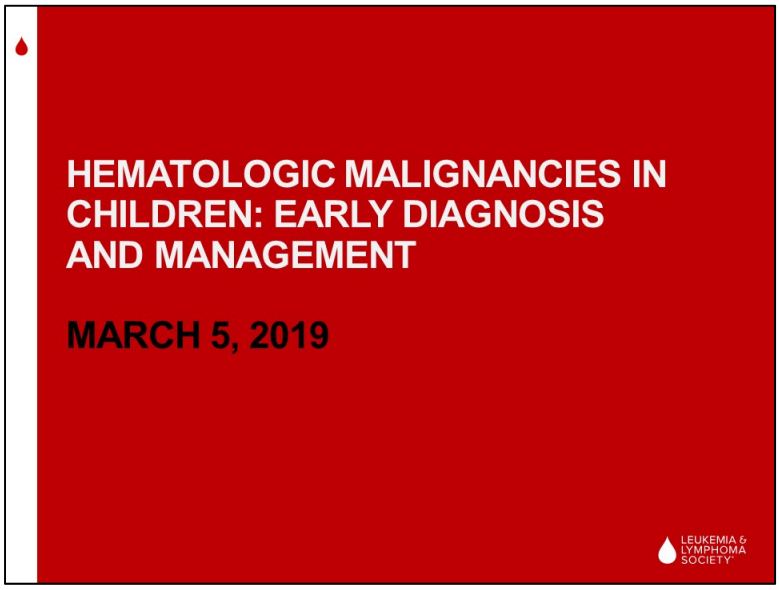
LEUKEMIA & LYMPHOMA SOCIETY®

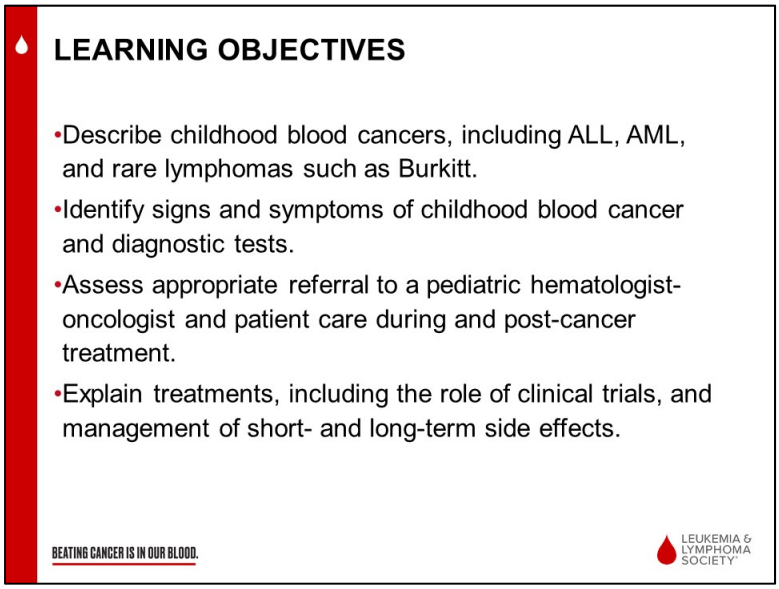
TRANSCRIPT

WELCOME AND INTRODUCTION

Valarie Leishman, RN, BSN, MBA



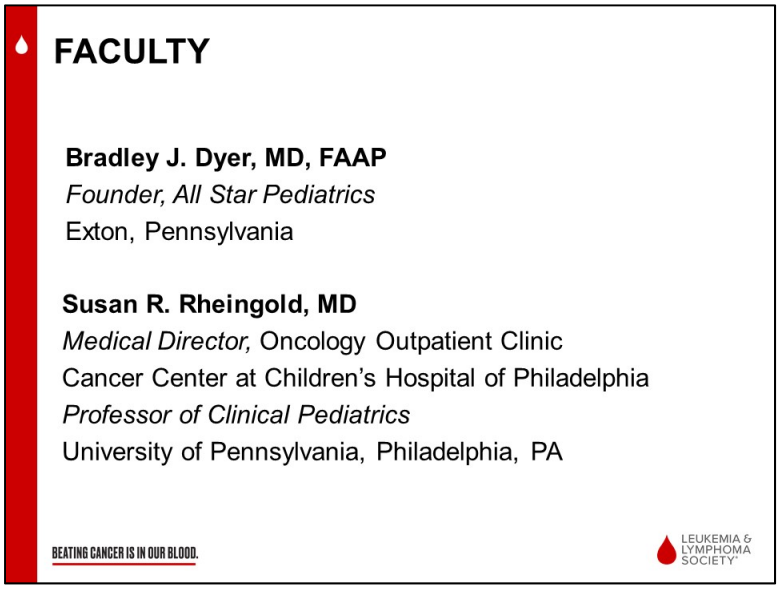
Good afternoon. On behalf of LLS (The Leukemia & Lymphoma Society), thank you for joining us today. The LLS is committed to improving patients' quality of life through programs such as this one and other professional and support education programs. We offer live and archived patient and professional programs for which you can earn CME, nursing, and social work credit. The LLS advocates for funding to accelerate the discovery and development of blood cancer therapies. To date, the LLS has invested more than $1.3 billion in research to advance therapies and save lives.



Today our presenters will address the learning objectives as outlined on this slide.

To receive physician, nursing, and social work credit for this program, please complete the evaluation at the end of this program. Your feedback is important to help us plan future programs and is also required for you to receive continuing education credit. A certificate of completion will be issued to you after the evaluation is submitted. The certificate will be a downloadable PDF. In order to receive credit, you must be present for the entire webinar.

We would like to thank the Clinical Directors Network for partnering with us on this program.



I am honored to introduce our speakers today. Dr. Susan R. Rheingold is the Medical Director at the

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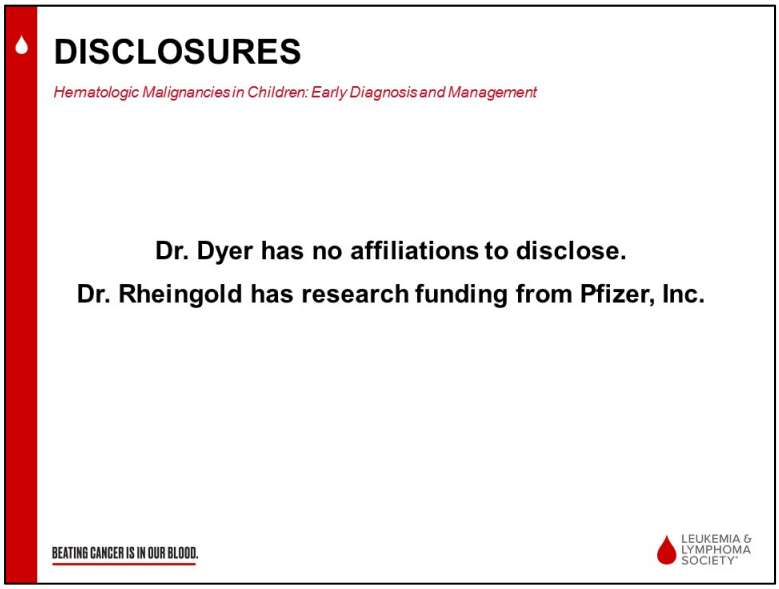
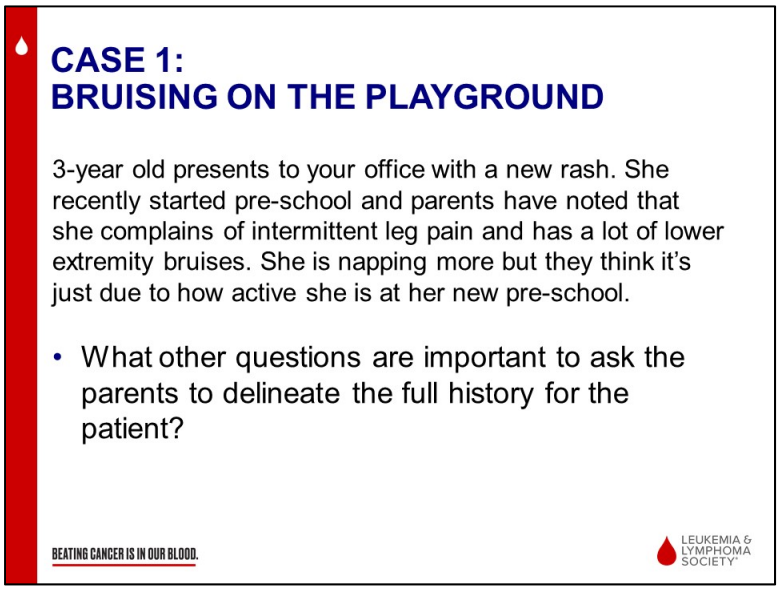
Oncology Outpatient Clinic and attending physician at the Cancer Center at Children's Hospital of Philadelphia in Philadelphia, Pennsylvania. Dr. Bradley J. Dyer is the founder of All Star Pediatrics in Exton, Pennsylvania. Thank you both for sharing your time with us today. It is my pleasure to turn the program over to you.



PRESENTATION

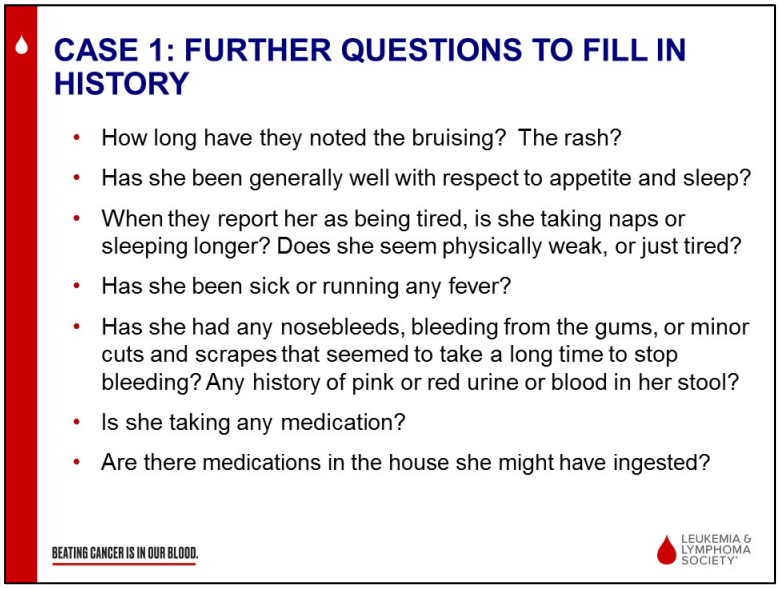
Susan Rheingold, MD

Thank you very much, and this is Sue Rheingold on the phone, the oncologist, and Brad Dyer is on the phone as well. And this is somewhat of a new kind of way to present these kind of conferences; and so teaming up with a general pediatrician to do some cases that might show up in the ER, in the general pediatric practice, in acute care practice, and really what kind of highlights or makes the general pediatrician begin to be concerned that this might be a diagnosis of malignancy and if it is or if you're highly concerned that it is, how do you get the patient referred to a tertiary care center.



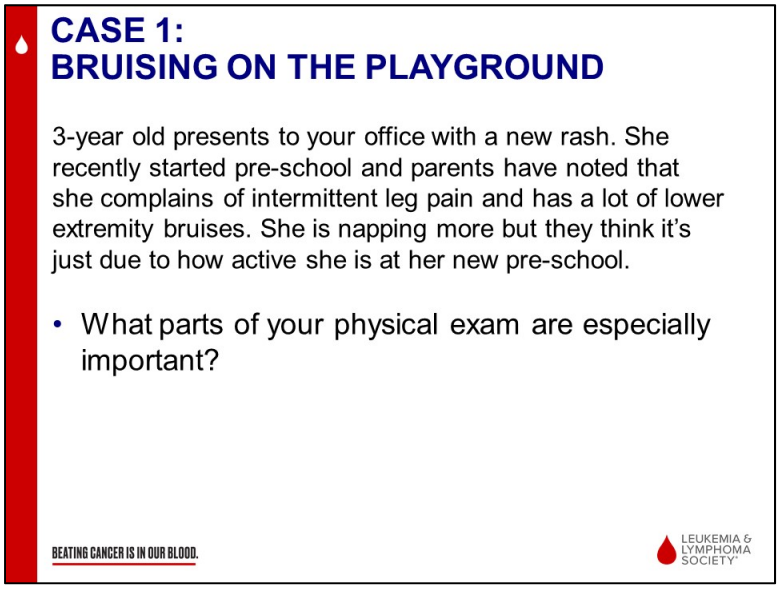
So, we'll start with the very first case, bruising on the playground. We have a three-year-old who presents to your office with a new rash. She recently started preschool, and the parents have noted that she complains of intermittent leg pain and has a lot of lower extremity bruises. She's napping more, but they think it's all just due to how active she is at her new preschool. So, Brad, what other questions are important to ask the parents to kind of delineate a more full history for this patient?

Bradley J. Dyer, MD, FAAP



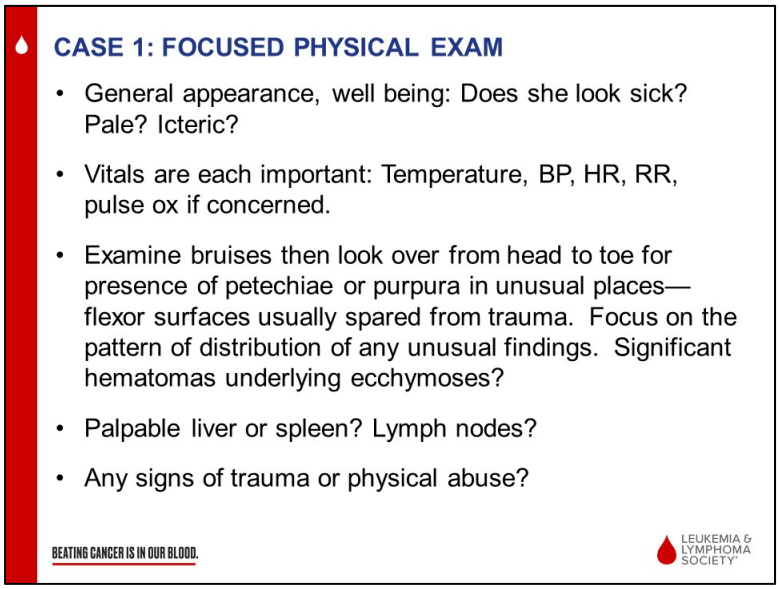
So, starting off as you would with any office visit, you want to really get a better history of both the rash, when it appeared, how long they've been noticing it for, has it changed at all, as well as the bruising and so forth. We want to get a good picture of that. Is that due to trauma, is that something that they expected, or is it kind of a surprise when they first saw it? And, also, the general health of their little girl. Has she been generally well with respect to her sleeping, eating, all the levels of energy, all that sort of thing. And then we want to really explore her being tired. Is she physically weak or is she just tired? Is she yawning all the time? Is she wanting to take naps where she wasn't napping before and kind of tease that out with them as well. And, also, has she been sick recently? Has she been running any fever? And then because of concerns of the rash, we're going to wonder if she's had any nose bleeds, bleeding from the gums, minor cuts and scrapes that seemed like they took too long to stop bleeding. Any history of pink or red urine or blood in her stool, any possibility or is she taking any medication, number one; and then also, number two, any possibility of poor ingestion?

Susan Rheingold, MD



And then, of course, after you get a more detailed history about the young lady, what parts of your physical exam are especially important?

Bradley J. Dyer, MD, FAAP



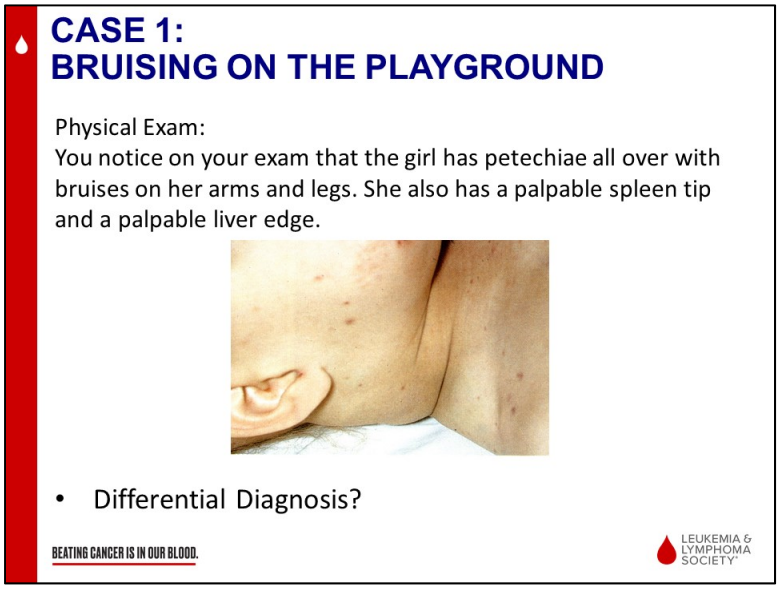
So, we're going to go over her from head to toe, just to really delineate physical findings just to see what's there as well as to look for things to make us feel better or worse about her case presentation. So, once again, in general, I mean how does she look in her terms of general health? Does she look

sick at all? Is she feverish looking? Is she pale? Is she jaundiced? Is she a carrot? And then looking at her vital signs, is she running a fever? And then, of course, the rest of your vital signs, pulse ox if you're concerned with her breathing in any way.

We look at the bruises that her parents brought her in for, and then you look for other bruises from head to toe. So, are they in places where you might expect them? Are they in what we call dependent areas on extensor surfaces or is there bruising in unusual places? And then you focus on the distribution of the rash as well and sort of what that looks like. Is that a head to toe? Is that just in certain spots? When we see or hear about petechiae, a lot of kids with a lot of intra-abdominal force with vomiting, they'll get petechiae in the face, but that never goes above the nipple line, things like that.

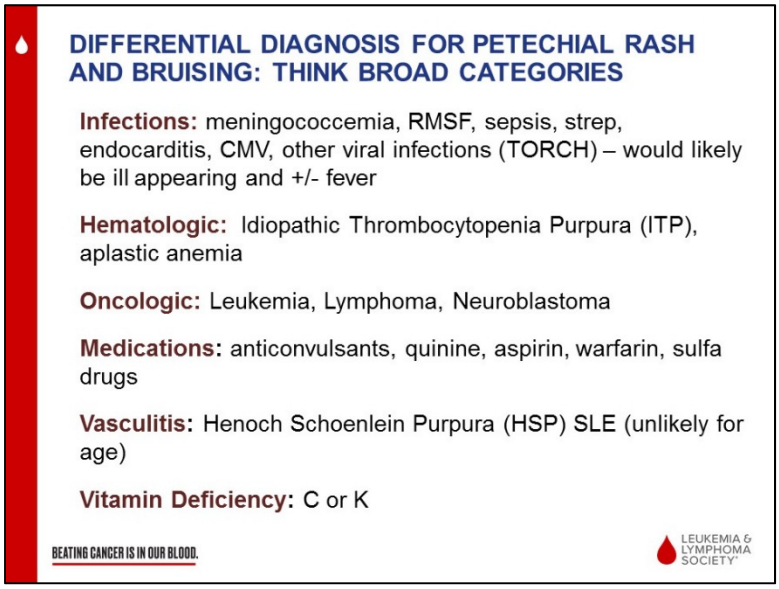
And so, we're looking for the rash, we're looking to describe the rash and see the rash as the parents are presenting it; but we're also looking for more than that. And then also feeling for liver or spleen, feeling for lymph nodes as part of the presentation; and then with any child with concerns for unexplained bruising, any signs of trauma or physical abuse. Where are those bruises? Were they inflicted by somebody else?

Susan Rheingold, MD



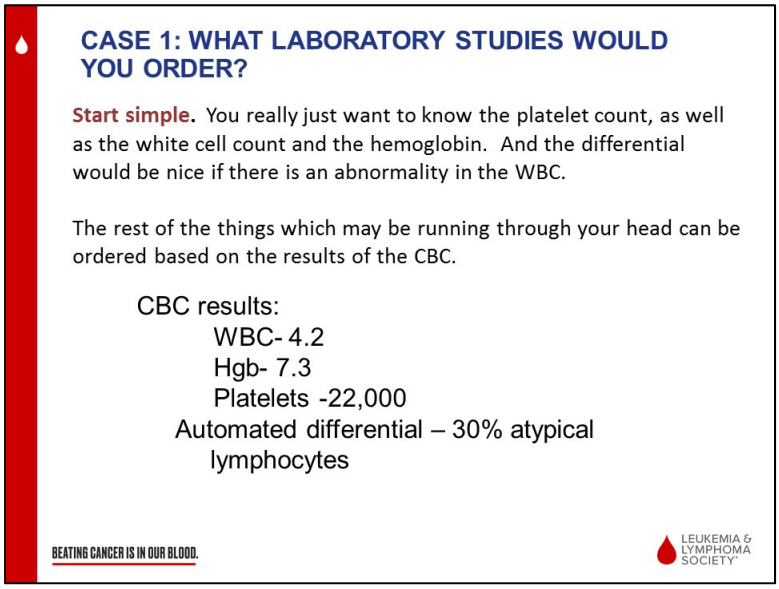
Thank you. And so, here's a picture of the young lady, and that rash is actually petechiae. Many parents will not walk into your office and be so kind as to say, "My child has petechiae." And she had significant bruises on her arms and legs, some over dependent sites but some not. On examination, she also had a palpable spleen tip and liver edge; and in a child who's three years old, that really, really needs to raise some kind of concern. The picture, which of course, is not the greatest, but there is some lymphadenopathy on the right side of this child's neck as well as the petechiae. So, now you have a little bit more history, and you can see the petechial rash on exam, what's your differential?

Bradley J. Dyer, MD, FAAP



So, on the next slide I've put together kind of a broad differential of just a petechial rash, somebody coming in, like what's going through your mind. Of course, sepsis, so meningococcemia, Rocky Mountain spotted fever, you know, any sort of other bacterial sepsis, endocarditis, those sorts of things. And then other things that might cause a rash, like this would be, you know, a streptococcal infection, viral etiologies, and so forth. With those, typically the child's going to be feverish and typically more ill-appearing, of course. Then we think of hematologic things, ITP (immune thrombocytopenia) probably being the most common thing. If I saw a child her age walking into my office with a, just solely the petechial rash, not the lymphadenopathy and the liver and the spleen, we do think about oncologic things as listed there. Any sort of medication ingestion, sort of, that would predispose her towards a bleeding diathesis. And then vasculitis HSP (Henoch-Schönlein Purpura), lupus, but unlikely for her. And then on the broad differential of vitamin deficiency, but in this case clearly, we're well beyond that.

Susan Rheingold, MD



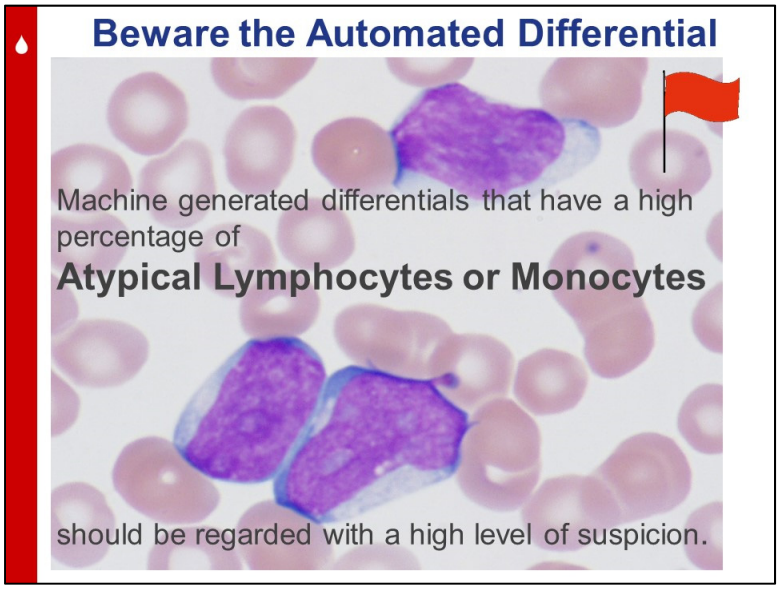
And so, you have the child there. You have this. So often the next step is you're going to order some labs on her. What kind of laboratory studies are you considering on a patient like this?

Bradley J. Dyer, MD, FAAP

So, again, a child that comes in with just a petechial rash and then maybe a little bit of adenopathy as well, you really want to start simple. You really want to know what the platelet count is, is it really low, is it way out of whack as well as other indices, and the complete blood count. The white cell count is going to be very helpful, and then if that is low or high, obviously, the differential there. But just starting with the CBC (complete blood count) is enough to go with, rather than trying to really test every hypothesis or every potential thing that you might have or that she might have.

Susan Rheingold, MD

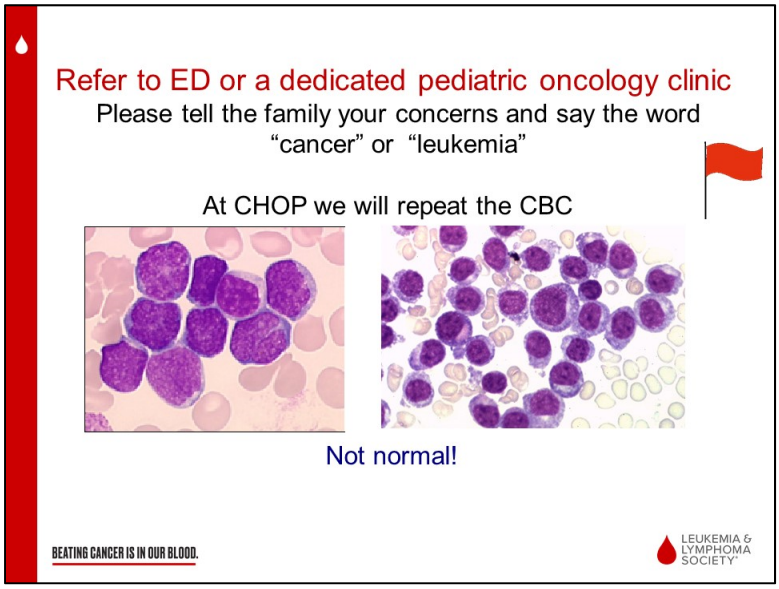
And so, I was kind enough to have the CBC results up there, and this child is generally pancytopenic. Platelet counts are in the double-digits, not the single-digits. And the automated differential, when you sent the kid to the local lab, had 30% atypical lymphocytes.



And I'm just going to put in here to everyone, beware the automated differential. Most LabCorp and Quests use a machine-generated differential; and it's hard enough for an oncologist to tell the difference between an atypical lymphocyte and a lymphoblast or a monocyte and a monoblast. How many of you looking at this picture right now can tell me which is which in that picture? The bottom two are the blasts, and the top one is the atypical lymphocyte. So, your machine certainly can't do it.

So, whenever you get on a differential a high number of atypical lymphocytes or monocytes, just regard it with a high level of suspicion. All of these labs are supposed to have hematopathologists where you can call and say, "Can somebody look at this?" But I've had issues where, "Yes, somebody can look at that on Monday," and it's now Friday. So just keep that in mind when you see something like that.

Bradley J. Dyer, MD, FAAP



And the other thing I'll sort of add in there too, Susan, going back to that CBC, she has, you know, the white blood cell count of 4.2 could be a little bit of a viral suppression. We see that a lot out in the office, but with at least two lines down, that's an immediate referral. That's not something that waits for tomorrow or next week to go see somebody. That's going to be, you're sending her in right away.

Susan Rheingold, MD

And she might be referred to an ED (emergency department) or a dedicated pediatric oncology clinic. If this child is somewhat well-appearing, I don't think it's the kind of thing that can wait until the next day. But I do think that if you have a relationship with your local pediatric oncologist, your tertiary care center, you can certainly call them and ask if they can see the child in their clinic that day. I think that's nicer for the families than being sent to an emergency room, but nights, weekends type of thing, the child may very well have to go to the emergency room.

We as oncologists and hematologists only request one thing. When you are sending a family in, voice your concerns. Let them know. I hate to say the scary words, such as, "I'm concerned your child might have leukemia. I'm concerned their blood counts are all down, and their bone marrow might not be making new blood cells." Because families who show up in an emergency room and sometimes are just told, "Well, there's something a little abnormal on the CBC" actually have said to us they would have been better prepared if somebody had given them some kind of idea that this was actually a little bit more serious than just a quick visit to the ED.

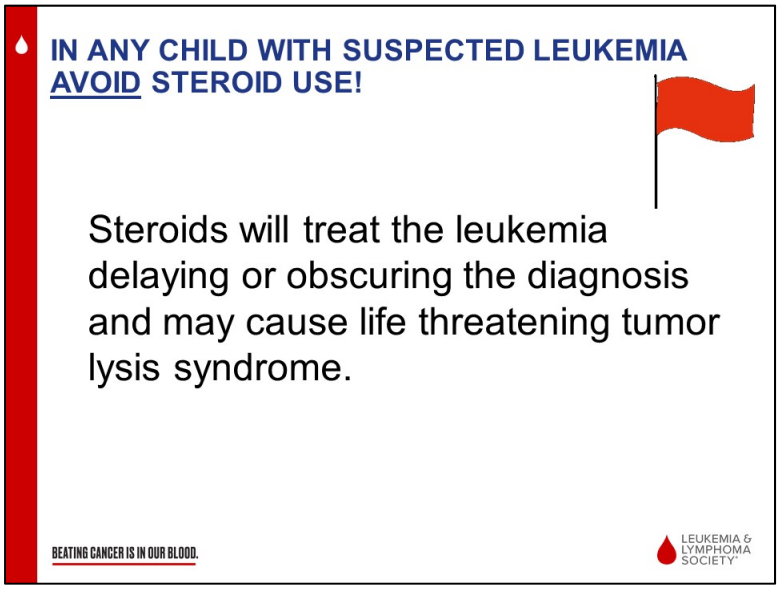
Bradley J. Dyer, MD, FAAP

And the art of doing that from my standpoint as well is you don't want to over worry parents at the same time; and, also, like if I get that CBC back, I know something's really wrong, I don't know if it's AML (acute myeloid leukemia), I don't know if it's ALL (acute lymphoblastic leukemia), I don't know if it's B-cell, T-cell, all that sort of stuff, they're going to have tons of questions. But I think it's important to broach the subject with them and say, "You don't have all the answers, but given the results of that one test, you know, it could be cancer, it could be aplastic anemia, it could be something else, and that she needs to get in right away.

Susan Rheingold, MD

So, when the child comes to the tertiary care center, and I'm just going to refer CHOP as the Children's Hospital of Philadelphia, we are going to repeat the CBC because I want to see what these cells look like with my own eyes under the microscope. And so, on the left-hand side, those are acute lymphoblastic leukemia cells. There are many of them. A typical blood smear has a variety of cells, and these are what we describe as homogeneous. These look alike.

For acute lymphoblastic leukemia, they're not much bigger than the red cells, maybe the size of those kind of faded red ghost-like cells. Those are actually your red blood cells. And they're pretty much all that dark purple middle, with a little bit of what we call the cytoplasm at the edge. On the right, on the other side, you're seeing what looks like acute myeloid leukemia under the microscope. A) you're not supposed to have that many cells, and there they all are out in the periphery looking very different. Myeloid leukemia is much bigger. Some of those are up to five times the size of the red blood cells, and that there's more of that lighter purple, what we call the cytoplasm on the round side. So, one look at that and I know that is not normal. But I'm not going to make a diagnosis that way.



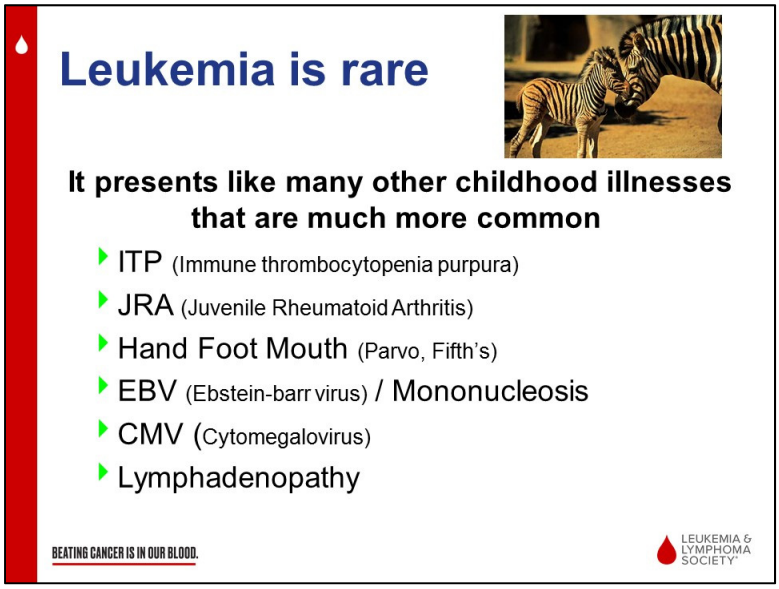
And I think in anyone, for any of these cases we talk about, that anyone out there in the community who is taking care or somewhere in your differential is a child with leukemia or even a lymphoma, we really want you to avoid steroid use because steroids are actually going to treat that leukemia or lymphoma; and, in fact, I might look at that CBC and it might look okay. It might not look that bad because the bad cells have died from the steroids themselves.

So, you can also get leukemia and lymphoma cell death, and if that occurs outside of the hospital without lots of fluids going, sometimes the kids can get into this situation called tumor lysis syndrome. It's a good thing. The cancer cells are dying. But when they're dying, they're releasing all these things into the blood stream; and eventually that will clog up the kidneys if the kids aren't on lots of fluids. So, for the generalists out there, you really want to know what you're treating when you start a pulse of steroids on a patient.

Bradley J. Dyer, MD, FAAP

Because we do give kids that have mono, that are having trouble swallowing certainly, maybe a little bit of difficulty breathing, difficulty lying down, that real discomfort that you can get with mononucleosis, we will treat them with short courses of steroids sometimes. We never do that without a CBC and a confirmation of either EBV (Epstein-Barr virus) titer series or Monospot.

Susan Rheingold, MD



And I think it's tough because leukemia is rare. I put the zebra up there. We all know the horses and the zebras, and leukemia is the zebra. It presents like so many other childhood illnesses that are much more common.

And for this young lady, if her platelet count was the only thing that was abnormal, we'd think ITP. But you also need to include JRA (juvenile rheumatoid arthritis), hand-foot-and-mouth, EBV, CMV (cytomegalovirus). All those things can cause the counts to be low, your hemoglobin to be low, your white blood cell count to be low, and they can all cause lymphadenopathy; and they're hundreds of times more common than leukemia.

Bradley J. Dyer, MD, FAAP

I think that as their primary care person, and if there are a lot of primary care people listening in, the difficult job of the primary care person is finding that zebra, you know, finding the needle in the haystack or whatever metaphor you want to use.

The incidence of childhood cancer, I think, at least, when I last looked, is about 1 in 3,000 children per year, newly diagnosed kids' kind of walking in. So, depending on the size of your practice, you might only see one new case of cancer every two, three years; or you might see three or four year, just based on the size of your actual clinic.

So, you never want to miss them, and I think that's what we're always worried about. But you also don't want to work everybody up that walks through the door that might potentially have something, and so that's the skill or, I guess, the focus of primary care is to do enough and not miss but not do too much.

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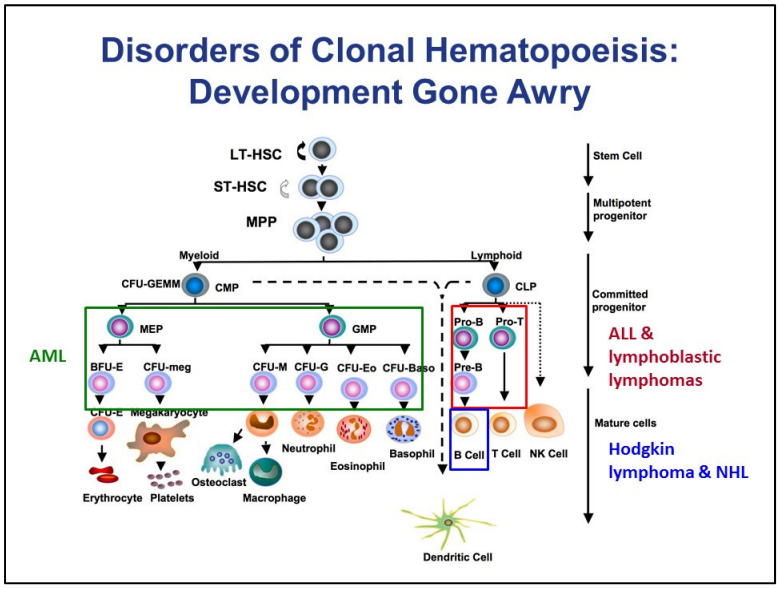
Susan Rheingold, MD



And, basically, leukemia, and even lymphoma to some extent, are disorders of early blood cells, early stem cells gone awry. I wish we knew why this happens, but the green box there represents the cells that go on to become AML; and these include cells like your neutrophils, eosinophils, basophils. But it also includes your megakaryocytes that make your platelets and the cells that make your erythroid cells. And those will all fall under AML.

ALL, acute lymphoblastic leukemia, kind of falls into two groups. There's B-cell and T-cell. You have B lymphocytes and T lymphocytes, and they can create the two different types of leukemia. And then a lot of the lymphomas stem from the more mature B-cells and T-cells that are actually circulating more and gone awry in the lymph nodes itself.

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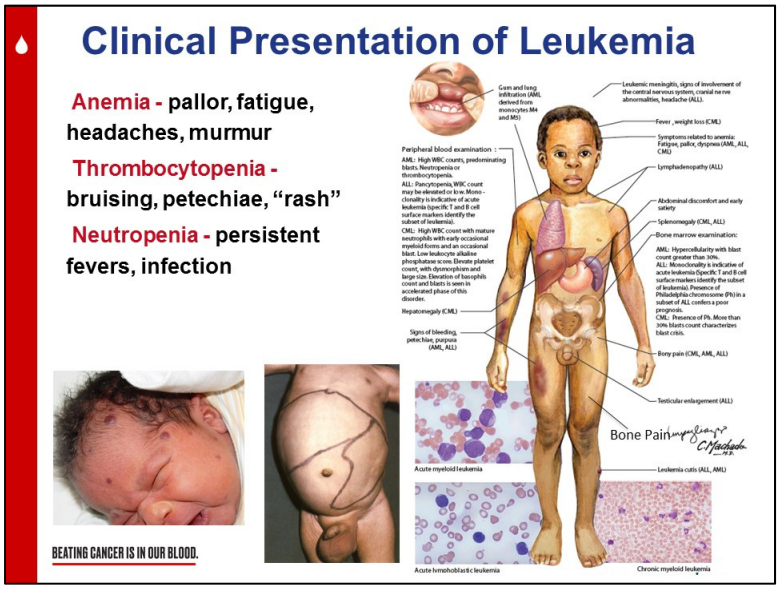
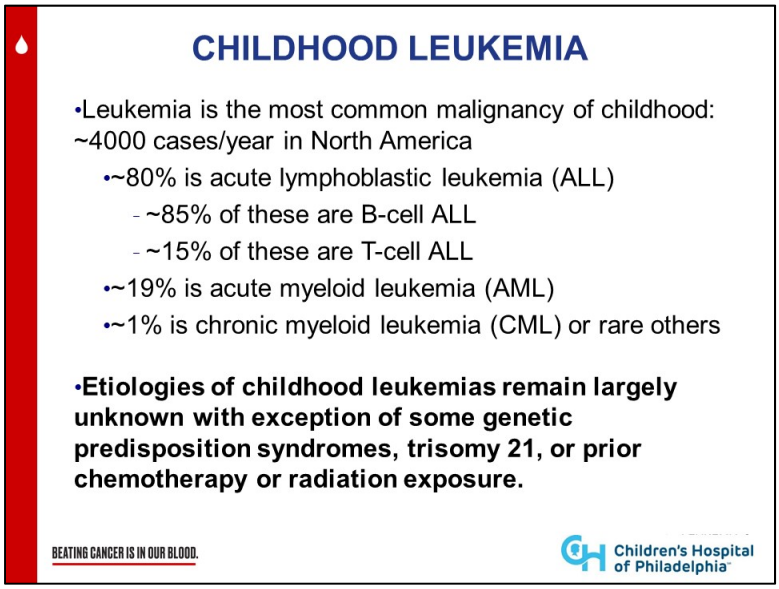


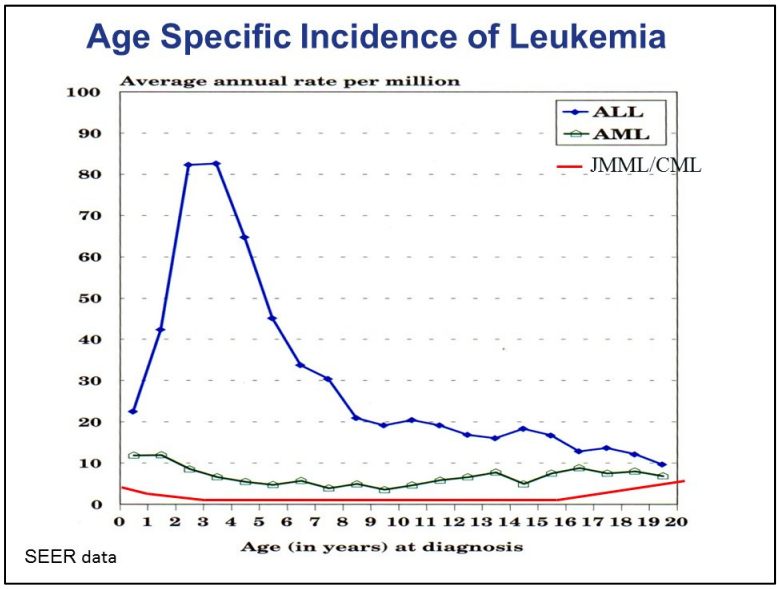
As we've talked about, there are so many different ways these kids present; and I just, both the diagram of the young man there with those kind of awful looking bruises that children get, they have, the bone pain is very common, especially in the toddlers age and refusing to walk. Children can have gum infiltration from the leukemia. The child there with the super impressive hepatosplenomegaly; one caveat I always put out is that very often when a child has significant hepatosplenomegaly, it often gets missed because we don't start low enough. We don't think we're going to look for a liver edge or a spleen edge way down in the inguinal area, but sometimes you need to get that low to feel the edge of it because it's just so large. And if you're feeling on top of it, you'll never feel an edge. It will feel homogeneous. It will feel okay.

The little baby on the left was what everyone thought was going to be what we call blueberry muffin or one of the TORCH titer in utero-type infections, but the white count was 200,000 on that little baby. And those are actually little skin tumors. Those are chloromas in what you call in the leukemia world of tumor. And so, some kids, those lesions end up getting biopsied by a dermatologist, and they can see that those are filled with leukemia cells.



Leukemia is the most common malignancy of childhood. There's about 4,000 cases per year in North America. The majority of leukemia is acute lymphoblastic leukemia (ALL), 80% of it is, followed by acute myeloid leukemia (AML), and then about 1% is chronic myeloid leukemia (CML); and there are some very, very rare others or preleukemia type things.

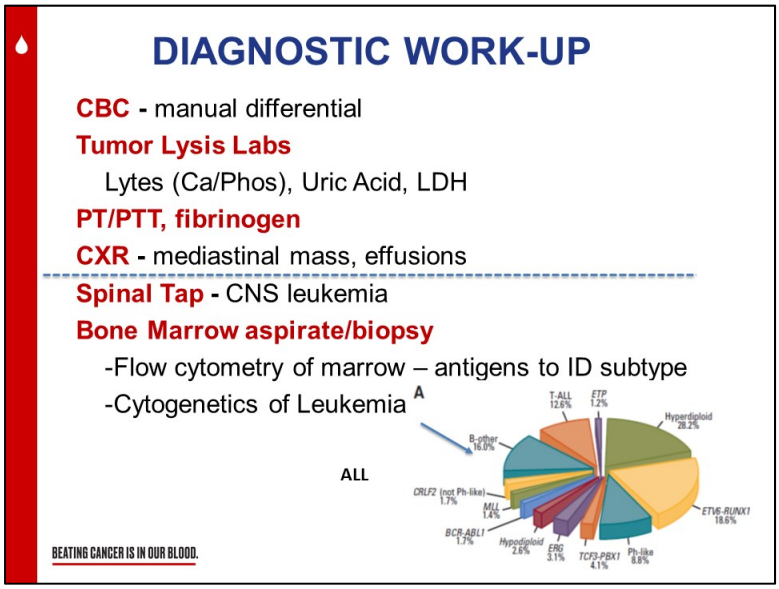
The etiology and why children get leukemia remains largely unknown. With the exception of some of the genetic predisposition syndromes, we know there's what we call chromosomal fragility syndrome. Children with Down syndrome and trisomy 21 are at increased risk of both getting AML and ALL; and that actually correlates with the fact that they have an extra chromosome 21, which is often abnormal in leukemia. Prior chemotherapy or radiation exposure is always a risk, so a child who may have survived one cancer, maybe a bone cancer or a liver cancer, may be at risk for developing a secondary leukemia.



Who gets leukemia differs by age. The blue curve on the top is showing there the incidence of ALL. And as you can see, there's a huge peak in the incidence in children in the toddler years, two, three, four, five. So that's why I gave you a case with a three-year-old. That is the primary age in which you see ALL. It evens off after that, and it even stays at a low rate through adults when you begin to get to 20-and 30-year-olds.

AML, which is less frequent, you have a little bit of an increased incidence in infants. And then as you begin to go into your teen years, it begins to increase again. But when you get into adults, AML rate really takes off. So, AML is more of an adult cancer. ALL is more of a pediatric cancer. But we both treat it, and we've really learned from each other as specialists across the continuum.

The red line at the very bottom, there's a form of CML that we call JMML (juvenile myelomonocytic leukemia). These kids are extremely rare, but they present with a monocytosis in a large spleen. And then CML is extremely unusual in small children, and again it kind of takes off in the adult age group.



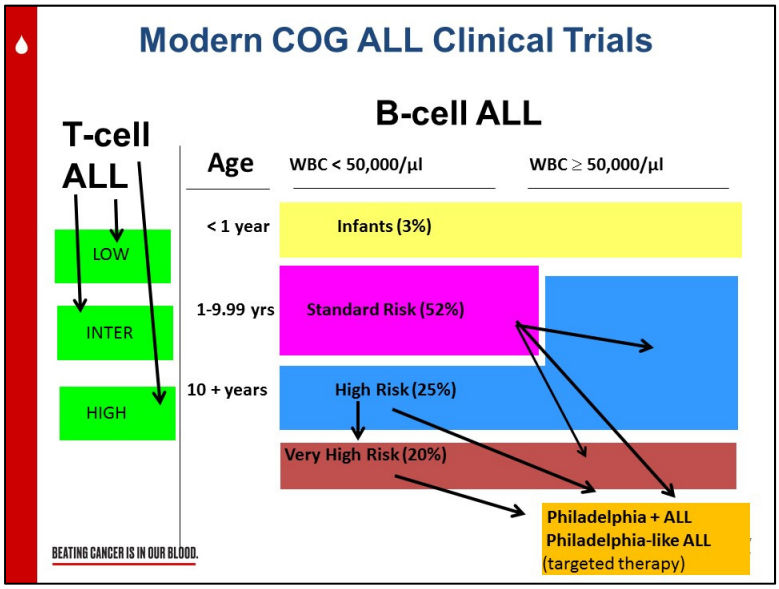
When the child gets to the Children's Hospital, our tertiary care center, as I said, we're going to do a CBC with a manual differential. We are also going to check a lot of their blood, their electrolytes, their creatinine to look if they're undergoing tumor lysis due to the cells dying. Even without starting therapy yet, you can have tumor lysis.

Uric acid is an excellent measure of cell turnover, and it's one of the screens we send along with an LDH, a lactate dehydrogenase, in patients when we're working them up for leukemia and lymphoma. So that's kind of a screening measure you can do.

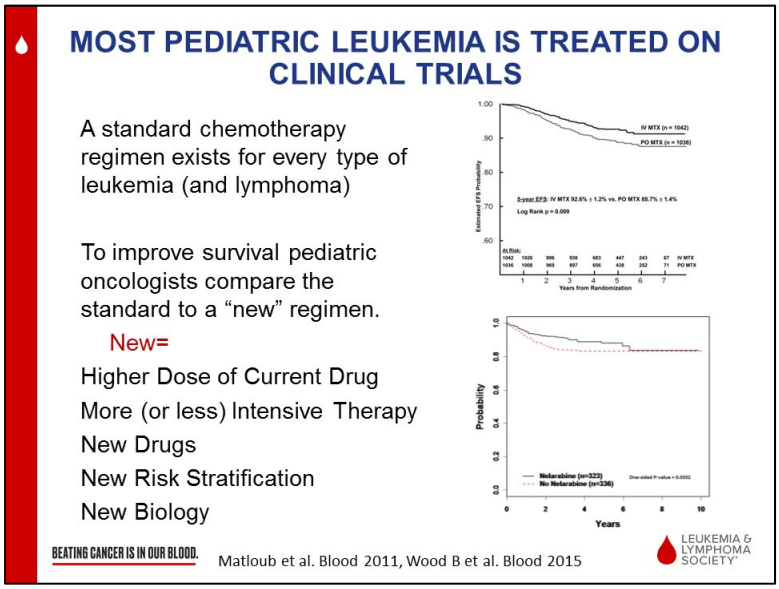
We check a PT/PTT (prothrombin time/partial thromboplastin time) and fibrinogen, in part, because AML can associate with bleeding disorders, and I personally do not want to do a diagnostic spinal tap on a child who has a PT of 2. I'm also going to get a chest x-ray on patients. Patients, especially with ALL and T ALL (T-cell acute lymphoblastic leukemia), are likely to have large mediastinal masses or pericardial or pleural effusions; and, again, I do not want to sedate a child or put a child under anesthesia with a large mediastinal mass. When we do see the child, generally the very next day, we do want to sedate or put a child under anesthesia to do a spinal tap to screen for CNS (central nervous system) leukemia; and we're going to do the final diagnostic part, which is really the bone marrow aspirate and biopsy. The leukemia is being made in the bone marrow, so we want the richest sample of where it's being made; and we do multiple things with the bone marrow.

We do testing of the proteins on the outside of the leukemia to identify exactly what subtype of leukemia it is. We don't just depend upon our eyeballs anymore. And we also do specialized testing on genetics of the leukemia. So, it's important these are not genetics of the child. It's genetics of the leukemia, and that chart graph there is kind of showing you in the breakdown of ALL all the different kinds of genetics you have.

And this becomes super important because we don't treat every child with ALL the same.



We, in fact, treat them very differently if they have T-cell ALL versus B-cell ALL. We treat infants differently. So, if you're a child with ALL and you're less than one year of age, you get treated differently than if you're a child over the age of ten. And you can move risk groups. We have risk groups within the therapy; and based upon a child's response to therapy and some of that genetic testing we do now, we move a child to higher-risk therapy, which often involves more chemo; and in the bottom right corner there, we have targeted therapy now. So, we have learned in the world of precision medicine and targeted therapy that there are some very, very specific drugs out there that can augment the classic chemotherapy and increase cure rate. So, we want to get all that testing at the start because once the leukemia goes away, I can no longer test it.



And when we have the information, kind of in the pediatric oncology world, we are the world's experts on what are called clinical trials. So, a standard chemotherapy regimen exists for every type of leukemia and lymphoma I could talk about in the pediatric, adolescent, and even really the young adult and adult world. But in the pediatric world, since the 1950s and '60s, we have always wanted to improve survival. So, to improve survival, the only way to show what might be better is to do a clinical trial and compare children to what was the standard best care we knew to a new regimen.

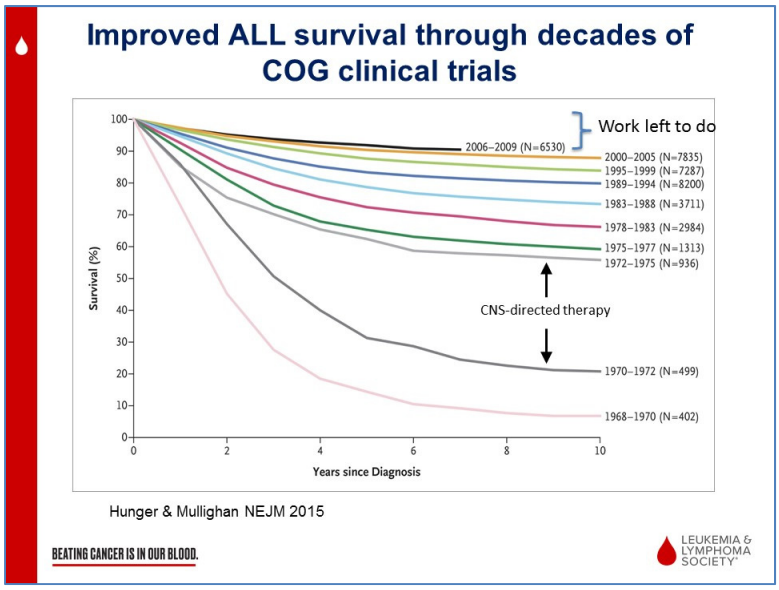
And the new regimen, sometimes people think, oh, you're comparing it to a scary new drug. That's actually only part of what the new regimen might be. Sometimes the new regimen is just a higher dose of a drug we use all the time. More or, in fact, now less intensive therapy, so when we can identify a child is very likely to be cured, we sometimes say, "Can we get rid of some of the chemotherapy that's going to cause late effects, problems with their heart, problems with their education, problems with their growth? Can we get rid of that chemotherapy and cure the same number of children?

Sometimes it's new drugs, and as an oncologist, I could go on forever about the exciting new drugs that are out there, many of them targeted to the leukemia and most of them having much less side effects.

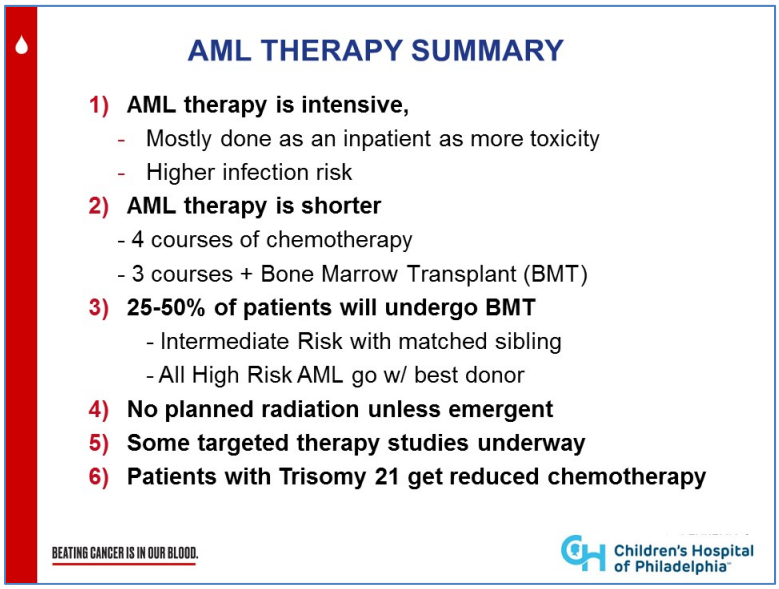
New risk stratifications. How do I decide if somebody might get away with less or might need some more? Well that's called risk, and so if I determine someone's higher risk, can I give them more, how can I do that more precisely? How can I make sure that I'm kind of putting the children and young adults into their right co-groups? And sometimes the clinical trial is just studying biology. Can we get some samples from the leukemia to help us understand for the next generation of trials something better?

And so, on the right I'm showing some slides of two of the Children's Oncology Group trials that have shown just changing the top one is IV versus oral, a chemo drug. And although that doesn't look like

a big survival group, when kids are surviving at that rate, to increase survival by 5 or 8%, to us is hugely significant.

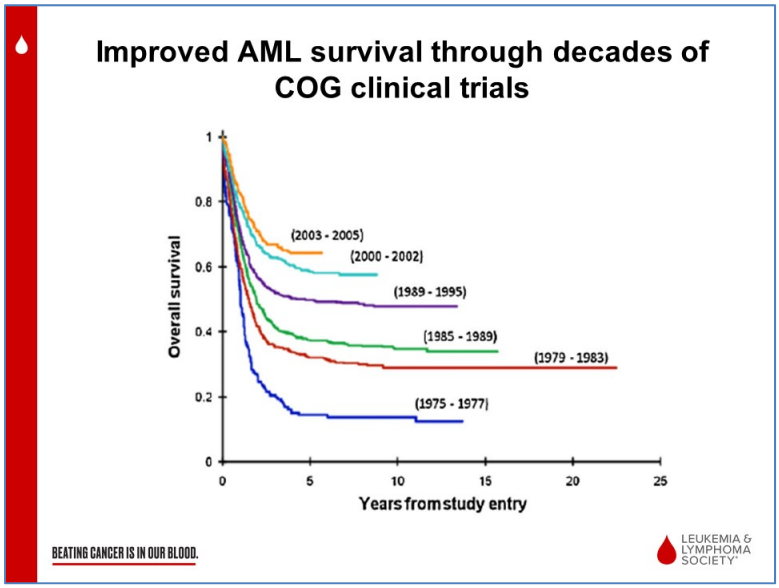


And doing this over the years, the Children's Oncology Group has improved survival, so you're going back to 1968 and all the decades of the trials have done, have improved overall survival to 92% for all children with ALL; but clearly there's work left to do, and then, getting back to the "can we reduce some of the intensive therapy that leave children with long-term late effects."

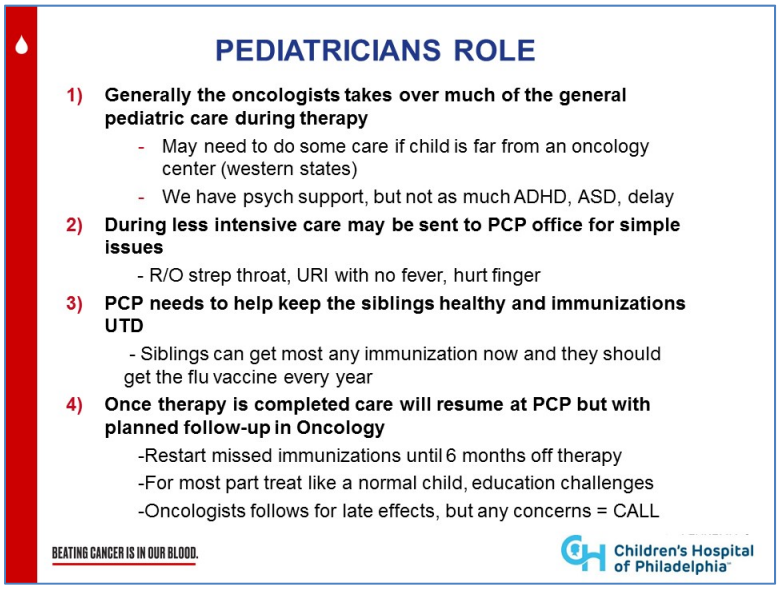


AML therapy is very different from ALL therapy. AML therapy is much more intensive. It's mostly done as an inpatient, requiring a pretty long four- or five-week hospitalization as it's much more toxic to the child and there's a higher infection risk. As a tradeoff, AML therapy is shorter. It can be four of these

courses or sometimes three courses and a bone marrow transplant. About a quarter to a half of children with AML will undergo a bone marrow transplant, and sometimes that relates to their risk or whether they might, in fact, have a sibling donor that's a good donor for a transplant. But some children with what we consider the high-risk AML, we'll always take to a transplant. Children with AML don't get radiated. We're also studying targeted therapies, and children with Down syndrome will actually get reduced chemotherapy because they do better and with less side effects.



We've come a long way with AML as well, but, unfortunately, it's not quite as good. Probably overall survival is closer to 65% in children with AML, but we are finding better populations and more challenging populations to treat.



Part of this was, okay, so I'm now taking care of this child. I've diagnosed them. What is the pediatrician's role? What is the acute care, you know, the doc at home's role? And to be honest, generally the oncologists do take over much of the general pediatric care during therapy. Some of you on this phone are probably four or five hours or across a state line to the primary pediatric oncology center. So, I know there are patients in Montana and far western Washington State who actually receive some of their chemotherapy through their pediatrician or get their CBCs or get transfusions locally. And that's fantastic that you can help work with the families.

We do have a ton of psychiatric and psychologic support, but pediatric oncologists aren't as good with some of the issues related to maybe ADHD (attention deficit hyperactivity disorder), autism spectrum disorder, developmental delay. So, some of those type issues may have to go back to the pediatrician to make sure the child's getting their proper dose of Adderall (dextroamphetamine saccharate/amphetamine saccharate).

Also, during less intensive care, like ALL in what we call the maintenance, if the child calls our clinic, we may send them to the PCP (primary care provider) office for a simple issue like everyone in the family has a Strep throat. The child has a sore throat. It's easier for them to go five minutes to your office to get a throat swab and a course of amoxicillin, or maybe a child has a cold with no fever or they fell and hurt their finger, and they really don't need to drive a whole hour to see us.

An important role for the pediatrician as well is to make sure to keep the siblings healthy and immunizations up to date. And I know immunizations can be a scary thing. Siblings can pretty much get any immunization now. It used to be there was some live and not live, and we've changed our immunization schedule. But I think the most important thing is to get the siblings their full vaccinations, so we don't leave the child at risk. And everyone in the family should get a flu vaccine every year. Generally, we will do the flu vaccine for our patients right here in the oncology clinic; but we do want you getting the siblings in.

Bradley J. Dyer, MD, FAAP

When we have a child diagnosed with a cancer, we really hand it over to the pediatric oncologist and expect that everything's going to be done with them. Now we keep communication with the family really more, almost as moral support as much as anything else and to be there to provide anything that they might need, like a vaccination or like a sick visit for a sibling or a cousin or whoever, to provide that sort of advice and also be there sort of with open arms when the treatment is over or referred in by the oncologist. But, really, and we're fortunate enough to be practicing within a half an hour of Children's Hospital and to have great care for those kids. But we really do sort of step back and let the oncologists do their work. You've become so great at looking at all the other health issues with kids and so forth by sort of being there for them when they step back into the realm, when they're out of their therapies.

Susan Rheingold, MD

And when they do return to your care, for the most part, they restart any missed immunizations when they're six months off all therapy. That's when we feel their B-cell population is enough to have some memory for it.

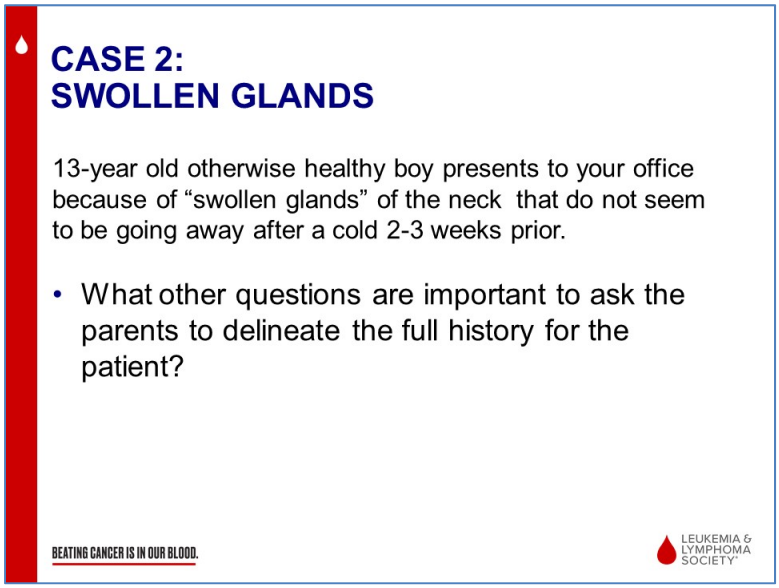
But we really recommend you treat this child like a normal child, kind of keep your ears open for any issues. Some of these children will develop educational issues due to their therapy. We are still seeing these children regularly. We haven't sent them away. We're seeing them every three months, but certainly anything you see at a visit that you say, "Wow, this is concerning, or this is unusual," just give us a call because we can probably get the child in for blood work or a test pretty quickly, which might take you a little longer to get.

Bradley J. Dyer, MD, FAAP

The other thing I will say too is reading all the letters that come from the specialists, I know, I'm sure everybody out there does that. But when they're getting those letters from the oncology clinics to kind of go through and see how are counts going, like why did they have to delay? You know, did they even know the child was in the emergency room last week because they had a fever and neutropenia, all that sort of stuff.

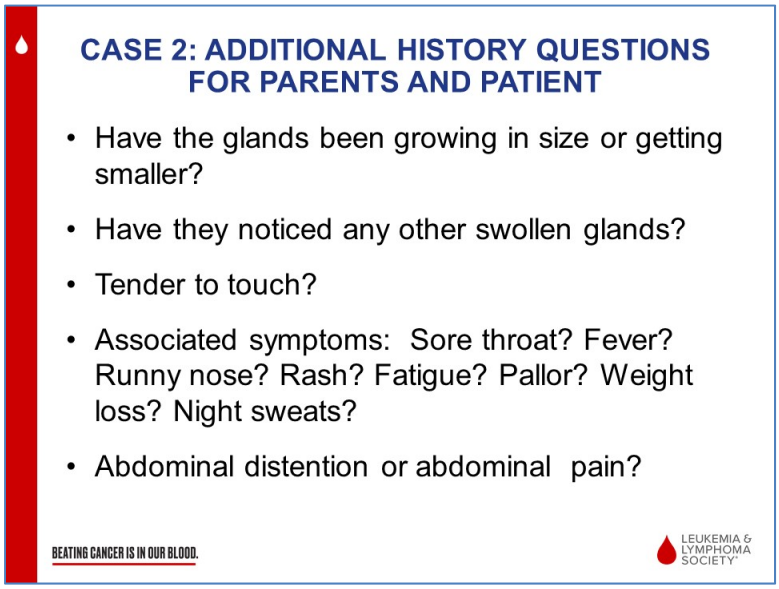
To keep yourself apprised of what's going on, even though you're not seeing the child, is huge in terms of your relationship with that child and with their family.

Susan Rheingold, MD



So, the second case, a 13-year-old, otherwise healthy boy, presented to your office because of swollen glands of the neck but do not seem to be going away after a cold two to three weeks prior. So what kind of questions in the history are you going to want to know?

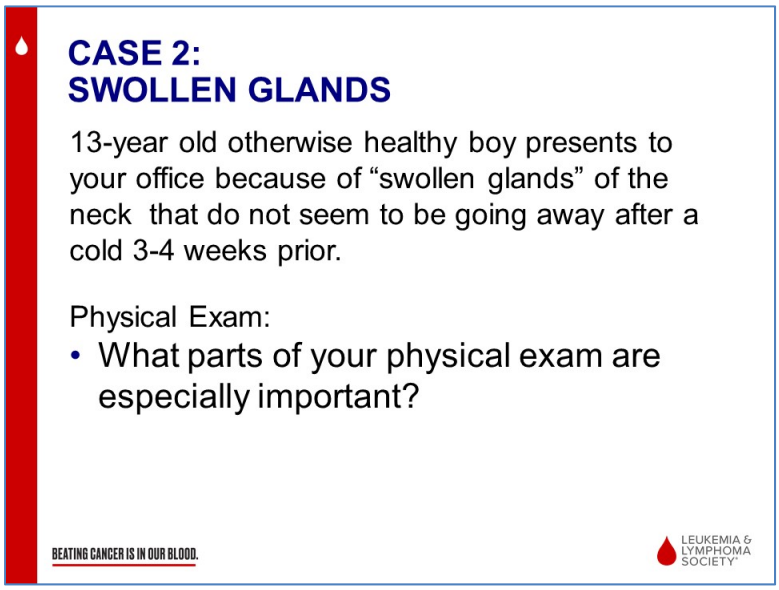
Bradley J. Dyer, MD, FAAP



So, what we want to do is to kind of really tease that out again, from the patient himself as well as their family. Like are the glands still growing in size, are they kind of the same, have they gone down

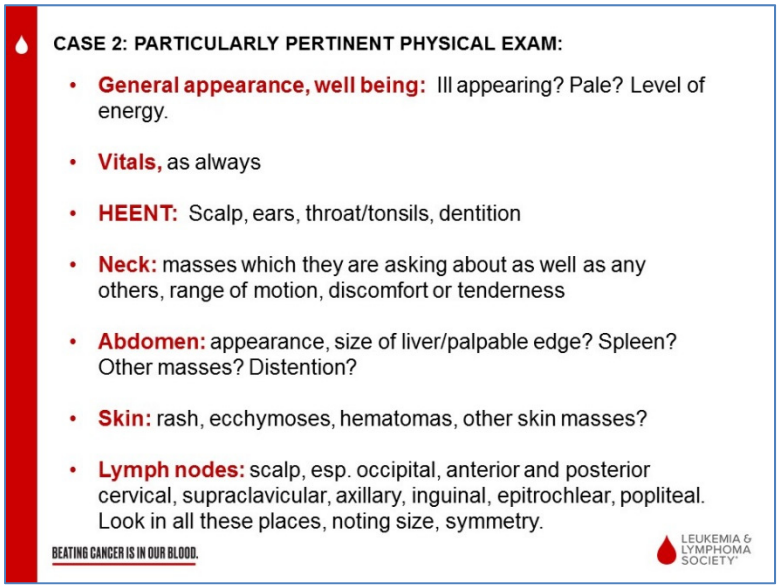
from the cold that was two, three weeks ago? Were they present before he had the cold or was this sort of the result of that or when did they really notice them? Have they noticed any other swollen glands anywhere in his body or has he noticed that? Are they tender, are they red, or are they warm feeling? All those sorts of things. And, you know, because the most common reason for having swollen glands is going to be an infection. Does he have a sore throat? Does he have fever, runny nose, rash? Is he tired? Is he pale? Any weight loss, weight gain, night sweats? Any sores in his mouth and so forth as well as any abdominal distension or abdominal pain?

Susan Rheingold, MD



And so what parts of the physical exam now are you kind of focusing on?

Bradley J. Dyer, MD, FAAP

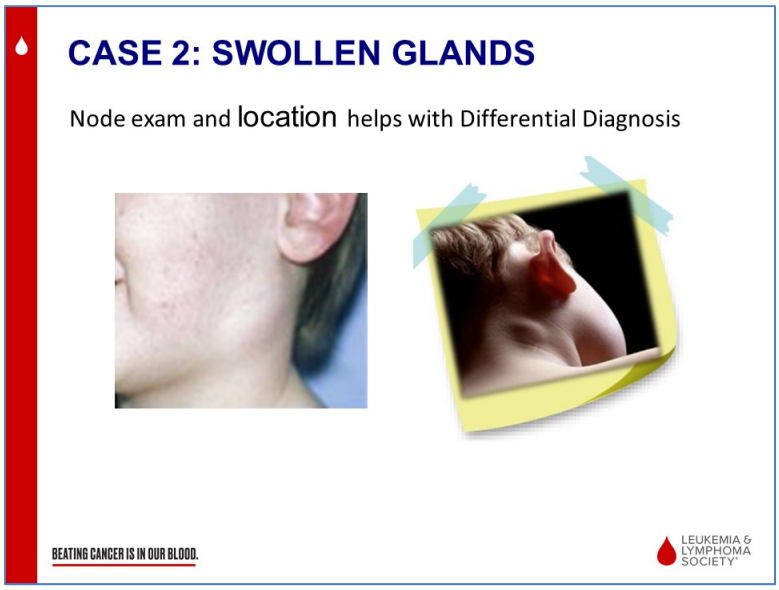


So really kind of focusing on those glands as presented. We're going to look at how big they are. We're going to look at where they are. We're going to look at any degree of discomfort and so forth. We're going to look for other glands.

Overall, but, you know, as I do in all of my slides here, I just, the general appearance of the child, I think, is just so important. What's his level of energy? Is he ill-appearing? Is he sick or is he just perfectly fine like, "Why am I here in the office?"

Looking at vitals, and then looking for a source of infection, sort of going from head to toe. So, looking in the scalp and the ears and the throat, tonsils, looking at the teeth. Looking at the neck, the masses in the neck that they came in for, as well as any other associated nodes or glands. Looking in the abdomen for liver or spleen. You know, palpable edges and so forth. Are there any other masses anywhere, and, yes, the abdomen distended? Does he have an associated rash or bruising or anything like that, other than just the swollen glands that we're seeing? And then I just kind of listed all the nodes that we're going to be looking for, knowing what the little guy looks like in the slide coming up.

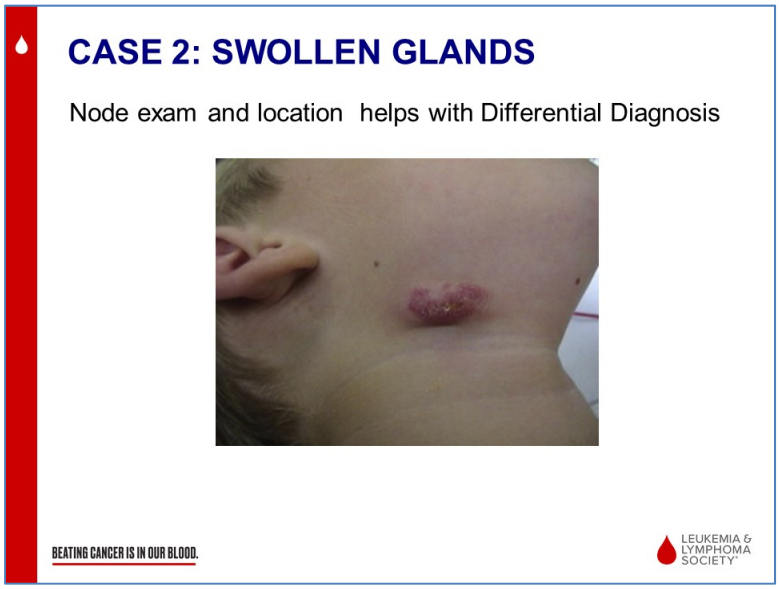
Susan Rheingold, MD



I think the hardest thing is, you know, we can talk forever about how you determine a benign versus a malignant node and when you worry, and you don't worry. And so, I think node exam and location helps tremendously with the differential.

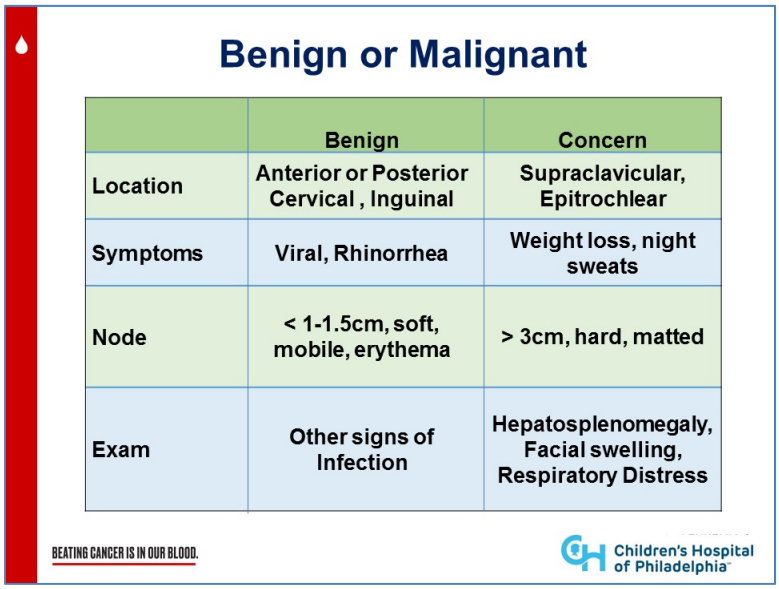
Bradley J. Dyer, MD, FAAP

It's huge. So, but I mean this is something you see in your office several times a day if you have a full schedule of patients. So, we see nodes all the time. People coming in for completely other things, you find lymph nodes on and so forth. And, you know, 99.99% of them are benign. So, looking at their distribution, looking at their size, number one. Looking at their distribution, are they in, you know, reassuring areas? Are they in concerning areas? Is there symmetry on both sides? And then is there any sort of other like tenderness, redness, swelling, drainage, all that kind of stuff?



And the ones that we're showing here, that was just a little anterior cervical node that was like a benign, unworrisome one. And then there's the posterior cervical node that could have been benign. It would depend if there was something up in the scalp also. You see something like this, obviously, you're worried that there's some sort of a typical or atypical infection there.

Susan Rheingold, MD

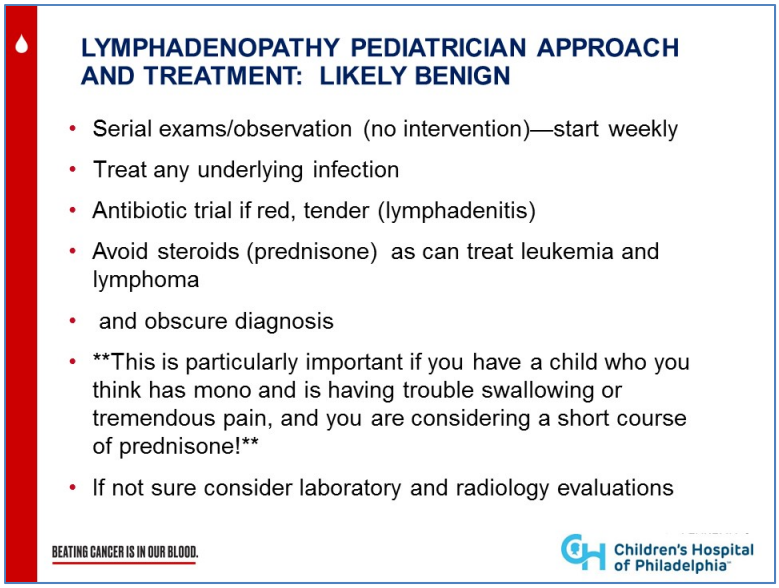


	Benign	Concern
Location	Anterior or Posterior Cervical , Inguinal	Supraclavicular, Epitrochlear
Symptoms	Viral, Rhinorrhea	Weight loss, night sweats
Node	< 1-1.5cm, soft, mobile, erythema	> 3cm, hard, matted
Exam	Other signs of Infection	Hepatosplenomegaly, Facial swelling, Respiratory Distress

Right. And so, in trying to break down kind of benign or malignant, I think the things that concern me location wise is supraclavicular. It's hard sometimes to tell the very low end of anterior chain, but if it's truly supraclavicular, that makes us worry that there's something going on in the chest. Also, of

concern, weight loss and night sweats. Those are commonly seen with Hodgkin's lymphoma. Large nodes, I've seen plenty of 1.5- and 2-centimeter nodes that are completely benign. I'm sure everyone has, but if you're getting up over 2 to 3 centimeters, if they're hard when you palpate them, they're not soft, they don't wiggle right under your fingers or they're matted together like a cluster of nodes, that concerns me as an oncologist.

And then the same thing on the exam. Hepatosplenomegaly, you shouldn't be feeling a liver and a spleen. Now with EBV, which is a big differential here, you may be feeling a spleen. So that you have to keep in mind, but otherwise, if you have hepatosplenomegaly, I'm going to be more concerned. Certainly, something like facial swelling, which would imply that the mass is actually obstructing the chest or respiratory distress, would make me even more worried about a child than just the node in the neck.



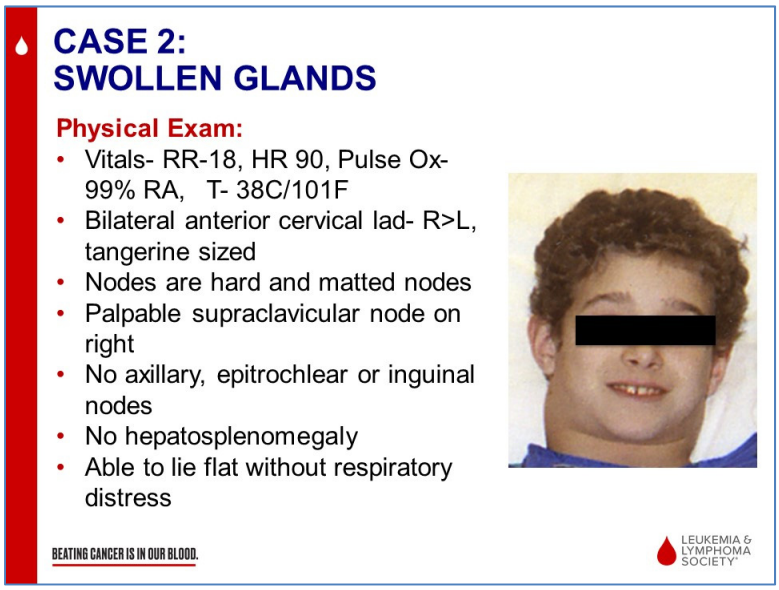
And so, you can kind of talk about what you do if you think this is a benign node.

Bradley J. Dyer, MD, FAAP

All right, so if you think this is benign and it's a small 1 to 2-centimeter node, it's mobile, it's rubbery feeling, it's not concerning, it's not tender, it's not draining off, so you can just watch it sometimes, a lot of times, depending on what the background story to that is. So typically you're going to watch it every week or couple weeks or so. If I do, then I'm sending the patient and parent out with the instruction like, "I want you to kind of look at this. It's the size of a lima bean right now, and I want you to feel it in a week or two and give me a call if you think it's getting bigger, if it's not getting smaller, if it becomes tender or whatever, or you start feeling more glands, you're going to give me a call about that." If you do think that there is bacterial adenitis, you're going to use an antibiotic for that, which we talk about. We talked about avoiding steroids unless you know that it's EBV by testing and the child is having some sort of, you know, swallowing dysfunction or breathing discomfort, things along those

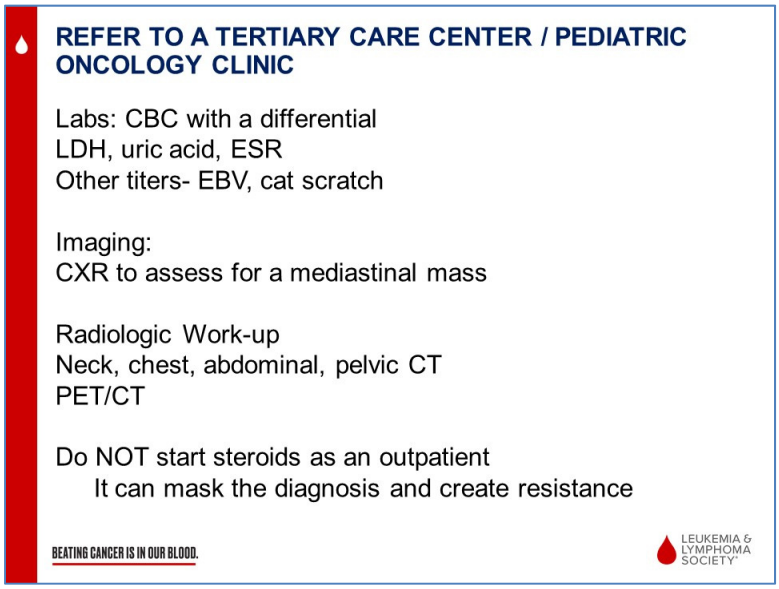
lines. And then sort of watching it and then if you're unsure of it, at least get a CBC. At least get something to kind of get a little bit of a look at what that node might be representing.

Susan Rheingold, MD



And so, this case was a young man who the nodes there are so prominent they're actually at the level of his ears, and he did have a supraclavicular node on the right which, as I said, is always concerning.

Importantly, he was able to lie flat, so that makes you, you know, here at this point, you're kind of trying to make the decision as the pediatrician about, okay, now I'm leaning a little bit more malignant, how quickly do I have to get him into an oncologist?

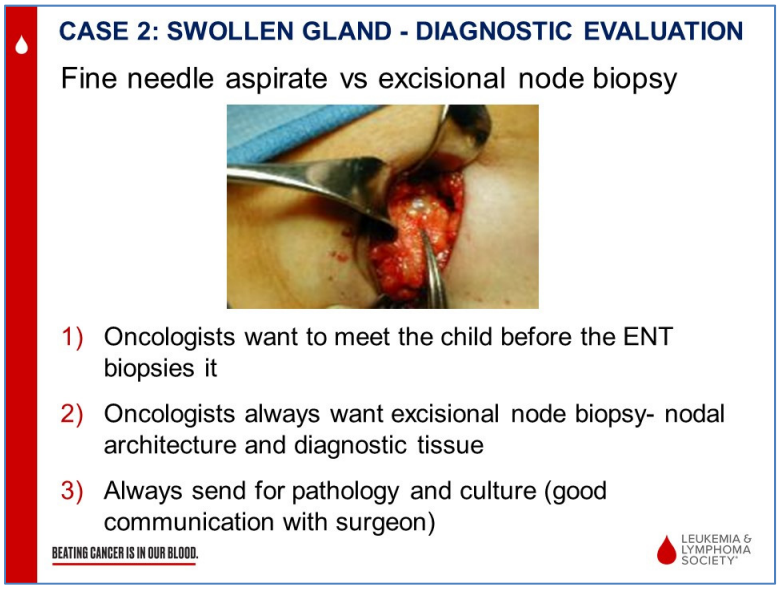


And we kind of talked about some of the things we see done as an outpatient. Certainly, the CBC, doing an LDH and a uric acid if you're worried about lymphoma because they'll be elevated, a sed rate. A sed rate can be elevated because of infection, but a sed rate is a marker for Hodgkin's lymphoma. And then certainly other titers like EBV and cat scratch, which are probably the second most common things that we send children home from our oncology clinic when we're asked to do a second check.

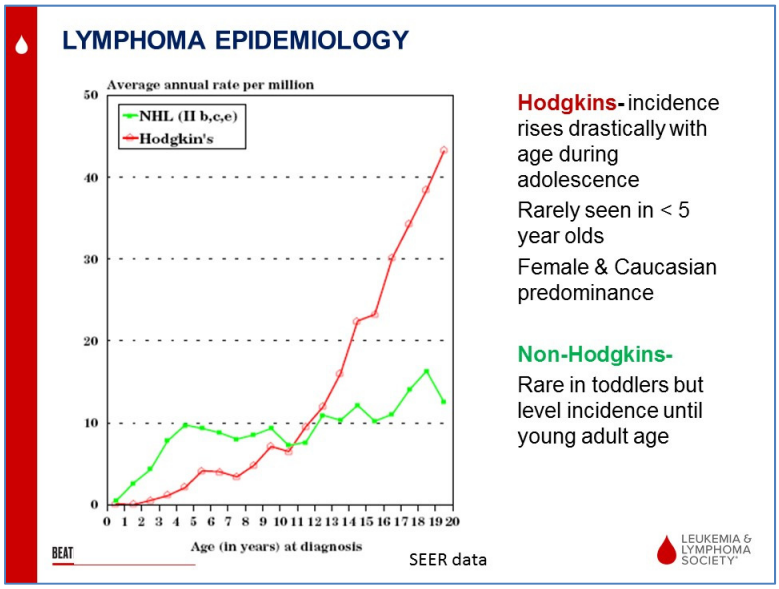
The other thing I always worry about, especially if there's any respiratory symptoms, is I always want to get a chest X-ray. If I have a child who's been referred to me here, then I'm going to get a chest X-ray to make sure the child doesn't have a mediastinal mass because that is someone who I can't send home. I can't let that child leave my office. If the child at your office has respiratory symptoms, well then, they need a chest X-ray. If they don't have any respiratory symptoms and they're more benign, then I don't think it's mandated to send every child.

If I'm concerned, I am going to begin to look for nodes everywhere. So I know it's on the neck, but if I'm putting him in the scanner here because I'm concerned, I am going to check the chest, the abdomen, and the pelvis, other places there can be nodes and areas of staging which we can also use the more modern PET (positron emission tomography) scanners or PET/CTs (computerized tomography) or MRIs (magnetic resonance imaging).

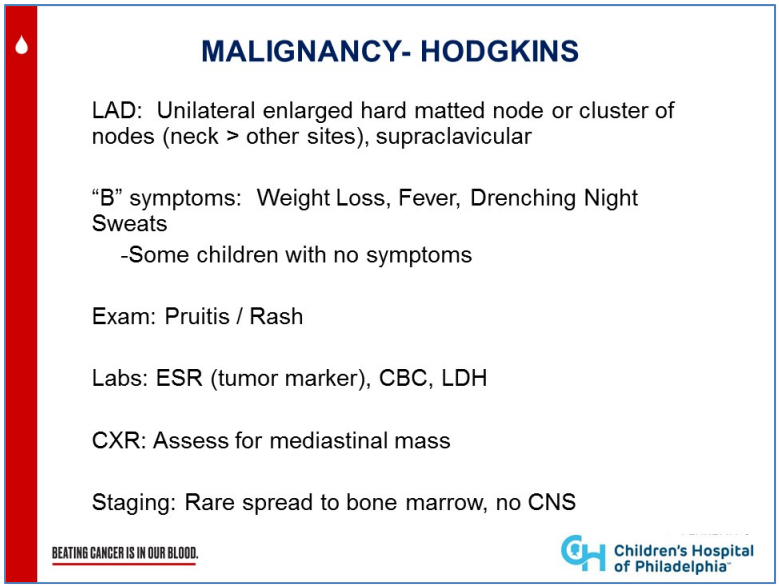
TRANSCRIPT



Lots of times we do have children who are first sent to an ENT (ear, nose & throat provider). So, you agree, you think the node's a little bit abnormal, you don't like, it, you've kind of been following it, and the child gets referred to an ENT. As oncologists, we would love to meet the child before the ENT biopsies it. And there's a couple of reasons for that. ENTs like doing what are called fine needle aspirates, but fine needle aspirates are really hard to look at the full architecture of the node and to get enough diagnostic tissue for us to send all the stuff off like I was talking about like genetics, some of the molecular biology of it. And so very often we then have to actually repeat an excisional node biopsy here. If an ENT on the outside does an excisional node biopsy, that usually is fine. We get enough tissue for that. And, of course, in communicating with the surgeon, you always want it sent for pathology. And if infection, like granuloma or something, is in your differential, you want to include that.



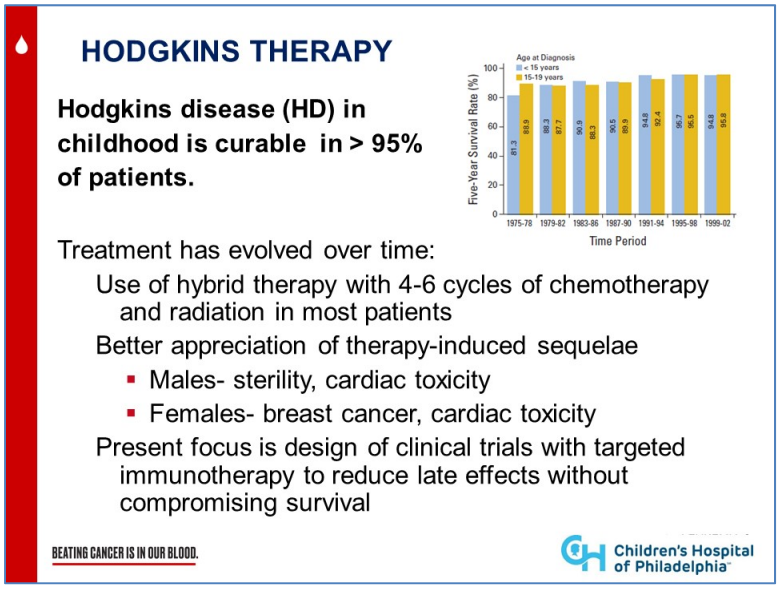
And I'll talk a little bit about lymphoma. There's two types. Lymphoma falls into two groups, Hodgkin's and non-Hodgkin's. As you can see, Hodgkin's is fleetingly rare. Seeing a child with Hodgkin's lymphoma less than five is notable. And as an oncologist, you might see one of them. It really is more of a double-digit teenager type diagnosis, and it is more common in females and white children. Non-Hodgkin's is also rare in toddlers, but as you can see by the green line, it has a pretty steady incidence across the age categories and will increase, of course, in adulthood.



What makes us concerned about Hodgkin's is it's usually unilateral in large hard-matted nodes and the supraclavicular nodes. The B symptoms, which is the weight loss, the fever, the drenching night sweats that are occurring night after night and the parents are changing the sheets are concerning,

and those do go along with Hodgkin's. Some children, though, will not have any of those symptoms; probably more than half of them.

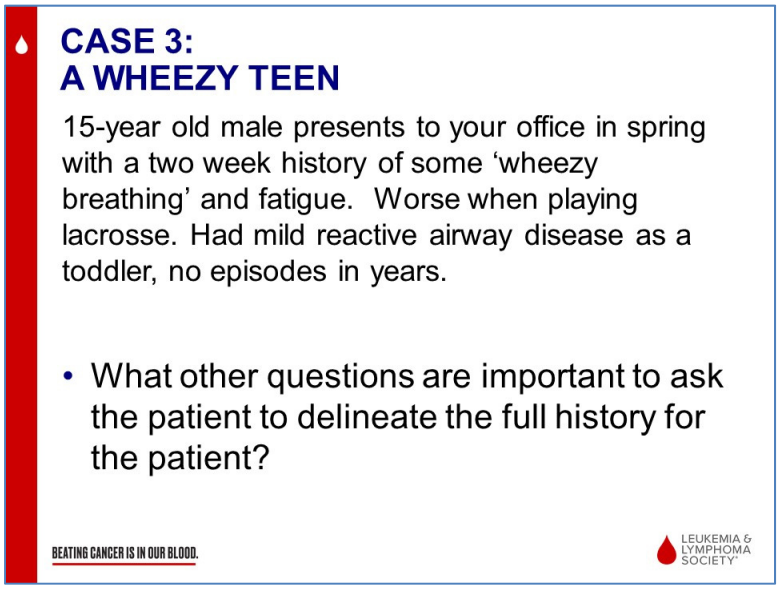
Another weird presentation is itching. We've had children who just are itchy for three weeks prior to their diagnosis. It's probably, you know, something being released by the Hodgkin's, but we'll have children who have excoriated scratched rashes on their legs.



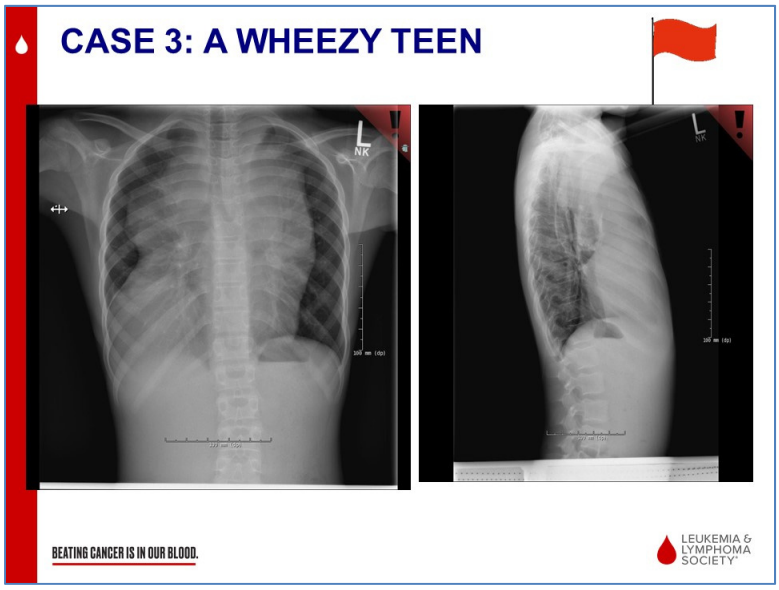
Hodgkin's is extremely curable. We cure greater than 95% of the children. And, in fact, if you look back at the graph there, we have done a good job in all age categories for decades now. Treatment has evolved. We kind of have the hybrid treatment with four to six cycles of chemotherapy and most patients will receive radiation. In this day and age, if your Hodgkin's completely disappears with a little bit of chemo, great. If it doesn't disappear with a little bit of chemo, radiation is what cured it back in the '60s and we'll still use it, although we use it in a much more isolated location. We have proton beams. We have all these new techniques in radiation. So, you don't just shoot it at the upper chest. You actually try to shoot it right at the field the Hodgkin's was in.

And we know that there are a lot of long-term effects that these children with Hodgkin's have to be followed for from sterility, to lung toxicity, to cardiac toxicity, especially if their lungs or their chest was in the radiated field. For females, breast cancer is a risk. So, Hodgkin's recipients who received radiation as teenage girls absolutely are monitored early and get mammograms at an earlier age than a typical woman.

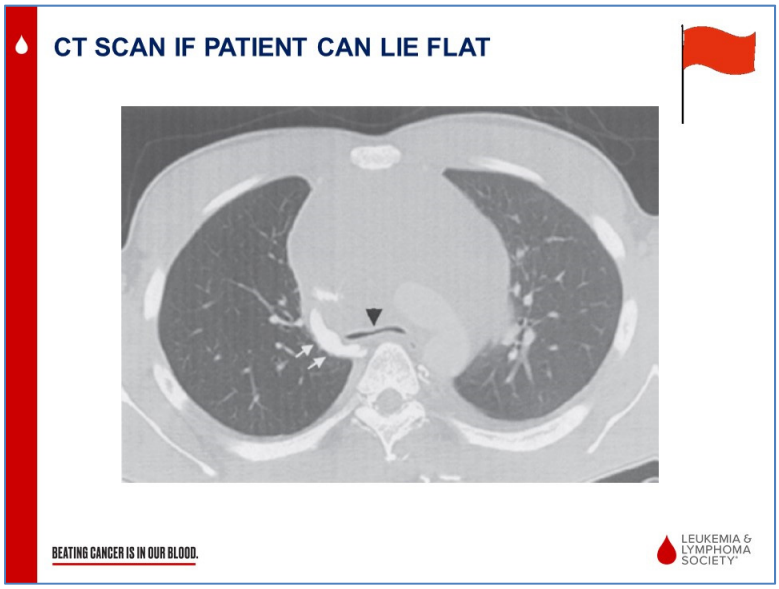
Luckily, our present focus, due to the highly curative rate here, is we're trying to design clinical trials with targeted immune therapy to kind of reduce the late effects without compromising survival in these patients.



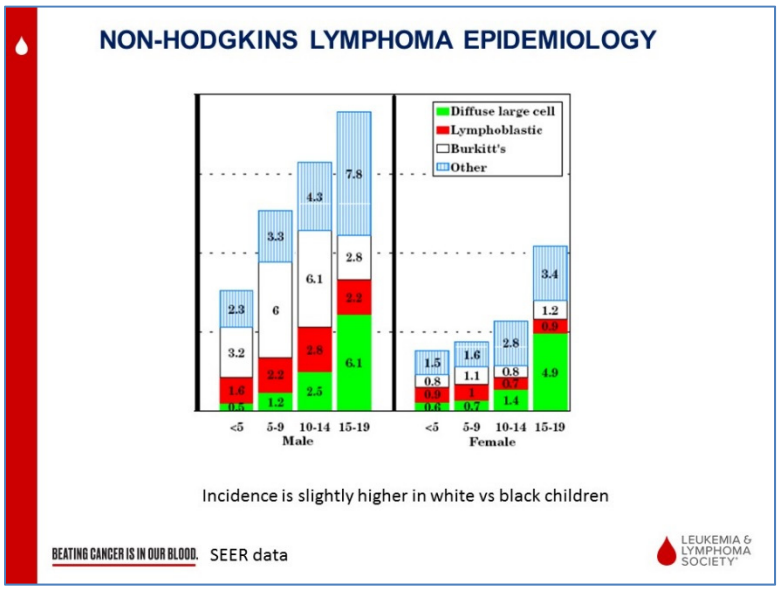
The same patient that we just talked about could also conceivably show up with some wheezing, trouble breathing, airway issues.



The person who shows up in the office, has the respiratory symptoms, and you do get a chest X-ray, or we get a chest X-ray here, and the child has a huge mediastinal mass.

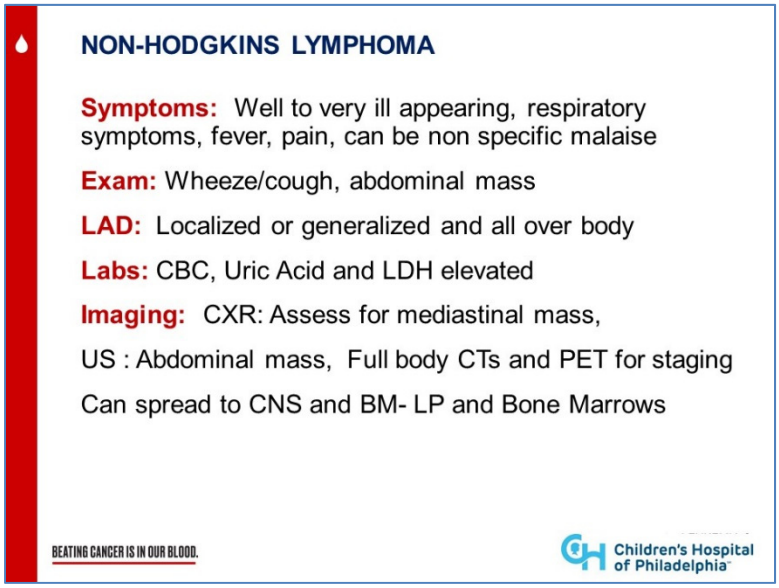


And kind of the concern with this is that black arrow was pointing to this child's airway, and it's why a lot of these children won't even lie flat. They're sleeping on pillows which Brad would've told you was an important thing to test. And this is a medical emergency. These children need to get to medical attention immediately because if they arrest on the outside, the chances of them surviving are small. And even the best of these cases like this with an airway like that, they go to our ORs, if they even go to our ORs, to try to get a piece of tissue with an ECMO (extracorporeal membrane oxygenation) team on call, with anesthesiologists, multiple anesthesiologists in the room. So, this is something you want to make sure is dealt with at a large tertiary pediatric care center.

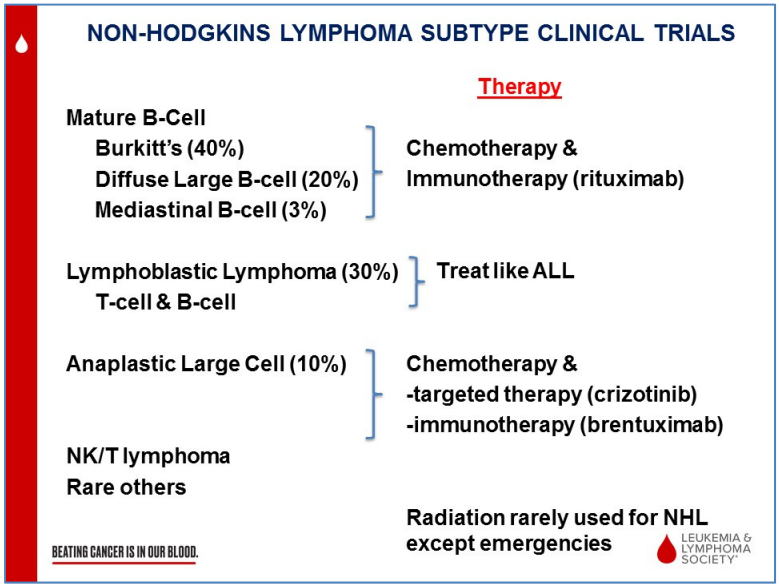


And I'll just end on the whole other group that causes neck nodes and mediastinal masses, which is the non-Hodgkin's lymphomas. More common in male patients than female patients. Again, more

common in white than black children. And the type, diffuse large B-cell, lymphoblastic, Burkitt's will differ by what the age is of a patient, although many of them can present in very similar ways and very similar to the kind of symptoms that a child with Hodgkin's might show up with.



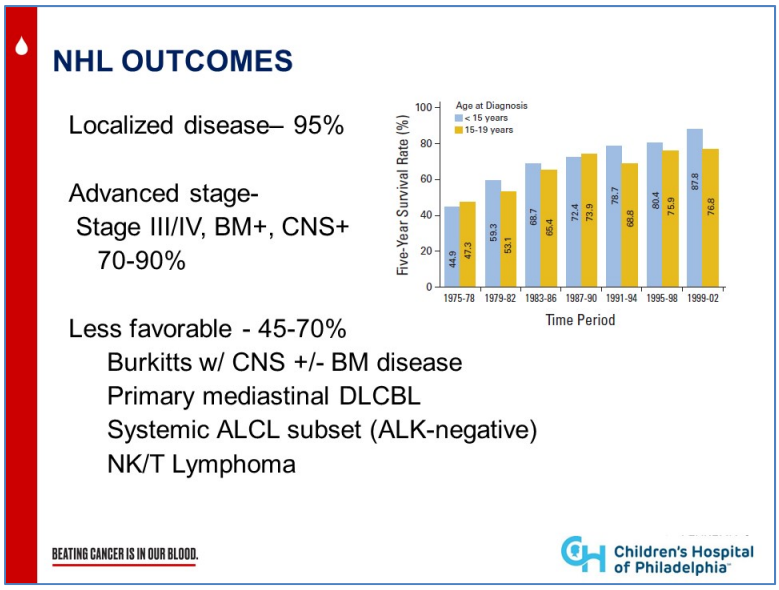
We don't see the B symptoms here. These children can be extremely well-appearing and just got the chest X-ray because they fell, and someone thought they fractured a rib, and the mass was there. Or they can be extremely ill. They can be getting worse and worse from a wheezing perspective and people have been thinking they're just having asthma attacks, so that kind of falls through.



We break it down as oncologists into a mature B-cell, Burkitt's, diffuse large B-cell and mediastinal B-cell, and these children in this day and age tend to get chemotherapy and immunotherapy, which is

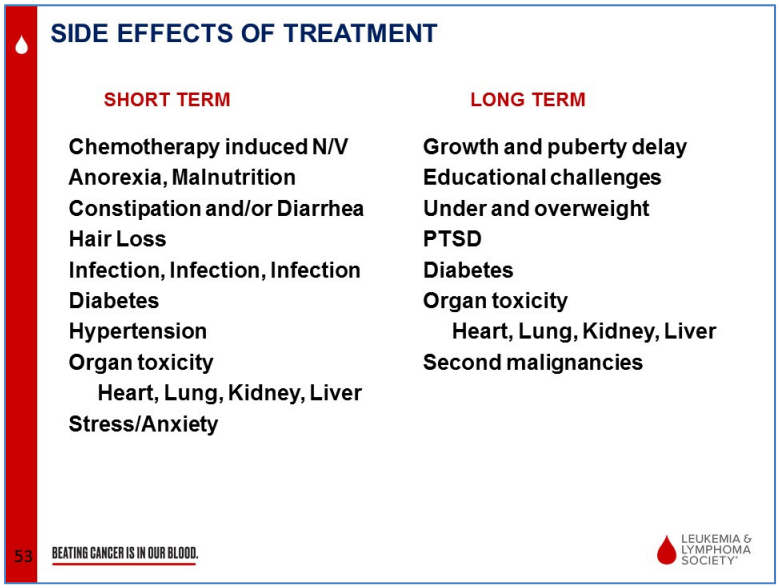
great because, again, when we can subtract chemotherapy and use some of our target immune therapy, we are probably going to have less long-term effects.

There's lymphoblastic lymphoma, which looks just like ALL, and we treat it like ALL. Very rare is anaplastic large cell lymphoma (ALCL), which, again, we're using both with chemotherapy-targeted therapy with agents targeted to an abnormality and immune therapy. And then we talk about a lot of other more rare types.



Cure rates will differ. Again, for the most part, localized non-Hodgkin's lymphoma is very curable, but when you get into advanced stage where it might have spread to the bone marrow or the spinal fluid, be masses in the chest and the abdomen, your cure rates are probably going to go down some. And then we do have some subgroups that always make us want to push to the next level and use these new immune therapies because we consider their cure rates not nearly as good as patients with ALL and Hodgkin's therapy.

Susan Rheingold, MD



So short-term side effects are certainly the chemo-induced nausea and vomiting, which can lead to anorexia and malnutrition. And we have nutritionists on board to help us with these patients. We have placed G-tubes (gastric), NGs (nasogastric) to just be able to feed these children. Constipation and/or diarrhea, we get both depending upon the chemo being used. As you know, all patients do lose their hair with chemo. Infection, infection, infection – there's no such thing as a benign fever anymore in these patients.

Less commonly, we do have children where things like high-dose steroids end up uncovering a diabetes. Some of these children will need insulin even after they come off therapy. High blood pressure while they're getting their therapy and they can be on high blood pressure meds. Organ toxicity so, you know, we know that the heart, lungs, kidneys, livers aren't quite the 100% they were before the child started the therapy so that has to be monitored and will be monitored with all our long-term follow-up visits. And, of course, short term, there's a lot of stress and anxiety. Many teenagers and many children these days come to us already with a history of anxiety and this just, of course, is going to intensify it.

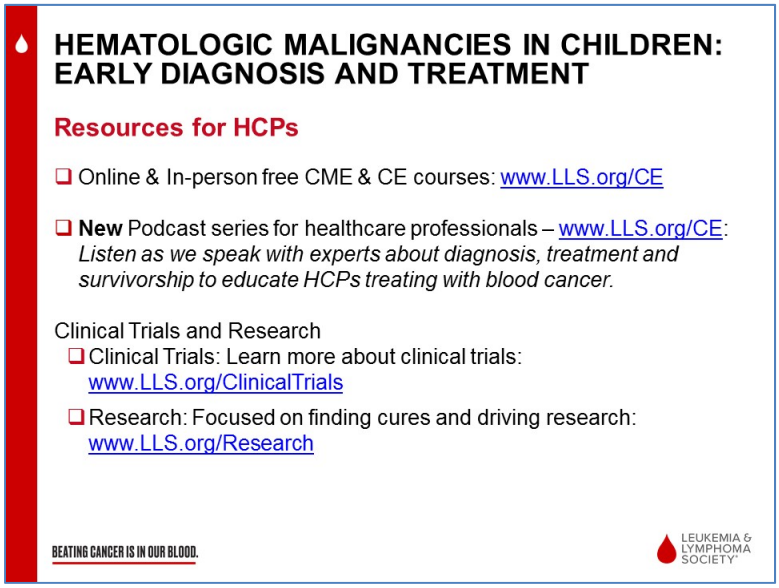
Long-term things that the general pediatrician is going to have to watch for is kind of growth and puberty delay. We do occasionally start children on growth hormone far out from their therapy. Educational challenges can be big. To prevent it from coming back in the spinal fluid, these kids get a lot of intrathecal chemotherapy and some get radiation, and there's no question that has effect on things like IQ and executive functioning.

In the long term, some of these patients are underweight, but some of these patients are overweight, and we do deal with kind of metabolic syndrome in these patients in part probably due to all the steroids they were exposed to, posttraumatic stress disorder is part of that anxiety. Things that might trigger a child, like somebody is coming at them to place an IV and it might trigger a child's, the

memories from what happened. And certainly, organ toxicity and second malignancies are all things we have to watch for.

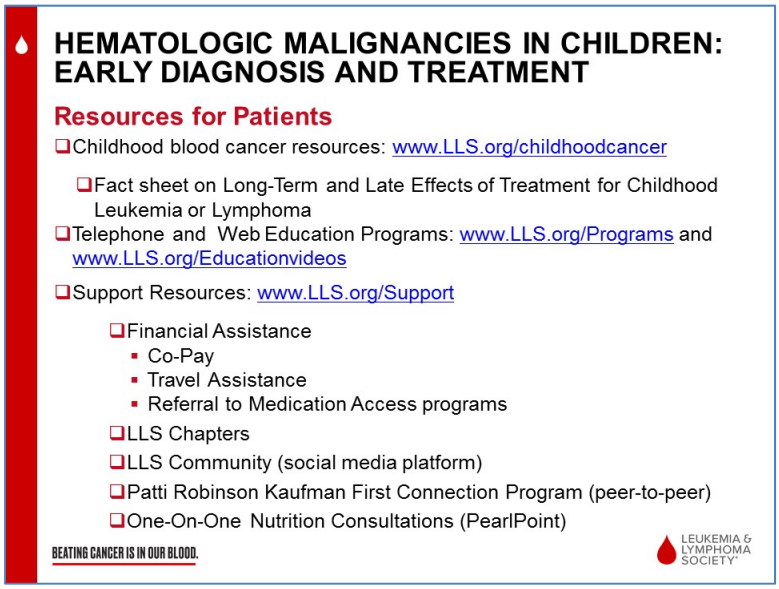
Valarie Leishman, RN, BSN, MBA

Thank you, Dr. Dyer and Dr. Rheingold for a very informative and comprehensive presentation. That was just fantastic. We really appreciate that.

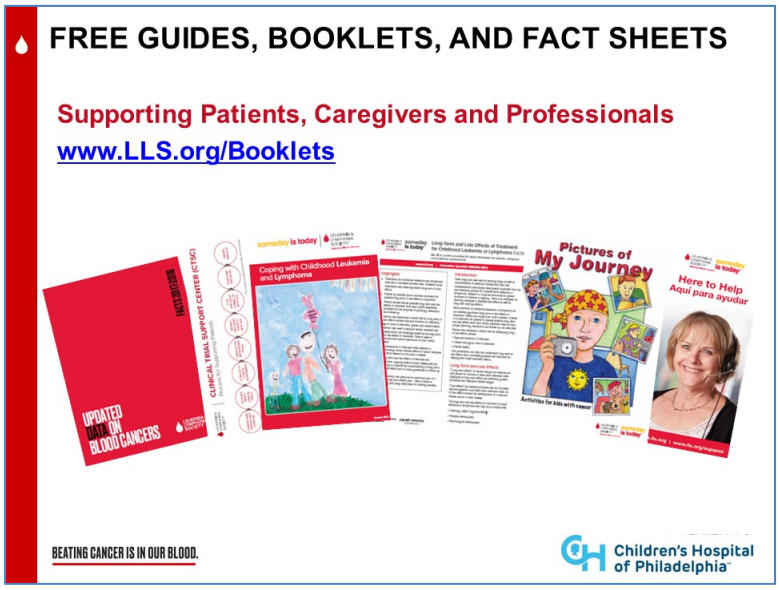


I am now pleased to share with the audience free resources for you and your patients. Visit The Leukemia & Lymphoma Society website to access web-based and in-person programs offering free CME and CE credit, our new podcast series for healthcare professionals, and also information on research.

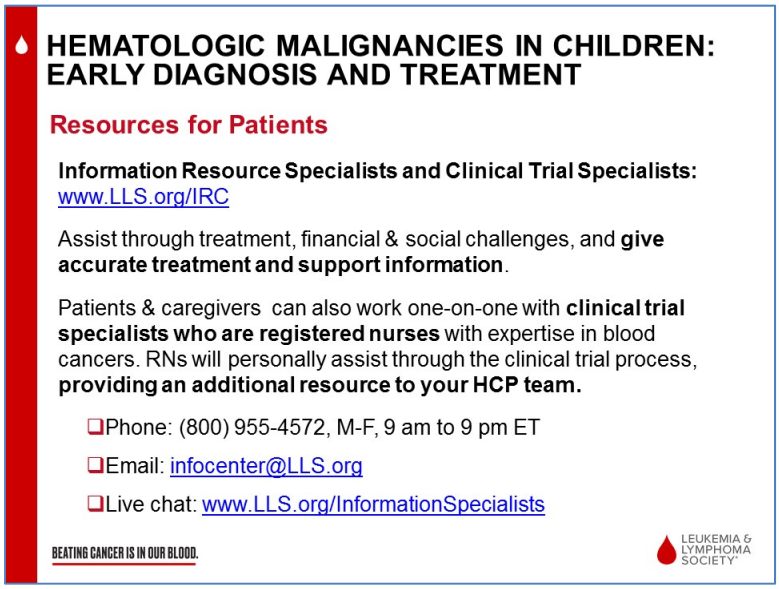
TRANSCRIPT



LLS offers childhood and other blood cancer disease-specific information, including booklets, telephone, Web education programs, videos, and podcasts for patients and their caregivers.

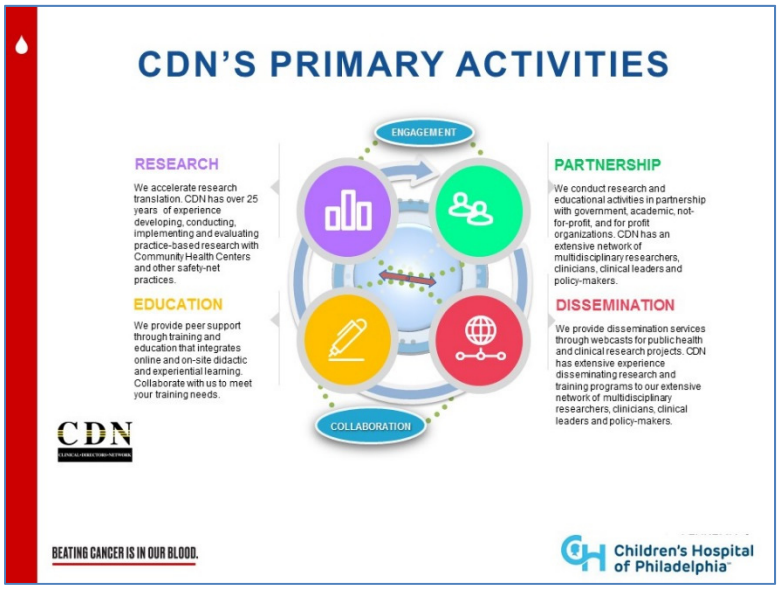


You can order booklets from LLS at no charge to give to your patients, or they can access these resources directly from LLS.



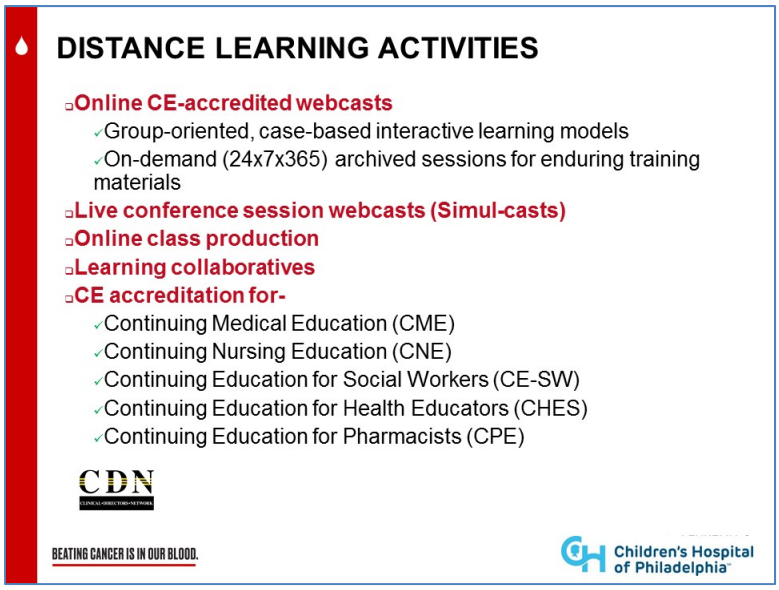
LLS information specialists who are oncology social workers, nurses, and health educators provide patients and their caregivers with personalized assistance for managing treatment decisions and side effects as well as for dealing with financial and psychosocial challenges.

All of these specialists, as well as booklets and online programs for patients and healthcare professionals, can serve as additional resources to you and your healthcare team. To refer your patients to LLS, use the contact information on this slide.



Our collaborator on this program, Clinical Directors Network, CDN, is an AHRQ-designated (Agency for Healthcare Research and Quality) Center of Excellence for practice-based research and learning. CDN develops, conducts, implements, and evaluates practice-based research with community health

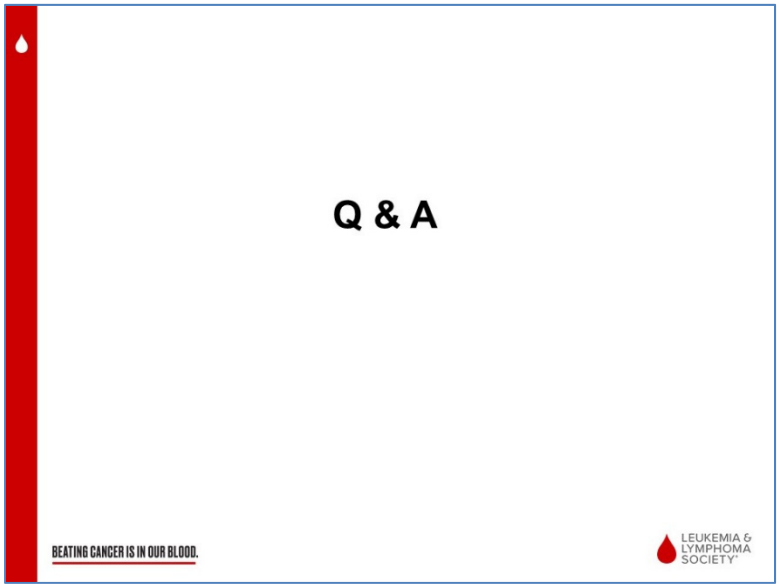
centers and other safety-net practices in partnership with government, academic, not-for-profit, and for-profit organizations.



CDN also provides continuing educational research and quality improvement QI (quality improvement) support to primary care practices and other healthcare professionals through developing and disseminating CME accredited trainings both onsite and online through interactive webcasts. CDN distance learning activities carry continuing education credits for physicians, nurses, social workers, health educators, dentists, and pharmacists.

QUESTION-AND-ANSWER SESSION

Valarie Leishman, RN, BSN, MBA



Again, thank you, Dr. Rheingold and Dr. Dyer for sharing your time and expertise with us today to update us on childhood cancers. It is time for the Q&A portion of our program.

Valarie Leishman, RN, BSN, MBA

Our first question is from Marlia. “I have a question about umbilical cord blood banking. Can you clarify how it is used for blood cancers and how helpful it is?”

Susan Rheingold, MD

That is a very loaded question. So, the odds that we would use cord blood for the patient themselves is almost null. If a child has leukemia, we’ve actually gone back in some cases and found some genetic abnormalities in rare blood cells in their cord blood. So, in fact, if a child’s diagnosed with leukemia or lymphoma, we often request that their cord blood get taken out of the bank and not used.

The very rare situations in where you might use cord blood is for a sibling. So, a sibling’s cord blood is stored, and the stored blood is needed for the sibling with the diagnosis of cancer. That can be used. I think a bigger problem is, is that often if the cord blood was collected 18 years ago and you have a 200 pound 18-year-old, you’re going to need a lot more than that one sample of cord blood, and you’re actually going to go to the source, the sibling itself.

And so, I do not routinely recommend that people go and make sure they bank their cord blood. I do recommend there are some centers that will for free bank cord blood if a sibling already has a diagnosis of cancer. And then it's being banked through different organizations who will help the family pay for it as it is expensive because then there is a chance that would actually be used for the sibling with cancer. That's my opinion. I imagine five different people would have five different opinions on that subject, but it's a good question.

Valarie Leishman, RN, BSN, MBA

Thank you, Dr. Rheingold. We have a follow-up question about vaccinations that you had spoken about earlier. "Can siblings of AML/ALL patients who are on chemotherapy, can their siblings get rotavirus vaccine, MAR, and Varivax?"

Susan Rheingold, MD

We are recommending it now. We often say to the family, "Maybe you can time it when the one patient's going to be in the hospital so if there is some mild shedding." But to us the bigger concern would be, for instance, the patient getting chicken pox. And so, given the likelihood that the chicken pox exposure would come from a sibling, more so from another source, we feel that the risk is greater than the actual risk of the child maybe shedding a little bit when they're vaccinated. So, again, we do now at this point recommend that pretty much all immunizations, typical immunizations for the United States – this certainly doesn't include international travel – should be given to the siblings in a timely fashion; and they can just think a little bit ahead about, well, he's going to be in the hospital for a couple days so why don't we have him, the sibling immunized, so if he sheds for the next two or three days, they're not playing together and all on top of each other?

Valarie Leishman, RN, BSN, MBA

One question from Victoria was "What is your definition of a high percentage of atypical lymphocytes or monocytes?" that you referred to in the beginning of this presentation.

Susan Rheingold, MD

That's a good question. I have seen mono go up to about 30%, but when you're getting up above 30%, I really feel someone has to take a look at it. And other than maybe mono and other kind of more classic infections, if a child doesn't have any symptoms of mono or like histoplasmosis or toxoplasmosis or something, then even a number probably higher than 20% I'd say, "Well, why in world's name does that child have that many atypical lymphocytes? They don't have a fever. They don't have a cold." Brad, I don't know if you have something.

Bradley J. Dyer, MD, FAAP

Yeah. You've got to ask, "So why was I getting a CBC in the first place?" And, "Is it a classic picture of mono for me?" I may feel better when an oncologist or at least a pathologist reviews that slide like what are those atypicals? But, yeah, I would say much above like 18-20% is sort of your radar.

Valarie Leishman, RN, BSN, MBA

Great. Thank you. And following on to the CBC issue, should a CBC be a routine part of a yearly wellness exam for children of every age?

Susan Rheingold, MD

Absolutely not. Four thousand children in the United States a year are diagnosed with leukemia. That's extremely rare. And so, getting CBCs every year from a cancer perspective, no. Getting them from your lead and your anemia perspective, I leave to Brad, but that's certainly not needed yearly.

Bradley J. Dyer, MD, FAAP

Right. So those screenings, obviously, are cost effective and so forth and you pick them up immediately. The other thing about annual screenings for something like leukemia and lymphoma, and, Susan, you can correct me if I'm wrong, you could miss it. I mean they could be getting them every year and two or three months out, they present with their symptoms and so forth and it would give you a false sense of security. But a lot of reasons not to do that.

Susan Rheingold, MD

We also get asked, "Should a sibling, therefore, get a CBC every year?" Or "When one child's diagnosed, should all the other children get looked at?" No, because it's so rare that we see cancer in siblings. There are extremely rare family type syndromes. And now, in fact, those rare syndromes are being picked up when we do the cancer genetic evaluation. So, if the cancer genetic evaluation actually shows us something that says, "This might be partially the cancer but, in fact, there may have been a predisposition genetically in the family," we will let you know, and we'll get you tested for that. But otherwise we do not do any kind of special screening for any siblings based upon a sibling having a cancer diagnosis.

Bradley J. Dyer, MD, FAAP

As the primary care like frontline person, you should have your relationship with the pediatric oncologist/hematologist established well in advance of having children like this come into your office.

And then you know who to call, you know what you're going to do, get that direction and so forth. So, if you don't have somebody already, get them now.

Valarie Leishman, RN, BSN, MBA

Great point. And I'd like to ask one final question of both of you. Dr. Dyer, as the pediatrician or primary care physician, what do you need from the oncologist when the oncologist transfers the patient care back to you? And likewise, Dr. Rheingold, what do you usually provide to the PCP or pediatrician?

Bradley J. Dyer, MD, FAAP

Really, I'm looking for a summary of their, you know, what their diagnosis was, what their treatment was, what their issues are now and expected screenings, where are they in their treatment? Are they presumably cancer-free, but what's the likelihood of a recurrence and so forth? How frequently are we doing screenings? We're not typically part of that screening protocol, but just to sort of know so that I can walk into the visit with the family and feel like I'm at least as informed as they are.

Susan Rheingold, MD

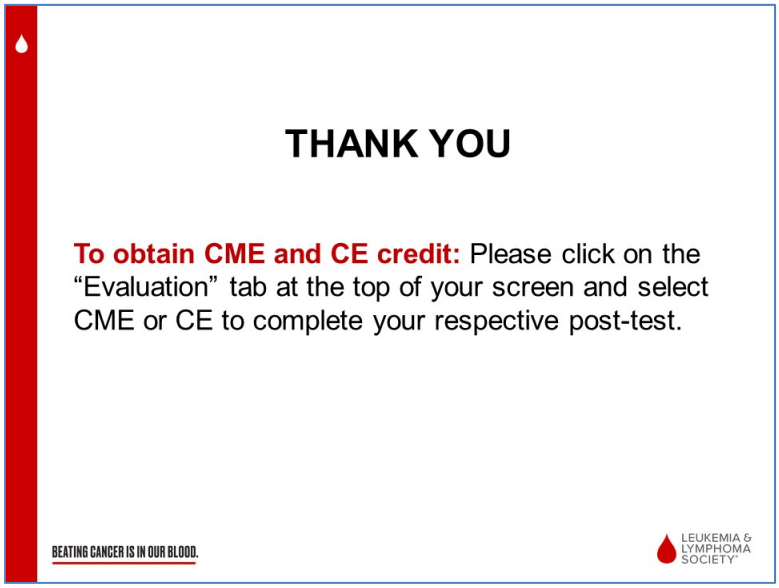
Exactly. And those go in the letters. And then at a certain point out, children do kind of- We have a survivorship program which is even taking on the screening for long-term late effects that, you know, they come in for the day and they might actually see three or four specialists – the heart specialist, the lung specialist, the oncologist when we're no longer worried about the cancer. We're focusing on the issues, what's going on with their thyroid and heart etc.? So, we even will offer that service. Sometimes when children are more remotely located and they're not actually able to get back to the office of, you know, an oncology office, there are national screening guidelines that are available that the pediatrician can get, and the primary oncology center can send. But if they're close to a survivorship type center, the oncology group really does take on all the survivorship screening of late effects.

Valarie Leishman, RN, BSN, MBA

Wonderful. Well, thank you all for your questions, and thank you, Dr. Rheingold and Dr. Dyer, for your continued dedication to patients and fellow healthcare professionals.

CLOSING REMARKS

Valarie Leishman, RN, BSN, MBA



We've come to the end of the symposium, and I'd like to thank everyone for participating. We hope that the information presented today will be useful in your work with patients and families.