Why Guidelines and Standardized Terminology Are Important

When Treating Patients With a Rare Disease, Like Immune Thrombocytopenia

By Jennifer DiRaimo

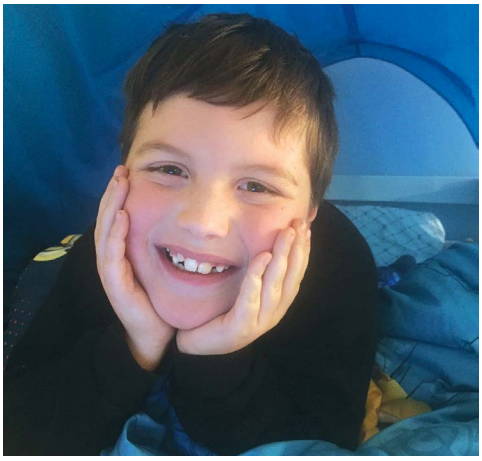
ITP is rare and affects individuals differently. This reduces opportunities for healthcare providers and hematologists to appreciate the broad range of ways ITP can impact individuals and families living with it. Serious bleeding is not common and is estimated to occur in only 3-4% of individuals with ITP, meaning most medical providers have very little exposure to this group of ITP patients. Since serious bleeding is infrequent, it is not surprising that policies and procedures are lacking for how to deal with such bleeds if and when they do present, and how to manage ITP moving forward after treating a serious bleed. Policies and procedures for how to manage ITP patients who are "at-risk" for a critical bleed are also lacking.

Luca's journey with ITP:
My son Luca was diagnosed with ITP in February 2015 when he was seven years old. He had developed petechiae after a fun day celebrating his birthday with his friends from school. I had a difficult time accepting that my healthy, energetic, playful boy had a medical condition with serious risks attached to it. Luca wasn't sick with a virus before he was diagnosed, he had not been recently vaccinated, and he wasn't taking any medication that could have lowered his platelet count. I spent many sleepless nights online trying to figure out how this happened to him all while reading as much as I could about ITP. Over time, I focused on how "lucky" we were that Luca was considered a "non-bleeder." Apart from a hematoma he developed on his side after jumping into a pool a few times wearing a life jacket, he usually only had some petechiae and a few bruises. His platelet count at diagnosis was 27,000 (µL).

Luca was eventually diagnosed with chronic ITP and while his symptoms worsened, his bleeding continued to be limited to petechiae and bruising. His average platelet count was usually below 10,000 and he followed a "watchful waiting" approach. Luca didn't require treatment, however he did use prednisone twice at my request. Once to see if he would respond should there ever be an emergency, and the second time was to elevate his platelet count so that we could go on our first family vacation, to Disney. Both times, Luca responded well to prednisone. His platelet count climbed into the normal range and then slowly dropped back to his baseline within a few months.

Luca struggled with his diagnosis. While he wasn't experiencing bleeding symptoms for most of his journey with ITP, he struggled with his limitations and occasionally with fatigue. Some days he only had enough energy to sit quietly on the sofa reading or playing with his tablet. We used to call them "low-key ITP days." He didn't seem tired mentally, but his body seemed exhausted on these days. He struggled with exercise endurance and this frustrated him in gym class at school. There were some sports he was unable to participate in, including dodge ball and competitive group contact sports. Since a lot of his good friends at school played sports whenever they could, he often spent recess alone feeling sad.

Luca didn't have many restrictions placed on him, but my husband and I implemented our own restrictions to keep him safe. Luca's hematology team indicated to avoid rollercoasters with a count less than 50,000 and competitive group sports when his counts were under 20,000. We made the decision Luca would stay close to home when his levels were below 10,000, which was most of the time. We stopped using the highway when his levels were under 10,000 and would only travel on country roads with significantly less traffic. This was difficult for us because all of our family live outside of our city, which meant family visits were few and far between. Over time, as my husband and I adjusted more to life with ITP, we became less anxious and allowed Luca to take more risks because we wanted Luca to enjoy his life and make the most of it. We allowed Luca to ride his bike with a helmet, swim but not dive, and learn beginners non-contact karate since everything was padded and modifications were arranged to keep him safe. His hematology team felt these activities were safe and they encouraged us to keep Luca active.



Luca DiRaimo, age eight, in January 2017 when he was considered a "non-bleeder."

Mid-October 2017, Luca became a "bleeder." He experienced a lot of spontaneous nosebleeds at school and home. By November, some were so terrible and long-lasting they

required a trip to the emergency department at our local hospital to stop. Prednisone stopped working. Luca had suddenly developed a resistance to it. IVIG alone also did not work, and caused aseptic meningitis. He developed dense and widespread petechiae and started to experience spontaneous oral bleeding, including bleeding from his gums, and developing tiny purple blood blisters inside his mouth and on his lips. If he had been treated for oral mucosal bleeding when it first appeared he may not have developed days later a spontaneous lump on his head alongside internal bleeding (specifically extensive hematuria and a gastrointestinal bleed in his stomach). This experience was terrifying. To treat his internal bleeding and the lump on his head, prednisone and IVIG (with Benadryl) were used in combination to elevate his platelet count. Sadly, a week later his platelet count was back down below 10,000 and the widespread petechiae returned. After the steroid/IVIG treatment wore off, we lived in fear another bleed would happen any day. In fact, Luca frequently would say, "Something bad is going to happen to me, and nobody is doing anything." While I too was scared, I reassured him that I would not let anything "bad" happen to him. I even ordered papaya extract in an attempt to feel in control and do something, but Luca did not like the taste and did not want to use it.

Six weeks following his internal bleeding scare, Luca was finally seen in the clinic and plans were made to access rituximab as a next step. He was also given a script for dexamethasone to use in the meantime if he experienced bleeding. One week later, Luca woke up feeling very tired with even more petechiae, and he had a broken blood vessel in his eye in addition to mild gum bleeding. He started dexamethasone. We were surprised to learn he did not respond well to dexamethasone because his petechiae completely cleared up for weeks, and the broken blood vessel in his eye resolved within 12 hours. However his platelet count only went up to 14,000. Unfortunately, Luca was denied financial coverage for rituximab through the province of Ontario, Canada where we live since it was not listed as an acceptable treatment for ITP and we were unable to access the drug through other avenues in a timely manner. Luca used tranexamic acid to manage occasional nose and oral bleeding and we waited for rituximab to come through. However, this did nothing for his platelet count. Sometimes he had multiple mild nosebleeds in a 24-hour period. Somedays he threw up quarter sized blood clots he said would "jet up" from his stomach. He continued to have small blood blisters, occasional oral bleeding, and widespread petechiae and bruising.

On the 1st of May 2018 Luca went for a bike ride with his helmet on. I had been encouraging him to ride his bike again even though he was worried about his ITP. During his bike ride he lost his balance while slowing down and steering around a few adults on the path and he ended up falling onto an adjacent set of parked bicycles. He didn't hit his head, but he did have a huge scrape on his chest even though he wasn't going that fast. When he got up, I could see the look of fear in his eyes as he walked towards me crying and lifting up his shirt to show me the damage. I froze. Anxiety rushed through me and I thought to myself "I broke him." It was another moment of sheer terror for us. Luca saw his hematology team following this bike accident and we learned his platelet count was less than 5,000. Luca had never been given such a low count. We also learned his hemoglobin was the lowest it's ever been. His team assumed it was a concentration issue. No treatment was provided since Luca did not appear to be actively bleeding even though he was covered in significant petechiae, large bruises, and had tiny blood blisters on his lips.

Five days later, a few things happened that I always wonder about. Luca hit his head with a light saber while playing casually with his best friend. I learned of this the following day when I questioned him about the teal-blue bruise above his left eyebrow. He didn't tell me because he didn't think it was a big deal since it did not hurt when it happened and he didn't want me to worry. He also had a heated argument with his dad that same day and he was very upset and angry. I kept telling him to breathe and calm down. I was afraid he could cause a brain bleed from stress at such a low platelet count. So, I was terrified when the following day (May 7, 2018) Luca had a mild headache in the morning. However, it quickly resolved with Tylenol so I began to relax. While at school, Luca experienced a lot of lethargy and I had to pick him up in the afternoon and take him home. He also wasn't eating much. I consulted with his hematology team over the phone before picking Luca up from school in case they wanted to reassess him. This was

Luca, age 9 in February 2018, one week before his 10th birthday with bruising and blood blisters.

not the case, and I was assured Luca's lethargy wasn't a concern since his headache resolved, and it sounded like he had "a bug." I accepted that, once again, I was unnecessarily worrying.

That night, Luca developed a second mild headache, and the light was bothering his eyes. We gave him more Tylenol. His headache did not worsen, in fact Luca said it felt better after taking Tylenol. However, the headache persisted before resolving again. My husband called the after-hours hematologist to be sure this wasn't a brain bleed. He was reassured when he called that since Luca's headache wasn't progressive and the Tylenol was working there was no need to bring him in for an assessment. Overnight, Luca vomited twice and his appetite continued to be non-existent in the morning. I thought this was further confirmation that he was "sick." Luca began slurring his words by late afternoon on May 8, 2018. This was a shock since throughout the day while he was quiet, he was able to navigate the remote to watch his favorite Netflix shows on TV and used his tablet. He put his own shoes on and got into the car himself when it was time to rush to the hospital, although he had a difficult time putting on his seatbelt. He had an intracranial bleed, and was possibly bleeding from the moment he fell off his bike.

We had been counseled previously by the hematology team that brain bleeds present as a progressive thunderclap headache described as causing "the worst pain ever." That is not what Luca experienced. In fact, Luca said his head hurt less than when he had aseptic meningitis with photophobia.

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When Luca presented to our local emergency department, he walked through the doors by foot himself. Soon after, he started to rapidly lose consciousness and eventually collapsed. He was intubated to maintain his airway, and was given oxygen, sedation, and a platelet infusion which alone did not increase his platelet count above 5,000. He was then given a steroid, and later provided with IVIG and factor V11 (for clotting). I was told dexamethasone was the steroid used, however his medical records indicate he was given methylprednisone which was a surprise given that we already knew he was resistant to prednisone. An urgent CT scan of his head revealed a large left frontal lobar hematoma with a small subarachnoid component and significantly increased intracranial pressure. A separate CT scan of his body also revealed a hematoma on his bladder wall. While waiting for his platelet count to increase high enough to perform a craniectomy (where part of the skull is removed temporarily to ease the pressure in the brain) his left eye became unresponsive to light, which isn't a good sign. A second CT scan showed more extensive bleeding deeper in the brain and multiple regions damaged due to a lack of blood supply from the intracranial pressure. Luca required at least one blood transfusion to manage his low hemoglobin levels.

Jenn and Luigi DiRaimo during their January 2017 trip to Disney World with sons Luca (front left) and Matteo.

His platelet count eventually elevated to 94,000 and, following his initial craniectomy, the pressure reduced and Luca's left eye became responsive again to light. We were told there was hope he would pull through but he could have personality changes. However, hours later his intracranial pressure spiked again, and a second craniectomy was required. Luca was then placed on life support and we were told he would likely not survive. While on life-support he was attached to many tubes, one that drained excess fluid. I remember asking why the fluid was green, and I was told it was "old blood" from his stomach. Luca progressed to "brain death" and life support was discontinued on May 15, 2018. He was only ten years old.

Looking back, I feel Luca should not have been allowed to maintain such a low platelet count, especially with a previous history of critical bleeding. Priority and urgency should have been placed on long-term prevention rather than relying on rescue therapies during a bleeding event. If Luca had been treated following his bike accident it might have made a difference. Awareness regarding how all types of brain bleeds present is needed. I also feel that a decision to perform a CT scan in a child with ITP who has almost no platelets should be made as soon as a headache or other neurological symptoms are experienced, even if the headache goes away, or if there is an unexplained drop in hemoglobin. Time is of the essence, and ultimately it was the increased intracranial pressure that built up that made Luca's brain bleed lethal. Was the choice (and sequence of) therapies provided to him during his brain bleed optimal for the best outcome? I am not sure. The truth is, there are no specific protocols for emergency management. There are no specific protocols for how to prevent a critical bleed either. Luca's story demonstrates how additional guidelines and protocols are needed to share knowledge about atypical ITP and establish a standard of care or best practice for managing individuals with ITP who have more than minimal bleeding.

Treating 'critical' bleeding and 'at-risk' bleeding in the emergency room:

In 2017, PDSA provided funding for a study led by Siraj Mithoowani, MD and Donald Arnold, MD at McMaster University in Hamilton Ontario, Canada to investigate emergency management of severe thrombocytopenia and bleeding in patients with ITP. The study included adult ITP patients presenting to one of four local emergency departments during an eight-year period (2008-2016). After reviewing outcomes and the sequence of therapies provided, it was confirmed that a standardized protocol for managing severe bleeding was urgently needed.

A dedicated group of patient representatives joined forces with a group of international physicians to form a committee called the ITP Emergency Management Guideline Panel, led by Dr. Arnold, a PDSA medical advisor, and Emily Sirotich, a PhD student supervised by Dr. Arnold. Included on the panel are seven hematologists (three pediatric and four adult), two emergency physicians, one nurse, four methodologists, a transfusion medicine physician, and five patient representatives including myself, PDSA board member Dale Paynter, and PDSA patient members Barbara Pruitt and Gail Strachan.

Our mission is to develop management guidelines for critical bleeding for both adult and pediatric ITP patients. Our first task was to define what a "critical emergency bleed" is so we could target who the guideline would apply to. We also wanted to standardize the term "critical bleeding." Currently, there are over twelve different terms used to reference "critical" bleeds including life-threatening, severe, serious, and high-risk bleeding. A working group searched the literature for systematic reviews of bleeding assessments and bleeding scores for ITP. The definition that was developed focuses on bleeds that are life-threatening or organ-threatening and require urgent intervention in the context of very low platelet counts (less than 20,000). The new definition is endorsed by the Platelet Immunology Scientific Standardization Committee (SSC) of the International Society for Thrombosis and Haemostasis (ISTH). *Once published, we will share this definition with the PDSA community.*

The committee is now in the process of collecting data over the last ten years on management and outcomes of ITP bleeds in both children and adults presenting to the emergency room from eight participating hospitals across Canada and the USA. In addition, a systematic review of published scientific literature will also be performed to further collect data on management and outcomes of "critical bleeds." The knowledge obtained will allow us to identify best practices for treating a critical bleed and identify risk factors for critical bleeding by looking at previous clinical history. In October 2021, data collection should be completed, and then work on the emergency management protocol will begin. ■