhibition is associated with long-term preservation of renal function in children with CKD. Proteinuria lowering should be considered an important target in the management of pediatric CKD. van den Belt, S. M., Heerspink, H. J. L., Gracchi, V., de Zeeuw, D., Wühl, E., Schaefer, F., & ESCAPE Trial Group. (2018, August). *Early Proteinuria Lowering by Angiotensin-Converting Enzyme Inhibition Predicts Renal Survival in Children with CKD*. https://www.ncbi.nlm.nih.gov/pubmed/29930161.

⁷⁷ NOTE: Proteinuria was identified as early as 11/22/18 during Lucas' acute HUS, and discussions regarding the future use of an ACE inhibitor were initiated by Rob Humphreys MD on 2/22/19.

⁷⁸ Coxa valga deformity can cause pain, limit mobility in the hip, and make one leg shorter than the other. If conservative treatment isn't enough to stop pain, surgery may be done to cut into the femur and decrease the angle of the femoral head. Hsieh, Hsiang-Chieh MD; Wang, Ting-Ming MD, PhD; Kuo, Ken N. MD; Huang, Shier-Chieg MD, PhD; Wu, Kuan-Wen MD, PhD Guided Growth Improves Coxa Valga and Hip Subluxation in Children with Cerebral Palsy, Clinical Orthopaedics and Related Research: November 2019 - Volume 477 - Issue 11 - p 2568-2576

BCCH – Dental procedures under anesthesia

On October 8, 2020, Kunal Chander, DDS performed a comprehensive dental exam, prophylaxis. fluoride, scaling, and tooth extractions with Lucas under general anesthesia in the OR, for Lucas' diagnosis of "advanced dental caries." The procedures were conducted in this manner to reduce the stress Lucas would experience if they were attempted without anesthesia.

EXPERT OPINIONS

Sharon P. Andreoli, MD – HUS Expert Opinion

We asked Sharon P. Andreoli, MD, Professor of Pediatrics at Indiana University School of Medicine, to provide an analysis of Lucas' clinical presentation, as well as his risks of long-term complications following his acute episode of HUS. After completing a review of the extensive medical records, Dr. Andreoli provided her opinion on December 31, 2019.

Dr. Andreoli began her report by summarizing the complexity of Lucas' clinical illness, beginning with his falling acutely ill while still in California and being seen in Olympia, Washington in an emergency department on the family's way home to British Columbia, Canada. Dr. Andreoli highlighted the urgency of Lucas' symptoms that drove the primary focus of treatment during increasingly acute episodes. This included the emergent admission to Richmond Hospital and then transfer to British Columbia Children's Hospital for evaluation and management of Shiga-toxin-associated *E. coli* O157:H7 hemolytic uremic syndrome. Dr. Andreoli noted the catastrophic brain injury that led to the devastating loss of Lucas' cognitive function, as well as numerous comorbidities, such as insulin dependent diabetes, hypertension, and acute renal failure, and the need to intubate Lucas for multiple procedures including the insertion of a peritoneal dialysis catheter.

A number of sections from Dr. Andreoli's report that are particularly significant to his renal function and prognosis are excerpted below:

... On October 22, 2018 Lucas went to the operating room for placement of a peritoneal dialysis catheter. Lucas underwent continuous EEG monitoring. On October 23, 2018 Lucas was treated with eculizumab 600 mg over 4 hours.

... On October 23, 2018 peritoneal dialysis was initiated. On October 25 to 26th, 2018 Lucas experienced episodes of hypotension and he was given a fluid bolus and his WBC count increased to 42,500 mm3 and he had recurrent hyperglycemia requiring multiple insulin adjustments. Lucas was started on intravenous vancomycin and cefotaxime.

... On November 2, 2018 ... Lucas received his second dose of eculizumab. A CT scan performed on November 1, 2018 demonstrated much more extensive white matter abnormalities compared to the prior CT scan. ... Since his disease seemed to have progressed while on eculizumab, therapy with pulse steroids was begun on

November 2, 2018 for a five-day course of pulse steroids.

... On November 6, 2018 Lucas was extubated and he demonstrated spontaneous respirations on room air. He began producing urine (see table) and he was transferred out of the ICU to a regular pediatric bed. With the increase in his urine output peritoneal dialysis was discontinued.

... On November 16, 2019 Lucas went to the operating room for removal of his peritoneal dialysis catheter and placement of a gastrostomy feeding tube.

... On November 22, 2018 Lucas was noted to have significant proteinuria and his physician recommended consideration of an ACE inhibitor. On November 28, 2018 a continuous EEG demonstrated severe encephalopathy. His blood sugars required adjustment of his insulin dose by endocrinology.

... On December 11, 2018 Lucas was transferred back to Sunny Hill Rehabilitation Center from BCCH. He received occupational therapy (OT), physical therapy (PT), Speech therapy, Music therapy, Social Work Services and Therapeutic Recreational Rehabilitation. It was noted that Lucas was severely cognitively impaired, scoring 1.8 on the Rappaport Coma/Near Coma Scale.

... On February 22, 2019, Lucas was seen for his first post-discharge follow up at the pediatric nephrology clinic. It was noted that he had severe neurologic injury as a result of his CNS involvement of his HUS. His urine contained 2+ protein on a dipstick and a protein:creatinine ratio was 0.93 (normal, less than 0.2) which was improved from a protein:creatinine ratio of 9.81 on November 23, 2018. It was also noted that his blood pressure was intermittently elevated for age and size and if persistent an ACE inhibitor might be indicated for the hypertension and proteinuria.

... Lucas was discharged from Sunny Hill Health Center for Children in patient services on March 1, 2019 and he was to continue to receive therapy as an outpatient as Sunny Hill Acute Rehabilitation Unit until community therapy could start working with him. In addition, he would continue to be seen by the neuromuscular team at Sunny Hill, as well as by Endocrinology and Nephrology at BCCH. It was recommended that Luca undergo a trial of botulinum toxin injections which was later initiated.

... Lucas was seen in pediatric endocrinology clinic on March 13, 2019 and his insulin was discontinued since it appeared that his pancreatic beta cells had recovered from the insult during his acute episode of HUS. Lucas was also seen in BCCH Outpatient Biochemical Diseases on April 5, 2019 by Dr. Horvath who reviewed his entire history and she noted that he had dystonic posturing, whole body tremor, clonus bilaterally, and it was really hard to watch how he was suffering.

Dr. Andreoli went on to describe Lucas's outpatient care after discharge from Sunny Hill

before turning to her analysis of the residual effects of his severe and devastating STEC HUS illness on his future health:

A normal urine output in Lucas would be 1.0 ml/kg/hour and based on a weight of 14.6 kg a normal urine output would be greater than 350 ml/24 hours; on few days urine output was described as 0 in some areas of the charts and small urine output in other areas of the chart. Thus, Lucas was anuric (no urine output) 13-15 days and oliguric (decreased urine output) for 3-5 days for a total of 18 days of oligo/anuria.

In summary, Lucas has significant residual kidney disease from his acute episode of HUS, he has pancreatic injury as a result of his acute episode of HUS and he has very severe residual CNS disease from his acute episode of HUS.

I will address the long-term risk of kidney complications from Lucas's acute episode of HUS and I will address the long-term risk of pancreatic complications from Lucas's acute episode of HUS. I will address the pancreatic injury first then the long-term consequences of the acute kidney injury.

IDDM resulting from pancreatic injury in HUS is a well described complication of HUS (see references). The IDDM can be permanent or transient. Children with IDDM are at risk for the development of complications from the IDDM. IDDM predisposes children to premature atherosclerosis (hardening of the arteries), retinopathy (decreased vision and blindness), neuropathy (decreased feeling and strength) and nephropathy (kidney failure). Lucas recovered from his pancreatic injury however it is quite important to note that many children with IDDM during the acute injury who have recovered will later develop re-occurrence of the IDDM at later time points (see references). Thus, it is likely that Lucas will develop IDDM in the future.

It is also highly likely that Lucas will development chronic kidney failure and end stage kidney disease in the future. Lucas has substantial kidney injury from his episode of HUS documented by his complications of prolonged hypertension and proteinuria. As described above, Lucas was anuric for 13-15 days and oliguric for 3-5 days for a total of 18 days of oligo/anuria.

One of the best predictors of later kidney problems following the acute episode of HUS, is the duration of anuria and/or oliguria/anuria, and residual kidney disease including hypertension and proteinuria.

Dr. Andreoli provided a review of the medical literature in her report, including multiple citations for the complications regarding the incidence of hypertension, decreased creatinine clearance, or proteinuria. Her complete analysis of the literature is contained in her full report. Some of the more significant findings are excerpted below:

• Severe sequelae occurred in children with oligo/anuria for more than or equal to 7 days.

- Many of the children with residual renal symptoms or chronic renal insufficiency/renal failure had appeared to have recovered normally at earlier checkups.
- Oakes, et al., determined the risk of later complications in children who had HUS several years earlier; they found that the incident of late complications increased markedly in those with more than 5 days of anuria or 10 days of oliguria.

Dr. Andreoli summarized her report by pointing out that many children who have recovered normal renal function following the acute episode of HUS have a high risk for the development of late complications from their acute episode of HUS. The risk is substantially lower in children who did not require dialysis and in children who were not oliguria or anuric while the risk is the highest in children who had oligo/anuria for more than 7 days. Dr. Andreoli summarized Lucas' specific renal diagnoses and prognosis, relative to what is known to occur in children who have suffered the kind of acute kidney injury and medical complications that Lucas has:

Lucas had prolonged oligo/anuria and required dialysis for 18 days. He has had intermittent hypertension requiring medication, and he has persistent residual proteinuria with elevated urine protein:creatinine ratios. Thus, as described above, studies have shown that such patients have a significant risk of later kidney complications. I would estimate his risk of later kidney complications at greater than 90% and that he will eventually develop end stage kidney disease and need a kidney transplant. It is likely that during his teenage years his kidney function will significantly decline as the growth spurt and hormonal changes that occur during puberty can be quite detrimental to kidney function.

Children and adolescents with chronic kidney failure face a number of complications from their chronic kidney failure (Andreoli SP, Acute and Chronic Kidney Failure in Children, 2001) including alterations in calcium and phosphate balance and kidney osteodystrophy (softening of the bones, weak bones and bone pain), anemia (low blood count and lack of energy), growth failure (final height as an adult substantially below normal), hypertension (high blood pressure) as well as other complications.

Renal osteodystrophy (softening of the bones) is an important complication of chronic kidney failure. Bone disease is nearly universal in patients with chronic kidney failure; in some children symptoms are minor to absent while others may develop bone pain, skeletal deformities and slipped epiphyses (abnormal shaped bones and abnormal hip bones) and have a propensity for fractures with minor trauma. Treatment of the bone disease associated with chronic kidney failure includes control of serum phosphorus and calcium levels with restriction of phosphorus in the diet, supplementation of calcium, the need to take phosphorus binders and the need to take medications for bone disease.

Anemia (low blood cell count that leads to a lack of energy, commonly called thin blood) is a very common complication of chronic kidney failure. The kidney makes

a hormone that tells the bone marrow to make red blood cells and this hormone is not produced in sufficient amounts in children with chronic kidney failure. Thus, children with chronic kidney failure gradually become anemic while their chronic kidney failure is slowly progressing. The anemia of chronic kidney failure is treated with human recombinant erythropoietin (a shot given under the skin one to three times a week).

Growth failure ultimately leading to short height as an adult is a very common complication of chronic kidney failure in children. The mechanisms of growth failure are complex and due to multiple causes. Poorly controlled kidney osteodystrophy (bone disease), inadequate nutrition (insufficient intake of adequate calories), chronic acidosis (blood system too acid) and abnormalities of the growth hormone axis (growth hormone deficiency) are each major contributors to poor growth in the child with chronic kidney failure. Growth hormone therapy with human recombinant growth hormone has been approved for use in children with chronic kidney failure and such therapy has been shown to accelerate growth, induce persistent catch up growth and lead to normal adult height in children with chronic kidney failure. Growth hormone therapy are rare but may include glucose intolerance (that is, a worsening of Lucas' diabetes), pseudotumor cerebri, and exacerbation of poorly controlled kidney osteodystrophy and perhaps a detrimental effect on kidney function with progression of glomerulosclerosis.

Hypertension (high blood pressure) is a common complication of chronic kidney failure and needs to be treated with medication. During the time that he is developing chronic kidney failure and progressing to end stage kidney disease, he will need to be followed by a pediatric nephrology with measurement of height, blood pressure, urine and blood test on a frequent interval.

Lucas is very likely to need kidney replacement therapy in the future. Kidney replacement therapy can be in the form of dialysis (peritoneal dialysis or hemodialysis) or kidney transplantation. Kidney transplantation can be from a cadaver or a living related donor (parent or sibling who is over the age of 18 who is compatible). Should Lucas have a living related donor available to donate a kidney, he can undergo transplantation without the need for dialysis (preemptive transplantation). Should he not have a living related donor, he will likely need to undergo dialysis (see below) while on the waiting list for a cadaver transplant. Fortunately, children have the shortest waiting time on the cadaveric transplant list. The average waiting time for children age 0-17 years is approximately 300-325 days while the average waiting time for patient's age 18-44 years is approximately 600 days (United States Kidney Data Systems, Am J Kidney Dis, 2003).

Following transplantation, Lucas will need to take immunosuppressive medications for the remainder of life to prevent rejection of the transplanted kidney. Medications used to prevent rejection have considerable side effects. Corticosteroids are commonly used following transplantation. The side effects of corticosteroids are Cushingoid features (fat deposition around the cheeks and abdomen and back), weight gain, emotional liability, cataracts, decreased growth, osteomalacia and osteonecrosis (softening of the bones and bone pain), hypertension, acne and very importantly in Lucas' case, alterations in blood glucose levels and difficulty in controlling diabetes. The steroid side effects, particularly the effects on appearance, are difficult for children particularly teenagers; and noncompliance secondary to the side effects of medications is a risk in children, particularly teenagers.

Cyclosporine and/or tacrolimus are also commonly used as immunosuppressive medications following transplantation. Side effects of these drugs include hirsutism (increased hair growth), gum hypertrophy, interstitial fibrosis in the kidney (damage to the kidney), as well as other complications. Imuran and/or meclophenalate are also commonly used after transplantation; each of these drugs can cause a low white blood cell count and increased susceptibility to infection. Many other immunosuppressive medications and other medications (anti-hypertensive agents, anti-acids, etc.) are prescribed in the post-operative period.

Lifelong immunosuppression as used in patients with kidney transplants is associated with several complications including an increased susceptibility to infection, accelerated atherosclerosis (hardening of the arteries), increased incidence of malignancy (cancer) and chronic rejection of the kidney. In this regard, it is highly likely that Lucas will need more than one kidney transplant during his life.

If Lucas does not have a living related donor for his first kidney transplant and when see needs a second kidney transplant after loss of his first transplant, he will need dialysis until a subsequent transplant can be performed. He can be on peritoneal dialysis or on hemodialysis. Peritoneal dialysis has been a major modality of therapy for chronic kidney failure for several years. Continuous Ambulatory Peritoneal Dialysis (CAPD) and automated peritoneal dialysis also called Continuous Cycling Peritoneal Dialysis (CCPD) are the most common form of dialysis therapy used in children with chronic kidney failure. CAPD/CCPC. In this form of dialysis, a catheter is placed in the peritoneal cavity (area around the stomach); dialysate (fluid to clean the blood) is placed into the abdomen and changed 4 to 6 times a day. Parents and adolescents are able to perform CAPD/CCPD at home. Peritonitis (infection of the fluid) is major complication of peritoneal dialysis.

Hemodialysis has also been used for several years for the treatment of chronic kidney failure during childhood. During hemodialysis, blood in taken out of the body by a catheter or fistula and circulated in an artificial kidney to clean the blood. Hemodialysis is usually performed three times a week for 3-4 hours each time in a dialysis unit.

Dr. Andreoli summarized by stating that Lucas has residual kidney disease as a result of his acute episode of HUS and he is at high risk for the reoccurrence of his IDDM in the future. He

is very likely to develop chronic kidney failure in the future. He will need lifelong monitoring of his kidney status (pre and post-transplant) as well as hospitalizations and surgeries for transplant, to place catheters for transplantations as well as for complications of transplantation and dialysis.

Dr. Andreoli concluded her report:

My opinions of Lucas's risk for complications from her HUS and his future medical care may be modified based on new information as it becomes available. If you have any questions, please do not hesitate to contact me.

Anthony A. Bouldin, MD – Pediatric Neurology Expert Opinion

We requested an independent pediatric neurological evaluation by Anthony A. Bouldin, MD. Dr. Bouldin is a board-certified pediatrician and a Diplomat of the American Board of Pediatrics. He is also a Diplomat of the American Board of Psychiatry and Neurology, with Special Qualifications in Child Neurology. He currently practices at Swedish Neuroscience Specialists and is affiliated with Swedish Medical Center First Hill Campus. Dr. Bouldin graduated from University of Louisville School of Medicine in 1997 and has been in practice for 22 years. He completed a Child Neurology Residency at University of Washington School of Medicine from 2000 to 2003. Dr. Bouldin is therefore uniquely qualified to render an opinion regarding Lucas' catastrophic, acquired brain injury and his neurologic prognosis moving forward. Dr. Bouldin provided his opinion on April 6, 2020.

Dr. Bouldin conducted a thorough review of Lucas' entire medical record, including his history of neurologic injury related to his *E. coli* O157:H7 infection and hemolytic uremic syndrome. He interviewed Lucas' parents Nathan and Karla and examined Lucas on January 24, 2020. He observed that Lucas' severe clinical course included progressive central nervous system involvement leading to a variety of neurologic symptoms and permanent brain injury requiring prolonged hospitalization in the intensive care unit and subsequent inpatient rehabilitation. Dr. Bouldin synopsized Lucas' evolving neurologic course and provided an assessment of his current condition.

Dr. Bouldin concluded his report with a summary of his impression and his thoughts about Lucas' likely prognosis:

Given the time that has passed since Lucas's acute *E. coli* infection and HUS and the nature of his brain injury, I would not expect his neurologic or functional status to improve significantly in the future. As of this assessment, Lucas remains in a quadriplegic state with severe spasticity and intermittent dystonic crises with dysautonomia though these latter issues have improved with time and treatment. I believe he will require continue medical treatment for his tone issues and autonomic issues for the remainder of his life. He remains fed entirely by gastrostomy tube and continues to suffer from severe cortical visual impairment and a limited ability to communicate his needs. I do not foresee these deficits improving with time and I believe he would require the same level of support he currently requiring on a lifelong basis.

Because of his language and motor impairments it is hard to directly test his cognitive skill to any great degree but given the severity of his more apparent neurologic deficits and the progressive loss of brain volume on his MRI scan, I believe his cognition is likely quite impaired as well. I would not expect any improvement with these issues over time.

In terms of future treatments, he continues to require treatment for his spastic posture particularly in the upper extremities which has included physical and occupation therapy, splinting, medications. Treatment for this issue would be required on lifelong basis for Lucas Parker. Furthermore, because of unsuccessful attempts at treating the spasticity in his upper extremities with botulinum toxin or lidocaine the possibility of a surgical treatment is currently being explored. His dystonia and dysautonomia will require the current treatment on a lifelong basis and depending his course and continued response to medical management of these, mention has been made of possible surgical treatment in the form of deep brain stimulation for dystonia when older or alternatively with transcranial magnetic stimulation (a non-invasive albeit specialized treatment only offered in center referral centers).

As far as other likely treatment for future complications given his overall neurologic state, there are likely orthopedic complications that will arise that will in the very least require regular monitoring and possible surgical intervention including risks for hip dislocation and scoliosis He remains at risk for the development of epilepsy which would in the very least require medical management and further electrophysiological testing.

LIFE CARE PLAN

Kenneth W. Reagles, PhD

We requested the assistance of Kenneth W. Reagles, Ph.D. to prepare a Life Care Plan for Lucas. Dr. Reagles received a Ph.D. from the University of Wisconsin-Madison in Rehabilitation Psychology in 1969 with majors in statistics and research, including specialization in the economics of vocational rehabilitation. From 1975 to 1996, he was Professor and past Chairman, Department of Rehabilitation Services at Syracuse University. He is presently Professor Emeritus of Rehabilitation Counseling at Syracuse University. Since 1969, Dr. Reagles has been the owner and president of K.W. Reagles & Associates, L.L.C., wherein he provides expert vocational (life-care planning), rehabilitation, economic, and related consultation services to attorneys and their clients, consultation, and training.

On May 8, 2020, Dr. Reagles completed an analysis and appraisal and prepared a Life Care Plan on behalf of Lucas. In preparing his report, Dr. Reagles conducted a full review of Lucas' social history, medical records, and expert reports. His report summarizes the nature of Lucas' disablement and provides an overview of his permanent enduring physiological and psychological consequences of his *E. coli* O157:H7 infection, including dysfunction and

associated phenomena. Dr. Reagles examines the economic consequences of the probable diminution of Lucas' future educational and vocational accomplishments attributable to the condition of his kidneys and related acquired brain injury secondary to the bacterial infection (loss of earnings capacity). He provides a synopsis of Lucas' diminished or lost capacity as an adult to independently perform his activities of daily living and carry out tasks in the home environment. Finally, Dr. Reagles outlines a life-care plan that sets forth the future cost and the present values of the future cost of anticipated medical and allied-health care.

Process

Dr. Reagles began his assessment with a thorough review of Lucas' family history, tracing it back through both the paternal and maternal familial lines to outline their social and educational history. He also reviewed Lucas' medical history since birth. Dr. Reagles identified a mostly unremarkable medical history, the most significant feature of which was a minor communication disorder that was manifested as using no more than four-work sentences and resulted in his being enrolled in speech therapy. He noted that Lucas was born at full term and met the majority of his developmental gross-motor skill milestones in a timely fashion, walking at one year of age and no issues with running and climbing as a toddler.

Dr. Reagles then reviewed the nature of Lucas' exposure to the *E. coli* O157:H7 bacteria, followed by the acute and chronic illnesses that ensued, including the complex twists and turns of the evolution and complications of his hospitalization for *E. coli* O157:H7 induced hemolytic uremic syndrome. This included but was not limited to his loss of kidney function, need for transfusions and peritoneal dialysis, and multiple medical comorbidities. Dr. Reagles examined in great detail the nature and course of Lucas' neurologic complications and catastrophic, acquired brain injury.

To assist him in his evaluation, Dr. Reagles relied on the expert opinions of Sharon Andreoli, MD and Anthony A. Bouldin, MD to identify the future medical care needs and social services needs that Lucas will encounter. He reviewed their reports and excerpted their opinions. Further, Dr. Reagles observed that Lucas currently remains under the care of a pediatric physiatrist (Dr. Li), a pediatric nephrologist (Dr. Humphreys), a pediatric neurologist (Dr. Datta), pediatric specialists in biochemical genetics (Drs. Horvath and Mishaal), an orthopedic surgeon (Dr. Pike), a pediatric ophthalmologist (Dr. Mulholland), a physiatrist with a specialty in nerve testing (Dr. O'Connor), a pediatric endocrinologist (Dr. Metzger), and a general pediatrician (Dr. Ramesh).

On January 27, 2020, Dr. Reagles met with Lucas' parents Karla and Nathan in their home in Richmond, British Columbia, Canada. The evaluation interview consisted of a detailed family history, including, especially, the educational and vocational accomplishments of Lucas' parents, grandparents, aunts, uncles, and close cousins. He commented:

It was abundantly apparent that Lucas' parents while coping as best as they can, are overwhelmed by their circumstances. They impressed me as caring and devoted parents who are making do with what they have but they expressed a desire for more optimal care and commodities for Lucas, as well as a wish that Lucas had never become impaired after he became infected with *E. coli* O157:H7 bacteria. It

is abundantly apparent that the medical complications that Lucas Parker has sustained as a direct and causal result of the *E. coli*-induced HUS in October 2018 have had a significant impact upon his life -- previously, presently, and for the duration of his life expectancy -- including, but not limited to, as it relates to his future educational and vocational accomplishments and his need for ongoing healthcare related goods and services, some for the remainder of his life expectancy.

Dr. Reagles forth his opinions regarding the economic consequences of Lucas' medical condition, including sections of "Loss of Future Educational Achievement" and "Pre-Subject Incident Future Expected Earnings Capacity," with accompanying tables and estimates of value and projected losses. The next sections discussed "Impaired Earnings Capacity," "Net Loss of Future Earnings Capacity," "Lost Capacity to Perform Household Work," "Future Health-Related Goods and Services," the latter of which was accompanied by "A Life-Care Plan" with multiple tables and estimations of needs and costs.

Recapitulation

Dr. Reagles concluded his report with a "Recapitulation" of the economic losses Lucas and his family have incurred as a direct and causal result of the injuries, disabilities, and corresponding cognitive and functional limitations that were incurred following his consumption in October 2018 when he became infected with *E. coli* O157:H7 bacteria. Dr. Reagles set forth his estimates of the present values of the future values of Lucas' economic losses, which are expressed in Canadian currency (dollars).

Present Value of Future Cost in C\$							
1.	Loss of Future Earnings Capacity:						
	a. Loss of Wages	=	C\$	1,743,341	to	C\$	1,894,656
	b. Loss of Fringe Benefits	=		131,542	to		142,959
2.	Future Health-Related Goods and Services	=	41,311,666				
	TOTAL	=	<u>C</u> \$ -	43,186,549	<u>to</u>	C\$ 4	<u>43,349,281</u>

Finally, for the purposes of the present determination, the future and present value costs of health-related goods and services were projected on an annual and aggregate basis as is set forth in Table 10 at the conclusion of Dr. Reagles' report. "The utility of such a table will be apparent in instances in which there is conjecture regarding Lucas Parker's future life expectancy given that the life expectancy of a person with his medical conditions may be significantly less than the general population."



A rare moment of family peace...



Lucas before illness

Life for Lucas now



Mom and son look-alikes before he got sick



Mom with her babies now (Lucas on right)



Daddy with Lucas in hot tub