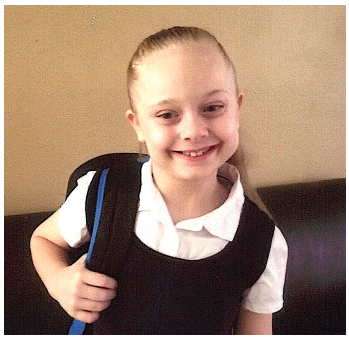
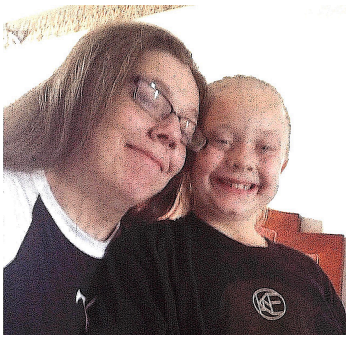
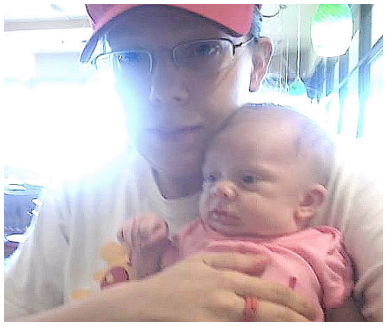
MAKAYLA JARBOE'S 2018 *E. COLI* O157:H7 ILLNESS CAUSED BY ROMAINE LETTUCE





Makayla Jarboe is a 9-year-old girl residing in Mesa, Arizona with her mom, Destiny Jarboe, and her two younger brothers, Carter and Tommy. The children's grandmother, Glenda Jarboe, also lives with the family. Makayla ate a salad from the Mesa, Arizona Souper Salad restaurant on April 11, 2018. It was one of Makayla's favorite restaurants. Unfortunately, the salad contained contaminated romaine lettuce, causing her to become severely ill. Makayla was just 7 years old.



Destiny with 1-month-old Makayla at Souper Salad in 2010

Symptom onset

Makayla had been diagnosed with gastroesophageal reflux (GERD) and was accustomed to occasional stomachaches and acid indigestion. The first indication that something more serious was wrong came on April 14, 2018, when she developed painful abdominal cramping and loose stools. She had diarrhea once or twice the first day and on the second day the diarrhea turned watery. Destiny assumed her daughter had a stomach bug that all kids get, but she began to worry when it did not resolve quickly. Over the next 24-48 hours, Makayla developed worsening diarrhea and stomach cramping, and ran intermittent fevers. Soon it became clear she needed to see a doctor.

Banner Desert Medical Center / Cardon Children's Hospital

Makayla and Destiny arrived at Banner Desert Medical Center on April 16, 2018, just before 11:00 PM. Makayla was evaluated by Nachman Ullman, DO, and Destiny described Makayla's symptoms, noting that her daughter had multiple episodes of watery non-bloody and non-bilious diarrhea that day, experiencing eight of them just since arriving in the ER. Makayla had not been vomiting, but her diarrhea symptoms were exacerbated by eating and drinking. Destiny had been giving Makayla Imodium, with the last dose being 10 hours earlier. She also reported that Makayla was having left-sided abdominal pain and ran a fever that morning of 100.4ºF. Additionally, Destiny reported that Makayla had a history of urinary tract infections, but the last one was four years ago. Makayla did not think she had symptoms of that now.

On exam, Dr. Ullman found Makayla's abdomen tender in the left lower quadrant, but she had no rebound tenderness or guarding. She did not have a fever at the time of the examination. Makayla was started on intravenous fluids and blood and urine samples were sent to the lab. At 2:33 AM, the lab reported mostly normal values, but a urinalysis was significant for protein, bacteria, and blood. Dr. Ullman chose not to treat Makayla for a UTI at that time, given her lack of symptoms and acute diarrheal illness, advising instead to wait for the results of the urine culture. Makayla's renal function panel was normal (BUN 11, creatinine 0.53) and her complete blood count and electrolytes were unremarkable. A KUB (kidney-ureters-bladder) X-ray was done just after midnight that showed a mildly distended colon and rectum with an otherwise unremarkable bowel gas pattern. After observation in the ER, Dr. Ullman considered Makayla sufficiently stable to go home and push fluids. She was drinking Pedialyte at that point without difficulty, so she was provided with Zofran to take at home as needed for nausea. Dr. Ullman recommended probiotics to help restore the normal gut flora after significant diarrhea. Dr. Ullman diagnosed acute diarrhea and abdominal pain and discharged Makayla from the hospital at 4:23 AM with instructions to Destiny to take her daughter to her pediatrician in 1-2 days for a recheck and to return for any new or worsening symptoms.

Home but not better…

Destiny returned home with Makayla and followed the doctor's orders to hydrate and rest, but the little girl only got worse. Throughout the day, her diarrhea became voluminous and as frequent as every 1-2 hours and turned frankly bloody. Makayla continued to experience intermittent fevers and sharp abdominal cramping, and if she was not in the bathroom with diarrhea, she was lethargic and sleeping. Destiny worried about dehydration, a warning echoed by the ER doctor. Fewer than 24 hours after being discharged, Makayla was back in the same ER.

Return to ER…

On Tuesday, April 17, 2018 at 11:32 PM, Destiny returned to Banner Desert Medical Center with Makayla. Destiny explained to Zola Trotter, M.D. that they were in the emergency department early that morning and described how Makayla's condition worsened following her discharge. Dr. Trotter resumed IV fluids and her blood was rechecked with a CBC and metabolic panel. Makayla provided another urine sample for analysis. This time, the CBC returned with an elevated white blood cell count of 20.4. Her metabolic panel showed a low CO2 level of 17 and low albumin of 2.6. A coagulation panel was mildly elevated with an INR of 1.2 and PT of 13.5.[1]

[1] Normal reference ranges for this lab: WBC 4.5-13.5K, hemoglobin 11.5-14.5 g/dL, hematocrit 33-43%,

Makayla's urine sample continued to exhibit white blood cells and was now leukocyte esterase positive, suggestive of infection. It later grew only mixed lower urethral flora (a contaminant). A stool for occult blood was positive.

Hospital Day 1 – admitted from ER with bloody diarrhea

Just after midnight on April 18, 2018, Adrienne Timothy, RN attempted three times to get a peripheral intravenous catheter inserted into Makayla's left hand and finally succeeded with a small gauge (22g) catheter. Dr. Trotter then administered a bolus of IV fluid and observed her in the ER for three hours. During that time, Makayla had two episodes of large volume diarrhea. The PA consulted with the hospitalist to admit Makayla to the hospital for observation for "bloody diarrhea, leukocytosis, acidosis, abdominal pain, pyuria, hypoalbuminemia" and "dehydration." Makayla was transferred from the ER to the main hospital at 3:08 AM. Before leaving the ER, a stool sample was collected and sent to the lab.

Mona Nourani, DO formally admitted Makayla to the hospital and spoke with Destiny and Makayla about how the child's diarrheal illness had started and progressed to bloody diarrhea over the previous four days. Dr. Nourani found it notable that, after going home from the ER in the early morning hours on April 17, 2018, Makayla had gotten worse and had to come back later the same night. Her diarrhea now contained frank blood, which was confirmed by guaiac testing. Dr. Nourani thought that most of the abnormal labs could be explained by dehydration, especially since her white count and hemoglobin were elevated from hemoconcentration, although the blood sample was suboptimal because it had hemolyzed in the tube. Dr. Nourani observed that a KUB X-ray from the night before showed only a mildly distended distal colon and rectum with unremarkable bowel gas patterns.

Dr. Nourani also found it notable that Makayla had experienced mild tactile fevers (unmeasured) while in Nevada, but none of the other family members she was with were sick. Destiny stated that Makayla had not been exposed to lake water and she had not been out of the country. Dr. Nourani admitted Makayla to the pediatric floor for observation with a plan to follow-up on the stool studies started in the ER. These included testing for *Giardia*, *Cryptosporidium*, parasites, Shiga toxins, and enteric bacterial pathogens. At this point, Dr. Nourani still awaited the results of the urine culture. Meanwhile, Makayla continued on IV fluids and she was given Zofran for nausea. Tylenol and ibuprofen were employed for abdominal pain. Dr. Nourani thought it likely that Makayla had bacterial gastroenteritis and they would defer additional treatment pending the culture results.

Hospital Day 2 – first signs of hemolytic uremic syndrome (HUS) – oliguria, TTP, AKI

On Thursday, April 19, 2018, pediatric hospitalists Satya Vittala, MD and Alan Graham, MD visited Makayla. She had only had one loose stool during the night, however the abdominal pain continued and was worse. Her eyes looked puffy that morning, and the doctors noted that her urinary output was very poor—only about 100 mL—and she was taking very little oral fluids.

---

platelets 130-450K, CO2 20-28 mmol/L, albumin, LDH 129-137 IU/L, PT 9.4-12.5 seconds, INR 0.9-1.1, D-Dimer <500 ng/mL FEU, BUN 5-25 mg/dL, creatinine 0.50-0.90 mg/dL, ALT 10-35 IU/L, AST 10-41 IU/L, haptoglobin 43-212 mg/dL, schistocytes are normally not present

The doctors continued Makayla on IV fluids. On exam, she exhibited both tachypnea and tachycardia (respiratory rate 40, heart rate 160) and she appeared to be in "mild distress due to pain." The doctors observed that Makayla had also been tachycardic the day before, with heart rates in the 120-140s throughout the day. On exam that morning, her abdomen was distended, soft and diffusely tender in all quadrants, but she exhibited no guarding or rebound tenderness to suggest an underlying inflammatory process.[2]

Makayla's labs were concerning for mild anemia, with a hemoglobin and hematocrit of 12.5. Her renal function was abnormal, with a serum creatinine that jumped up to 1.91 from her admission value of 0.59, "likely due to AKI." Her liver function tests were in the normal range. Pediatric nephrologist Ayah Elmaghrabi, MD was consulted, and she recommended several follow-up labs to assess acute kidney injury (AKI) and possible hemolytic uremic syndrome. These included LDH, haptoglobin, CBC with differential, ANA with reflex, ANCA, C3 and C4 complement proteins, urinalysis with urine protein/creatinine ratio, and a renal ultrasound. She recommended that Makayla's IV fluids be changed to D5 ½ NS at a rate of 60 mL/hr and directed medical personnel to keep strict track of her I/Os. [3]

At 1:50 PM, the lab reported a new set of results that demonstrated a severe worsening in Makayla's clinical condition, showing a sudden drop in her platelet count to 56K, down from a normal admission value of 256K. Equally worrisome was Makayla's renal function, which was worse (BUN high normal 25, creatinine further elevated to 2.40), and her LDH, which was markedly elevated at 1195. The labs were repeated in the afternoon and again in the evening, at which time her BUN and creatinine rose further to 29 and 2.73; additionally, her liver transaminases were now elevated (AST 165, ALT 48), but her bilirubin was normal.

Confirmation of Shiga toxin 2 – *E. coli* O157

At 5:36 PM, the hospital lab reported a positive result from the stool collected on April 18, 2018, showing it contained Shiga-toxin 2 by PCR testing. The lab report carried the warning:

> Positive Shiga-toxin results are most commonly due to Shiga-toxin producing *E. coli* (O157 or non-O157 STEC) which may cause enterohemorrhagic disease and Hemolytic Uremic Syndrome (HUS). Antimicrobial therapy is not required unless the corresponding stool culture is also positive for *Shigella*.

Satya Vittala, MD discussed these lab results with Destiny and explained that Makayla had likely developed hemolytic uremic syndrome related to Shiga toxin-producing *E. coli* based on the clinical findings and labs and required closer monitoring. She explained that the elevated LDH was caused by hemolysis.

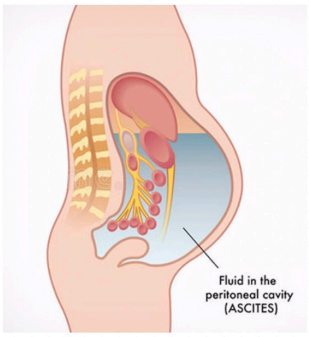
---

[2] One of the 3 cardinal "peritoneal signs," *guarding* is a body defense method to prevent movement of an injured part, esp. spasm of abdominal muscles when an examiner attempts to palpate inflamed areas or organs in the abdominal cavity. Venes, Donald. Taber's Cyclopedic Medical Dictionary (Taber's Cyclopedic Medical Dictionary (Thumb Index Version)) (Page 1056). F.A. Davis Company. Kindle Edition.

[3] I/O – "intake and output" refers to measurement of a patient's fluid intake by mouth, feeding tubes, or intravenous catheters and output from kidneys, gastrointestinal tract, drainage tubes, and wounds.

X-ray evidence of medical renal disease, ascites, pleural effusion

At 8:40 PM, radiologist Christine Kassis, MD performed a transabdominal ultrasound of Makayla's kidneys and bladder, taking careful measurements and inspecting the organs. She identified "small, echogenic kidneys, suggestive of medical renal disease."[4] She observed a lobular contour of the posterior bladder wall, possibly reflective of renal diverticuli. There was small to moderate ascites, including right perinephric fluid, and fluid in Morison's pouch and the pelvis. Dr. Kassis also observed a pleural effusion in her right lung.



- 60% of lean body weight = water
  - →(2/3) intracellular.
  - →(1/3)extracellular (interstitial fluid)
  - →5% blood plasma.
- *edema* = an accumulation of interstitial fluid within tissues.
- Extravascular fluid collection in body cavities:
  - pleural cavity (*hydrothorax*)
  - the pericardial cavity (*hydropericardium*)
  - peritoneal cavity (*hydroperitoneum*, or *ascites*).
- *Anasarca* is severe, generalized edema marked by profound swelling of subcutaneous tissues and accumulation of fluid in body cavities.

Moved to PICU for increasing respiratory distress, worsening labs, HUS

Late in the evening of April 19, 2018, Makayla developed increasing respiratory distress and was started on 3 liters/min of oxygen by nasal cannula. A chest X-ray revealed a new large left-sided pleural effusion and possible left lower lobe infiltrate. Makayla was transferred to the pediatric ICU (PICU) for acute renal failure, metabolic acidosis, progressive anemia, and thrombocytopenia due to hemolytic uremic syndrome. At 12:30 AM on April 20, 2018, Jonathan Matyac, RN inserted a second, small 22g peripheral IV catheter into Makayla's right hand, requiring two attempts, and "saline locked" it for future use.

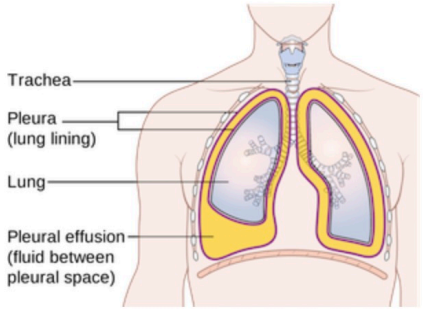


Diagram showing where pleural effusions form

Hospital Day 3 – PICU Day 2 – continued oliguria, respiratory distress

In the early morning hours of April 20, 2018, pediatric critical care intensivist Alan

---

[4] *Medical renal diseases* are those that involve principally the parenchyma (functional tissue) of the kidneys. Vincente, Flavio, MD. "Diagnosis of Medical Renal Disease." *Diagnosis of Medical Renal Disease.* Armina Hypertension Association, 2016. Web. 31 Jan. 2017.

Graham, MD was summoned urgently to the PICU by Dr. Surapeneni to evaluate Makayla's hemolytic uremic syndrome and respiratory distress with left-sided pleural effusion and anasarca. The PICU staff reported that she had been moved there a few hours earlier when she developed respiratory distress with low blood oxygen levels requiring increasing amounts of supplemental oxygen. Dr. Graham observed that Makayla was a previously healthy seven-year-old girl who had been having diarrhea since the 15th. He found it notable that she was afebrile except for one elevated temperature of 100.4ºF at home. He reviewed the ultrasound showing echogenic kidneys but no other specific renal abnormalities.

On exam, Dr. Graham found Makayla in "moderate distress," waking easily and appearing anxious with intermittent episodes of crampy abdominal pain. Her chest was clear to auscultation on the right, but her breath sounds were very diminished on the left, and she exhibited nasal flaring, bilateral intercostal, and subcostal retractions, consistent with significant respiratory distress. She was in sinus tachycardia with a heart rate of 160, but her peripheral pulses were palpable, and she had brisk capillary refill. Dr. Graham observed "central edema" with abdominal distention and periorbital edema.

Periorbital edema (example, not Makayla)

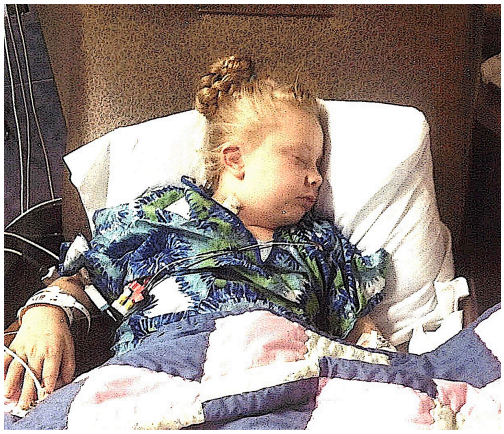
Makayla's abdomen was moderately distended with some tenderness in the epigastric and left upper quadrant, but Dr. Graham could not evaluate for hepatosplenomegaly as the exam was too painful for her. Dr. Graham agreed with the diagnoses of acute kidney injury, dehydration, hemolytic uremic syndrome (HUS), Shiga toxin-producing *Escherichia coli* infection, and sepsis of unspecified origin. Although Makayla's diarrhea made it difficult to measure urinary output, it was clear to Dr. Graham that she was oliguric and fluid overloaded, as evidenced by central edema, pleural effusions with respiratory distress, and hypoxia.

Dr. Graham was concerned that Makayla might need to be emergently intubated to secure her airway and reduce her metabolic stress. He decided she needed to undergo the insertion of a chest tube to relieve her pleural effusions.

Nephrology determines need for urgent hemodialysis, trial of Lasix to induce urine output

Dr. Graham consulted with nephrology, who concurred that Makayla was already fluid-overloaded and oliguric/anuric with uremia and "thus meets criteria for dialysis." They agreed that they would first trial a "single (large) dose" of Lasix to see if they could induce any urinary output and maintain her renal pressure. They chose not to insert a Foley catheter because it posed an infectious risk and would not add to the management decision already made that Makayla met the criteria for dialysis.

In coordination with pediatric surgery, the doctors planned to coordinate Makayla's chest tube insertion with hemodialysis catheter placement, for which she would be sedated and intubated under general anesthesia. They ordered serial chest X-rays and arterial blood gas measurements. Dr. Graham anticipated that Makayla would need a cardiac ECHO to assess her cardiopulmonary function and assess her for pericardial effusions. Given her acute renal failure, he planned to monitor her closely for the development of hypertension. He requested the insertion of a PICC line and central venous catheter for therapeutic and monitoring purposes.



Makayla looking edematous

Neurologically, Dr. Graham thought Makayla was stable but needed to be watched for signs of neurologic involvement as she was potentially at risk for a stroke or CNS hemorrhage. To that end, he asked for the head of her bed to be elevated and to do serial neuro checks. He wanted to keep her pain level down with judicious pain control with Tylenol and opiates, avoiding NSAIDs and other nephrotoxic agents.

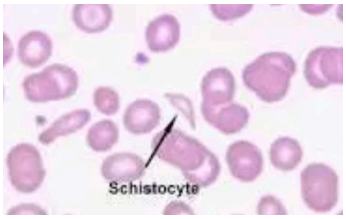
Pediatric surgical consultation for chest tube and dialysis catheter

Just past noon on April 20, 2018, pediatric general surgeon Tuan Pham, MD evaluated Makayla and prepared her for surgery, in anticipation of the chest tube and dialysis catheter. Makayla's morning labs showed multiple abnormal values, including an elevated white count of 45.2, mild anemia with a hemoglobin and hematocrit of 11.6 and 32.6, and platelets 55K. Her renal function labs were significantly abnormal as well, with a BUN 43 and creatinine 3.89. A quantitative D-dimer was extremely elevated at >7650.[5] A peripheral smear showed the presence of 1+ schistocytes and Makayla's haptoglobin level was low at 14 mg/dL.[6]

---

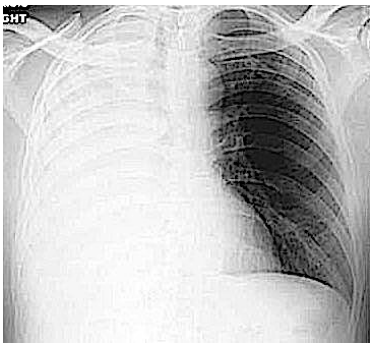
[5] Normal D-dimer is <500 ng/mL FEU. D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross-linked D fragments of the fibrin protein. D-dimers and FDP can become elevated whenever the coagulation and fibrinolytic systems are activated. Adam, S., Key, N., & Greenberg, C. (2009). D-dimer antigen: Current concepts and future prospects. *Blood, 113*(13), 2878-2887

[6] The hemolytic-uremic syndrome (HUS) is defined by the association of hemolytic anemia (low haptoglobin levels, high lactate dehydrogenase levels, and schistocytes), thrombocytopenia, and acute renal failure. Olivia Boyer and Patrick Niaudet, "Hemolytic Uremic Syndrome: New Developments in Pathogenesis and Treatment," International Journal of Nephrology, vol. 2011, Article ID 908407, 10 pages, 2011. doi:10.4061/2011/908407



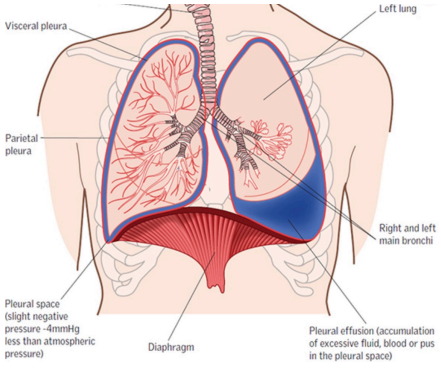
To the OR for multiple HD and central line procedures

Just before 1 PM, Dr. Pham took Makayla to the operating room, where a 20-French left chest tube, 12-French "permanent" right internal jugular hemodialysis catheter, and 10-French right basilic PICC line were placed under general anesthesia. The clinical indications for the procedures included "acute kidney injury," "bilateral pleural effusions," "hemolytic uremic syndrome," and "Shiga toxin-producing *Escherichia coli* infection." Makayla was first premedicated for the procedure with a cephalosporin antibiotic (IV Ancef). Radiologist Amal Jabra, MD was present to provide fluoroscopic guidance during the procedures, during which he observed a moderate left-sided pleural effusion throughout the visualized left hemithorax, as well as "residual confluent airspace disease in the left lower chest."

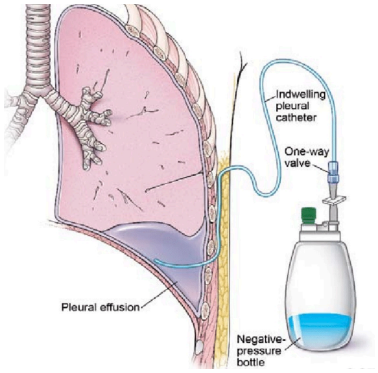


Hemithorax (illustration - not Makayla)
Shows a right lung opacification

Dr. Pham first inserted a left chest tube. Approximately 500 mL of clear pleural fluid was drained, and the chest tube entry point was secured at the chest wall and dressed.



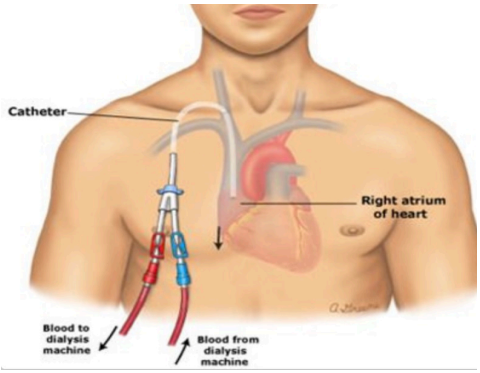
Left pleural effusion



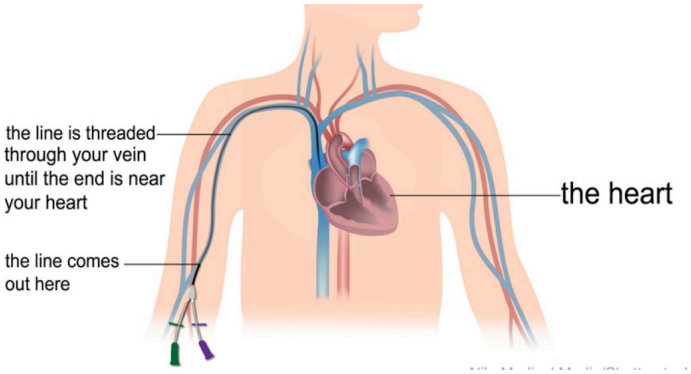
Chest tube insertion

Difficulty with dual central line insertions…

After the chest tube was secured, at 2:15 PM Dr. Pham placed a double hemodialysis/pheresis catheter in Makayla's right internal jugular vein, with the tip terminating in the right atrium of her heart. He followed this with the insertion of a peripherally-inserted central catheter (PICC line).



RIJ HD catheter in right atrium



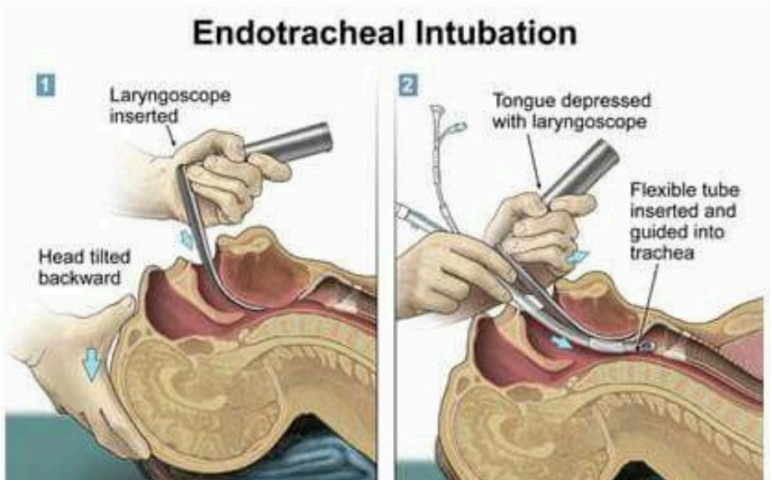
Right basilic insertion of PICC line in right atrium

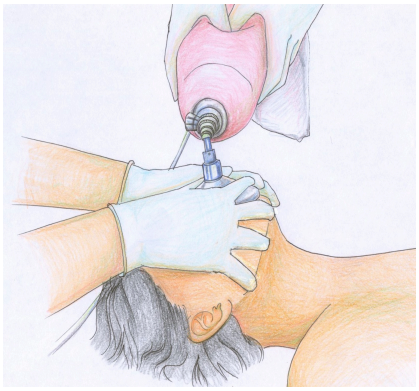
Dr. Pham's first attempt to insert the PICC line failed when the guide wire/catheter would not thread through Makayla's left basilic vein; he therefore instead utilized her right basilic vein, threading the catheter alongside the previously-placed RIJ HD catheter, with both tips terminating in the right atrium of her heart. Dr. Pham encountered some difficulty with kinking of the HD catheter in Makayla's neck, although the dual line insertions both drew blood easily.

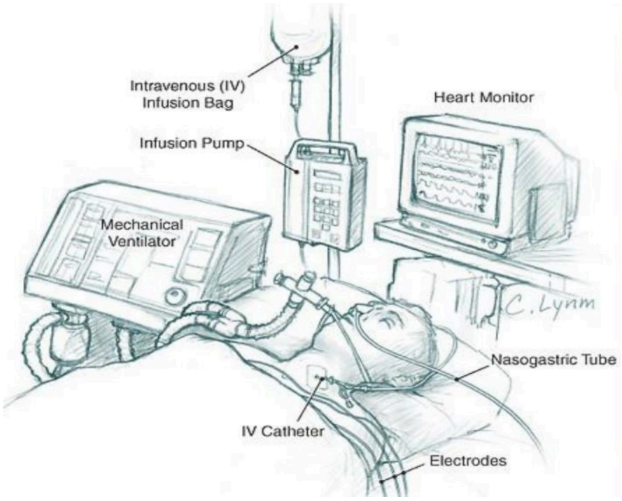
Dr. Pham dictated his operative report at 3:09 PM, describing the difficulties he encountered:

> There were 2 dialysis catheters; 1 was a 10-French and 1 a 12-French. The 12-French was what the ICU requested for her dialysis. It is slightly long. I tunneled the catheter from the anterior chest to the neck venotomy site. Under fluoroscopy, I dilated the track over the wire up to a size 12-French. The peel-away sheath was with the dilator. Once the peel-away was in place, I inserted the catheter into the peel-away sheath and the peel-away sheath was broken. Initially there was a kink in the neck. As such, I had to enlarge the incision to manipulate the surrounding soft tissue so that the catheter can make a gentle curvature. With multiple manipulations, I was able to confirm that there was no more kink in the neck by visual inspection, as well by fluoroscopy. The distal tip of the catheter was in the atrium. Both ports drew blood easily. They were appropriately heparinized with 10 units per mL of heparin. The catheter was secured in place. The cuff was approximately 2 cm away from the skin incision. The neck incision was closed in multiple layers. Dressing was applied. She tolerated procedure well. All counts were correct.

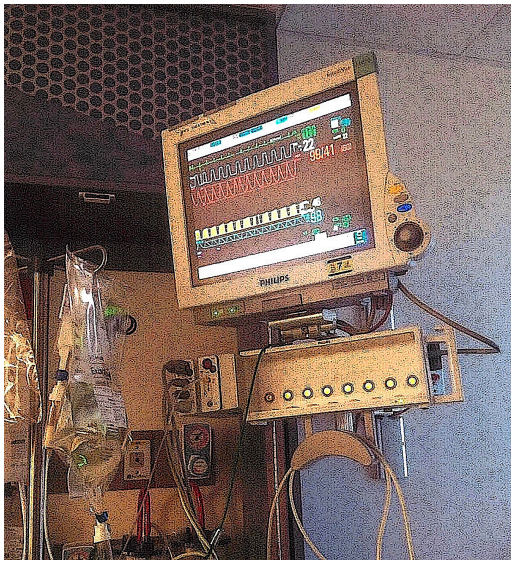
Live imaging confirmed correct catheter placement, after which insertion sites were dressed. At the end of the procedures, Makayla remained intubated and was provided with ambubag oxygen delivery en route to the post-anesthesia care unit (PACU), where she was connected to mechanical ventilation.







Mechanical ventilation



Makayla's monitors and IVs

Pediatric Nephrology Consultation – kinked HD line – CRRT ordered

At 4:20 PM on April 20, 2018, pediatric nephrologist Ayah Y. Elmaghrabi, MD arrived to find Makayla still intubated and sedated post-procedure. She noted that the chest tube was draining blood-tinged serous fluid and her lungs sounded better to auscultation. Dr. Elmaghrabi was unhappy with the placement of the current HD line and wanted it to be adjusted or replaced before dialysis could be started. She wrote orders to start hemodialysis in the form of CVVHDF.[7] In addition, she wanted Makayla started on TPN the following morning.

Continued volume overload – low C3 complement, normal C4

Dr. Elmaghrabi observed that Makayla continued to exhibit volume overload (periorbital edema) and had very little urinary output. She ordered additional lab work to follow her LDH, haptoglobin, anemia, peripheral smear for schistocytes, and autoimmune testing (ANA, ANCA, complement C3 and C4 proteins), as well as a renal ultrasound. Commenting that Makayla had TMA,[8] Dr. Elmaghrabi ordered blood transfusions if her hemoglobin dropped below 7 g/mL, but she wanted to avoid platelet transfusions. Makayla's C3 complement proteins came back marginally low normal at 86 (RR 90-180 mg/dL) and her C4 was normal at 19 (RR 16-47).

Repeat imaging at the bedside – HD catheter non-functional – failed repositioning

Just before 7 PM, Christine White, DO repeated Makayla's chest X-ray at the bedside for the purpose of repositioning the RIJ hemodialysis catheter. She observed that her endotracheal tube was in satisfactory placement, as was the left apical chest tube. She also identified a right upper extremity venous catheter (PICC) with the tip at the junction between the superior vena cava and right atrium of Makayla's heart, as well as a double lumen central venous catheter (CVP/HD line) ending at the lower aspect of the right atrium. She noted significant clearing of the left hemithorax; however, confluent airspace opacification remained visible in the mid to lower left lung field, mostly at the retrocardiac level. Dr. White observed that Makayla's left lung was smaller than her right and that there was a probable minimal residual pleural effusion on the right side, with "mild streaky somewhat confluent opacification" at the base. Dr. White

---

[7] CRRT has become the preferred modality for managing hemodynamically unstable patients with AKI. The different CRRT modalities can use diffusion, convection, or a combination of both for solute clearance. Unlike [intermittent hemodialysis], CRRT is performed continuously (24 hours per a day) with a typical blood flow of 100 to 300 mL/min and a dialysate flow of 17 to 40 mL/min if a diffusive CRRT modality is used. It is performed most commonly through a venovenous vascular access. The most commonly applied modalities of CRRT are continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Harshman L.A., Brophy P.D., Symons J.M. (2016) Management of Pediatric Acute Kidney Injury. In: Geary D., Schaefer F. (eds) Pediatric Kidney Disease. Springer, Berlin, Heidelberg

[8] Thrombotic microangiopathy (TMA). "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/.

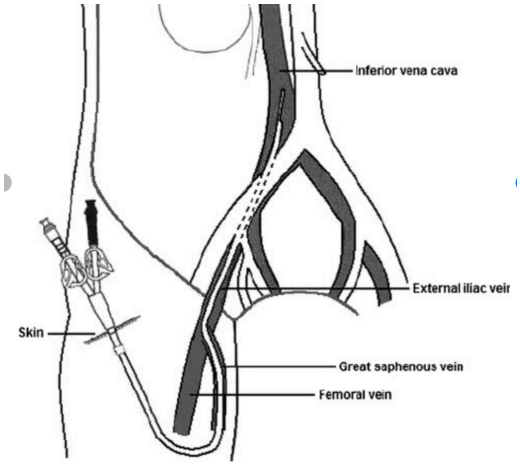
successfully retracted the right intrajugular HD line to the level of the cavoatrial junction; however, the line was clotted and could not be flushed or draw blood, making it non-functional for hemodialysis.

Back to the OR for femoral placement of HD catheter

At 10 PM on April 20, 2018, Dr. Pham brought Makayla back to the operating room for her diagnosis of "malpositioned and kinked tunneled catheter placed in the neck" and "hemolytic uremic syndrome, requiring renal dialysis." Dr. Pham commented:

> The patient has HUS and I initially placed a tunneled double-lumen hemodialysis catheter in the right IJ. In order for it to not kink at that neck position, the catheter needed to be placed deep with the tip in the right atrium. It was found that the tip flipped into the right ventricle. As such, I pulled the catheter back, but then it kinked at the neck incision. It was not usable. I recommended insertion of a temporary catheter in the femoral region in order to preserve the right IJ in case she needs a more permanent catheter. I discussed the procedure and indication with her mother.

As Makayla remained intubated, the anesthesiologist induced general anesthesia with the current intubation. In addition, she was already on antibiotics (Ancef) since the initial procedure. Dr. Pham successfully placed a 12-French Mahurkar hemodialysis catheter in the right femoral vein, with the tip terminating in the common iliac vein. The port flushed easily and drew blood readily. It was therefore secured in place.

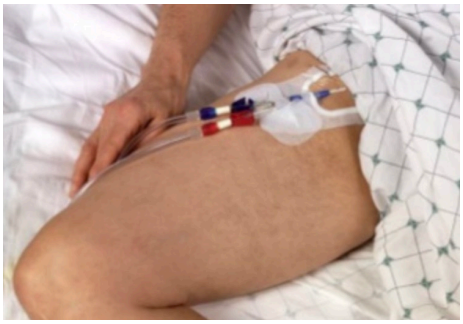


Location of Makayla's femoral vein HD catheter

After completing the placement of Makayla's femoral line, Dr. Pham removed the right internal jugular vein hemodialysis catheter, leaving the right basilic vein PICC line in place. He commented:

> Of note, if she does [need a] more permanent catheter, she needs a shorter catheter length, preferably approximately 18 to 22 cm from the cuff. There was no 12-French 18 to 22 cm in stock at this time, only 28 cm. There is a 10-French 18 cm

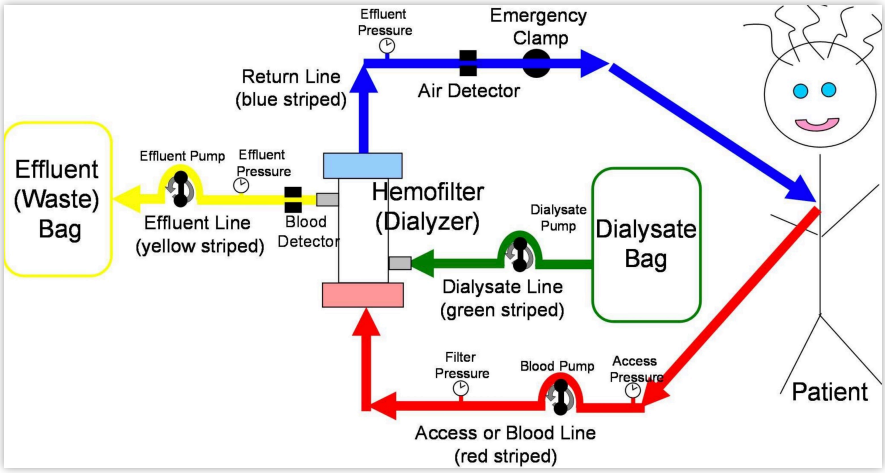
in stock at this time which can also be used."



Femoral hemodialysis catheter
(illustration, not Makayla)

Hemodialysis begins: CRRT/CVVHDF Day 1 – transfusion pRBCs

Just before midnight on April 20, 2018, Makayla was started on CRRT – CVVHDF[9] (continuous venovenous hemodiafiltration) at 11:35 PM. She also received one unit of packed red blood cells (pRBCs).



Continuous venovenous hemodiafiltration (CVVHDF)

Hospital Day 4, PICU Day 3, CVVHDF Day 2 – continued mechanical ventilation

On April 21, 2018, at 4:59 AM, pediatric critical care intensivist Jose Gutierrez, MD arrived as part of the PICU team and reviewed Makayla's hospital course to date. He discussed

---

9 Continuous veno-venous hemodiafiltration (CVVHDF) uses the principles of both hemofiltration and hemodialysis, as described. As this mode enable the ultimate removal and replacement of solutes and fluids within the blood, it is the most common mode chosen for CRRT. It is recommended that this mode is always selected, even if the clinician would like to run only hemofiltration or only dialysis. This is because the other modes can be achieved within this mode through the programming of dialysate and/or replacement fluids. However, this mode cannot be achieved in the other modes unless the whole filter is re-started. Adeel Rafi Ahmed, Ayanfeoluwa Obilana, and David Lappin, "Renal Replacement Therapy in the Critical Care Setting," Critical Care Research and Practice, vol. 2019, Article ID 6948710, 11 pages, 2019. https://doi.org/10.1155/2019/6948710.

her case with Dr. Elmaghrabi, Dr. Graham, pharmacy, and the nursing staff. Makayla was sedated on Precedex and on a neuromuscular blocker. She remained orally intubated on ventilator support and her left chest tube was draining serous pleural fluid. She was afebrile with stable vital signs, although she was intermittently tachypneic with somewhat labored breathing and nasal flaring over the ventilator. A sample of the pleural fluid had been collected for Gram stain and culture the day before; the culture was pending, but the Gram stain showed rare WBCs and no organisms.

Multiple co-morbidities…

Makayla's diagnosis list was long and included the following:

- Respiratory failure/acute post procedure
- Hypoxemia
- Hemolytic uremic syndrome
- Thrombocytopenia
- Pleural effusion
- Acute kidney injury
- Acute kidney failure

Dr. Gutierrez continued Makayla's admission to the PICU to manage her respiratory failure, acute kidney injury, and hemolytic uremic syndrome. He ordered continued sedation with Precedex, and frequent neuro checks and seizure precautions. Ventilator support was set for normal oxygenation and minute volume[10] (MV), but Dr. Gutierrez hoped to extubate Makayla later that same day. Meanwhile, he would monitor her chest tube output and cardiopulmonary function on telemetry. CRRT/CVVHDF was ongoing at this point.

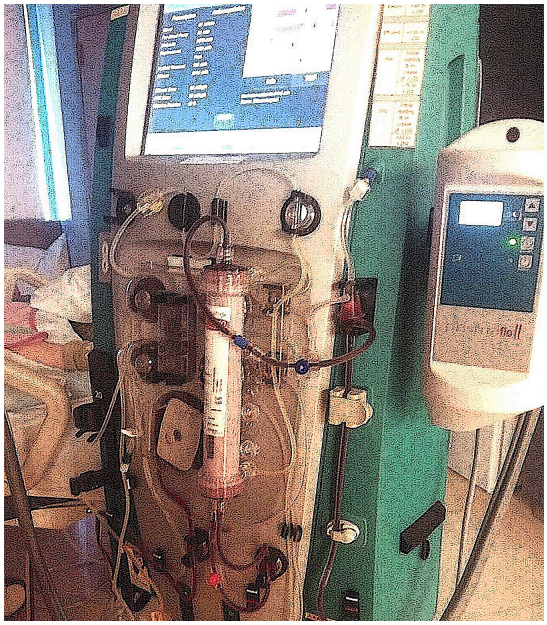
Pediatric Nephrology – anuric but no further bloody diarrhea

At 10:45 AM on April 21, 2018, Karen Papez, MD observed that Makayla's initial HD line was too deep and then was not working. The femoral line was placed because of the nonfunctioning line and she was receiving ongoing CRRT. Dr. Papez also observed that Makayla was not producing any urine. She no longer had bloody diarrhea. The chest tube that was placed for her left pleural effusion was draining abundant fluid, more than 610 mL over the prior 24 hours. She noted that Makayla remained intubated for respiratory failure.

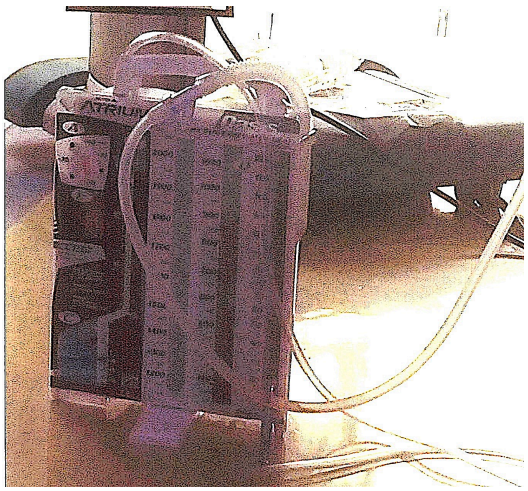
Dr. Papez reviewed Makayla's morning labs, which showed a WBC 29.4, hemoglobin 8.2, hematocrit 24.1%, platelets 63K, BUN 52, creatinine 4.33. Makayla appeared to be well-oxygenated and her vitals were stable. Dr. Papez deferred the management of her mechanical ventilation to the PICU team.

---

[10] Respiratory minute volume (or minute ventilation or minute volume) is the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute. It is an important parameter in respiratory medicine due to its relationship with blood carbon dioxide levels. Bateman, N T, and R M Leach. "ABC of oxygen. Acute oxygen therapy." *BMJ (Clinical research ed.)* vol. 317,7161 (1998): 798-801. doi:10.1136/bmj.317.7161.798



Makayla's CRRT machine, multiple monitors, lines and tubes on mechanical ventilation



Makayla's chest tube drainage, negative pressure system

Pediatric Surgery

Nicole Hayes, PA evaluated Makayla for the surgery service, finding Makayla intubated and sedated on mechanical ventilation with her family at the bedside. She inspected the chest tube drainage, which exhibited no air leaks and the insertion site was clean, dry and intact under the occlusive dressing. The PA asked the PICU team to alert her and Dr. Pham to consult when they deemed the chest tube no longer necessary, although she approved the team removing it on their own if Makayla was not tolerating the discomfort.

KUB Imaging for increasing abdominal distention

At 8:44 PM on April 21, 2018, radiologist John Wendel, MD completed an X-ray evaluation of Makayla's kidneys-ureters-bladder (KUB) to assess her increasing abdominal distention in the setting of HUS. He compared the imaging to that done on April 16, 2018. Dr. Wendel identified gaseous distention of the large bowel, with a relative paucity of bowel gas in the right lower quadrant. The chest tube was visible and correctly positioned, as was the femoral HD central catheter. He suggested follow-up with an ultrasound if there was increasing concern overnight.

Pediatric Critical Care – continues to require mechanical ventilation – continued anuria

Just before 9 PM, Richard Betters, MD evaluated Makayla for critical care and reviewed Makayla's oxygen requirements and other PICU needs. As part of his examination, Dr. Betters discussed her physiologic trends with Dr. Papez, Dr. Gutierrez, respiratory therapy, and the nursing staff. Dr. Betters commented that Makayla was still critically ill and required continued intubation and sedation, although she was stable on CRRT. She had experienced intermittent hypotension overnight but was now improved after a 300-cc bolus of albumin administered intravenously. A morning chest X-ray confirmed that Makayla's endotracheal tube was still in good position between T1 and T2, with a left-sided chest tube in situ and draining abundant serosanguinous fluid. She remained anuric but was not having any bloody diarrhea.

Respiratory failure unspecified cause – perioperative antibiotics stopped

Dr. Betters observed that Makayla's respiratory failure was unspecified as to whether it was related to hypoxia or hypercapnia (low oxygen vs. elevated CO2). She remained on ventilator support with SIMV[11] pressure control plus pressure support mode. The PICU team was observing ventilator-acquired-pneumonia (VAP) precautions, including head-of-bed elevation and chlorhexidine skin prep use to reduce skin bacteria, with daily chest X-rays while she was intubated. Dr. Betters agreed with nephrology's recommendation to start Makayla on nutritional support with TPN[12] plus intralipids (IL), with a plan to wean her off intravenous fluids once those were well established. Now that she was postoperative and afebrile, he discontinued her antibiotic (Ancef), with consideration of an infectious disease consultation if Makayla was not improving or developed additional symptomatology.

Hospital Day 5, PICU Day 4, CVVHDF Day 3 – increasing left pleural effusions

On April 22, 2018, Makayla's morning chest X-rays showed her endotracheal tube in a slightly elevated position, and she had an increasing left base atelectasis and left pleural effusions. There were mild hazy infiltrates in her right lung and an increase in a small right pleural effusion. Her right PICC line had been adjusted and was in good position in the high right atrium. Her left

---

[11] Synchronized Intermittent Mandatory Ventilation (SIMV) is the most common mode of ventilation used for conscious patients who don't require 100% of the work being done for them. This mode allows the patient to breath on their own between the set rate of breaths given by the machine. *Ibid*.

[12] TPN by definition is nutrition given intravenously. It typically consists of dextrose, amino acids, emulsified fats, trace elements, vitamins, and minerals to patients who are unable to assimilate adequate nutrition by mouth. Because TPN solutions are concentrated and can cause thrombosis of peripheral veins, a central venous catheter is usually required. Venes, *supra* Note 84 at 1650.

chest tube was stable. Makayla's ET tube was adjusted and a tracheal aspirate was sent to the lab for Gram stain and culture. The Gram stain result was reported showing the expected gram positive and gram negative mixed lower respiratory flora,[13] but a culture was pending results.

Desaturating O2 levels – pulmonary edema, tracheitis – started on abx (ceftriaxone)

Dr. Papez came in for nephrology and observed that Makayla still was not producing any urine. She was concerned about Makayla's condition as she "desaturated" every time she was moved and her left lung appeared more concerning for pulmonary edema on the current imaging. Her morning labs were relatively stable, with a WBC 22.6, hemoglobin 8.5, hematocrit 24.9%, platelets 78K, BUN 34, creatinine 2.21. Her liver enzymes were elevated (AST 213, ALT 172). Makayla was about to be started on TPN.

At 2:48 PM, Dr. Gutierrez arrived for critical care and listened to Makayla's lungs, finding them coarse-sounding with diminished breath sounds in the bases. He was concerned about her unstable oxygen levels and the radiologic appearance of her lungs, so he consulted with the PICU team and decided to start Makayla on IV ceftriaxone, to be given "IV push" every 24 hours for a possible pulmonary infection.

Hospital Day 6, PICU Day 5, CVVHDF Day 4 – continued antibiotics for tracheitis

Imad Haddad, MD came in for critical care on April 23, 2018 and noted a slight improvement in Makayla's left lung pleural effusions since the day before. She remained on mechanical ventilation and CRRT/CVVHDF. Dr. Haddad observed that Makayla's low blood pressures had persisted, making it difficult to "pull fluid off" with ultrafiltration. She was therefore started on an epinephrine drip to facilitate excess fluid removal. Makayla was also given two more infusions of 25% albumin.

Dr. Haddad consulted with Dr. Gutierrez, as well as Dr. Elmaghrabi and general surgeon Jonathan Greenfeld, MD, and he continued Makayla's IV ceftriaxone for "tracheitis." The doctors also continued sedation with Precedex and fentanyl as needed for comfort, as well as Ativan for anxiety. Makayla was transitioned to PRVC[14] ventilation to monitor her oxygenation and ventilation. Dr. Elmaghrabi discussed with Dr. Greenfeld that Makayla was going to require a permanent dialysis catheter, which he planned for the following Wednesday.

Hospital Day 7, PICU Day 6, CVVHDF Day 5 – still intubated – blood transfusion pRBCs

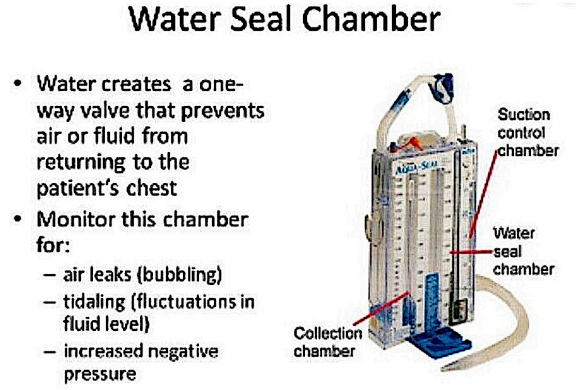
On April 24, 2018, Dr. Elmaghrabi came in for nephrology in the morning and noted there had been no acute events overnight. Makayla remained anuric/oliguric. She was afebrile. Her systolic blood pressures were still labile, ranging from 70-110s on the epinephrine drip. She was

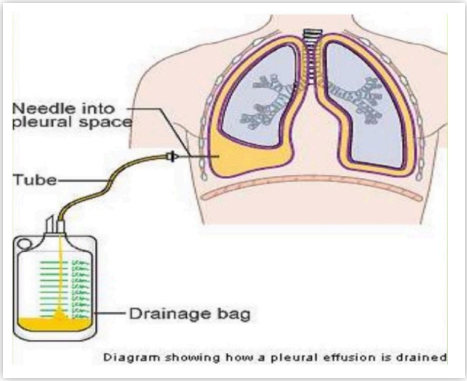
---

[13] The presence of normal upper respiratory tract flora should be expected in sputum culture. Normal respiratory flora include *Neisseria catarrhalis, Candida albicans,* diphtheroids, alpha-hemolytic streptococci, and some staphylococci. *Manual of Laboratory & Diagnostic Tests (7th Edition): Fischbach, Frances Talaska*. Lippincott Williams & Wilkins: 2004. Makayla's sputum culture was positive for pathogens – see DOS 4/26/18.

[14] Pressure-regulated volume control (PRVC) is a form of an adaptive pressure-controlled ventilation in which tidal volume is used as a feedback control to continuously adjust the pressure limit. "Pressure Regulated Volume Control (PRVC): Set It and Forget It?" *Respiratory Medicine Case Reports*, Elsevier, 8 Mar. 2019

tolerating CRRT/CVVHDF, but the circuit had clotted that morning and interrupted the procedure for a time. Makayla's morning lab values revealed a WBC 16.6, hemoglobin 7.2, hematocrit 21.5, platelets 58K, BUN 30, creatinine 1.06, AST 66, ALT 63, INR 1.3, PT 15.2. Makayla received another blood transfusion of pRBCs for the severity of her hemolytic anemia.





Dr. Greenfeld came in for the surgical service and found Makayla stable on mechanical ventilation. He inspected the chest tube and drainage system, observing that there was no air leak and there was positive "tidaling."[15] He also evaluated her femoral catheter insertion. The circuit had clotted during CRRT, which required clearing the line and restarting the dialysis. Dr. Greenfeld discussed the risks of major vascular injury with life threatening bleeding with Makayla's mom, if they kept the HD catheter in its current location. He therefore planned to take Makayla back to the OR for the insertion of a "permanent" HD catheter the following day.

Hospital Day 8, PICU Day 7, CVVHDF Day 6

On April 25, 2018, Makayla's morning chest X-ray continued to show left lower lobe confluent airspace opacification, with more patchy areas in the remainder of the lung fields of both lungs. The radiologist found the appearance of Makayla's lungs consistent with pneumonia. She remained in critical condition on CRRT and sedated on mechanical ventilation. Dr. Haddad wanted to try and wean her epinephrine drip as tolerated to keep her mean arterial pressures above 55.[16] He also hoped to start the weaning process to get Makayla off mechanical ventilation. Although she was currently sedated, she was responsive during exam. Her morning labs showed a WBC 16.5, hemoglobin 9.0, hematocrit 26.4, platelets 65K, BUN 45, creatinine 1.33. The peripheral smear continued to show 1+ schistocytes.

---

[15] Tidaling—fluctuations in the water-seal chamber with respiratory effort—is normal. The water level increases during spontaneous inspiration and decreases with expiration. However, with positive-pressure mechanical ventilation, tidaling fluctuations are the opposite: the water level decreases during inspiration and increases during expiration. If tidaling doesn't occur, the tubing might be kinked or clamped, or a dependent tubing section has become filled with fluid. F.J. Brims, S.M. Lansley, G.W. Waterer, et al. "Empyema thoracis: new insights into an old disease" Eur. Respir. Rev., 19 (2010), p. 220

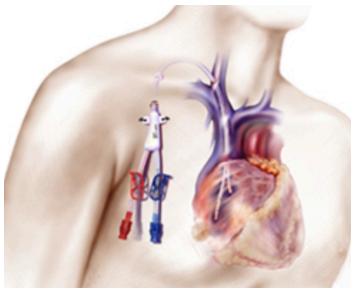
[16] Mean arterial pressure (MAP) is defined as the average pressure in a patient's arteries during one cardiac cycle. It is considered a better indicator of perfusion to vital organs than systolic blood pressure (SBP). MAP functions to perfuse blood to all the tissues of the body to keep them functional. Mechanisms are in place to ensure that the MAP remains at least 60 mmHg so that blood can effectively reach all tissues. DeMers D, Wachs D. Physiology, Mean Arterial Pressure. [Updated 2019 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538226/

Pediatric nephrologist Stephanie Hsieh, MD evaluated Makayla in the morning and spoke with her mom and the nursing staff. Makayla was experiencing diarrhea but still had no urine output. Dr. Hsieh reviewed the morning labs and addressed the plan to replace her HD catheter that afternoon. Makayla had been exhibiting elevated potassium levels on TPN, so nutritional adjustments were made. Dr. Hsieh made no changes to Makayla's dialysate but planned to reassess after the new HD catheter was in place.

To OR for removal of femoral catheter, placement RIJ HD/pheresis catheter – pRBCs

At around 12 noon on April 25, 2018, Dr. Greenfeld took Makayla to the operating room where general anesthesia was induced using her existing endotracheal intubation. Dr. Greenfeld did not administer additional antibiotics as she was still on ceftriaxone. Makayla received a blood transfusion during the procedure.

Dr. Greenfeld began the procedure with the insertion of a new right internal jugular 14-French HD/pheresis catheter. He found the new insertion difficult because Makayla's normal anatomy was distorted by a hematoma from the previous hemodialysis catheter attempt into the right internal jugular (RIJ) vein. This required Dr. Greenfeld to make a 3 cm transverse incision over the RIJ vein on Makayla's neck. After removing several sutures left behind with the last RIJ closure, he met stiff resistance when trying to thread the new catheter; however, after ligating the vein and dissecting it free, he was able to introduce the catheter under fluoroscopic guidance, after which it was easily flushed with saline and successfully aspirated blood.



Long-term HemoSplit HD RIJ catheter

Dr. Greenfeld finished the RIJ procedure without further difficulty, sutured the catheter in place, and applied an occlusive dressing with "biopatch." After the RIJ line was secured and placement confirmed by fluoroscopy, Dr. Greenfeld removed Makayla's right femoral vein HD catheter, ensuring hemostasis of the site prior to redressing the wound. She was taken to the PACU in stable condition but remained intubated.

Restarted CRRT with new right internal jugular HD catheter

Makayla's CRRT/CVVHDF was resumed by 3:32 PM. Dr. Hsieh came in for nephrology after Makayla was returned to the PICU. CRRT/CVVHDF was in process with good flow, "except when coughing." Dr. Hsieh made adjustments to her TPN, eliminating the added potassium as Makayla was still hyperkalemic on her labs.

Sputum culture growth of beta-lactamase-positive *H. influenzae* – continued antibiotics

Dr. Haddad returned for pediatric critical care during the late afternoon. He noted that Makayla was now on day 4 of 7 of IV ceftriaxone to treat her pneumonia and tracheitis. The laboratory reported that her sputum culture was growing *Haemophilus influenza* and *Streptococcus pneumoniae.* Makayla remained afebrile and Dr. Haddad ordered that she be transitioned off mechanical ventilation as tolerated.

Hospital Day 9, PICU Day 8, CVVHDF Day 7 – continued anuria

On April 26, 2018, Makayla's morning chest X-ray confirmed proper placement of her multiple tubes and lines, except for the right upper extremity PICC line, with the catheter tip slightly misplaced at the mid aspect of the right atrium. Amal Jabra, MD, performed the exam and observed improved lung volumes, with the worst residual bilateral airspace disease still in the left lower lobe. He called the results to the PICC nurse, Claudia Carlin, RN.

Chest tube removal after reduction in drainage noted

Dr. Greenfeld came in for the surgery service after the chest X-ray, noting that Makayla was still not producing any urine, but the CVVHDF had successfully removed 3664 mL of excess fluid. Her chest tube was still draining fluid at the rate of 50 mL in the past 24 hours. There was no leak in the negative pressure system, and the drainage was straw-colored and slightly serosanguinous. He consulted with the PICU team about his observations and went ahead with removal of the chest tube at the bedside. The chest X-ray was repeated in the early afternoon and demonstrated a slight readjustment of the PICC line and mild clearing of the lung fields. Incidentally noted was a dilated bowel loop in Makayla's upper abdomen.

Falling blood counts – another transfusion of pRBCs

Dr. Hsieh arrived for nephrology and requested another blood transfusion of pRBCs after reviewing Makayla's morning labs and observing a hemoglobin of 7. She also approved the initiation of trophic feeds[17] that day, which could utilize a "regular formula" while she was on CRRT. Dr. Hsieh was hopeful that Makayla might be extubated in the next 24-48 hours. Once that occurred, she wanted to transition Makayla to intermittent hemodialysis. Physical therapy and occupational therapy began visiting Makayla to initiate the process of mobilizing her and getting her started with everyday activities and self-care.

On April 26, 2018, the hospital lab issued a final report on Makayla's sputum culture, which showed heavy growth of *Haemophilus influenzae* – beta-lactamase-positive, scant growth of *Streptococcus pneumoniae*, and scant growth of *Streptococcus pyogenes* (Group A

---

[17] The generally accepted definition of trophic feeding is a small volume of balanced enteral nutrition insufficient for the patient's nutritional needs but producing some positive gastrointestinal or systemic benefit. If more than 25% of the patient's nutritional needs are administered enterally, the feeding should no longer be considered trophic. "A Critical Perspective on Trophic Feeding : Journal of Pediatric Gastroenterology and Nutrition." *LWW*, https://journals.lww.com/jpgn/Pages/ArticleViewer.aspx?year=2004&issue=03000&article=00001&type=Fulltext.

Streptococcus). The report stated:

> Penicillin and cephalosporins are universally active against beta hemolytic Streptococci. Microbiology lab tests susceptibility studies only if an agent such as clindamycin or gentamicin is being considered for therapy. Testing was in fact done, which showed the bacteria was "Intermediate" to ceftriaxone meningeal, "Susceptible" to ceftriaxone nonmeningeal, "Resistant" to erythromycin, "Susceptible" to levofloxacin, and "Resistant" to oral penicillin.

Hospital Day 10, PICU Day 9, CVVHDF Day 8 – normal complement proteins

On April 27, 2018, Kelly Benedict, MD evaluated Makayla for pediatric nephrology, first visiting in the morning and then again later in the evening. During the morning visit, she noted that Makayla had been weaned off epinephrine and her blood pressures were still labile. She was still anuric. Although still intubated and sedated, her narcotic medications were being weaned. Her lungs sounded clear to Dr. Benedict's auscultation and her breathing was nonlabored on the vent. She reviewed Makayla's morning labs, noting her WBC had normalized to 8.0. She was still significantly anemic with a hemoglobin of 8.8 and hematocrit 26.1, but well above transfusion range. Her platelets were 71K. Her BUN and creatinine were 49 and 1.18. Makayla's complement proteins were repeated, with return to normal C3[18] (C3 complement 135, C4 complement 21).

Alan Graham, MD examined Makayla on behalf of critical care at 10 PM, noting that Makayla was now on day 6 of 7 of antibiotic therapy with ceftriaxone for tracheitis and pneumonia. He commented: "No fever but on CRRT circuit." Makayla was not tolerating enteral feeds, which had caused vomiting episodes, so those were held for the time being. She remained on TPN.

Hospital Day 11, PICU Day 10, CVVHDF Day 9 – still anuric

On April 28, 2018, Thant Lin, MD, came in for pediatric critical care, finding Makayla still on Precedex sedation on the ventilator, but she had been started on methadone overnight and was weaning off fentanyl. She was receiving CRRT/CVVHDF without any problems but was still not producing any urine. She was on her final day of ceftriaxone.

Dr. Elmaghrabi rounded for nephrology and made no changes to Makayla's dialysis orders. Of concern, the doctor found her abdomen too tender to permit a thorough exam. However, her CBC was stable with a WBC 7.9, hemoglobin 8.3, hematocrit 24.1, and platelets 65K. Her BUN and creatinine were 47 and 1.24, respectively.

---

[18] HUS vs. aHUS: Hemolytic uremic syndrome (HUS) is characterized by the clinical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Atypical Hemolytic Uremic Syndrome (aHUS) refers to non-Shiga-toxin HUS and is a primary thrombotic microangiopathic disease due to chronic, uncontrolled activation of the complement system. Complement-mediated HUS is a relatively rare, life threatening disorder caused by mutations in the genes that encode complement proteins. Davis, D. O., Dunn, D. O., & Schreiner, D. O. (2016). Intermittent Recurrent Renal Failure: Diagnosing Atypical Hemolytic Uremic Syndrome.

Hospital Day 12, PICU Day 11, CVVHDF Day 10 – extubated – platelets normalizing

Dr. Graham returned to see Makayla on April 29, 2018. Although the PICU team had hoped to stop the ceftriaxone prophylactic antibiotic therapy the day before, Dr. Graham noted that she was still on the medication out of their concerns for pneumonia. He wrote orders to go ahead and discontinue the medication.

Makayla was in the process of being weaned from fentanyl with methadone, but she was experiencing some agitation so was placed on Versed as needed for that. The morning labs showed a stable CBC with continued significant anemia, but her platelets were up to 153K. Her BUN and creatinine were 50 and 1.28. Dr. Graham noted that the PICU staff had begun spontaneous breathing trials that morning, hoping to extubate Makayla soon, and they were successful at doing that in the early afternoon. After a brief trial on room air, Makayla was taken off mechanical ventilation and transitioned to supplemental oxygen delivery via high flow nasal cannula.

Hospital Day 13, PICU Day 12, CVVHDF Day 11 – extubated, but remains in PICU

On April 30, 2018, Jose Gutierrez, MD examined Makayla for critical care and noted that Makayla had been successfully extubated the night before. She was still on Precedex and appeared to be reasonably comfortable on supplemental oxygen. She continued to exhibit tachycardia with a pulse of 130, but she appeared to be well-oxygenated with pulses equal in all extremities and brisk capillary refill.

Dr. Gutierrez wanted to keep Makayla in the PICU for the time being to continue management of her acute renal failure secondary to HUS. He wanted to wean her from sedation as tolerated, including the Precedex and the methadone. Dr. Elmaghrabi visited Makayla later in the day for nephrology and reviewed her morning labs, which showed a WBC 11.0, hemoglobin 8.7, hematocrit 24.9, and a platelet count in normal range at 223K.

Hospital Day 14, PICU Day 13, CVVHDF Day 12 – anuric and hypertensive, ascites

Makayla's morning chest/abdomen X-ray on May 1, 2018 showed her tubes and lines in proper alignment. There continued to be mild diffuse gaseous distention of her large and small bowel; however, there was no free air in her abdomen to suggest perforation. Her lungs exhibited improved aeration compared to the prior exam.

Makayla's CRRT/CVVHDF continued uninterrupted, but she had some difficulty with agitation and needed to be "well-sedated" for optimal infusion rates. Her morning labs showed continued stable but significant anemia and her platelets were still in normal range at 229.

Preparations for intermittent hemodialysis – still anuric and fluid overloaded

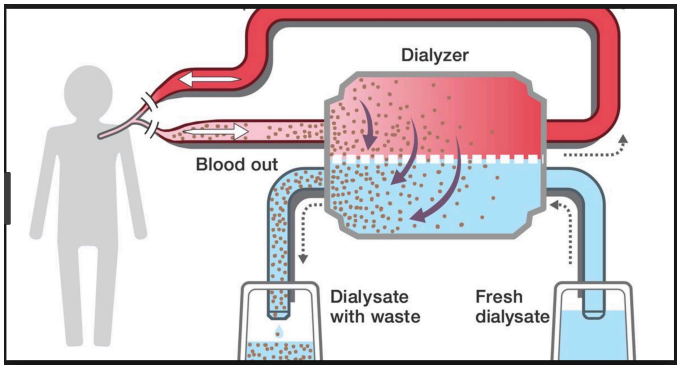
Dr. Elmaghrabi came in to see Makayla and began to ready her for intermittent hemodialysis scheduled to begin on May 3, 2018. Makayla was not producing any urine since she was started on CRRT and remained fluid overloaded, despite their attempts to balance her fluids with ultrafiltration. Dr. Elmaghrabi ordered the CRRT circuit to be discontinued at noon, with a

renal function panel and CBC to be drawn after that was done. Later in the day, Lisa Niebergall, MD performed a retroperitoneal ultrasound, comparing it to that done on April 19, 2018. Makayla's kidneys continued to exhibit the persistent echogenicity of underlying medical renal disease. There was sludge in her gallbladder and mild ascites.

At 9:26 PM, Sandra Buttram, MD evaluated Makayla on behalf of critical care, finding her with mild hypertension but not high enough to require hydralazine. Dr. Buttram added "hypertension" to her problem list and kept a standing order to give the medication for systolic pressures over 140. She observed that Makayla was having some difficulty with weaning of her sedation. She was still on Precedex and methadone, and required a dose of Dilaudid for pain overnight. Makayla had developed gingival hyperplasia (gum swelling) since she was admitted, prompting Dr. Buttram to order dental care and regular brushing before considering a dental consultation.

Hospital Day 15, PICU Day 14 – intermittent HD No. 1 incomplete (line occlusion)

On May 2, 2018, Makayla's morning labs showed a WBC 13.1, hemoglobin 8.3, hematocrit 23.9, platelets 295K, and BUN and creatinine 95 and 3.15. Her serum lipase level was elevated at 500. Dr. Elmaghrabi started Makayla on her first hemodialysis procedure in the morning. Unfortunately, a catheter malfunction occurred in the early afternoon that halted dialysis before it was able to be completed. Dr. Elmaghrabi thought they might need to consider peritoneal dialysis (PD[19]) if intermittent hemodialysis did not progress well. Meanwhile, she asked the PICU team to decrease Makayla's IVF rate that night as they had been unable to remove fluids via ultrafiltration that day. Yuki Yasaka, MD came in for critical care and recommended that they put Makayla back on CRRT/CVVHDF if she developed electrolyte abnormalities, fluid overload requiring respiratory support, and/or fluid overload causing malignant hypertension.[20]



Intermittent hemodialysis

[19] 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.

[20] A form of HTN that progresses rapidly, accompanied by severe vascular damage. It may be life-threatening or cause stroke, encephalopathy, cardiac ischemia, or renal failure. Venes, *supra* note 84 at 1173.

Just before 3 PM, pediatric surgeon Dr. Greenwald was called to consult about the malfunctioning HD catheter, noting that intermittent hemodialysis had to be stopped because the pump was not infusing. Nursing staff were unable to draw back from either the proximal or distal port. The lumens were then packed with tPA paste (Alteplase[21]) in hopes of improving catheter flow. Dr. Yasaka called for an ultrasound while waiting for Dr. Greenwald.

Ultrasound evidence of blood clot around RIJ HD catheter tip – treated with tPA

At 4 PM, radiologist Amal Jabra, MD performed an ultrasound venous doppler exam of Makayla's neck and upper extremities, looking for blood clots around the tip of the hemodialysis catheter. He observed evidence for echogenic material consistent with a nonocclusive blood clot measuring 4 cm x 5-6 mm within the right lower internal jugular vein and surrounding the indwelling venous catheter. Dr. Greenwald arrived to consult about the clot, finding Makayla awake and somewhat confused-appearing. He inspected her RIJ HD catheter, which had no drainage surrounding the insertion point, no surrounding erythema, and it had an occlusive dressing with biopatch. Her right upper arm PICC line dressing similarly had no drainage or surrounding erythema. Dr. Greenwald called Dr. Elmaghrabi and the two developed the following plan:

1. Altepase infusion for 2 hours through both the proximal and distal port of the hemodialysis catheter after priming both lumens.
2. Once the infusion was complete, they would pack both lumens with standard orders of Altepaste for this age group and leave the catheter packed overnight.
3. Pull back the PICC line to make it a deep peripheral line and avoid congestion around the dialysis catheter ("completed at the time of this note").
4. In the AM, an attempt would be made to switch back to CRRT; if unsuccessful, they would consider peritoneal catheter dialysis catheter placement in the OR.
5. This plan was discussed with mom, bedside nurse, and intensivist.

Hospital Day 16, PICU Day 15 – acute hyperkalemia – Intermittent HD No. 2

Dr. Yasaka came in on May 3, 2018 during morning rounds at 6 AM. Makayla was continued on minimal IV fluids overnight to cover for insensible[22] water loss only, due to persistent anuria. Makayla's follow-up potassium level had been increasing gradually over the course of 24 hours up to 6.3 that morning. No arrhythmia was noted at that time. Because of worsening hyperkalemia, Kayexalate, sodium bicarb, calcium chloride, and insulin glucose

---

[21] Alteplase, also known as tissue plasminogen activator (t-PA), catalyzes the conversion of clot bound plasminogen to plasmin, which then activates the fibrinolysis cascade. Already approved for treating acute myocardial infarctions, alteplase was studied to determine its efficacy as a means to clear catheter occlusions. In one of the initial studies, alteplase was found to be superior to urokinase for the treatment of radiographically proven thrombotic occlusion of a CVC. Baskin, Jacquelyn L et al. "Thrombolytic therapy for central venous catheter occlusion." *Haematologica* vol. 97,5 (2012): 641-50. doi:10.3324/haematol.2011.050492

[22] *Insensibles* refers to a loss of body fluid that is not easily measured, e.g., the moisture released in exhalation and perspiration. The amount of fluid typically lost is about 200 mL a day. Insensible fluid losses increase in any disease or condition that increases diffusion of liquid from the skin or the lungs, e.g., in burns, climatic changes, fever, or heavy exercise. Venes, *supra* note 84 at 1420.

infusions were initiated.

Makayla's labs showed other abnormalities in the morning on May 3, 2018, including a BUN and creatinine of 116 and 4.95, although her lipase was about the same at 498. Makayla continued to produce no urine whatsoever. Her HD catheter cleared somewhat with TPA overnight. The dialysis nurse came in and was able to run the hemodialysis pump at lower pressure rates, but she was able to power flush[23] through both ports and was currently succeeding with usage.

Dr. Greenfeld's initial plan was to see how Makayla's HD pump functioned for the rest of the day and, if there was continued difficulty with it, he would perform operative placement of a peritoneal dialysis catheter. However, after a discussion with the PICU team including Dr. Yasaka and Dr. Yoon, the consensus decision of the doctors was to proceed with the PD catheter in any event, since Makayla was likely going to require long-term dialysis.

Back to the OR… insertion of peritoneal dialysis (PD) catheter – transfusion pRBCs

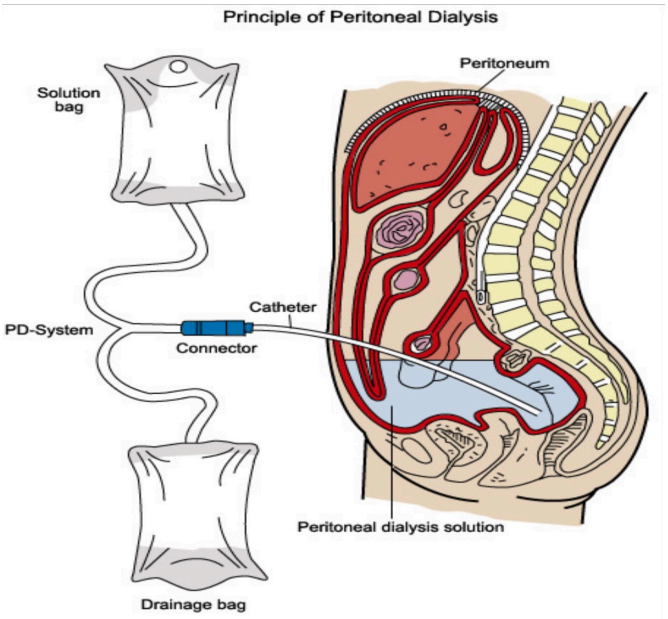
Just before 2 PM on May 3, 2018, Dr. Greenfeld brought Makayla back to the operating room for a "laparoscopic-assisted peritoneal dialysis catheter placement with partial omentectomy[24]" under general anesthesia. Makayla received a unit of pRBCs during the procedure. Dr. Greenfeld documented his surgical findings:

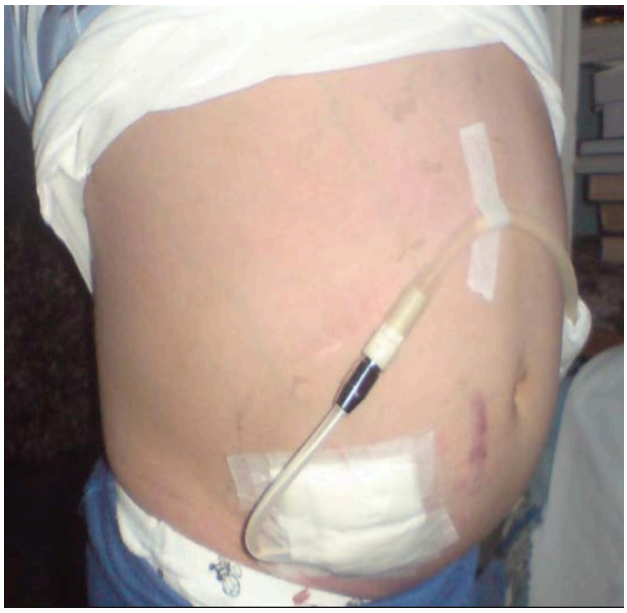
> The patient is a critically ill 7-year-old in renal failure. Her colon remains inflamed with hyperuricemia and what appeared to be indurated tissue, mostly of the transverse colon. The small intestine was inspected and did not appear to have any significant abnormalities except for some mild dilation. The [peritoneal dialysis] catheter was allowed to dwell 1 L, which rapidly entered the abdominal cavity and then drained readily and rapidly.

---

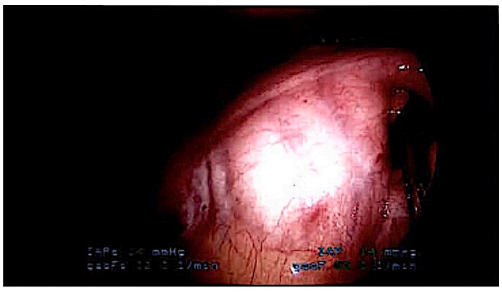
[23] Flushing and locking of intravenous catheters are thought to be essential in the prevention of occlusion. The clinical sign of an occlusion is catheter malfunction and flushing is strongly recommended to ensure a well-functioning catheter. Goossens, Godelieve Alice. "Flushing and Locking of Venous Catheters: Available Evidence and Evidence Deficit." *Nursing research and practice* vol. 2015 (2015): 985686. doi:10.1155/2015/985686

[24] A partial omentectomy is partial surgical removal of the greater omentum.

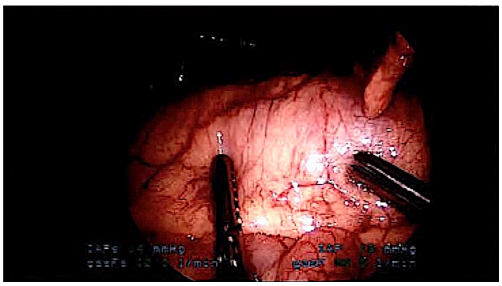




Example of PD catheter apparatus (not Makayla)



IMG001



Makayla's laparoscopic imaging

Pediatric Hematology Consultation

Just before 7 PM, Naresh Reddivalla, MD arrived for a hematology consultation after Makayla's ADAMTS13[25] test was reported low at 39%. He reviewed Makayla's history of

[25] In nearly all patients, aHUS can be distinguished from TTP on the basis of an ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) enzyme activity measurement. It is essential that aHUS and TTP be differentiated quickly, as they require markedly divergent treatments. The standard treatment for TTP is plasma exchange, a therapy that has no role for patients with a diagnosis of aHUS established by ADAMTS13 activity levels. Laurence, Jeffrey. "Atypical Hemolytic Uremic Syndrome (AHUS): Making the

bloody diarrhea (started 4/15/18) that progressively worsened, followed by the development of anuric AKI and diagnosis of Shiga-toxin-induced hemolytic uremic syndrome. He observed that Makayla's platelet count was currently normal, but she continued to exhibit anemia with no features of hemolysis. Dr. Reddivalla commented:

> She has low ADAMTS13 activity of 39%. There is no ideal cutoff value for ADAMTS13 above which TTP is eliminated or below which TTP is assured, but most widely, levels less than 10 percent are noticed in patients with TTP. Low activity between 10 to 60 can also be seen in the setting of sepsis or acute illness. Patients with hereditary TTP has typically, undetectable activity in the absence of inhibitor. It is very unlikely that Makayla's low ADAMTS13 activity is due to hereditary or acquired TTP. Will repeat ADAMTS13 activity with reflex inhibitor testing. Will send Von Willebrand panel and multimers

Hospital Day 17, PICU Day 16 – Intermittent HD No. 3 – again incomplete, circuit clotting

On Friday, May 4, 2018, Makayla resumed intermittent hemodialysis via her right internal jugular HD catheter. Unfortunately, the run had to be discontinued after two hours of the intended three-hour treatment when the circuit again clotted. The line was flushed with TPA after the session was over. Stephanie Hsieh, MD evaluated Makayla for nephrology and discussed the previous day's successful surgical insertion of the peritoneal dialysis catheter with Dr. Greenfeld and questioned when it could be implemented. Dr. Greenfeld stated that the PD catheter could not be used until after appropriate healing had occurred of the surgical site, so the plans were for Makayla to continue with CRRT or intermittent HD until the following Monday. Makayla reported that she continued to experience abdominal pain from the surgery. She remained anuric. Her renal function labs had improved on dialysis, but the values remained "quite high." Her morning labs showed a BUN and creatinine of 71 and 4.03. Her WBC was 8.1, hemoglobin 9.0, hematocrit 25.4, platelets 291K. She remained afebrile, but she continued to exhibit tachycardia with a heart rate of 139. Her blood pressure was stable at 121/63.

Hospital Day 18, PICU Day 17 – Intermittent HD No. 4 – success, but increasing lipase level

On Saturday, May 5, 2018, Dr. Greenfeld assessed Makayla's postoperative recovery and was concerned to see that her lipase level had climbed to 1063 IU/L (up from 398 over a couple of days). Her BUN and creatinine were 97 and 5.39. Her white count was normal at 8.0, and she was still significantly anemic, if stable, with a hemoglobin of 8.5 and hematocrit 22.5%. Dr. Greenfeld did not think the PD catheter was ready for use and advised continued intermittent hemodialysis that day. Radiologist Lisa Niebergall, MD performed an abdominal ultrasound that afternoon at 3 PM, comparing it to the last one on May 1, 2018. She observed decreased echogenicity of Makayla's kidneys and continued to see gallbladder sludge. A hepatitis panel came back negative for all varieties of viral hepatitis (A, B, C), and her liver enzymes remained in normal range. Makayla had some intermittently elevated blood pressures and had standing orders to be treated with prn antihypertensive medications (hydralazine). She was able to tolerate three hours of hemodialysis on May 5, 2018, with successful removal of 1.7 liters of excess fluid

---

Diagnosis." *Clinical Advances in Hematology & Oncology: H&O*, U.S. National Library of Medicine, Oct. 2012, www.ncbi.nlm.nih.gov/pubmed/23187605.

by ultrafiltration. She was still not producing any urine.

Hospital Day 19, PICU Day 18 – Intermittent HD No. 5 – deferred PD for site healing

On Sunday, May 6, 2018, Makayla continued to receive intermittent hemodialysis. Dr. Greenfeld noted that her lipase levels were still elevated, so he recommended her enteral feeds be held that day and to repeat her levels after that. Critical care intensivist Dr. Gutierrez agreed with that plan and ordered a lipase for the following morning. Makayla had finally completed methadone and Precedex weaning and remained on a clonidine patch to help with any residual narcotic withdrawal symptoms. She continued to receive TPN for her nutritional needs and replacement electrolytes through her PICC line as needed.

Dr. Hsieh came in for nephrology and was concerned that Makayla had ongoing abdominal pain, but she was working with PT/OT to sit up in a chair and start moving around more. She continued to be anuric, but her blood pressures were doing better, and she did not need any antihypertensives that day. Her abdominal wounds were healing well, but Dr. Hsieh wanted to continue intermittent dialysis with ultrafiltration. The plan was to start peritoneal dialysis on May 7, 2018, but since Makayla's HD catheter was currently functioning well, Dr. Hsieh thought they could defer starting peritoneal dialysis. She wanted to use the RIJ HD catheter until it stopped functioning entirely. The doctors began planning for outpatient dialysis, which would need to be continued until Makayla's renal function recovered, at which time they could remove the HD and PD catheters simultaneously.

Hospital Day 20, PICU Day 19 – psych consult – anxiety but no treatment necessary

On Monday, May 7, 2018, Medina Kamau, NP conducted a psychiatric assessment at the request of the PICU team. Dr. Yoon had been concerned about a mood disorder. NP Kamau observed symptoms of anxiety in Makayla, as she documented:

> [Makayla] reports, "I am scared... I am scared..." When asked what she is scared about, [she] continuously states "I am scared."

NP Kamau talked to Makayla about having poor sleep, but Makayla did not elaborate about having nightmares, or being unable to fall asleep or stay asleep; when asked, she stated "'I don't know… I don't know.'" Makayla was cooperative with the assessment and denied feeling depressed. NP Kamau did not consider Makayla appropriate for inpatient psych treatment but promised to remain available for consultation during her hospital course.

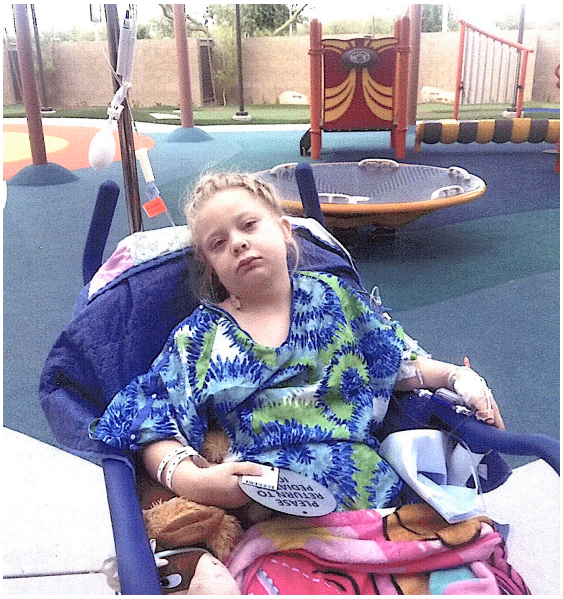
Successful intermittent HD No. 6, deferred trial of PD – rising lipase levels

Dr. Hsieh came in for nephrology while Makayla was receiving intermittent hemodialysis and observed that the HD catheter continued to work well; however, any attempt to increase the ultrafiltration rate (fluid removal) caused Makayla to become nauseous and start vomiting. Her lipase level was still elevated. Dr. Hsieh thought Makayla appeared to be increasingly anxious, despite being taken off continuous HD. Her blood pressures were still labile but in acceptable range. Dr. Hsieh planned to trial peritoneal dialysis that afternoon so that, if Makayla had

difficulty tolerating it, she would already have had her dialysis treatment that day. She started the day with labs showing a BUN and creatinine of 78 and 4.81, respectively. Her lipase continued to rise and was at 1433 (up from 1379 on the 6th).

Hospital Day 21, PICU Day 20 – spontaneous urine production – hemodialysis deferred

On Tuesday, May 8, 2018, Dr. Greenfeld came in to see Makayla in the morning and examined her surgical incisions, which appeared to be healing well. She was tender in the mid epigastrium only, which he did not think was excessive. Dr. Hsieh came in for nephrology around 11 AM and was happy to find that Makayla had produced 350 mL of spontaneous urine that morning. Her blood pressures were in normal range. She was working with PT daily at this point and was planning to go to the playground that day. Dr. Hsieh reviewed Makayla's morning labs and determined that she was sufficiently stable to skip hemodialysis that day, especially since she had produced some urine. Her BUN and creatinine that morning were 87 and 4.81. Her lipase was still elevated but down to 1269.



Makayla miserable, but outside at last with PT

Pediatric Gastroenterology – continued elevated lipase – pancreatitis vs. peritonitis

At 2:35 PM, Vinay Bandla, MD came in for a gastroenterology consultation at the request of Dr. Graham, for concerns of pancreatitis. He met with Makayla and her mother at bedside. Dr. Bandla noted that Makayla had presented with bloody diarrhea and was found to have *E. coli* that then progressed to HUS with subsequent acute kidney failure. He documented:

> She is status post respiratory failure, extubated on 4/29, septic shock on renal replacement therapy initially with CRRT, now on hemodialysis status post PD cath placement on 5/3 but has not been used. She has no significant past medical hx except for ongoing constipation. She is currently receiving TPN and lipids and has been allowed po, initially only water and since yesterday has been a liquid diet and diet [*sic*]. She reports having no appetite and also complains of some pain with

> eating. Mom reports her having eaten 1 grape, 6 oz of apple juice, and 3 oz of blueberry Naked Juice since yesterday. She denies current pain but mom reports that her pain comes in waves which is usually periumbilical in location, sharp in quality and during my interview today, she had an episode where she was crying with pain. Her lipase has been elevated for the last week and in the last few days has climbed up despite being mostly npo. Her US on 5/5/18 was normal other than decreased echogenicity of the kidneys and gallbladder sludge. Her lipase levels remain elevated at 1,269, down from 1433.
>
> Michaela [*sic*] has abdominal pain which could be secondary to pancreatitis as evidenced by her increased lipase. Her symptoms do not typically fit with pancreatitis as well as the fact that her lipase is currently increasing despite being mostly npo. Non-pancreatitis causes of elevated lipase include but are not limited to peptic ulcer disease, acute kidney injury including HUS, multiorgan involvement of critical illness, sepsis and peritonitis.

Dr. Bandla requested additional labs to include amylase, isoamylase, urine amylase, serum trypsinogen, and stool elastase. He also ordered an abdominal X-ray. Dr. Bandla advised that she could continue an oral regular diet and be encouraged to take oral fluids, and they should only continue with nasogastric tube enteral feeds if she did not take enough orally. He prescribed an oral antacid (Protonix 40 mg) in addition to famotidine in her TPN. Dr. Bandla also ordered continued TPN/intralipids for now

Pediatric Critical Care – encourage oral intake but continue parenteral nutrition

At 5:42 PM on May 8, 2018, Thant Lin, MD evaluated Makayla on behalf of critical care and reviewed the recommendations made by gastroenterology and nephrology. He agreed with the plan to encourage oral intake and supplement Makayla's calories with TPN/IL. The current plan was to implement another session of intermittent hemodialysis the next day, but to transition to peritoneal dialysis prior to discharging her home.

Hospital Day 22, PICU Day 21 – Intermittent hemodialysis No. 7 – transfer out of PICU

On Thursday, May 9, 2018 at 5:48 AM, radiologist Amal Jabra, MD performed a KUB X-ray to evaluate the source of Makayla's continued abdominal pain. The peritoneal dialysis catheter was visible and properly placed in the pelvis. Dr. Jabra observed that Makayla's bowel loops were "somewhat gassy," but there was no significant bowel dilatation. A small amount of stool was visible in her colon. There were no abnormal air collections or abdominal calcifications.

Dr. Bandla returned for gastroenterology in follow-up of the consultation from the day before. Makayla reported very little oral intake since then, taking only 60 mL of water during the afternoon, "and then getting upset and spitting it back out." She had been drinking juices as well, which the nurse stated she tolerated better. "She did have a bite of mac & cheese but then had small amount emesis." Dr. Bandla reviewed Makayla's abdominal X-ray and found it largely reassuring. He also looked at her labs, which continued to show an elevation of her lipase (1152

IU/L), as well as an amylase level that was elevated at 252 IU/L.[26] Makayla's liver enzymes had not been elevated since they normalized around April 26th. Dr. Bandla opined that Makayla's abdominal pain could be secondary to pancreatitis, as evidenced by increased lipase; however, he went on:

> Her symptoms do not fit with typical pancreatitis and her lipase is remaining fairly consistent despite being mostly NPO. Non-pancreatitis causes of elevated liver enzymes include, but are not limited to, peptic ulcer disease, acute kidney injury including HUS, multiorgan involvement of critical illness, sepsis, and peritonitis. Continue encouraging p.o. Boost breeze 2-3 cans a day since she is lactose intolerant and does not like milky drinks RD consult to ensure that this is within her K and phosphorus restrictions. We will need to place NG tube if she does not show any interest in eating/drinking.

Out of PICU to regular ped bed…

Makayla was transferred out of the PICU to a regular pediatric bed that afternoon. Satya Vittala, MD arrived for pediatrics just before 2 PM and reviewed Makayla's hospitalization to date, noting that she was currently on every-other-day intermittent hemodialysis. She observed that she was also receiving TPN and IL because of poor oral intake. She saw that Makayla carried a current diagnosis of pancreatitis with elevated lipase levels that were now slowly trending down. Makayla also had significant anemia (hemoglobin 7.4 and hematocrit 19.5 that morning) and was scheduled for another pRBC transfusion with hemodialysis that day. Dr. Vittala saw that Makayla was very anxious with dressing changes and HD catheter accesses, and she noted that she was crying during her exam. She complained of abdominal pain that was intermittent and located in the epigastrium and mid abdomen. Makayla had spontaneously voided again that morning, but it did not get collected to measure it. Dr. Vittala noted that, although Makayla had very poor oral intake, she continued to enjoy juice. She remained on room air without the need for supplemental oxygen. Dr. Vittala planned to place a nasogastric tube the next day if Makayla continued to take insufficient calories and fluids orally.

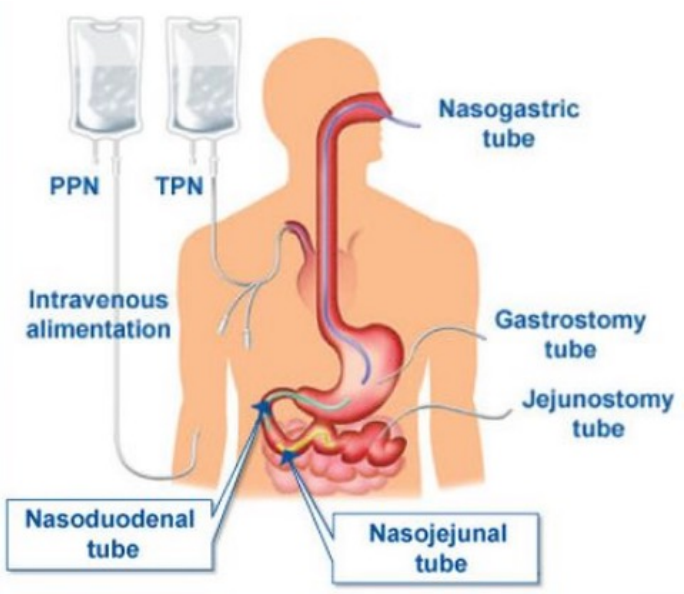
Makayla's BUN and creatinine were 126 and 6.68 that morning. Kelly Benedict, MD arrived for the nephrology service that day and was concerned about the BUN level being over 100. She planned a four-hour hemodialysis treatment that day for clearance, as well as the blood transfusion, and she hoped for ~2000 fluid removal via ultrafiltration. Dr. Benedict also noted Makayla's continued anxiety. She saw that the surgical had weighed in on Makayla's enteric intake and recommended that, "because of pancreatitis," they wanted her to eat a regular diet and avoid giving her liquid formula through an NG tube. Therefore, Dr. Benedict placed Makayla on a regular diet and ordered monitoring of how much and what she ate—"if she is consuming large amounts of K and PO4, may need to restrict or start a PO4 binder." If she had to go on "formula," she recommended a low potassium/phosphorus variety.

Hospital Day 23 – No hemodialysis – urinating small amounts – petechial rash

On Friday, May 10, 2018, Dr. Bandla returned for gastroenterology in the morning and

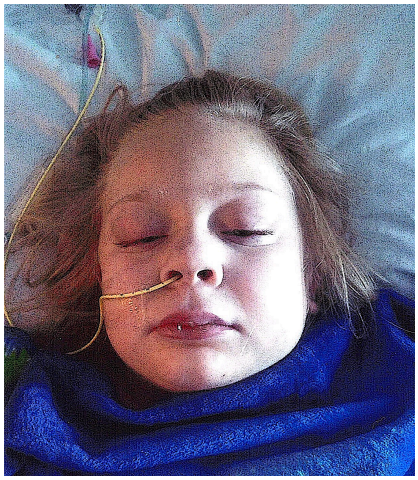
[26] Reference ranges: Lipase 104-176 IU/L, amylase 18-102 IU/L

met with Makayla and her mom, who reported some improvement in her oral intake since the day before. She had been drinking water, apple juice, and a "V8 Splash." Nevertheless, Dr. Bandla commented that her mom was eager to get a nasogastric tube inserted to make sure her daughter received sufficient nutrition. Makayla reported one large pasty stool that morning, as well as some urine output (reportedly about 100 mL). Makayla did not want to have an NG tube inserted and so was trying hard to eat to avoid it.



Mark Joseph, MD came in for nephrology and was happy to see that Makayla had voided a small amount, although her urine did exhibit gross hematuria. Dr. Joseph indicated that was to be expected and was not a bad sign. Makayla did not have hemodialysis that day and Dr. Joseph delayed flushing the peritoneal dialysis catheter for another day, although it had originally been scheduled for May 10, 2018.

Dr. Joseph reviewed Makayla's morning labs and was concerned to see that her platelet count had been lower the past few days (138 on the 7th, 155 on the 9th, and 105 on the 10th), but wondered if it could be a lab error. She had also developed a petechial rash and he discussed this with the hospitalist. Makayla underwent the insertion of a nasogastric tube that evening, after which she felt nauseated and vomited soon after. She was started on half strength Vivonex.



Makayla gets an NG tube…

Hospital Day 24 – Intermittent hemodialysis No. 8 – PD catheter flushed – still oliguric

On May 11, 2018, Dr. Joseph came in for nephrology and ordered the peritoneal dialysis catheter to be flushed that day. Makayla was to undergo 3.5 hours of intermittent hemodialysis through the RIJ HD catheter. Her platelets were back up to 170. Makayla urinated again that morning, which was measured at 180 mL and still represented oliguria.[27] Although her PD catheter permitted filling and draining unimpeded, it caused Makayla discomfort.

Dr. Bandla came in for gastroenterology and noted that Makayla's oral intake remained essentially unchanged, "with her having a couple of bites of lunch yesterday and 165 mL of water and V8 Splash in the past 24 hours." He observed that the Vivonex was running at half strength at 20 mL/hr, with a goal of 85 mL/hr. She continued to receive TPN and IL. Dr. Bandla checked Makayla's morning labs and saw that her lipase was down slightly. He planned to recheck it the next morning.

Hospital Day 25 – No hemodialysis – continued oliguria

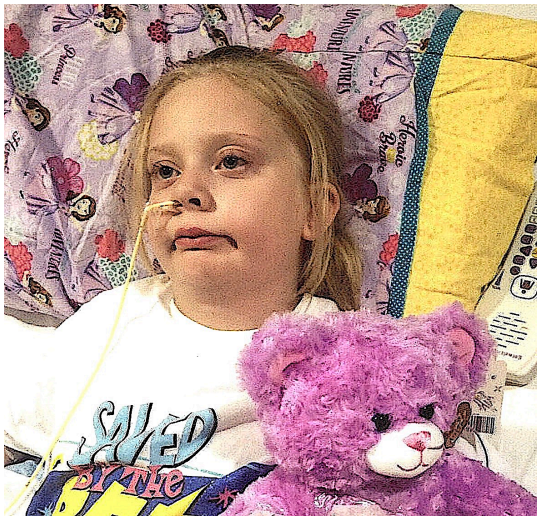
On Sunday, May 12, 2018, Dr. Joseph was back in to see Makayla again in the morning around 10 AM. She had yet to produce any urine that day. He observed that the peritoneal dialysis catheter flush was successful, with fluid instilled and drained without issue, but he did not comment on Makayla's response. He also noted that her hemodialysis session had not presented any problems, and they had been able to remove 1000 mL excess fluid via ultrafiltration. Makayla remained afebrile and her blood pressures were acceptable (i.e., labile but not elevated enough to require medicating). Her morning labs revealed a WBC 10.1, hemoglobin 8.3, hematocrit 21.9, platelets 174, BUN 98, creatinine 5.92.

Hospital Day 26 – Intermittent hemodialysis No. 9 – worsening anemia – 2 units pRBCs

---

[27] 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

Makayla's morning labs on May 13, 2018 were significant for a drop in her platelets to 101K, and her hemoglobin and hematocrit were down to 6.2 and 17.9. She therefore underwent transfusions of two units of pRBCs that day. She also vomited that morning and expelled her NG tube in the process. Dr. Joseph came in to see her at 10 AM during her first blood transfusion of the day, noting that she had eventually urinated 210 mL the day before and already voided 290 mL that morning, and her urine was now yellow without gross hematuria. Dr. Joseph observed some edema, however. Makayla's BUN and creatinine were 103 and 7.52 that morning, and Dr. Joseph ordered a hemodialysis run for 3.5 hours, with fluid removal of 0.8 liters via ultrafiltration. Makayla's pancreatitis was improved, with a lipase of 352. Dr. Joseph deferred TPN that day, as well as IV fluids, as her fluid balance was almost in normal balance, if slightly hypervolemic. At 11:27 AM, radiologist Christine White, DO performed a KUB X-ray just after Makayla's NG tube was replaced, finding it in proper placement. She noted a nonobstructive bowel gas pattern.



Makayla none too happy about NG tube

<u>Hospital Day 27 – No hemodialysis – oliguria but producing urine – hypertensive</u>

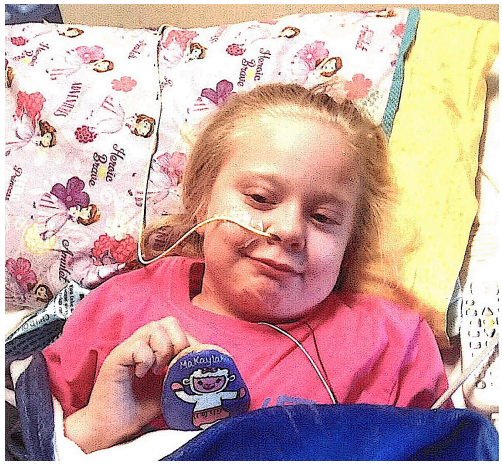
On Tuesday, May 14, 2018, Dr. Bandla came in for gastroenterology in the afternoon and was happy to see that Makayla's lipase continued to downtrend. She was now on full strength formula feeds through the NG tube. She had vomited the past two mornings, but otherwise was tolerating enteric feeds well and was having non-diarrheal stools. Dr. Bandla increased the strength of her formula to a higher calorie version of Vivonex and ordered a continuous drip overnight. To avoid fluid overload, he had the nurses subtract any oral fluid intake from her bolus feeds.

Dr. Hsieh was back on duty for nephrology and came in to see Makayla during the afternoon. She was happy to see that Makayla had more than 400 mL of urinary output estimated (mixed with stool) that morning. She noted that intermittent hemodialysis the day had successfully removed about a liter of excess fluid via ultrafiltration. The dialysis circuit had clotted twice and Dr. Hsieh opined that her decreasing platelet counts might have something to do with that problem. She ordered an increase in Makayla's heparin HD line flush. In addition, Makayla had

been running high blood pressures and had to be medicated (prn isradipine[28] ordered) twice since the day before. She had also gained weight and looked more edematous, and her mom had noticed a petechial rash since the previous Thursday that appeared to be spreading. Dr. Hsieh ordered a Lasix drip to improve Makayla's urinary output and decrease her fluid overload.

Hospital Day 28 – Intermittent hemodialysis No. 10 – pancreatitis improving

On Wednesday, May 15, 2018, Dr. Hsieh noted a positive response to the Lasix dosing from the day before. She thought Makayla looked less edematous and she had produced a liter of urine after it was given. She observed that Makayla remained hypertensive (currently 151/108), but her mom stated that she stiffened and tensed up when the nurses tried to take her blood pressure. Therefore, there were multiple attempts, and so not all "high" blood pressures were treated with isradipine if the nurses thought the readings were inaccurate. Makayla still struggled with oral intake. She was tolerating her current NG enteric formula. Dr. Hsieh ordered 3.5 hours of hemodialysis that day with an ultrafiltration goal of 2 liters of excess fluid removal.



Makayla doing better with her NG tube feeds

Swati Kolpuru, MD arrived for the surgery service and noted that Makayla was tolerating NG tube feeds of 225 mL full strength Vivonex over 90 minutes, as well as continuous night feed infusions of 65 mL/hr. She had not had any emesis for 24 hours. Her lipase was still elevated but slowly declining, and her abdomen was now soft and nontender to examination.

Hospital Day 29 – continued anuria/oliguria off Lasix

Dr. Elmaghrabi returned to evaluate Makayla for nephrology on May 16, 2018. Makayla had produced approximately 375 mL of urine in the preceding 24 hours. She was tolerating NG formula feeds but had vomited after eating a sandwich the night before. Her blood pressures were still elevated and required medicating with isradipine, currently at 157/104. Dr. Elmaghrabi observed that Makayla remained anuric/oliguric, despite the "brisk UOP" after Lasix dosing. Makayla was currently on intermittent hemodialysis three times a week, with the next one scheduled for the following day for a 3.5 hour run and 1.5-2L ultrafiltration. Dr. Elmaghrabi

---

[28] Isradipine is a calcium channel blocker used to treat high blood pressure.

agreed that the drop in Makayla's platelets had been caused by the dialysis circuit clotting, which resulted in their increasing her heparin dose, and she planned to monitor that. She agreed with the NG feeds. If Makayla's urinary output increased, the doctor planned to liberalize her oral fluid intake. She was not surprised that Makayla was having difficulty with oral intake, stating, "this is quite common in HUS." She noted that GI had prescribed Periactin to help increase Makayla's appetite.

Hospital Day 30-31 – Increased UOP – Intermittent HD No. 11 done on the 18th

On May 17, 2018, Makayla was noted to have 1.1 liters of urinary output. Dr. Elmaghrabi deferred hemodialysis that day, although Makayla's renal function labs remained significantly abnormal (BUN 53, creatinine 7.20). Her lipase was also increased for the past couple of days, and her blood pressures reflected hypertension (142/104). Makayla received one dose of isradipine overnight.

Dr. Elmaghrabi re-assessed Makayla in the morning on May 18, 2018 while she was on intermittent hemodialysis. She had produced 1.35 liters of urine since the day before, but her BUN and creatinine were increased to 61 and 8.32, so the doctor went ahead with dialysis.

Dr. Elmaghrabi planned to also do a run of low volume peritoneal dialysis later in the day. She returned to see Makayla and her mom Destiny to answer questions about peritoneal dialysis and training. She met with Destiny and the bedside nurse to discuss further plans for Makayla. Dr. Elmaghrabi explained the short-term goal would be to continue dialysis while allowing kidney recovery. She also explained long-term goals to plan for home discharge and possible need for dialysis as an outpatient for period of time, which was unknown at that time "and could be days, weeks or months."

Dr. Elmaghrabi wanted to move forward with home preparation and training of two family members. Destiny expressed her concerns that the other caretaker was Makayla's grandma who was taking care of Makayla's two siblings (ages 3 and 4), and thus they would not be able to do training simultaneously. Dr. Elmaghrabi also contacted the hemodialysis unit at Phoenix Children's Hospital for their availability, as Makayla was to be discharged home on hemodialysis and they had some lab requirements prior to registration (QuantiFERON Gold TB testing and hepatitis B testing).

Trial PD run causes discomfort

The dialysis nurse attempted a trial run with Makayla's PD catheter that evening at 8 PM. Shortly after the fill, during drainage, Makayla complained of abdominal discomfort and she had to be repositioned to complete the process.

Hospital Day 32 – No hemodialysis – continued urinary output

On May 19, 2018, Makayla had continued spontaneous urinary output, although it decreased from 1350 mL to 625 mL. Ever since the trial PD run the night before, Makayla reported an increase in her abdominal pain. Dr. Elmaghrabi came in for nephrology and noted

that she had not tolerated peritoneal dialysis very well the day before. In addition, her blood pressures had remained quite elevated, requiring two doses of antihypertensive medications overnight. Makayla complained of abdominal and shoulder pain, but a chest X-ray was unrevealing. Dr. Elmaghrabi planned her next intermittent hemodialysis for Monday the 21st.

At 11 AM, radiologist Matthew Lynn, MD performed a repeat chest X-ray, comparing it to that done on the May 2, 2018. He observed Makayla's enteric tube properly placed in the gastric fundus (body of the stomach).

Hospital Day 33-34 – Intermittent HD No. 12 – continued urinary output

On May 20, 2018, Dr. Elmaghrabi returned for nephrology and concluded that Makayla's enteral intake was improved but still suboptimal. She had tolerated nasogastric tube feeds overnight. She continued to produce urine but was still fluid overloaded. Makayla continued to exhibit elevated blood pressures requiring medication twice during the night. Makayla's morning labs continued to reflect significantly abnormal renal function (BUN 46, creatinine 6.61). Dr. Elmaghrabi ordered another dose of Lasix. Makayla tolerated 3.5 hours of intermittent hemodialysis with removal of 1.6 liters of excess fluid via ultrafiltration.

On May 21, 2018, Dr. Greenfeld evaluated Makayla on behalf of surgery service and was happy to hear that her abdominal pain had improved. He deferred to nephrology, but thought she was ready for outpatient dialysis. Makayla's urinary output was up to 1125 mL that day, and she was tolerating nasogastric formula feeds. She continued to be hypertensive and was medicated two times overnight once again. Her labs were stable, with a WBC 9.2, hemoglobin 10.1, hematocrit 30.3, platelets 157, and a BUN and creatinine of 24 and 3.52.

Dr. Kolpuru came in for gastroenterology on May 21, 2018 and was satisfied that Makayla's oral intake and interest in eating had progressed well enough to defer bolus formula feeds via the NG tube. She wasn't having any stools, so she was started on MiraLAX. Her lipase had decreased to 291 and she had no current signs of pancreatitis. The doctors discussed transferring Makayla to the hemodialysis program at Phoenix Children's Hospital (PCH). Meanwhile, her peritoneal dialysis catheter was scheduled for regular flushes with three passes of 300 mL/fill, with 500 units of heparin per liter to keep the lines patent.

Hospital Day 35-36 – Intermittent HD No. 13

Dr. Elmaghrabi returned to evaluate Makayla on May 22, 2018 and made no changes in her care plan. Her last HD was on May 20, 2018 and her morning labs showed a BUN and creatinine of 45 and 5.77. She continued to produce increasing volumes of urine, and her blood pressures had been good enough to avoid medicating her during the night. Makayla tolerated intermittent HD No. 13 that day with 700 mL fluid removal via ultrafiltration.

On May 23, 2018, Makayla had an exciting day, looking forward to a visit from her school classmates who were coming to see her. It was getting near the time her peritoneal dialysis catheter was due to be flushed again. Nephrologist Mark Joseph, MD planned to discuss this with Destiny, as the family was reluctant to even consider utilizing that method of dialysis, given

Makayla's negative response to the trial run. He opined that, if the family had no intention of utilizing PD, they should just go ahead and remove the catheter. He ordered another dose of Lasix that day, hoping to improve her urinary output so they could avoid ultrafiltration during intermittent hemodialysis. Dr. Lukacik came in for the surgery service that afternoon and discussed the PCH hemodialysis program with Makayla and her mom.

Hospital Day 37-38 – Intermittent HD No. 14

Dr. Joseph returned on May 24, 2018, and Makayla reported that she was trying to eat but did not have any appetite. He observed that she was eating less than 50% of her three meals. They had been holding her nasogastric tube feeds on the assumption she would eat. Dr. Joseph discussed this with the hospitalist and they decided to restart her night formula that night. Unfortunately, the Lasix had not helped increase Makayla's urinary output overnight, so Dr. Joseph discontinued it. Makayla tolerated intermittent hemodialysis with ultrafiltration that day.

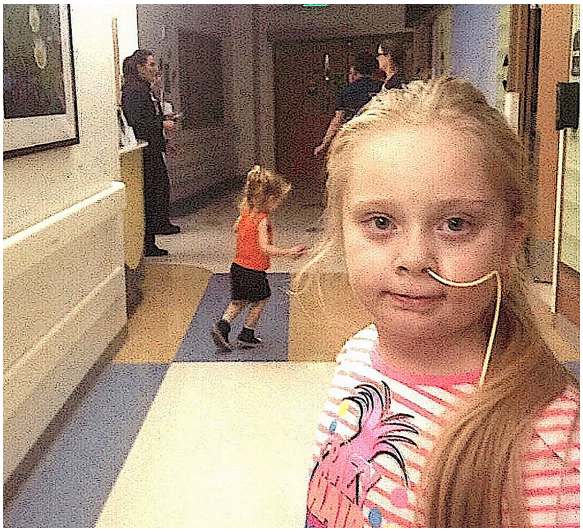
Dr. Lukacik returned to see Makayla that afternoon to assess her oral intake and address what they could do to improve it. She had only taken in 600 mL of fluids in 24 hours, which was far under goal. As a result, her urinary output was decreased. She was going to be discharged soon, but Dr. Lukacik restarted her nighttime NG tube feeds in the meantime.

On May 25, 2018, Dr. Joseph came in for nephrology and visited with Makayla's grandma in the lobby. They discussed her discharge from the hospital, which was set to occur the following day. Makayla's urinary output was only 550 mL since the day before. She was now having bowel movements, which helped her abdomen feel better, and she had no return of diarrhea.

Hospital Day 39 – Going home

On May 26, 2018, Kelly Benedict came in for nephrology in the morning to assess Makayla for discharge home that day. She arrived around 9 AM to find Makayla out of bed, sitting in the bedside chair, and asking to walk around the unit. She had not had much fluid intake in the past 24 hours, which was reflected in little urinary output, but she continued to urinate without difficulty. Makayla was tolerating the nighttime nasogastric feeds, and the plan was to discharge her with the NG tube in situ. Makayla's PICC line was removed at the bedside.

Makayla was excited to go home and sleep in her own bed. Her morning labs showed a normal white count, but she was still quite anemic with a hemoglobin of 10 and hematocrit 29.7. Her platelets were stable at 140K. Her BUN and creatinine were 43 and 6.42. Dr. Benedict discussed the use of the peritoneal dialysis catheter with Makayla and Destiny, which had never actually been utilized for dialysis while in the hospital because it caused her too much discomfort. The family concluded that they would like Makayla to remain on hemodialysis and forego the peritoneal dialysis altogether. After some discussion, Dr. Benedict indicated that she would arrange to have the catheter removed as an outpatient as Makayla and her family were eager to leave the hospital. They planned for intermittent hemodialysis at Phoenix Children's Hospital three times a week for 3.5 hour runs each time.



Makayla ready to go home, NG tube and all

Satya Vittala, MD examined Makayla for discharge in the early afternoon and did a discharge physical and summary of her hospitalization. She listed Makayla's discharge diagnoses in her chart note:

1. Shiga toxin-producing *Escherichia coli* infection
2. Hemolytic uremic syndrome
3. Acute renal failure secondary to hemolytic uremic syndrome
4. Acute pancreatitis that resolved
5. Bilateral pleural effusion with respiratory failure requiring intubation that resolved
6. The patient is NG-tube fed due to poor p.o. intake
7. *Haemophilus influenzae* and *Strep pneumoniae*, status post-treatment

Dr. Vittala advised Destiny to take Makayla to see her pediatrician, Dr. Rios, in 3-4 days, with a follow-up visit with nephrology in 1-2 weeks. She was scheduled to see pediatric gastroenterology as an outpatient in 3-4 weeks. Outpatient hemodialysis was scheduled to occur intermittently on Tuesdays, Thursdays, and Saturdays.

Makayla was prescribed Renvela[29] 1600 mg to take with each meal and she was advised to continue with MiraLAX to avoid constipation. Dr. Vittala wrote a prescription for Periactin to keep up Makayla's appetite and she was to continue with Suplena formula at half strength to be delivered via the NG tube over 10 hours (overnight).

Phoenix Children's Hospital Dialysis Center

On Tuesday, May 29, 2018, Makayla presented to Phoenix Children's Hospital for her first outpatient hemodialysis treatment. Her systolic blood pressure was marginally elevated at 130/55. Labs were also done that day, which showed WBC 8.3, hemoglobin 9.2, hematocrit 26.9,

[29] Renvela (sevelamer) is a phosphate binder. Sevelamer helps prevent hypocalcemia (low levels of calcium in the body) caused by elevated phosphorus. Renvela is used to control phosphorus levels in people with chronic kidney disease who are on dialysis. http://www.renvela.com/

platelets 234, BUN 45, and creatinine 6.76. Makayla and her mom reported that she was going to have her peritoneal dialysis catheter removed the following day.

Banner Medical Center – outpatient surgery – removal of PD catheter

On May 30, 2018, Makayla returned to the hospital to have her peritoneal dialysis catheter removed by Dr. Greenfeld. This was done in the operating room under general anesthesia with additional local anesthetic. She tolerated the procedure well and was discharged to the PACU for recovery before going home.

Happy Kids Pediatrics

Makayla went to see Klint L. Webb, PA-C at Happy Kids Pediatrics on May 30, 2018. PA Webb reviewed her hospital course with admission for Shiga-toxin *E. coli*, HUS, respiratory failure, and kidney failure and noted that she had been intubated for over a week. He found it notable that Makayla was currently NG fed and just had her PEG removed that very day. She was advancing with feeds and had been cleared to start solids. PA Webb also observed that Makayla was still undergoing dialysis treatments three times a week at Phoenix Children's Hospital as an outpatient. Destiny reported that Makayla was supposed to be followed by both nephrology and gastroenterology, but she needed a referral to Banner gastroenterology within the next week. She already had an appointment with nephrology for June 16, 2018. Makayla's examination that day was unremarkable other than her surgical scars, NG tube in situ, and her still-present central line, which was clean and dry. PA Webb deferred to nephrology and dialysis for those portions of her care, as well as gastroenterology for continued evaluation and treatment. He advised Destiny to proceed slowly while advancing Makayla's diet to solids and to continue the NG feeds as directed by her doctors at hospital discharge. She was advised to return as needed, with the next appointment in a week. Makayla received flu, Kinrix, and MMR vaccines before being discharged from the visit.

Phoenix Children's Hospital Dialysis Center

Makayla returned for her next dialysis treatment on Saturday, June 2, 2018. Her CBC was stable, and her serum creatinine was 2.03. She was scheduled to return every Tuesday, Thursday, and Saturday for intermittent hemodialysis. She had HD on June 5, June 7, June 9, June 12, and June 14, 2018 before her first outpatient nephrology follow-up.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On June 15, 2018, Dr. Elmaghrabi saw Makayla as an outpatient for a nephrology visit in follow-up of her hospitalization for STEC HUS. Makayla was there that day with her mother and two siblings. She reported that she had done well since her hospital discharge, having received regular hemodialysis treatments three times a week since she left the hospital on that date. In addition, she had undergone the surgical removal of her peritoneal dialysis catheter on May 30, 2018, which had never been used for that purpose during her hospitalization. Destiny reported that her daughter remained on overnight nasogastric tube feeds with Suplena 325 mL/325 water, as well as her medication to increase her appetite (Periactin). She was drinking three bottles of

water a day and taking MiraLAX and she had been having non-diarrheal stools regularly. She denied having any headaches, dizziness, chest pain, or palpitations.

On exam, Dr. Elmaghrabi found Makayla without tenderness, guarding, masses, or rebound tenderness, and her abdomen was soft and nondistended. Her surgical wounds appeared to be healing well from the removal of her PD catheter. Makayla had normal blood pressure. A dipstick[30] urinalysis was done in the office that showed significant proteinuria (100 mg/dL, or 2+), with leukocytes but no nitrites or blood.

Dr. Elmaghrabi diagnosed Makayla with acute renal failure syndrome, diarrhea associated hemolytic uremic syndrome, secondary hypertension, disorder of electrolytes, anemia and feeding problems. She explained that Makayla's renal function was slowly recovering, with a "good" urinary output (described as 1800 mL/day); however, her BUN and creatinine remained significantly elevated, the most recent values from the 14th showing levels of 33 and 3.47, and the calculated urine creatinine clearance remained low (~15 mL/min/1.73m^2 [Cr 0.49 gm/24hr]). Dr. Elmaghrabi noted that Makayla's complement proteins C3 and C4 were within normal range when last evaluated, although her ADAMTS13 had initially been low (39%) but more recently had been near normal range on May 3, 2018 (63%). A renal ultrasound revealed that her right kidney was smaller than her left.

Turning to Makayla's blood pressure and diagnosis of secondary hypertension, Dr. Elmaghrabi observed that her systolic pressures were now ranging in the 120s. Terming it permissive hypertension, she indicated that they adopted expectant management and tolerance of Makayla's otherwise seriously hypertensive episodes as temporary and necessary to allow her kidneys to recover. She recalled that, in the hospital, Makayla was managed on amlodipine (5 mg daily) and prn isradipine for systolic pressures greater than 145 mmHg, but the amlodipine had been discontinued prior to discharge as no longer needed. Dr. Elmaghrabi thought they could continue to watch her pressures and would start an antihypertensive if needed.

Makayla's hyperkalemia appeared to have resolved with dietary control, with her most recent value of 4.5. She also exhibited hyperphosphatemia and was managed on Renvela. Her calcium was normal at 9.5. Dr. Elmaghrabi continued Makayla on a low potassium, low phosphorus diet and continued her Renvela with meals, three times daily through her NG tube.

For Makayla's anemia, Dr. Elmaghrabi continued to diagnose her with MAHA[31] that was

---

[30] Dipstick tests for trace amounts of protein yield positive results at concentrations of 5 to 10 mg per dL—lower than the threshold for clinically significant proteinuria. A result of 1+ corresponds to approximately 30 mg of protein per dL and is considered positive; 2+ corresponds to 100 mg per dL, 3+ to 300 mg per dL, and 4+ to 1,000 mg per dL. Dipstick urinalysis reliably can predict albuminuria with sensitivities and specificities of greater than 99 percent. Anderson MJ, Agarwal R. Urinalysis. Lerma EV and Nissenson AR. *In Nephrology Secrets*. Third Edition. Elsevier Mosby: 2012.

[31] "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*

in part from iron deficiency and in part due to her AKI and being on dialysis. She was currently being given EPO[32] at her dialysis treatments. Dr. Elmaghrabi found it concerning that Makayla's last values showed a hemoglobin and hematocrit of 8.8 and 26, but these were being appropriately treated at her HD treatments with loading doses of Ferrlecit[33] in the HD unit and would continue on EPO for the time being.

Finally, Dr. Elmaghrabi discussed Makayla's diminished appetite and feeding problems, explaining that this was "quite common in HUS." Makayla had been doing well and continued on Periactin by gastroenterology. She noted that the pancreatitis she had been diagnosed with in the hospital had resolved prior to being discharged. She was changed from a proton pump inhibitor (PPI) while still in the hospital and started on an H2 blocker. Dr. Elmaghrabi wanted Makayla to stay on her nightly NG tube formula feeds for now and to continue the Periactin. Makayla did not drink milk as she had a lactose intolerance.

Phoenix Children's Hospital Dialysis Center

Makayla continued receiving intermittent hemodialysis on a regular schedule through Tuesday, June 26, 2018. During this time, her CBCs reflected stable but significant anemia, normal platelets, and continued abnormal renal function values that were very gradually improving, with a BUN and creatinine of 30 and 2.68.

Banner Desert Medical Center

Makayla's abdominal pain worsened and her blood pressure spiked, prompting Destiny to take her to Banner Desert Medical Center on June 27, 2018. Raz Guy, MD evaluated her in the emergency department for her primary complaints of abdominal pain and high blood pressure. Destiny reported that her daughter's most recent hemodialysis was the day before and, when she noticed high blood pressures at home, the dialysis center told her to bring her to the hospital. Dr. Guy reviewed the records from her STEC-HUS hospitalization. Makayla described her current abdominal pain as mild, and stated that she also had a headache. Destiny reported that Makayla's blood pressure was elevated in the low 130/80 range. She explained that, although Makayla was scheduled for Tuesday/Thursday/Saturday dialysis, her labs had been good enough for the last several weeks that she was allowed to skip dialysis the previous Saturday. Dr. Guy reviewed the lab values from the day before, with a sodium 139, potassium 4.6, chloride 106, blood urea nitrogen 30, creatinine 2.6, glucose 9.4, phosphorus 7.7. "Neurology is aware of her hyperphosphatemia as well as remainder of lab values and has not intervened at this time." Dr. Guy determined that Makayla had strep pharyngitis. He consulted nephrology to discuss appropriate antibiotic dosing; they recommended 720 mg of amoxicillin once a day for the next 7 days, advising the family to call them should anything worsen. Makayla was then discharged

---

Hemostasis, U.S. National Library of Medicine, Mar. 2013, www.ncbi.nlm.nih.gov/pubmed/23390027/.

[32] 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. https://www.themmrf.org/multiple-myeloma-knowledge-center/myeloma-treatments-guide/growth-factors/erythropeietin/

[33] Ferrlecit is an iron replacement product for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy. http://products.sanofi.us/ferrlecit/Ferrlecit.html

home. Makayla resumed hemodialysis at Phoenix Children's Hospital on June 28, July 5, and July 12, 2018.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On July 17, 2018, Makayla returned to Dr. Elmaghrabi and reported good urinary output and fluid intake since her previous visit. Her NG tube was now out. Her current labs showed a parathyroid hormone 282, hemoglobin 11.5, and near-normal electrolytes. Her serum creatinine was 2.38, and her eGFR was 23.6. Dr. Elmaghrabi thought her AKI was recovering and wanted her to continue with her current dietary restrictions. She thought that Makayla's good urinary output and improving renal function warranted the removal of her HD catheter the following week.

Banner Desert Medical Center

On July 19, 2018, Makayla presented for surgical removal of her RIJ HD catheter by Dr. Greenfeld. This was done under general anesthesia in the OR. She tolerated the procedure well and was returned to the PACU in stable condition. She was discharged home the same day.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

Makayla returned to see Dr. Elmaghrabi on July 20, 2018 and reported that she had had her HD catheter removed the day before in the hospital. Of note, as per Dr. Greenfeld, subcutaneous dissection was needed and thus Makayla had bruising around the HD cath site with blood on the gauze. Destiny had made sure she took her prescribed medications and followed her dietary advice. She was eating better with improved appetite, and she was no longer on formula feeds. Since the NG catheter was removed at home, Dr. Elmaghrabi wanted Makayla to resume the formula (Suplena) by mouth to avoid replacing the NG tube. Makayla proudly reported that she had completed first grade and had been doing well as the top student in her class.

Makayla reported good urinary output and Dr. Elmaghrabi observed that her serum creatinine had been measured at 2.38 on the 17th with an eGFR of 23.6. It had gone up slightly with fasting for surgery. A dipstick urinalysis in clinic that day showed continued proteinuria and leukocytes but no hematuria, which Dr. Elmaghrabi indicated were related to her acute kidney injury. She thought that Makayla was doing well and could continue with supportive care with good hydration and nutrition on a low potassium, low phosphorus diet. She continued her Renvela for now. She advised her to avoid NSAIDs and other nephrotoxic medications, and a "safe" list was given. She advised weekly lab monitoring for now.

In addition, Dr. Elmaghrabi advised continued blood pressure monitoring at home. Makayla exhibited secondary hyperparathyroidism, as her PTH remained elevated. She was taking Zemplar (synthetic vitamin D) with dialysis, and Dr. Elmaghrabi adjusted her dose accordingly. She continued Makayla on supplemental iron. Makayla was no longer taking Periactin, and they discussed restarting if her appetite was not sufficient to meet her nutritional needs.

Banner Desert Medical Center – Ultrasound

On August 1, 2018, radiologist Asmaa Aamir, MD performed a retroperitoneal renal aorta node ultrasound, comparing it with the renal ultrasound from May 1, 2018 and the abdominal ultrasound done on May 5, 2018. Dr. Aamir identified increased cortical echogenicity of the kidneys bilaterally, "which may be seen with medical renal disease." He observed that Makayla's kidneys were decreased in length compared to the prior studies, but he pointed out that the discrepancy might be secondary to differences in measurement technique or interval resolution of swelling in the kidneys. He recommended follow-up imaging to further evaluate renal size. Dr. Aamir also observed a fluid-containing structure in the upper pole of the right kidney, which was new and suggestive of focal caliectasis.[34] The right renal pelvis was not significantly dilated, but Dr. Aamir recommended attention on follow-up imaging.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On August 10, 2018, Makayla returned to the clinic, this time seeing Mark Joseph, MD. He went over her intermittent hemodialysis at Phoenix Children's Hospital that had concluded in July, followed by removal of her RIJ HD catheter by Dr. Greenfeld at Banner. Makayla's most recent serum creatinine was done recently and was 2.01 with a calculated eGFR of 37. Her labs also showed she was acidotic with a CO2 of 18 and potassium 5.7, so he started her on Cytra 25 mL twice daily, "which should help both." He continued her low potassium, low phosphorus diet and continued her Renvela. He wanted to continue with weekly labs for now. He made no changes to her other medications (Calcitriol and iron). Makayla's in-office dipstick urinalysis continued to show proteinuria, currently at 1+. Makayla had labs drawn on the 22nd that showed a cystatin C[35] elevated at 2.92, serum creatinine 2.05, and BUN 35.

Makayla saw Dr. Joseph again on August 29, 2018. She had done well since her last visit. Her mom had kept her adherent to her prescribed medications and dietary advice. Makayla was not taking cyproheptadine (Periactin) and her appetite was still poor—she had lost 2 pounds. Makayla was voiding good amounts of urine, but she was not stooling regularly without MiraLAX. She had occasional encopresis.[36] Destiny was currently homeschooling Makayla because her school did not want to take responsibility for hydration or medication delivery, despite there being a 504 (state plan) in place. Other issues for Makayla included having a sore arm from all the blood draws and her insurance had not yet provided the right size blood pressure cuff. She was also having right ear problems. Dr. Joseph referred her for the ear problem and

---

[34] Dilatation or distension of the calyces of the kidney, which is mainly associated with hydronephrosis and usually demonstrated by ultrasound or intravenous urography. This is the region of the kidney were urine production originates. Venes, *supra* note 84 at 362.

[35] The National Kidney Disease Education Program has recommended the use of the estimated GFR (eGFR) rather than measurement of serum creatinine alone. Until recently, estimating methods were based on serum creatinine as a marker of kidney function. However, because creatinine is also affected by diet, muscle mass or breakdown, and tubular secretion, it is not ideal, and a variety of estimating equations have been used. Recently, cystatin C, a nonglycosylated protein consisting of 120 amino acid residues encoded by *CST3*, has gained traction as an alternative marker. Ingelfinger, Julie R, and Philip A Marsden. "Estimated GFR and risk of death--is cystatin C useful?." *The New England journal of medicine* vol. 369,10 (2013): 974-5. doi:10.1056/NEJMe1308505

[36] *Encopresis* is a condition associated with constipation and fecal retention in which watery colonic contents bypass the hard-fecal masses and pass through the rectum. This condition is often confused with diarrhea. Venes *supra* Note 84 at 803.

made no other changes to Makayla's care plan. He wanted to see if she still had proteinuria at her next visit before prescribing an ACE inhibitor to treat that. Makayla's in-office dipstick urinalysis continued to show proteinuria of 100 mg/dL (2+).

Makayla turns eight years old

Makayla on her birthday 9/1/18

Banner Desert Medical Center – ER

On September 2, 2018, Destiny returned to Banner Desert Medical Center with Makayla, concerned about dark stools that started earlier in the day. In the emergency department, Makayla did not have any pain complaints, fevers, nausea, or vomiting. Her appetite appeared to be normal, and it was noted that she had been allowed to have a slice of birthday cake the day before. Dr. Ullman evaluated Makayla and reviewed a urinalysis, which was significant for 30 mg/dL proteinuria and a large amount of leukocyte esterase and white blood cells. X-rays of her abdomen and chest were unremarkable. Dr. Ullman reassured Destiny that her daughter appeared to have a simple urinary tract infection, for which the doctor prescribed a course of Keflex antibiotics. A CBC reflected normal values. Dr. Ullman also diagnosed Makayla with constipation and overflow diarrhea, and reassured her there was no blood in her stool by guaiac testing. He advised her to keep her visit with her PCP the following week but to come back if she had additional concerns.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

Accompanied by her mom and little brother Tom, Makayla returned to see Dr. Elmaghrabi on September 4, 2018 and discussed her most recent ER visit. They discussed her labs, dietary restrictions, and medications. Dr. Elmaghrabi spoke with the registered dietician and switched Makayla's Suplena supplement to half water, as full strength was too strong for her. Makayla was responding well to an appetite stimulation with an improvement in her appetite.

Happy Kids Pediatrics – well child exam

On September 6, 2018, Klint L. Webb, PA-C at Happy Kids Pediatrics evaluated Makayla for a routine child health exam. The visit was notable for a resolving urinary tract infection, for

which she was put on antibiotics (Keflex) a few days earlier. The ER advised her to follow-up with her pediatrician. Her basic exam was unremarkable, with the exception of hematuria. PA Webb advised Destiny to keep Makayla on the antibiotic through its completion.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On September 11, 2018, Makayla returned to the pediatric nephrology clinic and saw Dr. Elmaghrabi, addressing the same issues as on September 4, 2018.

Makayla returned to see Dr. Elmaghrabi on October 10, 2018. She was still taking Periactin and had an improved appetite. She was voiding well with "good" amounts of urine. Her latest serum creatinine was slightly improved at 1.97 mg/dl which calculated to an eGFR of 29. Dr. Elmaghrabi thought this was consistent with continued, if slow, renal recovery. She commented on the renal ultrasound in August that showed a renal size discrepancy, with the right kidney being smaller than the left. Makayla also continued to have proteinuria, although this was improved (1+), and her urine protein/creatinine ratio was elevated at 0.9. Dr. Elmaghrabi discussed low dose ACE inhibitor therapy if the proteinuria persisted. As such, she wanted to recheck a urine protein/creatinine ratio on an early morning void. She continued Makayla's vitamin D and low potassium, low phosphorus diet. She continued her Renvela.

On October 22, 2018, Makayla was called back to the clinic early because of elevated blood pressures at home, and the last episode was accompanied by a headache. Dr. Elmaghrabi measured Makayla's blood pressure in the clinic that day with a systolic of 119. She observed that Makayla was not currently on antihypertensives because she had experienced low blood pressure on amlodipine, which had been discontinued for that reason. She therefore thought they could continue to monitor her pressures at home and keep a log, and they could consider a low dose ACE inhibitor for hypertension and proteinuria, depending on how she did, allowing for further renal recovery. Her dipstick UA[37] that day showed stable proteinuria of 1+ (30 mg). Makayla came back and met with the dietician on October 27, 2018.

Repeat labs were done on October 31, 2018, which showed an increase in Makayla's proteinuria to 100 mg (2+), as well as leukocyte esterase and white cells. A random urine protein test was measured at 128 and protein 124, with a "normalized" urine protein elevated at 969.[38] The following day, blood tests showed that Makayla was still anemic, with a hemoglobin 10.8, hematocrit 32.1, BUN 33, creatinine 1.90, and she exhibited hyperparathyroidism with a PTH[39]

---

[37] Dipstick tests for trace amounts of protein yield positive results at concentrations of 5 to 10 mg per dL—lower than the threshold for clinically significant proteinuria. A result of 1+ corresponds to approximately 30 mg of protein per dL and is considered positive; 2+ corresponds to 100 mg per dL, 3+ to 300 mg per dL, and 4+ to 1,000 mg per dL. Dipstick urinalysis reliably can predict albuminuria with sensitivities and specificities of greater than 99 percent. Anderson MJ, Agarwal R. Urinalysis. Lerma EV and Nissenson AR. *In Nephrology Secrets*. Third Edition. Elsevier Mosby: 2012.

[38] Normal reference range for protein in the urine, normalized, is 15-220 mg/g/creatinine

[39] Renal hyperparathyroidism (rHPT) is a common complication of chronic kidney disease characterized by elevated parathyroid hormone levels secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D. Yuen, Noah K et al. "Hyperparathyroidism of Renal Disease." *The Permanente journal* vol. 20,3 (2016): 15-127. doi:10.7812/TPP/15-127

of 124.[40] On November 27, 2018, Makayla's PTH level was measured closer to normal range at 76.

Phoenix Children's Hospital – renal ultrasound

On November 28, 2018, Makayla presented to Phoenix Children's Hospital for a renal ultrasound with Mostafa Youssfi, MD. He identified bilateral hyperechoic kidney parenchyma suggestive of nonspecific medical kidney disease. There was no hydronephrosis. He identified a simple cyst on her right kidney. Dr. Youssfi also observed the size discrepancy between the right and left kidneys with the right being at the lower range of normal and the left at the upper limits of normal. He also saw an incidental omental cyst. Dr. Youssfi also performed a nuclear medicine renal DMSA[41] scan, which confirmed the discrepancy of renal sizes but otherwise was a normal DMSA study.

Pediatric Kidney Disease & Hypertension Outpatient Clinic – slow renal recovery

Makayla returned to see Dr. Elmaghrabi on December 4, 2018. The doctor noted that her serum creatinine was still trending down, with the most recent reading on the 29th of November of 1.66, observing that she continued on a slow trajectory of renal recovery. She continued to exhibit proteinuria of 100 (2+).

Happy Kids Pediatrics – home glucose monitoring

On December 7, 2018, Makayla returned to see Klint L. Webb, PA-C at the pediatric office, referred by her nephrologist to get a glucose monitor. She was prescribed a home kit, and the PA referred her to endocrinology for further evaluation and management of her elevated blood sugars.

Pediatric Endocrinology Consultation – diabetes ruled out

On December 18, 2018, Makayla presented for an endocrinology consultation with Aruna Poduval, MD. Destiny provided Makayla's medical history, adding that she had been on antihypertensive medications during her hospitalization but had been able to discontinue them and had not needed them since—however, at the last nephrology visit, there had been discussion of restarting them for intermittent elevated pressures if the trend was on the rise.

Dr. Poduval found it notable that Makayla had been on and off appetite stimulants since her NG tube was removed in August, and she was currently on a renal diet at home. She had been referred by her pediatrician for the possibility of developing diabetes. Destiny reported that they had been keeping track of Makayla's blood sugars, and there had been a couple of high fasting

---

40 Normal reference range for PTH is 16-65 pg/mL.

41 *DMSA* is a method of testing the kidneys for evidence of pyelonephritis, e.g., in children suspected of having kidney damage resulting from vesicoureteral reflux. A small dose of dimercaptosuccinic acid (DMSA) linked to radioactive technetium (technetium-99m) is injected intravenously and allowed to circulate to the kidneys. Several hours later, uptake of the tracer by the kidneys is measured with a gamma camera. Venes *supra* Note 84 at 2015.

values (120-130). Makayla did not exhibit excessive thirst or urination to suggest overt diabetes. Dr. Poduval checked Makayla's hemoglobin A1c,[42] finding it in normal range at 5.1. She told Destiny and Makayla that they did not need to continue monitoring her blood sugars, since there was no current evidence of hyperglycemia on the HbA1c.

Pediatric Kidney Disease & Hypertension Outpatient Clinic – starting ACE inhibitor

On January 8, 2019, Makayla and her mom met with the dietician, who noted improvement in many areas, including her weight (gain) and serum creatinine. She was continued on a low sodium and potassium diet. The following day, Makayla's lab results exhibited continued proteinuria. Her anemia was improved (hemoglobin 12.8, hematocrit 39.4), her renal function panel continued to show abnormal values (BUN 32, creatinine 1.51), and her PTH was still elevated at 84.

On January 16, 2019, Makayla returned to Pediatric Kidney Disease & Hypertension Outpatient Clinic. Since her last visit, she was reportedly doing well. Her appetite and fluid intake were improved, but Makayla reported that she continued to have fatigue. She was now attending public school half days. The ear problem reported earlier had resolved. Destiny was worried about Makayla's grades being worse (Ds and Fs, where she had As before). Her constipation was improved on supplemental fiber and MiraLAX. Dr. Elmaghrabi explored the issue of fatigue (intermittent napping), but Makayla had not been having fevers, no significant weight changes, and no respiratory problems. Her urine output was good and there were no voiding problems. She had no increased thirst, temperature intolerance, or other signs of endocrine problems. She did have occasional headaches, but no dizziness, syncope, gait problems, or weakness. She had no developmental delays, and no known heart murmurs.

Dr. Elmaghrabi documented that Makayla's CKD (chronic kidney disease) was of an "undetermined" stage, as her serum creatinine was still trending down. Her latest value was improved to 1.5 mg/dL, calculated to an eGFR of 38. She considered her renal status stable but with "quite slow renal recovery." She discussed with Destiny the preventive measures needed to protect Makayla's kidneys from the development of AKI and progressive CKD. She wanted to get another renal ultrasound in six months. Dr. Elmaghrabi was concerned about possible underlying etiologies of CKD such as renal scarring from her past urinary tract infections. She thought they could go 6 weeks between blood draws at this point, with return visits afterwards. Makayla continued to exhibit proteinuria (100 mg/dL, 2+) with a urine protein/creatinine ratio elevated at 1.4, which was worse (last was 1.2). Makayla's blood pressure was slightly elevated in clinic that day, with home measurements running around 110/80. Dr. Elmaghrabi again discussed starting an ACE inhibitor and prescribed Enalapril at 1 mg daily for blood pressure control, renal protection, and proteinuria.

Finally, Dr. Elmaghrabi discussed obtaining genetic studies for aHUS if Makayla were to redevelop features of HUS or any other clinical concerns: "On 10/10/18, I spoke with personnel

---

[42] HbA1c, aka glycated hemoglobin, is a form of hemoglobin that is chemically linked to a sugar. The usual sugar is glucose. The formation of the sugar-Hb linkage indicates the presence of excessive sugar in the bloodstream, often indicative of diabetes. A1C is of particular interest because it is easy to detect. Normal range is under 5.8. https://www.mayoclinic.org/tests-procedures/a1c-test/about/pac-20384643

in the genetic lab at Cincinnati children and stated that, testing has to be done through an institution." Makayla was scheduled to get an evaluation for her learning difficulties on January 24, 2019.

Banner Desert Medical Center

Makayla was seen in the ER on January 17-18, 2019 for constipation and was evaluated by Zola Noni Trotter, MD and Jennifer Meeks, PA. The providers were concerned that Makayla presented with right lower quadrant pain, but a full history and physical were consistent with constipation. An abdominal X-ray confirmed the presence of a "moderate stool burden" and a nonobstructive bowel gas pattern. She was encouraged to continue with MiraLAX.

Happy Kids Pediatrics

On January 31, 2019, Makayla returned to the pediatric office to follow up on a cough she had for a couple of weeks. She reported that she had been on Enalapril for a couple of weeks for blood pressure and protein in her urine, but she had stopped it three days earlier because of her cold. PA Webb diagnosed her with an upper respiratory infection and advised a cool mist humidifier but no medications. Makayla returned for a follow-up on February 4, 2019 and was given Delsym children's cough syrup for symptom relief.

Lab Results

Makayla had repeat labs done on February 19, 2019, which showed continued proteinuria (urine protein, normalized 1530), BUN 28, creatinine 1.30, and PTH 85. A cystatin C eGFR was reported abnormal (low) on the 23rd, showing a value of 34.[43]

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On February 26, 2019, Makayla returned to see Dr. Elmaghrabi in follow-up of hyperphosphatemia, electrolyte disorder, proteinuria, and acute nontraumatic kidney injury. She and her mom reported that she had been doing well the past month; however, X-rays in the ER had showed constipation and she was working on getting more fiber in her diet, as well as taking MiraLAX. Her blood pressures at home had a few systolics in the 120s. Dr. Elmaghrabi discussed Makayla's renal function labs, including the cystatin C eGFR calculation of 34-38 (normal being greater than 60). Makayla had a great deal of protein in her urine in the clinic that day (>300), so she wanted to recheck her urine protein on an early morning void. She planned another kidney ultrasound in May.

Wayne R. General, PhD – Licensed Psychologist

On March 20, 2019, Destiny brought Makayla to Wayne R. General, PhD, based on a request by an Arizona Department of Economic Security/Disability examiner for a mental examination regarding Makayla's claim: "E-coli; kidney failure; learning delays." Dr. General interviewed Destiny and Makayla, who explained that Makayla was earning As and Bs prior to

[43] The normal reference range for eGFR using cystatin C is >60 mL/min/1.73m2

her *E. coli* infection, and she was now earning mostly Ds and Fs. Destiny described Makayla's critical illness and hospitalization as best she could, as well as her current impaired kidney function and general health after being discharged from the hospital. Destiny told the doctor that she was home-schooling Makayla at the time of the visit. Dr. General performed a formal mental status examination, observing her affect and mood, which he followed by the administration of the Wechsler Intelligence Scale For Children-V test and Vineland Adaptive Behavior Scale-II. At the conclusion of his assessment, Dr. General documented:

> [Makayla's] ability to perform school related tasks is quite limited, given her history as related by Mother. On the basis of this evaluation, Makayla is seen as being quite delayed in all areas of academic functioning and these findings are consistent with her overall Wechsler Intelligence Scale for Children-V performance, [and she has] an IQ in the Mildly Intellectually Impaired range.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On April 6, 2019, Makayla's cystatin C eGFR was stable at 35 mL/min/1.73m2. Her BUN and creatinine were 23 and 1.38. Her PTH was in normal range. She continued to have 2+ proteinuria, with a urine protein "normalized" of 1200 (normal is 15-200 mg/g creat).

Dr. Elmaghrabi saw Makayla on April 10, 2019, noting a "good" appetite and adequate fluid intake. Her blood pressures at home had been in normal range on the ACE inhibitor. She commented: "The CKD is now stage 3 but creatinine is still fluctuating. Her latest creatinine stable at 1.38 (prior 1.3 mg/dL) which calculates to an eGFR of ~42 bedside Schwartz. Adding cystatin C which is elevated at 2.1 would change eGFR to 34-38. Discussed with mom the preventive measures needed to protect the kidneys from the development of AKI and progressive CKD." Dr. Elmaghrabi increased Makayla's enalapril dose to 1.5 mg daily for blood pressure control, renal protection, and proteinuria. She discussed her electrolytes, which were normalizing, and started weaning her off Renvela.

Banner Desert Medical Center

On April 12, 2019, Makayla was back in the ER with vomiting since the night before. James Reingold, MD evaluated her and kept her under observation long enough to confirm that she was hemodynamically stable and able to keep down fluids. She was discharged home after she was noted to have normal urine output and no signs of urinary tract or other infections. Her proteinuria showed improvement (30 mg/dL – 1+), and a urine culture grew only mixed lower urethra flora, suggestive of a contaminated specimen. Since her lab work also showed an increased serum creatinine of 1.44 mg/dL, Makayla was advised to see her nephrologist in follow-up.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On May 8, 2019, Makayla's urine creatinine was 50 and protein 40, which correlated to a "urine protein normalized" value of 800 (RR 15-220 mg/g/creat). On the 11th, her Cystatin C was

2.13, with a calculated eGFR of 35 (note that Dr. Elmaghrabi adjusted the value to an eGFR of 44 given the Cystatin C value).

Makayla returned to see Dr. Elmaghrabi on May 15, 2019. She reviewed Makayla's recent lab studies and the ER visit in April, at which time she was advised to see nephrology sooner than previously scheduled. Destiny reported that Makayla had been doing well since the ER visit, had improved constipation, but still had occasional episodes of encopresis. Makayla continued her current dose of enalapril.

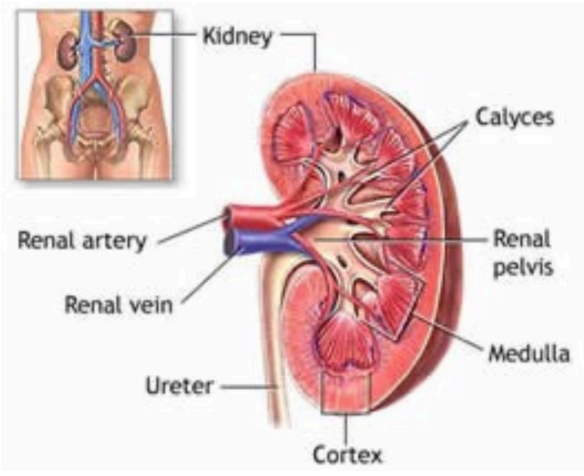
Banner Desert Medical Center – referred for a neuro check

Makayla was sent over to the ER by nephrology on June 10, 2019 when Destiny reported that Makayla was having problems with short term memory loss. This had been especially noticeable for the prior couple of weeks, and for a couple of days she had been "repeating questions and not gathering answers to material she most certainly knows." Jayson Luma, MD, evaluated Makayla, considering a differential diagnosis (diagnostic possibilities) of "viral syndrome, colic, bacterial infection." Her labs showed a BUN 26.4, serum creatinine 1.52, negative proteinuria, moderate urinary leukocyte esterase, with white blood cells. Dr. Luma reported the results to nephrology and sent Makayla home in stable condition. He reassured Destiny that this did not look like a relapse of HUS.

Makayla left the ER with instructions to follow-up with pediatric neurologist Jeremy Timothy, MD the following week to schedule and complete an MRI. Destiny was advised to bring her back to the ER for worsening headaches, persistent vomiting, suspicion for seizure activity or changes in her level of consciousness.

Renal ultrasound still abnormal

On June 19, 2019, Makayla returned to Banner Desert Medical Center for a retroperitoneal renal ultrasound. Asmaa Aamir, MD, performed the exam and compared it to the ultrasound on August 1, 2018. Dr. Aamir identified increased renal cortical echogenicity bilaterally, compatible with Makayla's history of medical renal disease. She saw no pelvocaliectasis (dilatation of the renal calyces).



Dr. Aamir observed an anechoic cystic structure in the upper pole of the right kidney that was minimally increased in size from the prior study. She thought it was likely a cyst, which had a few thin septations within it. There were also several non-obstructing stones in both kidneys. She also observed some "debris" in the urinary bladder, which could be consistent with infection or hemorrhagic product, so she advised correlation with a urinalysis.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

Makayla returned to see Dr. Elmaghrabi on June 26, 2019. They reviewed the evaluation in the emergency department for memory loss, which had worsened over the prior few weeks. She was evidently referred to neurology but had not been able to schedule a visit. Makayla's CKD-III was unchanged, with recent lab test results similar to the last time she was seen. Dr. Elmaghrabi discussed the renal ultrasound that showed a continued size discrepancy between Makayla's kidneys (right 8.3 cm and left 10.5 cm) and a stable cystic structure on the right, with a normal DMSA (right 45% and left 55%). Makayla's UA dipstick in the office that day showed trace proteinuria. Dr. Elmaghrabi noted that her urine protein/creatinine ratio was still elevated at 0.64 but improved from prior 0.8 to 1.2. She made no changes to Makayla's ACE inhibitor and lab scheduling. Turning to the neurologic issues, she told Destiny that her PCP would need to make the referral to neurology. Makayla was also still having learning difficulties that she "previously underwent cognitive testing" for, which problem was also managed by her PCP. Makayla was scheduled to return for another visit with Dr. Elmaghrabi in August.

Happy Kids Pediatrics

Makayla returned to Happy Kids Pediatrics on July 16, 2019 to arrange for a neurology referral. Nabor Rios, PA-C saw her that day and gave her a referral, indicating specifically that the referral be made to a neurologist other than Dr. Timothy at Banner.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

On August 20, 2019, Dr. Elmaghrabi saw Makayla at Pediatric Kidney Disease & Hypertension Outpatient Clinic and Destiny reported that Makayla had been doing well but still had problems with intermittent loss of short-term memory. She had been referred to neurology at PCH and a visit was pending. Makayla's urinalysis that day showed only a trace of protein on the dipstick, but the sample was very dilute, and her last urine protein/creatinine ratio had been more elevated at 0.67 (previously 0.64). Dr. Elmaghrabi therefore increased Makayla's enalapril dose to 2 mg/daily.

Phoenix Children's Medical Group – Neurology Outpatient

Destiny brought Makayla for a neurology visit with Christopher Inglese, MD at Phoenix Children's Medical Group on September 12, 2019. He documented that Nabor Rios, PA-C had requested referral for "evaluation of new onset seizures." However, Destiny told him she was unaware of any seizures and did not think this had ever been of concern to her medical providers, family members, or teachers. Destiny explained that the concern, as she was aware of, was

memory loss that became apparent after Makayla's critical illness, "specifically Shiga-toxin related *E. coli* enteritis with subsequent HUS and AKF." Dr. Inglese found Makayla "delightful" and reviewed her history of hospitalization, including the multiple complications she suffered through the ordeal. His interpretation of the records was that she had developed situational anxiety and an adjustment reaction that had required intervention from Psychiatry, as well as fentanyl-related abstinence syndrome.

Dr. Inglese also observed that, prior to her illness, Makayla was faring well academically. Subsequently, she was struggling and seemed to have difficulties with retrieving previously mastered information and, to a lesser extent, difficulty with registration and facility with newly learned academic tasks. Destiny provided him with examples but, specifically, Makayla appeared to be doing as well as her peers in the 1st grade, but was now getting mostly Ds and some Fs.

Dr. Inglese made reference to a recent evaluation by a neuropsychologist in Mesa: "and soon mother will review the results, and this will impact whether a 504 plan is implemented." Destiny stated that she did not know the extent to which or the specifics of Makayla's intellectual dysfunction or academic challenges, but that she was told that her daughter had intellectual disabilities qualifying her for extra help.

During the interview, Dr. Inglese found Makayla "inattentive, distractible at times fidgety and restless but not intrusive, rude or aggressive." Destiny was asked about whether Makayla exhibited any "internalizing behaviors, anxiety or depression or mood volatility," but she indicated she had noticed none of those things. Her stated understanding of the referral was that the question to be answered was whether Makayla's brain had been affected by the critical illness, in addition to her hypertension and other toxic metabolic factors. Destiny denied that Makayla was having episodes of "activity arrest with or without automatisms" and informed Dr. Inglese that she had not noticed any episodes of "increased or decreased tone, myoclonus [muscle twitching], or clonic manifestations [sustained, rhythmical jerking] of an epileptic disturbance with altered awareness and a period of disorientation and fatigue." Evidently, Makayla was having nightmares but could not recall them well enough to describe them.

Dr. Inglese reviewed Makayla's discharge summary, looking for mention of neurologic involvement or central nervous system imaging, and specifically for seizures being suspected or diagnosed, finding nothing. He also reviewed Makayla's birth history, noting she was born at term but remained in the hospital for 5 days after being found to have a murmur and a ventricular septal defect; however, she was cleared by cardiology and sent home. Destiny did not smoke or drink during pregnancy or use recreational substances. Makayla's developmental history revealed she crawled and walked a bit late, according to her mom. A neurologic examination was unremarkable, and aside from looking somewhat pale, her physical exam was unrevealing. Dr. Inglese noted her renal function labs were improving.

Dr. Inglese documented his impression and plan:

> As this delightful child has a nonlateralized and nonfocal exam with no features of increased intracranial pressure or seizures, neither [EEG] nor imaging will be ordered. I asked mother to ask the neuropsychologist who has tested her in Mesa

contact me if she finds concerning findings suggestive of focal of regional cortical networks and if this is so, I of course will order an MRI without contrast of the brain.

If psychologist based upon test results feels that imaging may be helpful with regard to defined deficits or assist in the diagnosis of a specific neurocognitive problem, please call to discuss ordering an MRI. If episodes as reviewed are noted concerning for seizures, please call and I shall order an EEG.

After examining this child and conversing casually and performing Slosson-graded spelling tests, she appears to be grossly intact and possibly having specific learning disabilities or remediable attention problems. Mother recalls filling out a Vanderbilt or Connors rating form so it seems as if ADHD will be addressed as well.

Dr. Inglese concluded the visit by advising Destiny not to overuse Tylenol for minor headaches and asked her to keep a diary of Makayla's headaches, if any. He did recommend follow-up neuropsychology testing.

Pediatric Kidney Disease & Hypertension Outpatient Clinic

Makayla returned to see Dr. Elmaghrabi on October 21, 2019, at which time Destiny told the doctor about Makayla's visit with the neurologist. She explained that the neurologist ultimately told her that Makayla did not need an MRI. Makayla's blood pressures at home were reportedly in normal range, and she had a good appetite and adequate fluid intake. Dr. Elmaghrabi reviewed recent labs that were drawn the week before the visit that continued to show an abnormally low Cystatin C calculated eGFR of 39. Makayla's serum creatinine was fluctuating and still elevated, but more stable (currently 1.45 mg/dL), and her electrolytes and albumin were normal. Her urine protein/creatinine ratio was still abnormal but slightly better at 0.56 (previously 0.67). Makayla's UA continued to exhibit proteinuria, although improved on the ACE inhibitor (enalapril). Dr. Elmaghrabi and Destiny went over the preventive measures needed to protect Makayla's kidneys from the development of AKI and progressive CKD, including good hydration and nutrition, and minimizing the use of nephrotoxic medications such as NSAIDs. Destiny was following the "safe meds" list previously given to her by the doctor. Dr. Elmaghrabi told Destiny she wanted to get another renal ultrasound in July of 2020, and another clinic visit after the first of the year. Meanwhile, she increased Makayla's enalapril dose to 2.5 mg daily for blood pressure control, renal protection, and proteinuria. Destiny would continue to keep a blood pressure log.

2020 OUTPATIENT MEDICAL VISITS

On January 7, 2020, Makayla returned to the clinic, this time seeing Mark Joseph, MD. Destiny reported that Makayla continued to struggle at school and was likely going to be retained in the third grade the next school year. She was attending Leading Edge, and her mom was pleased with the support she was getting there. Destiny told Dr. Joseph that Makayla had not had any gross hematuria or edema since the last visit, and she had been adherent to the prescribed medications and dietary recommendations. Makayla had some difficulty with constipation, but

this was improved on fiber and MiraLAX.

Makayla had blood work and urine tests the week before this visit, and Dr. Joseph took the time to review all the results in detail with Destiny. Makayla's latest cystatin C was 209, "which calculated to an eGFR of 35-37 mL/min/1.73m^2, depending on formula." Her serum creatinine was slightly more elevated at 1.60 (previously 1.45 mg/dL). Dr. Joseph saw no evidence of acidosis or any other electrolyte abnormalities, but he noted that a phosphorus level had inadvertently been omitted from the lab tests. Dr. Joseph noted that Destiny had no evidence for renal osteodystrophy with an "intact" parathyroid hormone level of 50, and her magnesium was "normal" at 2.2. Makayla's hemoglobin was "normal" and Dr. Joseph was happy with an improvement in her iron stores, decreasing her supplemental iron to 2 pills a day. He observed that Makayla's current urine protein/creatinine ratio was calculated at 0.504 (previously 0.56), commenting: "This is the lowest value she has ever had since her acute injury." Destiny was concerned about an elevated blood glucose reading at home, so Dr. Joseph added a hemoglobin A1c to the next lab requests. He indicated he would like to transition Makayla's ACE inhibitor to a pill form at her next visit. Although she was stable and doing well, he cautioned:

> We anticipate that Makayla will have progressive kidney disease with time. Her rate of decline is unknown. It is imperative that we continue to follow her closely at all times. We plan to see her back in our nephrology clinic in 3-4 months with laboratory studies just prior to that visit.

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 Makayla's clinical presentation, as well as her risks of long-term complications following her acute episode of HUS. After completing a review of the extensive medical records, Dr. Andreoli provided her opinion on November 22, 2019. A Summary of her findings follows:

> To summarize her medical records related to *E. coli* O157:H7, Makayla had very severe HUS as manifested by the need for dialysis for over five weeks and a history of significant oligo/anuria. Makayla was anuric for 10-12 days and oliguric for 13 days for a total of 23-25 days of oligo/anuria. In another area of the chart, some urine output is reported on days when she was reported as anuric. According to these records, she had 12 days of anuria and 13 days of oliguria for a total of 25 days of oligo/anuria. The physician's progress notes repeatedly describe that she had prolonged anuria. At a weight of 36.8 kg and normal urine output of 0.5 mL/kg/hours, a normal urine output in Makayla would be approximately 440 mL per day. Thus, as described above, Makayla had 25 days of oligo/anuric [see Table in Dr. Andreoli report]. In addition, she required dialysis for over five weeks. Very importantly, Makayla had residual hypertension requiring antihypertensive therapy, residual overt proteinuria, and residual renal insufficiency, with an elevated BUN and creatinine, and stage 3 chronic kidney disease.
>
> 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 renal disease including hypertension, proteinuria, and residual renal insufficiency.

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. Some of the more significant findings are excerpted below:

- Children with a history of oliguria had a 44% incidence of proteinuria, 35% incidence of a decreased creatinine clearance, and a 47% risk of any renal sequelae including proteinuria, decreased creatinine clearance, or hypertension.
- 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 incidence of late complications increased markedly in those with more than 5 days of anuria or 10 days of oliguria.
- Other studies (Caletti, *et al.*, Pediatric Nephrology, 1996) have demonstrated that histological finding of focal and segmental sclerosis, and hyalinosis are observed several years following HUS. In that article, only 25% of the children had normal renal function during long term follow-up.

Dr. Andreoli summarized her report by pointing out that many children who have recovered normal renal function following an 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. Finally, she concluded:

> Makayla had prolonged oligo/anuria and required dialysis for over five weeks. She has hypertension requiring therapy and residual significant proteinuria requiring therapy with an angiotensin converting enzyme inhibitor. Thus, as described above, studies have shown that such patients have a very significant risk of later renal complications. I would estimate her risk for late renal complications, including end stage renal disease (ESRD), at 95-100%.

Dr. Andreoli took the time to address the special circumstances that apply to Makayla that are specific to young women as they approach puberty and adulthood. As she describes, the potential adverse effects of having severe HUS at such a young age as Makayla are far-reaching and life-altering. As a result, her hopes to have a normal life and raise children, or even to achieve advanced educational goals and lead a productive life as an adult, will likely be seriously compromised by the damage done to her vital organs in her formative years.

Dr. Andreoli described what Makayla might expect as she becomes a young woman and mature adult:

> Successful pregnancy is possible for young women with ESRD during their reproductive years. However, these pregnancies remain high-risk and require multidisciplinary care, given high rates of preeclampsia, cervical incompetence, preterm delivery, and small for gestational age offspring in this population. Further, the need for emotional support of these vulnerable young women cannot be overstated. Carrying a pregnancy on intensive dialysis requires commitment and the challenges associated with raising a young child can be extremely daunting for a young woman with chronic illness. In addition, pregnancy in young women prior to the need for renal replacement therapy can result in loss of renal function.
>
> Adolescents and young adults with chronic kidney disease face a number of complications from their chronic kidney disease failure (Andreoli SP, Acute and Chronic Renal Failure in Children, 2009) including alterations in calcium and phosphate balance, and renal osteodystrophy (softening of the bones, weak bones and bone pain), anemia (low blood count and lack of energy), hypertension (high blood pressure), as well as other complications.
>
> Renal osteodystrophy (softening of the bones) is an important complication of chronic renal failure. Bone disease is nearly universal in patients with chronic renal 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 renal 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) is a very common complication of chronic renal failure. The kidneys make 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 renal failure. Thus, children with chronic renal failure gradually become anemic, while their chronic renal failure is slowly progressing. The anemia of chronic renal failure is treated with human recombinant erythropoietin (a shot given under the skin one to three times a week or once every few weeks with a longer-acting human recombinant erythropoietin).
>
> Makayla is very likely to need renal replacement therapy in the future. Renal replacement therapy can be in the form of dialysis (peritoneal dialysis or hemodialysis) or renal transplantation. Renal transplantation can be from a deceased or a living related donor (parent or sibling who is over the age of 18 and who is compatible). Should Makayla have a living related donor available to donate a kidney, she can undergo transplantation without the need for dialysis (preemptive transplantation). Should she not have a living related donor, she will

likely need to undergo dialysis while on the waiting list for a deceased donor transplant. Children have the shortest waiting time on the deceased donor transplant list. The average waiting time for children age 0-17 years is approximately 275-300 days while the average waiting time for patient's age 18-44 years is approximately 700 days (United States Renal Data Systems, Table 7.8, 2005).

Following transplantation, Makayla will need to take immunosuppressive medications for the remainder of her 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 difficulty in controlling glucose levels. The steroid side effects, particularly the effects on appearance, are difficult for children, particularly teenagers, and noncompliance to the side effects of medications is risky in children, particularly teenagers.

I would estimate that Makayla will need her first kidney transplant in 5-10 years. By that time, she will be a teenager and the growth, development, and hormonal changes that occur during the onset of puberty can be very detrimental to kidney function and it is common that kidney function declines significantly during the teenage years.

Tacrolimus (also known as FK506) is commonly used as an immunosuppressive medication following transplantation. Side effects of this drug includes hirsutism (increased hair growth), gum hypertrophy, interstitial fibrosis in the kidney (damage to the kidney), as well as other complications. Meclophenalate is also commonly used after transplantation (sometimes Imuran is used); each of these drugs can cause a low white blood cell count and increased susceptibility to infection. Many other immunosuppressive medications and other medications (antihypertensive agents, anti-acids, etc.) are prescribed in the postoperative period.

Life-long 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.

Makayla may need more than one kidney transplant during her life. United States Renal Data Systems (USRDS) report that the half-life (time at which 50% of the kidneys are still functioning and 50% have stopped functioning) is 10.5 years for a deceased transplant in children age 0-17 years and 15.5 years for a living related transplant in children 0-17 years. Similar data for a transplant at age 18 to 44 years is 10.1 years and 16.0 years for a deceased donor and a living related donor,

respectively. Thus, depending upon her age, when Makayla receives her first transplant (and updated information at that time), she may need 1-2 transplants.

If Makayla does not have a living related donor for her first kidney transplant and if/when she needs a second kidney transplant after loss of her first transplant, she will need dialysis until a subsequent transplant can be performed. She can be on peritoneal dialysis or on hemodialysis. Peritoneal dialysis has been a major modality of therapy for chronic renal 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 renal failure. In this form of dialysis, a catheter is placed in the peritoneal cavity (area around the stomach) and 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 renal failure during childhood. During hemodialysis, blood is 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.

Finally, Dr. Andreoli stated:

In conclusion, Makayla had severe renal disease during her acute episode of HUS. She currently has stage 3 chronic renal disease. She will need life-long monitoring of her renal status (pre and post-transplant), as well as hospitalizations and surgeries for transplant, to place catheters for renal replacement therapy as well as for complications of transplantation and dialysis. If you have any questions, please do not hesitate to contact me.

Elizabeth L. Leonard, PhD – Neuropsychological Consultation

We asked Clinical Neuropsychologist Elizabeth L. Leonard, PhD, Faculty Fellow at the Center for Law, Science & Innovation at Arizona State University's Sandra Day O'Connor College of Law, to provide an analysis of the extent of any cognitive dysfunction after Makayla's acute episode of HUS that resulted in her prolonged hospitalization dialysis. After completing a review of the extensive medical records, Dr. Leonard provided her opinion on March 20, 2020.

In conducting her analysis, Dr. Leonard first met with Destiny for two hours on February 19, 2020 to obtain a comprehensive development, educational, and medical history prior to seeing Makayla. She then conducted a six-hour neuropsychological examination of Makayla at Neurocognitive Associates in Phoenix, AZ on 2/20/20 and 2/21/20 for about three hours each day. Dr. Leonard reviewed Makayla's full medical records from Banner Desert Medical Center, Arizona Kidney Disease and Hypertension Center, Happy Kids Pediatrics, Phoenix Children's Hospital, and Sonoran Pediatric Endocrinology. She also reviewed Makayla's educational records

from Sequoia Edkey Schools, as well as a Psychological Evaluation dated 3/20/19 conducted by Wayne General, PhD.

Dr. Leonard provided her Summary and Opinions:

> Makayla Jarboe is a 9.5-year-old girl who was healthy and doing well in school when she developed bloody diarrhea and became acutely ill after eating tainted lettuce at a local restaurant. Makayla was diagnosed with Shiga-toxin-producing *E. coli* infection resulting in hemolytic uremic syndrome with secondary development of acute renal failure and acute pancreatitis requiring nasogastric feeding and bilateral pleural effusions, and respiratory failure requiring intubation and chest tube placement. She was hospitalized for about 39 days and continues to require care with a pediatric nephrologist for stage 3 chronic renal disease. She required outpatient dialysis for several months after her hospitalization. She will ultimately require renal transplantation when her renal function deteriorates to the point where she will be eligible to be placed on a transplantation list. She is on a restricted diet and needs to remain well hydrated. She is not allowed to become overheated and is restricted from playing in the hot Arizona sun.
>
> Since her illness, Makayla's performance in school has declined and grade retention is being considered. Ms. Jarboe expressed concerns about Makayla's inability to retain information and poor comprehension. She has been teased at school for not being able to answer questions. A consultation with a pediatric neurologist did not identify any specific neurological illness and was relying on results from neuropsychological testing to guide treatment, and a determination as to whether neuroimaging might be indicated.
>
> Makayla has mild intellectual disability. Her profile on neuropsychological testing is markedly uneven with average performance on tasks assessing verbal understanding, reasoning, and processing speed, and mild impairments in visual spatial and fluid reasoning, and working memory.
>
> Immediate and delayed recall for complex verbal information was average. Verbal fluency and receptive and expressive vocabulary knowledge were average. Visual memory was mildly impaired. Mild to moderate deficits were present on tasks assessing visual memory, visual sequential processing, and auditory working memory. Verbal learning and memory were intact for rote learning.
>
> Visual-spatial processing was low average to mildly impaired. Makayla has mild impaired executive functions on tasks requiring conceptualization and abstract reasoning. Academic skills were average for reading and writing. Performance was borderline impaired on tests of math fluency and calculation.
>
> Makayla meets diagnostic criteria for mild intellectual deficiency with essentially two independent intelligence tests one year apart confirming impaired intelligence. Neuropsychological testing confirms multiple neurocognitive deficits affecting

principally visual learning and memory, visual spatial processing, some components of executive reasoning, and verbal and visual working memory. These deficits are more likely than not permanent. Makayla will require serial neuropsychological examinations approximately every three years until she exits school to monitor her progress and make developmentally appropriate recommendations as she matures, and her cognitive and emotional needs change.

Makayla's neurocognitive deficits do not appear to be the result of excessive school absences due to her illness or lack of educational opportunity but rather to central nervous system impairment. She requires special education and should be eligible for federally mandated services under the categories of Intellectual Disability and Other Health Impaired. Her disabilities will be most effectively remediated with a combination of learning with typical children and resource room participation where she can receive individually administered special education. This should be done under the auspices of an Individualized Educational Plan and not a 504 Accommodation Plan which does not assure the same legal protections. Makayla will require special education until she exits the educational system. If she is able to be employed, workplace accommodations can be provided under the Americans with Disabilities Act.

Some individuals with mild intellectual disability can work and live independently with intensive community and family support. Employment opportunities are generally restricted to low wage, non-skilled occupations. Whether Makayla can be employed will be highly dependent on her physical health and the limitations that are imposed by living with progressive kidney disease in addition to the demands of any job, which would be unskilled. It is more likely than not that she would be unable to sustain requirements necessary for gainful employment even at an unskilled level.

It is extremely likely that Makayla will require assistance to manage her illness with regard to supervised medication, maintaining special diets, and medical regimens like dialysis or taking immunosuppressive medications necessary to successfully deal with renal transplantation.

Additionally, maintaining healthy psychosocial development is critical in chronically ill children. Such factors that need to be managed include issues like maintaining self-esteem and a healthy body image, desire for normalcy, impact of stress imposed by illness, and treatment compliance. Further, children with intellectual deficiency deal with additional stressors such as bullying, lack of an adequate peer group, social isolation, and rejection.

The combination of intellectual disability and chronic illness predisposes Makayla to psychiatric illnesses like depression, and anxiety. All of these factors will collectively impact her quality of life and family function and may require appropriate interventions including psychiatric care and psychotherapy.

Dr. Leonard went on to describe her comprehensive clinical interview with Destiny, including the circumstances of her daughter's exposure to *E. coli* O157:H7 from romaine lettuce, which led to fulminant HUS, and the multiple medical complications she endured. She described Destiny's observations of Makayla's ongoing difficulties at school and the negative impact her illness had on her previously above average academic performance. Dr. Leonard also discussed Makayla's family history with Destiny, as well as her daughter's health history before the HUS, and her developmental, educational, and social history.

Kenneth W. Reagles, PhD

We requested the assistance of Kenneth W. Reagles, Ph.D. to prepare a Life Care Plan for Makayla. 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 for the 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 (including consultation and training).

On April 17, 2020, Dr. Reagles completed an analysis and appraisal, and prepared a Life Care Plan on behalf of Makayla. In preparing his report, Dr. Reagles conducted a full review of Makayla's social history, medical records, and expert reports. His report summarizes the nature of Makayla's disablement and provides an overview of the permanent enduring physiological and psychological consequences of her *E. coli* O157:H7 infection, including dysfunction and associated phenomena. He considers the probable diminution of Makayla's future earnings and benefits, as well as Makayla's probable future diminished capacity as an adult to perform 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 Makayla's entire medical history, including the complex twists and turns of the evolution and complications of her hospitalization for *E. coli* O157:H7-induced hemolytic uremic syndrome, including but not limited to her loss of kidney function, need for hemodialysis, and multiple medical comorbidities. On December 10, 2019, Dr. Reagles met with Makayla and her mother, Destiny, in their home in Maricopa, Arizona. Makayla participated actively in the interview.

Dr. Reagles commented:

> It is abundantly apparent that the medical complications that Makayla has sustained as a direct and causal result of the *E. coli*-induced hemolytic uremic syndrome in April 2018 have had a significant impact upon her life – previously, presently, and for the duration of her life expectancy, including, but not limited to, as it relates to her future worklife expectancy and her need for ongoing health-care

> related goods and services, some for the remainder of her life expectancy. Set forth below are my opinions regarding the economic consequences of her medical condition.
>
> In sum, Makayla is a delightful child who, while having survived a horrific infection, faces a future that, in all probability, will include medical procedures and potential complications that will rival her fight against the economic consequences.

Dr. Reagles followed the medical review with a thorough review of Makayla's academic record and noted that, secondary to her acute illness, Makayla missed the final ~5.5 weeks of 1st grade at Sequoia Elementary Charter School. Her mother requested extra help from the school during the final weeks, which did not materialize. Dr. Reagles went on to project Makayla's future earning capacity as she moves into adulthood, taking into account her likely-impaired educational accomplishments or career pursuits that cannot be known with certainty at present, but with reasonable scientific certainty based on several relevant factors and variables.

Dr. Sharon Andreoli's November 22, 2019 opinion was considered by Dr. Reagles in the formulation of his opinion about Makayla's future earning capacity, and he quotes:

> Dr. Sharon Andreoli, pediatric nephrologist, on November 22, 2019, opined that Makayla's ability to attain her educational goals or to lead a productive life has been seriously compromised by the damage to her vital organs in her formative years. She will be unable to work on a full-time basis within the competitive labor market secondary to chronic fatigue from stage 3 chronic kidney disease, attending healthcare appointments, undergoing dialysis therapy treatments (viz., presently at a frequency of three, three-hour sessions per week), and missing extended periods of time from the workforce prior to and following kidney transplantation surgeries.

Dr. Reagles commented: "It is my professional opinion, with a reasonable degree of scientific certainty within the field of vocational rehabilitation that Makayla will be able to work in the competitive labor market, but with important restrictions." He listed several criteria that would likely need to be met for Makayla to succeed in the work environment, including but not limited to a quiet and unstimulating environment, clear routines, stress reduction, and the promotion of a sense of importance and accomplishment.

The latter part of Dr. Reagles assessment focuses on "A Life-Care Plan," based on Makayla's projected need for "Future Health-Related Goods and Services." He again relies on Dr. Andreoli's assessment of Makayla's future healthcare risks and the likelihood of requiring an initial kidney transplant within 5-10 years, and an additional one or two kidney transplants over her lifetime.

Recapitulation

Dr. Reagles concluded his report with a "Recapitulation" of the economic losses Makayla and her family have incurred as a direct and causal result of the injuries, disabilities, and

corresponding cognitive and functional limitations that were incurred after she became infected with *E. coli* O157:H7 bacteria on or about April 11, 2018. Dr. Reagles set forth his estimates of the present values of the future (undiscounted) values of Makayla's economic losses:

Future Losses		**Present Values**		
1. Net Loss of Future Earnings Capacity:				
a. Net Loss of Expected Earnings	=	$ 915,497	to	$ 1,660,285
b. Net Loss of Expected Fringe Benefits	=	239,767	to	410,611
2. Future Health-Related Goods and Services:				
Scenario I: Maximum of 2 Transplants	=	N/A		26,653,949
Scenario II: Maximum of 3 Transplants		21,992,344		N/A
3. Future Pain and Suffering	=	? ? ?		? ? ?
TOTAL	=	**$ 23,147,608**	**to**	**$ 28,724,845**

Future Reproductive Health

It is worth repeating here that Dr. Reagles also comments regarding the unique adverse consequences on the future reproductive health that female patients incur following severe kidney damage, even when such damage occurs at an age that predates their eventual fertility. He reiterates:

> Although pregnancy is possible for young women with ESRD, the pregnancies are high-risk, including the potential for a loss of renal function; require multidisciplinary care, including emotional support; and can be especially challenging if undergoing dialysis. It is possible that in the future her treating OB-GYN physician will recommend against her becoming pregnant, so should she desire children, she may have to consider surrogacy and/or adoption.