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An Approach to Bleeding and Bruising, Part 2

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Introduction:

Welcome to part 2 of our PedsCases episodes on an approach to bleeding and bruising. I am Gabriel Blank, a fourth-year medical student situated at the University of British Columbia. Many thanks to Dr. Tom McLaughlin, a general pediatrician at BC Children's Hospital, for helping to develop this podcast.

Our last episode discussed coagulation cascade problems and non-hematologic causes of bleeding and bruising. This episode is devoted to platelet pathology that cause abnormal bleeding, including low platelet number and abnormal function.

Learning Objectives:

1. Describe how bleeding secondary to platelet pathology presents clinically.
2. Establish an approach to platelet pathology, using the overarching categories of increased destruction, decreased production, sequestration, and qualitative dysfunction.
3. Know the treatment for some notable thrombocytopenia causes, including DIC, HUS, and ITP.
4. Recognize the red flags that could point you to more sinister thrombocytopenia causes, such as malignancy.

Clinical Case:

Let's start with a case. You walk into the pediatric ED, keen and ready to start your night shift. The first patient for you to see is Jenny, a 4-year-old girl brought in by her parents with concerns of a new rash and bruises. You walk in and notice Jenny is responsive, energetic, and does not appear in acute distress. You also get a brief look at her skin, which shows small to moderate sized ecchymosis on the arms, and small, non-palpable, non-blanchable reddish-purple dots throughout the body. You recognize that the rash the parents mentioned is in fact petechiae and purpura. The parents say that the rash came on quite suddenly 2 days before. Since then, the rash seems to be getting denser and bruises have developed. The parents have also noted some gum bleeding when they floss Jenny's teeth. Jenny did have a sore throat about 2 weeks ago, though she has not taken any antibiotics or other medications within the past few months. Otherwise, Jenny has been well with no fatigue, fever, weight loss, loss of appetite, bone pain, hematochezia, melena, or hematuria. She has no known history of a bleeding disorder, such as cephalohematoma at birth and has not had episodes like this before. Jenny has no known medical conditions, and there is no known history of bleeding disorders in the family.

On exam, Jenny appears well with vitals in normal limits. You again note the bruises on her arms and legs. The petechiae and purpura are present throughout the body, though seem particularly dense on the extensor surfaces. You do not find any swelling of the joints or hematomas. There is no axillary, cervical, or clavicular lymphadenopathy and no hepatosplenomegaly. There are no skeletal injuries or dysmorphisms that you can visualize.

You review this with your preceptor, who, after seeing the patient, decides to order a CBC with blood smear. The platelet count comes back at 18,000, with normal hemoglobin and WBC's. Alarmed by this number, you rush over to grab your preceptor.

The Approach to Platelet Problems, Low number and Abnormal Function:

Let's keep that case in the back of our minds as we discuss an approach to platelet abnormalities. Bleeding and bruising secondary to platelet problems can be caused by a low number of platelets or abnormally functioning platelets. Remember, in contrast to the deep bleeds of coagulation defects, platelet pathology classically causes mucocutaneous bleeding,

like petechiae and gum bleeding.

Let's first look at causes of low platelet number, or thrombocytopenia. Buckle up. Thrombocytopenia causes can be broken down into increased destruction, decreased production, sequestration, and false thrombocytopenia.

Causes of Increased Platelet Destruction/Loss:

For increased destruction, you can first assess whether the patient looks sick or relatively healthy. Causes of platelet destruction in a very ill-appearing patient includes DIC, severe infections, HUS and TTP.[1]

Disseminated intravascular coagulation, or DIC, is thought to be caused by inflammation induced microthrombi that deplete platelets along with pro- and anti-clotting proteins. The main causes of DIC are really the things that cause systemic derangements in homeostasis--sepsis, major trauma, malignancy, and, in neonates, perinatal complications like asphyxia. What you see is a systemically ill child with bleeding that sometimes starts from venipuncture sites. This can progress to severe bleeding in the skin, GI tract, and central nervous system. Remember, DIC creates blood clots throughout the vasculature. What do you think happens when red blood cells move through this microthrombi laden highway? They become these sheared RBCs known as schistocytes. Conditions that cause schistocytes are called microangiopathic hemolytic anemias, also known by its much more fun to pronounce acronym, MAHA. Along with Schistocytes, DIC also causes low fibrinogen, low clotting factors, and an elevated D-Dimer. Though blood products can be given to support the patient, the bedrock of DIC management is aggressive treatment of the underlying etiology.[2,3,4]

While life threatening infections can cause DIC, certain severe infections can cause thrombocytopenia and bleeding abnormalities independent of DIC. A big infection of note in this category is Meningococcemia, a disseminated bloodstream infection with *Neisseria meningitides*. Roughly 80% have a non-blanching or petechial rash known as purpura fulminans. *Neisseria meningitidis* is the most common cause of purpura fulminans, though other bacteria can cause it. This rash commonly affects the trunk and lower limbs. While rare,

meningococcemia is a scary condition. It can quickly progress over hours from fever with nonspecific symptoms to full blown septic shock. Children can also have concurrent meningitis.[3,5]

Finally, TTP and HUS both cause platelet destruction in an ill appearing patient. Hemolytic uremic syndrome, or HUS, is most commonly caused by Shiga toxin producing E-Coli. The Shiga toxin damages endothelial cells promoting thrombus formation that, much like in DIC, leads to a microangiopathic hemolytic anemia. Platelets also get destroyed in the vasculature, while the glomerular endothelia are selectively damaged by Shigatoxin.[6] Collectively, this produces the classic triad for HUS--renal failure, thrombocytopenia, and a MAHA. HUS classically presents with bloody diarrhea, cutaneous bleeding, hypertension, and occasionally CNS changes. Thrombotic thrombocytopenia purpura, or TTP, is a rare illness usually seen in adults, but occasionally in adolescence. It is caused by low levels of ADAMTS13, a protein that cleaves large von-Willebrand factor multimers into smaller molecules.[6] These large multimers clump with platelets in the vasculature to cause symptoms very similar to HUS. Its classic pentad includes CNS changes, fever and the three features of HUS (thrombocytopenia, MAHA, and renal impairment). Unlike HUS, severe acute kidney injuries are rare in TTP. This makes sense, since TTP does not have Shiga toxin selectively attacking the glomeruli.[3,7] In contrast to DIC, both TTP and HUS have normal coagulation tests, that is to say normal PT and aPTT.[8] Treatment in HUS is supportive, including IV fluids and red cell transfusion. Platelets are avoided in HUS over a theoretical risk of adding to clot burden and worsening disease, while antibiotics are not used because the widespread death of E. Coli could lead to a sudden increase in Shiga toxin levels. The cornerstone of TTP management is plasma exchange.[3,8]

Alright, we covered DIC, infections, TTP, and HUS as four causes of platelet destruction in a sick patient. In contrast platelet destruction in relatively healthy patients classically involves immune mediated platelet attack. Four causes in this area are ITP, neonatal alloimmune thrombocytopenia purpura, thrombocytopenia secondary to another medical illness, and drug induced.[1]

ITP stands for Immune Thrombocytopenia (also known as Immune Thrombocytopenic Purpura, and sometimes referred to by its outdated name – Idiopathic Thrombocytopenic Purpura). It is thought to be due to antibody mediated platelet death. ITP is believed to be the most common acquired disorder of coagulation, with a peak age of onset between 2-5 years. Regarding

symptoms, 90% of cases presents with sudden onset generalized petechiae, purpura, and ecchymoses. In contrast to non-immune causes of platelet destruction, like DIC and HUS, children are often otherwise healthy in ITP. The thrombocytopenia can be notable, with most cases having platelet counts less than 20,000/microL. Interesting, this very low platelet count is less common in some more severe conditions such as leukemia and bone marrow failures, which usually feature a platelet count between 40,000 and 90,000.[9] 90% of ITP cases resolve in 6 months without sequelae. Watch and wait is recommended in children with no symptoms or mild, cutaneous bleeding regardless of platelet count. For more severe ITP, the three first line treatment options for children are IVIG, corticosteroids, and anti-D immunoglobulin in Rh positive, non-anemic children.[9,10] For more information on ITP, see our previous podcast dedicated to it.[11,12]

Neonatal Alloimmune Thrombocytopenic Purpura is a condition where the name says it all. It is thought to be due to the baby's platelets displaying the father's antigens on the surface, which are then recognized as foreign by the mom's immune system. The incidence is about 1:4500 live births. It presents with an initially well looking newborn who develops generalized purpura and petechiae within the first few days of life.[13] In contrast to low platelets secondary to maternal ITP, mom will have normal platelet counts.[3]

The last two immune causes of platelet destruction are either secondary to a medical illness or drug induced. Autoimmune thrombocytopenia can be the initial manifestation of Systemic Lupus Erythematosus. In contrast to ITP, Lupus induced thrombocytopenia can also target red blood cells, typically has higher platelet counts, and has fewer hemorrhagic complications.[14] In contrast to Lupus without hematologic involvement, Lupus with autoimmune anemia and thrombocytopenia is more likely to present with constitutional symptoms, including fever, weight loss, and hepatosplenomegaly.[14] Drugs that induce antibody mediated platelet demise include antibiotics and antiepileptics, with frequent perpetrators being beta-lactams, vancomycin, and carbamazepine. Heparin induced thrombocytopenia, while possible, rarely occurs in kids.[3,11]

One last cause of platelet loss is them simply leaving the body, as can happen with major trauma or surgery. It is a diagnosis based on history and tends to have mild to moderate thrombocytopenia (think 50,000 to 100,000 range), with no overt bleeding.[15]

Summing it up, we discussed some causes of platelet destruction in a very sick patient including DIC, infections like meningococcemia, HUS, and TTP. In patients who are largely, but not always, less ill appearing, we mentioned immune causes, which were ITP, neonatal thrombocytopenia, and platelet death secondary to a condition or drugs. Separate from this, platelet loss can be due to notable hemorrhaging, as can happen in trauma or surgery. As a rapid-fire review, what does a sick patient with schistocytes on blood smear, low platelets, low coagulation factors and low fibrinogen point to? Its DIC. How about schistocytes on blood smear with low platelets but normal factor levels. It could be HUS or TTP. Bloody diarrhea and acute kidney injury suggests HUS, while neurologic deficits are more common in TTP. And finally, a 2-day old who suddenly develops generalized petechiae and low platelet counts with no thrombocytopenia in mom. Why it's neonatal alloimmune thrombocytopenia purpura.

Causes of Decreased Platelet Production:

Next on our differential is low platelets due to decreased production. I break these into acquired and congenital causes. Three categories of acquired causes are bone marrow infiltration, from conditions like leukemia or myelofibrosis, bone marrow injury from infections or drugs, and poor bone marrow nutrition from low folate or low B12.

Big bone marrow suppressing malignancies to consider are leukemias and lymphomas, most notably the two clinically similar malignancies of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL). Both conditions can present with bone pain, fatigue, and B symptoms, like fever, drenching night sweat and weight loss. Lymphadenopathy and splenomegaly are commonly present in both. The Lymphadenopathy is classically non-painful, firm, and rubbery. If you have a malignancy taking over the bone marrow, what do you think a CBC will show? Well, thrombocytopenia, neutropenia and leukopenia can all occur, with lymphoblasts on blood smear.[3,16,17]

Viral Infections, most notably cytomegalovirus and Epstein-Barr virus, can also cause systemic symptoms like fatigue with co-occurring lymphadenopathy and splenomegaly. As a potential contrast to malignancies, these symptoms and signs are new onset. You can also do specific viral testing for diagnostic aid.[3,18]

And poor bone marrow nutrition, more specifically severe B12 and folate deficiency, is our third acquired cause of decreased platelet production. While the fortification of grains and cereals makes folate deficiency unlikely, a diet low in animal products can lead to B12 deficiency. There are also various malabsorption causes of B12 and folate deficiency including bowel resection and celiac disease.[19,20] Both B12 and Folate deficiency are differentiated on labs by megaloblastic anemia.[21]

Now the moment you've been waiting for, congenital causes of low platelet production. I break up the aetiologies into those that affect the whole bone marrow and platelet specific pathology. Congenital bone marrow aplasias, like Fanconi anemia, can cause bone marrow failure in multiple cell lines. Fanconi anemia is thought to be the most common inherited pancytopenia. Along with the pancytopenia, many of the hallmark presentations seem to be related to abnormal bony development. This includes skeletal abnormalities, atypical thumb and radii, and a predisposition to malignancies, among other things. Skin hyperpigmentation can also be present in Fanconi anemia.[22] Congenital thrombocytopenias are one of the few processes that affect marrow cell production and specifically decrease platelets without causing a broad pancytopenia.[3] We can't touch on all of them but think of them with a family history of thrombocytopenia and chronic low platelet counts. Children also often have co-occurring features—with more common ones being immunodeficiencies, skeletal abnormalities, and sensorineural hearing loss. Just in case you recognize the names, examples of congenital thrombocytopenia's include Wiskott Aldrich Syndrome, and Thrombocytopenia -Absent Radius Syndrome.[15]

The Other Platelet Categories—Sequestration, Pseudothrombocytopenia and Qualitative Platelet Defects:

Alright, so we talked about conditions that destroy platelets and impair thrombopoiesis. Our next three categories are platelet sequestration, pseudothrombocytopenia and qualitative platelet defects, but don't worry, they're much quicker.

Splenomegaly is the main cause of platelet sequestration. Splenomegaly is interesting in that it is a symptom of some thrombocytopenia causes, like Epstein Barr Virus or malignancy, yet can also independently cause thrombocytopenia. Medicine is complicated. Usually patients have

mild anemia and leukopenia accompanying the thrombocytopenia.[3]

Pseudothrombocytopenia is where labs say a patient has low platelets, but they are not actually thrombocytopenic. This is due to platelets clumping in a test tube, and it can be detected on a blood smear. You can correct for this by collecting the next sample in a tube with an anticoagulant other than EDTA.[23]

Qualitative platelet disorders refer to conditions where the platelet number can be unaffected, but the platelet function is abnormal. Acquired causes include NSAID consumption, uremia and liver disease.[24] Two inherited causes of note are von Willebrand Disease and Glanzmann Thrombasthenia. We talked about von Willebrand Disease in our last episode. In short, it is caused by deficiency or abnormal function in von Willebrand factor and leads to mucocutaneous and, occasionally, joint bleeding.[25]

And lastly, I mention Glanzmann Thrombasthenia as its thought to be the most severe genetic platelet function disorder in which platelet number and morphology is normal. It is caused by a defect in platelet glycoprotein IIb/IIIa, which is responsible for binding to fibrinogen and promoting platelet aggregation. My weird mnemonic to remember this glycoprotein is to think of a Canadian dreaming of freedom—they are wondering what it is like to be free, eh? That's glycoprotein IIb/IIIa. What you see clinically is extensive bruising and petechiae early in life.[2] Labs show absent platelet aggregation to everything except ristocetin. Just because I can't help myself from giving one more mnemonic, I remember this as Glanzmann sounds like grabs man, grabbing someone by the wrist, for ristocetin. A slightly uncomfortable visual, but it helps for remembering.

Alright, we discussed conditions that destroy platelets, those that impair platelet creation, platelet sequestration in the spleen, pseudothrombocytopenia, and qualitative platelet defects. As a quick sum up of some more noteworthy conditions, nonimmune death of platelets, like HUS or DIC, commonly have multiorgan effects in a sick appearing kid, and bone marrow suppression from conditions like leukemia usually affects multiple cell lines. In ITP, you see an otherwise healthy child with new onset, generalized cutaneous bleeding. Constitutional symptoms, splenomegaly, and lymphadenopathy raise red flags for malignancies, though could also be emblematic of infections like Epstein-Barr Virus, or inflammatory conditions like Lupus. Let's shake out our legs and do a little stretch break before we go back in to see young Jenny.

The Case Revisited:

Remember Jenny? She is the previously healthy 4-year-old with new onset generalized petechiae and purpura and a platelet count of 18,000. Let's think through what this could be. It is relatively sudden and new onset, making congenital conditions unlikely. Jenny also does not have that systemic, very ill appearance we would see in DIC, meningococcemia, and HUS. There are no new drugs that could cause thrombocytopenia, and there is no fever, weight loss, hepatosplenomegaly or other constitutional symptoms that could suggest malignancy or inflammatory conditions like Lupus. The isolated thrombocytopenia also rules against conditions that broadly impair bone marrow function, such as Fanconi anemia or malignancy. New onset petechiae, and very low platelet counts in a previously healthy child. Is there anything these findings make you think of? You discuss this case with your attending, and they agree that this is likely Immune Thrombocytopenia, or ITP. It is a diagnosis of exclusion though they concur that the history, physical and CBC with blood smear make ITP the most likely diagnosis. Regarding treatment, a watch and wait approach would not be unreasonable considering the primarily cutaneous bleeding without other active bleeds. Most understandably, the parents really want to try something to help raise Jenny's low platelets. Mindful of this and the history of gingival bleeding, the team starts IVIG. Jenny responds well to IVIG. Over the next few days, her cutaneous bleeding subsides, and her platelet counts come well above 50,000.[9,10,26]

Conclusion and Review:

Phew, we did it. Let's give each other virtual high fives and conclude with a very brief review of what we learned. In contrast to coagulation defects that present with bleeding into joint spaces and deep tissues, platelet abnormalities cause mucocutaneous bleeding. This can be due to low platelet number or abnormal platelet function. Thrombocytopenia causes can be categorized as increased destruction, decreased production, sequestration, and pseudothrombocytopenia. Destruction causes can be subcategorized based on if there is systemic pathology causing a very ill appearing patient, like in DIC and HUS, or if the patient appears relatively healthy, as classically happens in certain auto-immune causes like ITP and neonatal thrombocytopenic purpura. Decreased production can be due to acquired causes, with three big categories being

bone marrow infiltration, injury, and B12 or folate deficiency. Malignancy is a notable cause of infiltration, and is suggested based on constitutional symptoms like fever, weight loss, fatigue, and boney pain, hepatosplenomegaly and lymphadenopathy on exam, and pancytopenia on labs. Congenital causes of decreased platelet production include those that broadly affect multiple cell lines in the bone marrow, such as Fanconi anemia, and the congenital thrombocytopenias, which more specifically affect platelets. Qualitative platelet defects can be from acquired causes like NASID consumption, uremia, and liver disease or inherited conditions like von Willebrand Disease and Glanzmann Thrombasthenia.

As a rapid-fire treatment review, the cornerstone of DIC management is treatment of the underlying illness, with blood products given as support. In HUS, the best things you can do is supportive care—do not give platelets or antibiotics. And in ITP, IVIG, anti-D immunoglobulin or corticosteroids can be used if you decide to step beyond watchful waiting.

This was a dense episode, and I invite you to read the show notes at pedscases.org to help make this information stick.

That's all for now. Thanks for listening!

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