[MUSIC PLAYING]

STEVEN ALLEN: Hello, my name is Steven Allen. I'm a physician at Children's Hospital. I'm the director of our pediatric Bone Marrow Failure Program. And today, I'm going to be talking to you about bone marrow failure syndromes. So quickly, some just brief objectives. So first, I just want to discuss the definition of bone marrow failure as well as then I want to talk about the clinical findings, the laboratory findings, the diagnosis and management of both the single cytopenia bone marrow failures as well as the pancytopenia bone marrow failure syndromes.

So first, very simply put, bone marrow failure is failure of the bone marrow to adequately produce one or more of the cell lines. So you can either be hypoplastic, where you have still some partially functioning bone marrow, or aplastic, where there's no functioning marrow whatsoever. It can be congenital slash inherited, or acquired. And for the focus of this talk, I'm going to be talking about the congenital syndromes, the inherited syndromes.

So first, I'm going to break it down to red blood cells, white blood cells, platelets, and then pancytopenia. So first, red blood cells. The three main ones I'll talk about, and then a couple extra rarer ones are Diamond-Blackfan Anemia, Congenital Dyserythropoietic anemia, and Pearson Syndrome.

So Diamond-Blackfan Anemia, essentially, it's an aplasia or a hypoplasia of red blood cells. You typically see patients that have a normochromic and a macrocytic anemia in childhood accompanied with a reticulocytopenia. So they're just not producing red blood cells. When you do a bone marrow evaluation, or an aspiration biopsy, you tend to have normal cellularity, but you just do not have those red blood cell precursors. Sometimes you have some slightly decreased white cells, but that's variable. And sometimes you have some normal, and maybe increased, platelet counts as well.

Typically these kids present pretty early on, since they're not producing red blood cells. A good amount are noted in infancy. So about 10% are severely anemic at birth, 25% by one month, 50% by three months, 75% by six months, and then up to 90% by 18 months are typically presenting with this anemia. Mostly in the Caucasian population, but has been seen in all. And then that inheritance pattern can actually vary too. So there's autosomal dominant inheritance as well as recessive. And there's even some sporadic inheritance throughout these patients too.

So in addition to just the hematologic features of the syndrome, these patients also have a variety of clinical features as well. Some, not all, have cleft lip, cleft palate, micrognathia-- it's a small jaw-- microcephaly or macrocephaly, essentially craniofacial dysmorphia. You can also have some limb abnormalities. A good amount of these patients are short statured and small for age, essentially. And you can also have different eye, kidney anomalies, GU anomalies, and heart disease. Things like that, too, in the later years.

So lab findings, like I mentioned, you see that macrocytic anemia with a reticulocytopenia. So again, you're not producing these red cells. And other things you can find are you have an increased hemoglobin F, an increased erythrocyte ADA-- so there's multiple ways of ordering an ADA, you want, for these, specifically, the ADA on the erythrocytes-- and sometimes, check this antigen I, which is increased, but it's rarely checked.

Path findings. So when you look in the blood in the microscope, you see this macrocytic anemia, you see no reticulocytes, you see lots of different teardrop cells, you can see different shapes and sizes of the red blood cell. Because the bone marrow is trying to produce whatever it can, essentially. And then when you do the marrow, like I said, the majority you have a normal cellularity, but you have a paucity, or an absence of the erythroid precursors.

Pathophysiology is, for Diamond-Blackfanned, a good amount is tied to mutations and abnormality in the ribosome protein subunits. So it's erythropoietic defect, so the bone marrow is just not able to produce these red blood cells. So you see a compensatory elevation in the erythropoietin. About 25% of patients have this heterozygous mutation in one of the ribosomal protein subunits, so the RPS19. And then there's also another locus as well as several others that have been discovered, but I just wanted to talk about the general, most common one.

Therapies. So therapies are-- at least early on-- usually pretty supportive. If you're severely anemic, we treat these patients by giving them blood transfusions. Typically in the younger age, we tend to maintain a hemoglobin greater than seven or eight. And the younger, I tend to lean more toward the greater than eight threshold.

And then also, we can treat this-- and it's been shown, and I'll talk about it a little bit-- to be responsive to steroids. So corticosteroids at varying different regimens. This is one that I mentioned here, as a starting point you start high and try and get their hemoglobin high to make sure that they're safe. And then slowly, over time, wean them to the minimal and the lowest dose, but most effective dose, essentially. So like I mentioned, you can have a very varying response to steroids in this disease.

The great majority-- you should see it, the third bullet point-- you tend to have a response, and then as you start to wean the steroids, you can't get them completely off. But you can get them to a pretty manageable dose, but they're dependent. Some patients, you have a really rapid response, and then you wean them off, and they go into complete remission and they're off of steroids. And they do well from that standpoint, but you can see that's about less than 5%. Also less than 5% you have some intermittent responses.

You could also have patients that are responsive to steroids, but then are dependent on it for a while. And then later in life they fail to respond. So they start having difficulty keeping their hemoglobin up on their steroid dosing. And then there's a good portion of patients that just don't respond to steroids, or just require very, very high dose steroids, which in the long run, can cause lots of significant toxicity and morbidity, which is less than ideal, essentially.

There is a role for hematopoietic stem cell transplant in patients with Diamond-Blackfan Anemia. It's essentially those patients that, like I said, cannot respond to steroids or have significant steroid side-effects or other issues throughout their treatment course. And in these patients, if there's a matched sibling donor, there is at least a 75% survival and good outcomes with patients getting transplanted with Diamond-Blackfan. The overall best prognosis is those patients that were responsive to steroids and maintained on a lower dose and then those who spontaneously remit.

However though, from multiple reasons. From multiple parts of the treatment, from both the chronic transfusions, the steroids, to transplant, they all have their side-effects and their toxicities. Some of the more significant toxicities, when death can occur from iron overload from prior transfusions as well as pneumonia or sepsis due to immune dysfunction from either the steroids or post transplant course.

So that was a brief about Diamond-Blackfan. Next, I very briefly want to go through Congenital Dyserythropoietic Anemia, mainly because it's very rare. For the most part, if we have these patients, they become referred to me, essentially. But just briefly, Dyserythropoiesis-- is essentially just ineffective or abnormal erythropoiesis or development of red blood cells. So you have three different types that have these three different morphologic features. And I just want to go through one slide each. One or two slides each of the types.

So type 1 usually presents by 10 years of age. It's autosomal recessive. You have a macrocytic anemia. You also have some signs of some hemolytic anemia, so you have an elevated bilirubin. Excuse me. You have some slight icterus. You have moderate splenomegaly, you have some skin pigmentation. And then here on bone marrow, you have these megaloblastoid changes.

Treatment, essentially, is with transfusions, could have gallstones. You want to consider, again, for iron overload, phlebotomy and iron chelation for these patients if they have chronic transfusions. And then depending on the severity, you could consider a transplant, but there's also very minimal data for that in these patients.

Type 2 is this HEMPAS, which is hereditary erythroblastic multinuclearity with a positive acidified serum test. These kids tend to present a little bit later, later than type 1. So mean age is about 14 years. It's also autosomal recessive, and has some similarities. A treatment for this, for the most part, is supportive with blood transfusions and sometimes splenectomy is needed.

And then type 3 is later, so mean age is 24 years of age. This is autosomal dominant or recessive. Also have a macrocytic anemia associated with this. And these kids or individuals tend to be mostly asymptomatic and don't require any treatments. Rarely, you need to treat with transfusions or a splenectomy. But as I mentioned, these modalities are not without toxicity, et cetera.

Last in the red blood cells, or at least the big ones that I wanted to mention is Pearson Syndrome. This is a mitochondrial deletion disorder, so it's a very global disorder. One of the main hematologic features is a refractory aregenerative macrocytic sideroblastic anemia, but-- and with some of these bone marrow failure syndromes I'll talk about throughout this talk, there is some blending into-- some of these have major features of single cytopenias, but also can then progress to complete bone marrow failure. So Pearson Syndrome can also have neutropenia associated with this. And one big feature of the syndrome in general is that you have an exocrine pancreatic dysfunction. For these patients, cytopenias tend to resolve with age. So it's usually supportive care until their bone marrow starts to improve. With, as I mentioned, blood transfusions or G-CSF as needed.

So now going into the white blood cell cytopenias. One of the major ones is this general term Severe Congenital Neutropenia. It was initially diagnosed in 1956 by Rolf Kostmann. It was initially termed as Infant Genetic Agranulocytosis. He was studying this family-- this inbred family in Sweden. It was found that these children were having these severe infections early in infancy, to where he described it as a primary insufficiency of the bone marrow determined by a single recessive gene different just from the pattern, essentially. Then 50 years later, with the advent of genetic testing and screening, et cetera, it was found that these patients actually had a homozygous, so an autosomal recessive mutation in this HAX2 gene that I'll talk about in a second.

Severe Congenital Neutropenia. And this includes Kostmann Syndrome, which is that autosomal recessive form with HAX1 mutation that was initially described, plus also several other mutations. So in general, you see about two cases per 1 million people. This is usually less than 200 with a compensatory monocytosis. You can see some eosinophilia, some anemia, thrombocytosis can kind of vary, but the ANC less than 200 tends to be one of the hallmarks.

And just like with the initial presentations that were noted that these kids have very frequent infections within the first few months of life. So you can have omphalitis, pneumonia, skin infections, sepsis, meningitis. Commonly seen organisms are staph aureus, E. coli, pseudomonas. And historically, these patients were dead by the age of two due to infection. And other causes of death were then its predisposing syndrome to MDS or leukemia.

So briefly, the genetics. The great majority of these patients with the HAX1 gene have mutations in the ELANE gene, which essentially codes for the neutrophil elastase in neutrophils. So with mutations, it's essentially thought to be a misfolded protein, which then elastase accumulates in the cells and then causes increased apoptosis, or cell death of the neutrophil precursors.

Then like I mentioned before, the HAX1 gene is the autosomal recessive version. And this also can cause dis-regulation in the neutrophils which causes apoptosis early on in the precursors. You can also see mutations in the G-CSF receptor, activating mutation in the WAS, so those altered syndrome gene as well as this GFI-1 gene.

So diagnosis. Main diagnosis is through genetic testing. And specifically, also a bone marrow analysis because you'll see what's called this myeloid arrest, to where the myeloid cells are proliferating, and they get to a certain point in the myeloid phase, but they can't quite get past that to develop full mature neutrophils. That's a common finding on the bone marrow exam.

So treatment. Treatment. A majority of these patients respond to G-CSF. So just simulating the greatest light production. Usually it's not automatic, so sometimes you don't see a response until within the first seven days or so. I usually see within at least two to three days. And the goal is to have an ANC of between 1,000 and 2000 and no infections. So you start it in a standard dose, which is 5 micrograms per kilo per dose. And then you can adjust as needed-- and because within the half life of the medication, you can adjust as needed every one to two weeks essentially.

And then you want to wean these patients to the lowest, most effective dose. Over several weeks. Because these kids can be on this for a long time. You want to minimize toxicity as much as possible. Also you want to do a bone marrow evaluation prior to it, to make the diagnosis, and then at least annually to follow. Because like I mentioned before, these patients are predisposed to developing MDS or leukemia. So we want to look at the morphology and look at the cytogenetics to make sure that we're not seeing signs of transformation to there. I'll talk about this a little bit too is that-- it's been seen the patients in needing higher doses of G-CSF are usually at increased risk of developing MDS or AML.

So morbidity and mortality in these patients. Main issues with G-CSF are just side effects from that. A lot is like bone pain as well as-- we'll talk about this on the third bullet point-- so you have osteopenia and osteoporosis. Doesn't really relate to the dose of G-CSF, but you can just see this over time. So it's important to monitor that. Also you can see splenomegaly in these patients, where not only is it present sometimes at presentation before treatment, but also after treatment, you can see some increased incidence of splenomegaly. And then bacterial sepsis slash death as well as MDS and AML are also important to monitor for, which are big factors in long-term management in these patients.

Briefly about that, looking at the severe chronic neutropenia international registry between 2001 and '09, they actually divide up in these low risk and high risk groups. So low risk groups are essentially patients that were able to achieve an adequate ANC with lower doses of G-CSF. And high risk groups were those patients that needed higher and higher doses of G-CSF and were unable to maintain as adequate of an ANC response.

And it was seen that in comparison with these low risk and high risk groups, that in the high risk groups, you had a significantly increased risk and incidence of sepsis, death, MDS, and AML. And then patients in general who develop MDS or AML with this have a poorer prognosis.

Some risk factors to progression, as I alluded to earlier, if there's mutations in the receptor to the G-CSF. Because essentially if it's an abnormally functional receptor, than the G-CSF won't be as beneficial. And then any abnormalities that you're starting to notice in the bone marrow evaluation. Especially Monosomy 7. And then one way-- as you're following these patients, if you start noticing then becoming thrombocytopenic, or with low platelets, that can sometimes herald the development of MDS or AML. So it's good to keep a close eye on that.

And then there is a role for transplant in these patients. And these are typically the patients in that high risk group or the poorly responding group, essentially. So these patients with really high doses of G-CSF or refractory G-CSF, have developed AML or MDS, or have any of those poor prognosis genetic factors.

So this is just one slide of another genetic associated neutropenia that you can see in mutations in the G6 protein. Just wanted to briefly mention this, just so that you're aware of this. You usually can treat with prophylactic G-CSF, and you can have a variety of other clinical features as well with this.

Same thing with Reticular Dysgenesis, I just want to talk about with one slide. It's autosomal recessive, you can have very severe neutropenia, but also associated with some moderate to severe lymphopenia. A key feature of this is sensorineural hearing loss. And the treatment for at least the hematologic issues would be a transplant.

Another one slide for Dubowitz Syndrome. It's another syndrome with a slew of clinical features as you see here. These patients tend to have recurrent neutropenia. But like I mentioned with some of these syndromes, that you can have some blend between the single and the pancytopenia issues. These patients are also at increases of aplastic anemia and pancytopenic bone marrow failure as well as malignancy.

Cartilage-Hair Hypoplasia is really common in the Amish and Finnish population. So specifically of note in our patient populations. Main things to know with this, again, a slew of different clinical features. But you can notice this fine sometimes hypo-pigmented hair. And these patients can have a moderate or severe neutropenia associated with this. You also do have the general malignancy risk as well, as we discussed. Supportive care is used for treatment of this. So G-CSF, transfusion, steroids, but the only curative treatment is a transplant.

Jumping into platelets. Pretty briefly, because there's only three major ones. Two majors and one minor. First, Congenital Amegakaryocytic Thrombocytopenia. So this is an isolated thrombocytopenia in the neonatal period, to where again, amegakaryocytic, so you're not producing megakaryocytes, which then develop into platelets.

Most common age of diagnosis. So you typically see thrombocytopenia within the first month of age. And so you see clinical features like bleeding or petechiae. And then the actual diagnosis of Congenital Amegakaryocytic Thrombocytopenia is usually several weeks to months of age, depending on when it's caught and thought to do a bone marrow evaluation. Thrombocytopenia is usually very severe, and it doesn't resolve as some other neonatal thrombocytopenia conditions do.

You can have some physical anomalies, so some orthopedic, renal, or cardiac. But some are just completely without any physical distinguishing factors. On bone marrow evaluation, like I mentioned, you have normal cellularity, except you don't have any megakaryocytes. Then if you check a thrombopoietin level, it would be very high, because the body senses that there's no platelets being produced. And it's trying to from its other means, but it's unable to.

Genetics of this are mutations in the c-MPL gene, which part of the thrombopoietin receptor. It's an autosomal recessive. There's a high carrier frequency in Ashkenazi Jews. And essentially it causes a loss of function of this protein, which then causes increased precursor cell death, or apoptosis. Again, like I mentioned, a good amount these patients can progress to total aplastic anemia. So a total pancytopenia, which is thought to be from just the depletion of the stem cell reserve, essentially.

Treatments, can't really give thrombopoietin agonist, because again, it's an abnormality in that receptor. So most of it is supportive through platelet transfusions. The only curative treatment, as you can kind of sense is a theme in this talk, is transplants. And then again, I mentioned it may progress prior to that to a severe aplastic anemia, so you want to try and catch it early. Future directions are looking at potential gene therapy, but this is still a little ways away.

Thrombocytopenia Absent Radii, so TAR syndrome. Essentially this is, as the name implies, thrombocytopenia, plus bilateral absence of the radii bones. And you typically have normal thumbs, which-- as I'll talk about later-- which is compared to in Fanconi anemia, where you don't have abnormal thumbs, but similar features. Most cases are diagnosed either in utero or first day of life. It's pretty significant and pretty easy to see that these patients don't have the radii, or bone in the forearm. So sometimes you can see it on ultrasound, but when they're born it's a very clinically easy to notice clinical feature.

There's an autosomal recessive pattern for this. And you tend to have very significant bleeding with this. So you can have intracranial hemorrhage, you can have GI hemorrhage. This occurs in the first six months of life. And platelets tend to be less than 50, sometimes severely lower than that. You can sometimes have an associated anemia and also leukocytosis.

So treatment. The majority of these patients is-- treatment for these patients is supportive care at the very least until the first year of life. It's been seen that the natural course of this, for one reason or another, is that after the first year of life, the thrombocytopenia actually starts to improve and can actually have a normal platelet count beyond one year of age. So the main thing is to follow these kids closely early on and make sure that we support them with platelet transfusions. And to avoid significant or fatal hemorrhages until this point occurs.

So you want to maintain these kids' platelets at least over 50,000 to minimize that risk of bleeding. If you have the patients that are severely symptomatic and for one reason or another are not improving, or having issues with other treatment, you can consider transplants. But a majority of these patients don't need that. There's no lasting benefit for steroids or splenectomy.

Noonan Syndrome. It's a global syndrome that I just wanted to mention briefly, that can have this amegakaryocytic thrombocytopenia. So you have some thrombocytopenia early on. And also these patients are at risk for myeloproliferative disorders as well as JMML and AML too. I just wanted to give one slide just to make sure that that's at least known when managing these patients.

Jumping into the pancytopenia, so these are syndromes that, for the most part, developed with all cell lines ineffectively being produced. One major one is Fanconi Anemia. It has a varied spectrum of clinical features that include-- but not always-- you have short stature, microcephaly, this is like I mentioned, you can have what's called the dangling thumbs, where you have some thumb abnormalities. Epicanthal folds, a triangular face, you have some café au lait spots seen in these patients. You can have skeletal abnormalities, as well as GI and GU abnormalities from these patients.

The lab findings, like I mentioned, you have a pancytopenic bone marrow failure. So as a majority of these syndromes I'm talking about that develop into pancytopenia, for the most part, thrombocytopenia tends to be one of the earlier signs that you'll see as a progression to this. So these kids tend to present initially with thrombocytopenia within the first decade of life. Then you notice a development of macrocytic erythrocytes and anemia essentially. Could also have elevated fetal hemoglobin, that's a compensatory mechanism. And when you do a bone marrow of these patients, they're very hypoplastic and are a very hypo-cellular with substitution of fat in the marrow space.

Diagnosis. So the initial screen diagnosis is with the chromosome breakage testing. So either induced by DEB the mitomycin C. And then there's also genetic testing. So there's at least 19 different FANC genes that are identified and more are being identified all the time. As we're getting deeper and deeper into the pathogenesis of this disease and syndrome, the majority are either A, C, or G mutations.

Such it is a role and ubiquitin ligase, so the abnormality in this cause increased fragility of the chromosomes, essentially. So chromosomal instability. Especially with different stresses. And then here, FANCB is the only one that's x-linked recessive. The rest are typically autosomal recessive. This syndrome is also a member of this caretaker gene diseases, like I mentioned, including things like AT, Bloom syndrome, XP, BRCA1, BRCA2. Also good to kind of keep in the back of your mind.

Therapy. Median age of survival is about 20 years in these patients. Androgen therapy is one mainstay, even though it has its own significant side-effects and morbidities that need to be managed as you're treating these patients. But if these patients get severely low enough, there is some utility in androgen therapy, which is shown to help improve cell lines in these patients. For the most part too, supportive care, so transfusions as needed. You can consider G-CSF, but I usually reserve this for if they're very severely low or have very significant and recurrent infections too, to try and minimize the morbidity.

And then, again, common theme is the only curative treatments is for the hematologic manifestations is a transplant. This is important to know for stuff that I talked about before and then also going forward, is that the majority of these syndromes have lots of different organ systems involved. Transplant is curative from our standpoint, so the hematologic standpoint. But it doesn't particularly cure or treat any of the non-hematologic parts of the condition.

One big thing with Fanconi Anemia, is that there is a cancer predisposition with this, as is with a majority of the others that I have discussed. So about 15% are predisposed to cancer. In Leukemia, there's mostly AML, you have myelodysplastic syndrome, so MDS. But also you have solid tumors throughout, liver tumors, which is important to know because androgen therapy can cause liver dysfunction and liver adenoma. So it's always a balance and a consideration. So it's important to have these kids evaluated broadly by multiple sub-specialties for surveillance. So gynecologic exams, rectal exams, regular dental checks, oropharyngeal evaluations, and then from our standpoint, we follow blood counts and marrow.

Jumping into the next big pancytopenic bone marrow failure syndrome is Dyskeratosis Congenita, or DC. This is part of a group of disorders that we call the telomere biology disorders. So just briefly. So as you may or may not recall, telomeres are essentially the chromosomal caps. And they're repeating, non coding DNA sequences that are important in maintaining chromosomal stability during replication. So as the DNA polymerase gets to the end of the coding regions, they can't quite get to the ends of the specific coding regions without these caps to where it can kind of extend a little bit. But with each replication, you still lose a little bit of each telomere, essentially.

Our bodies compensatory mechanism is this enzyme complex called telomerase, which extends the telomeres and helps maintain their stability and preserve the telomeres with multiple replication. These telomere biology disorders typically involve deactivating or dis-functioning mutations in the telomerase complex or associating proteins.

So if you think about if you have a poorly or non-functioning telomerase complex, then the telomeres will be getting shorter and shorter as time goes by. And then once they're to a certain point, you start having chromosomal instability and breakage and damage, et cetera, which can cause global issues. In general these patients, in the first decade of life, they have what's called this ectodermal dysplasia.

So you see this triad of both Leukoplakia, so this white plaque typically on the tongue or the mouth. You have some dystrophic nail findings, so any kid that I'm concerned about for a bone marrow failure syndrome, any in general, you always want to check the nails to see if there's any dystrophic nail symptoms. Not in all patients, and not in all DC patients, but it's an important physical characteristic to evaluate.

And then you also can have a hyper-pigmented reticular rash. And then these patients, in about the second or third decade of life, then that's when they start showing signs of bone marrow failure. Either single cytopenia or pancytopenia. Usually again, like I mentioned before, with the others, we can see it start as a thrombocytopenia, and then progress to pancytopenia.

And then I mentioned here, down at the bottom, just some other findings for telomere biology disorders, including DC. So like I said, it's a global syndrome. So you have liver cirrhosis, short stature, pulmonary fibrosis is a common one to note. Vascular anomalies, you have dental issues, CNS, GI tract. Again, all organ systems are involved.

So diagnosis is we can actually test white blood cell DNA, essentially, for their telomere lengths. And we can test them in comparison to the different percentiles for what they should be for age, et cetera. And what you'll see for these patients is you'll see that the lengths are less than the first percentile in all different categories. When you do a bone marrow in these patients, you see a moderate pancytopenia and a hypocellularity. So typically less than 10% with reductions in all three lineages.

And then you can also do genetic testing, which is mostly focused at the components of the telomerase complex, as well as some accessory proteins that affect the telomerase complex. It has a wide variety of inheritance. 70% of these kids have germ-line mutations, so about 30% don't. But one of the most common, that's seen in 40% of cases with a known mutation, is this DKC1 mutation, which is actually an excellent inheritance.

Prognosis, and treatment. So prognosis is not great for these patients. Median age of survival or at death is 20 years, median age of aplastic anemia is about 11 years or so. These patients that are getting to older ages, we are also finding they have a predisposition to cancers as I mentioned before. Most notably, of the oropharyngeal or GI tracts in their 30s.

Treatments. Again, this is another syndrome and treatment that has shown response to androgen therapy. But again, like I mentioned, androgen therapy has a lot of its own known side effects that also can affect some of the things that already are dysfunctional in these patients. I mentioned here several. So you can have abnormalities in cholesterol, triglycerides, liver function is a big one, because again these kids have liver dysfunction at baseline sometimes. Or they develop it. As well as liver lesions like adenomas and things like that. So it's a balance in seeing how clinically well these patients are compared to what they would tolerate or what would be the best for them.

They also have very poor survival and toxicity from transplant. That's improving with better transplant preparations. So more reduced intensity transplants. As well as it can be improved depending on their baseline organ dysfunction. So if we catch this early on and their general clinical status is good and well, then there might be a better survival and less toxicity with transplant.

Like I mentioned, this is the only curative option for the bone marrow failure, but again this doesn't treat other organ systems. In general, preventative things. So avoiding DNA-damaging agents, such as different medications, but also specifically radiation. So we tend to minimize imaging as much as possible with these kids. This is not responsive to different types of immunosuppressive therapies that are used in other patients and other syndromes.

Shwachman-Diamond syndrome is another global syndrome that I mentioned the clinical features here very briefly or kind of extensively. This is another syndrome with pancreatic exocrine insufficiency. But you can see, again, you have a slew of other clinical features in this. I tend to think of these patients as those patients that you think have cystic fibrosis, but when you do the sweat-electrolyte test, it's normal. So they have clinical features that look like cystic fibrosis. Short stature, increased infections, and different things like that. But when you do the sweat-electrolyte test, it's normal.

You mostly see a neutropenia in these patients as kind of one of the main features, but also this progresses into pancytopenia as well. I wrote here for the diagnosis is mostly GI testing and things like that. You can also do genetic testing. So the majority of patients have a mutation in this SBDS gene that's inherited an autosomal recessively, but then there's also a couple other genes and several others too throughout the implicated.

The hematologic problems, like I mentioned. This is mostly from a combination of things. These patients have abnormal marrow, so you have abnormal support of the hematopoieses. And then you also have increased apoptosis of early progenitors. Like I mentioned, you start off with a neutropenia and then progresses to aplastic anemia, pancytopenia. And also has a risk for AML and myelodysplasia, as with some of the others. One of the bigger indicators or progressions of myelodysplasia are this chromosomal 7 abnormalities. Overall, incidence for both AML or myelodysplasia is about 25%. And this is usually a very chemo-resistant AML or myelodysplasia, and transplant is typically the first line for treatment.

So general treatments of the pancreatic enzyme replacements from the GI standpoint, G-CSF or GM-CSF from our standpoint. I mentioned the transplants, and this is usually, again, for those patients with myelodysplasia, or AML, or severe symptoms, et cetera. But again, it's a balance between what their clinical statuses is with the rest of their organ involvement. From our standpoint-- from a pediatric hematology oncology-- monitoring, we usually do at least an annual marrow, plus following regularly CBCs and retic, and I'll talk about a general a little bit later.

Last, I just wanted to briefly mention this term aplastic anemia, which is not a great term, because it's essentially a pancytopenic. So you have anemia, but it's also a pancytopenia bone marrow failure, essentially. These patients tend to have in general-- just with aplastic anemia-- no splenomegaly, hepatomegaly, or lymphadenopathy associated with this, where you would see with like a malignancy, essentially. And I put here just the definition of aplastic anemia and severe aplastic anemia.

Usually it's with a combination of the bone marrow findings as well as the peripheral blood findings. So you have bone marrow failure of less than 25%, or if it's in this 25% to 50%, you'd also have hematopoietic cells that are less than 30%. And at least two of the following cytopenias. So an ANC less than 500. If it's less than 200, that's classified as severe, versus just aplastic anemia. Platelet count less than 20, and then a reticulocyte count less than 20. There's varying definitions of this mild and moderate aplastic anemia, so I won't get into that. And you can have both a congenital inherited aplastic anemia or an acquired aplastic anemia. So I'm just not going to talk about the acquired during this discussion, just because of the general talk.

Syndromes that are see with this, so disorders that I mentioned above. And then also a slew of other different things. So I put this up here as kind of a reference, but also just to say to keep this in mind for several of these or any genetic syndrome that you're concerned about, essentially.

Treatment. So there's three main treatment modalities. So the only curative, as with the others, are bone marrow transplant, or hematopoietic stem cell transplant. Gold standard is a matched sibling donor. If a matched sibling donor is available and clinical status of the patient allows it, then transplant is actually first line treatment for this. If there's no sibling donor available and or the clinical status doesn't allow or they don't think-- they think that the toxicity and the risk of transplant outweigh the benefits, the next first line is immunosuppressive therapy, with the exception of the telomere biology disorders like I talked about before.

And this involves treatment with horse anti-thymocyte globulin as well as Cyclosporine. So typically it's a four day course of ATG, and then oral Cyclosporin monitoring level. And this duration can be typically it's at least three to six months, depending on their response. Then next, most recently was FDA approved, was Eltrombopag, which is the TPO agonist. Which is approved for patients with severe aplastic anemia who have had insufficient response to the immunosuppressive therapy.

Last couple of slides, I just wanted to give a general overview of just a pancytopenia workup. And then once you get a bone marrow failure syndrome, how I kind of monitor these kids. So if you have a patient as a persistent pancytopenia, so on recurrent checks, I usually check a CBC and diff, and a reticulocyte count to get more information about if the patient is anemic.

First you want to rule out other things, so like infections, drugs, medications, any other things that could potentially be causing these things. And one good way of ruling that out is if the patient's otherwise stable, repeating the count after like a week or two is a good way of trying to help rule some of that stuff out, in addition to viral testing, et cetera if need be.

Then on the history and physical exam, you want to look for the signs and symptoms of bone marrow failure syndromes, like we've talked about earlier. As well as signs and symptoms of bone marrow failure. So if there's thrombocytopoienic, there's more bruising, leading concerns for that [INAUDIBLE]. Fatigue from the anemia side, things like that.

If there is a big concern, obviously you can refer to us, hematology oncology. And then if there is concern for trying to work up for a bone marrow failure syndrome, this is kind of my baseline that I do for a majority, but also you can tailor it to more specific concerns if need be. But again baseline CBC, retic, a CMP, amylase and lipase. You can check the chromosomal breakage, and then if that's abnormal you can look into Fanconi gene testing. Telomere length for the DC, peripheral blood for PNH flow, SBDS gene testing. And then I do a baseline bone marrow aspirate and biopsy to look for histology, cytogenetics, molecular, FISH, flow, et cetera. And then I put here plus or minus a bone marrow failure genetic panel. I usually save that for later if there's still some question in other things and depending on timings and things like that.

So go through all that, say something hits that patient has [INAUDIBLE], or we diagnose an actual bone marrow failure syndrome in this patient. So what I do for monitoring these kids is again, I get a CBC, a diff, and a retic at baseline, as well as a baseline marrow. And then I kind of follow a couple different pathways. So here if you have normal and stable CBC, diff, and retic, and on the marrow, you have no dysplasia and no clonal cytogenetics, no concern for bone marrow failure, et cetera.

Then I tend to follow these kids-- it says here every three to six months, usually earlier on I start every three months and then potentially space out the six months if possible. So every three months with labs, the CBC, retic, and then a yearly bone marrow evaluation. Because again like we mentioned earlier, the earlier you catch some of these subtle changes, typically is better in helping manage these patients further on to help minimize toxicity, morbidity, mortality, et cetera.

If with stable counts, you do a marrow evaluation, and there is no dysplasia, and you see maybe a low risk clone, or a single low risk clone, or something of unclear incidence, then that's when you want to check more frequently, just to make sure that there's not anything significant. So I usually repeat within a month, or monthly. And then consider also a marrow evaluation between three to 12 months, depending on the concern. And then you can obviously reduce frequency if that stabilizes.

Next situation, if you're following these patients every three months, or initially where you notice the CBC, diff, and retic are declining and going the wrong direction, or the marrow evaluation shows increased dysplasia, a high risk clone, or concerning signs from what I mentioned earlier for possible bone marrow failure-- this is where I follow these kids just more frequently to make sure that this isn't continually getting worse and worse, and trying to catch subtle changes earlier on.

So I usually check these kids in two to four weeks and then a repeat marrow instead of just the yearly, repeat in maybe one to three months, depending on the severity of the findings, essentially. If this is consistent or concern is getting worse, treatment modalities would be considering transplant. Also want to consider chemotherapy depending on what you see. So if they're starting to develop like an MDS, or you notice that there's a new AML, sometimes you want to treat those conditions before going to transplant, essentially.

Last category is patients with severely low CBC, retic, and diff. Or they're symptomatic cytopenia, so needing to be transfused very frequently. Or on the bone marrow, you see MDS, AML, or overt bone marrow failure. Then this is where you-- if not earlier-- this is where the next treatment would be stem cell transplant. Or again, like I said, consider of bridging chemotherapy to get the patient into remission if they have AML. Get the patient into remission before going to transplant, essentially, to give them the best possible chance for outcome.

Hope this has been helpful, if there's any questions-- I believe my contact information is part of this. You can always reach out to us. I think in general, if there's a question or a concern, you can always call us to discuss or refer to our clinic and we can help evaluate from there. Thank you.