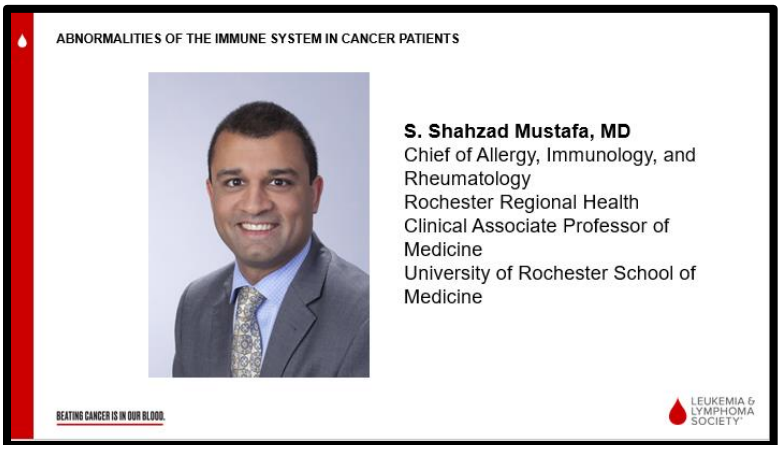
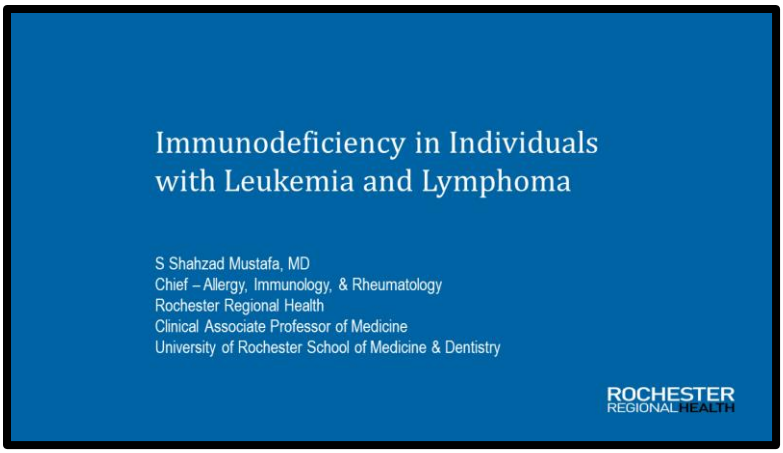
Angela Austin: Hello everyone and welcome to *Abnormalities of the Immune System in Cancer Patients*. My name is Angela Austin, with the Patient and Community Outreach team at The Leukemia & Lymphoma Society, and I will be your moderator today. We will have a Question & Answer session after the presentation, where our speaker will answer questions from the audience.

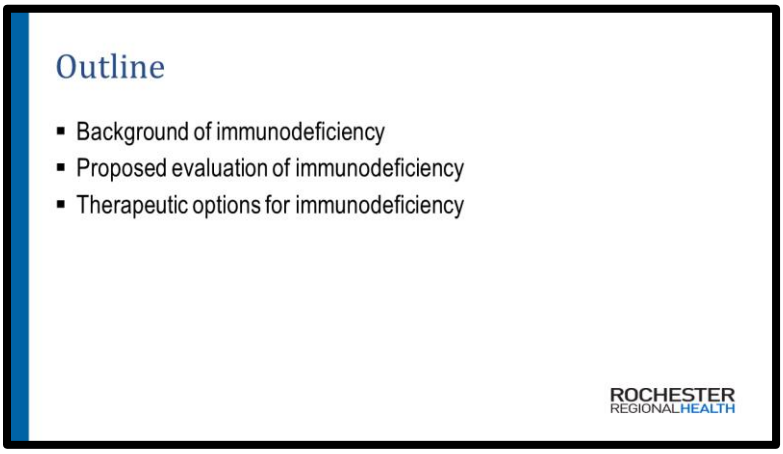


I am now pleased to introduce Dr. Shahzad Mustafa. Dr. Mustafa is the chief of allergy, immunology, and rheumatology at Rochester Regional Health in Rochester, NY, where he sees both pediatric and adult patients. He is also on faculty at the University of Rochester, where he is Clinical Associate Professor of Medicine, and the clerkship director for the medical student elective in allergy and clinical immunology. In addition to teaching and seeing patients, Dr. Mustafa is also a lead investigator on multiple clinical research projects, with a special interest in secondary immunodeficiency due to malignancy and chemotherapeutics.

On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Mustafa I am now privileged to turn the program over to you.

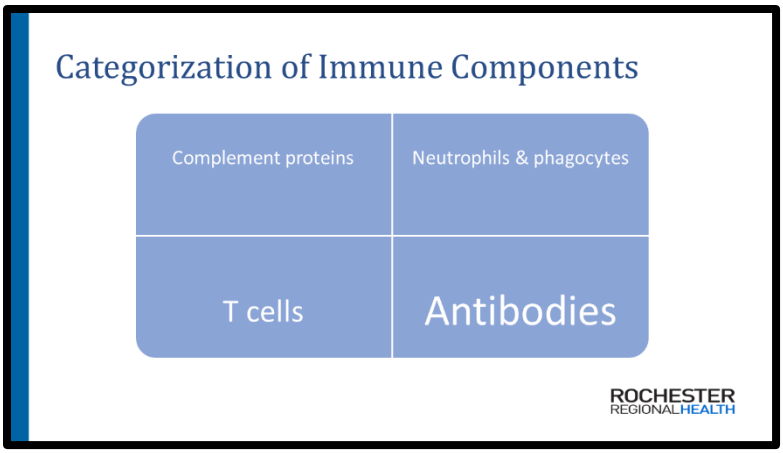


Dr. Shahzad Mustafa: Thank you so much, Angela, for the very, very kind introduction and for having me tonight and for The LLS [The Leukemia & Lymphoma Society] for again in the invitation. And for everyone for joining. I know evenings are busy it's a crazy time, the world is a little upside down so. Thanks for carving some time out. My goal is going to be to make this very, very practical and hopefully answer your questions and we will certainly have time at the end for Q&A. Feel free to put those in through the chat function throughout the talk.



So a little outline, a little roadmap of what we're going to do over the next 45 minutes or so. We're going to talk about some background of immune deficiency, which I think is important to just understand and then a proposed evaluation of immune deficiency. And then some therapeutic options. How can we manage this? This isn't just a talk about, there's actually things we can do.

I think my biggest disclaimer for the talk this evening is, I'm not an oncologist. I'm a clinical immunologist and I, by no means, want to manage you know your primary hematologic malignancy, but I do think clinical immunologists and oncologists can work very well together. So I've tried to give you a highlight of how that may look over the next few minutes.



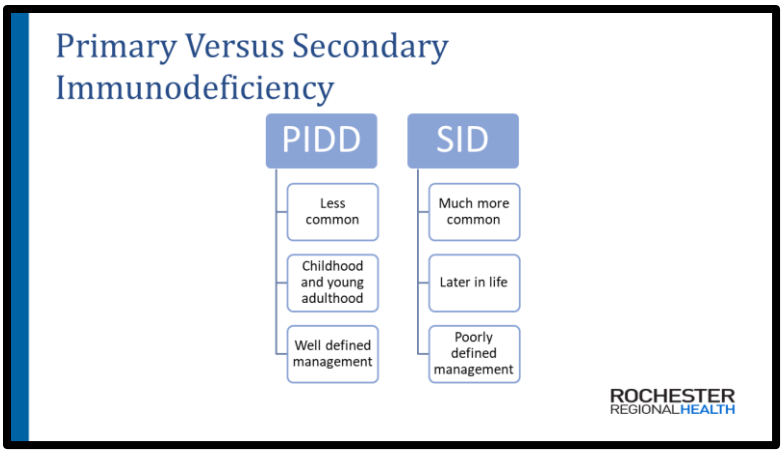
But if we're going to talk about immunity and defects and immune system, we should talk about some immune components and your immune system is very, very complicated with lots of different parts and I'm going to overly simplify it is that's actually how I understand it best.

There's these proteins called compliment proteins, these are proteins that help with innate immunity very early responds to danger signs, alarms. Very, very, very few immune deficiencies are due to complement defects or defects and complement protein, so we see it, we study we don't see a whole lot of it in clinical practice.

Then you have neutrophils and phagocytes which can also lead to defects, particularly things like abscesses and a predisposition to infections often and children. Again, pretty rare we don't see many of these defects and abnormalities in clinical practice. Now we're getting into two of the bigger parts and T cells. So, T cells are very big part of our immune system, particularly in responding to viral antigens We know all about a virus now, COVID.

T cells are a big part of our immune system. Our ability to evaluate T cells is decent, not great. But we certainly see these abnormalities in clinical practice, and then the really the biggest part of the immune system that we spend a lot of time talking about today is our antibodies.

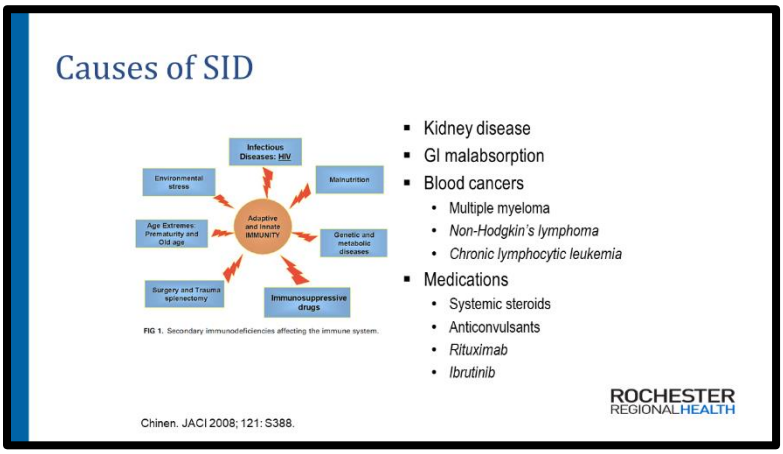
Antibodies work with T cells, they help us viral infections, but certainly bacterial infections. We are very well equipped to study antibodies, measure antibodies, measure levels, measure function. And many individuals with blood cancers, B cell malignancies, have antibody defect and a lot of our therapies lead to antibody defense, so this is really going to be the biggest focus of the talk tonight and that's why I've kind of the font sizes kind of categorize is how you know relevant this is.



So immunologists take care of a lot of conditions called primary immune deficiency. You guys have heard of the “bubble boy” in pediatrics. So you know, severe combined immune deficiency. And then their secondary immune deficiency. So primary immune deficiencies, we study a lot about, but they're pretty uncommon. We only have a handful of patients in our practice with primary immune deficiency.

Secondary immune deficiency is hugely common and there's millions of individuals, just in the US with secondary immune deficiency. So much, much more common. Primary presenting, again many children 2,3,4,5 years of age and then there's a second level of presentation and individuals in their 20s. Which, as I get older 20s is way young, so, young adulthood. Secondary presents much later in life, typically fourth, fifth sixth, seventh decades and because this presents later in life is due to the reasons it presents from and we'll talk about that.

We know a lot about primary immune deficiency, we know a lot about genetic defects, we know how we should evaluate it and likely we treat, alright. Secondary is really poorly defined. We don't know a lot about what causes it, potentially, how do we evaluate for it and how do we treat it. You know, and we don't know a lot and in medicine, we start seeing different people doing different things so that's what I’m going to try to ground this conversation today on a proposed approach to evaluating your immune system in the setting of blood cancers, chemotherapies, things like that.

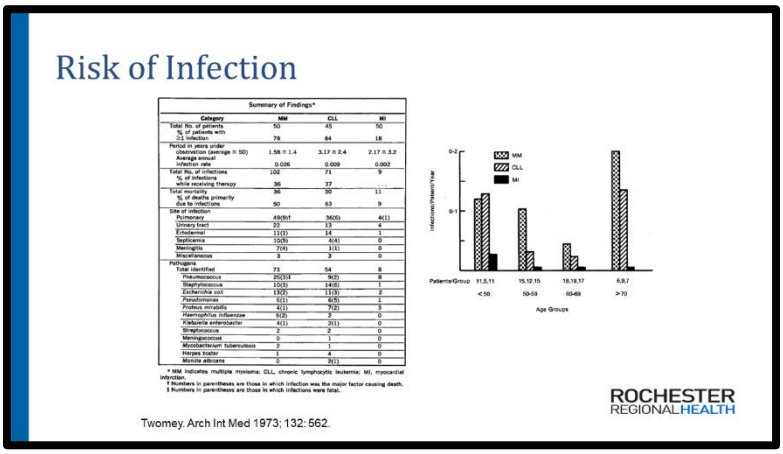


So, again there's been a lot of talk recently about individuals who are immunodeficient or you know people's immune deficiency, and this can rearrange a huge spectrum of children are

immunodeficient. Their immune systems mature over the first few months of life. Elderly, advanced age as we get older into our eighth and ninth decade our immune system actually has some glitches, so we become somewhat immunodeficient.

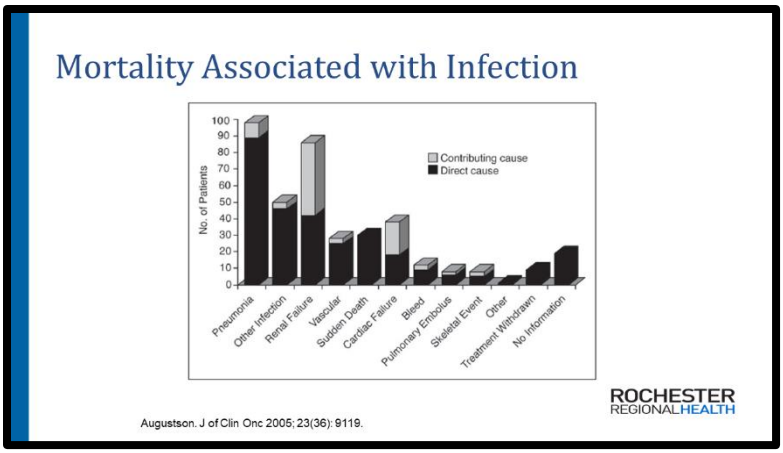
Multiple conditions, diabetes, has mild components of immune deficiency. Certainly malnourishment is a leading cause of immune deficiency in third world countries. Our antibodies are proteins, and if you're malnourished, you can't make protein. So there's a lot of reasons to be immune deficient. We're going to really focus on blood cancers, which unfortunately, I think you guys are familiar with. Myeloma, lymphoma and CLL. And then medications, the most common medication that can mess with the antibody levels is actually prednisone, or steroids. A medicine, many of us have gotten for asthma, croup or poison Ivy.

But we're going to talk about some specific medications used the treatment of blood cancers, particularly B cell defeating agents rituximab and ibrutinib. So lots of reasons for immune deficiency. We're going to really focus in on blood cancers and certain medications.

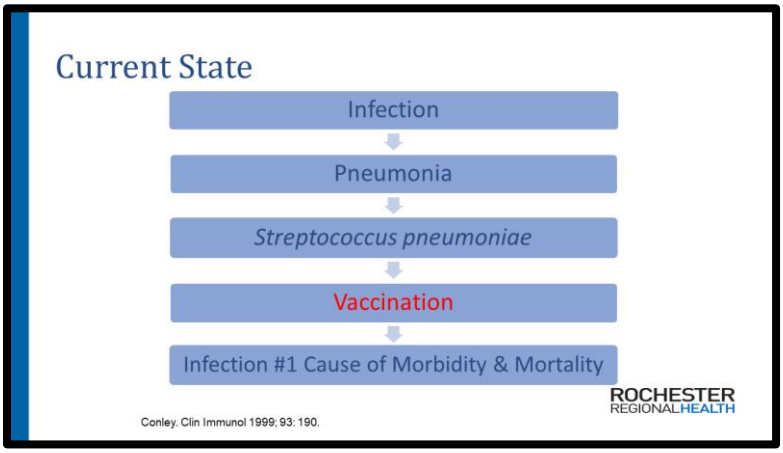


So I don't give many talks where I quote a study from 1973 and there's a point of that, the point is this is not a new thing. We've known this. This table is just a table of individuals with multiple myeloma, CLL, and heart disease, MI, myocardial infarction. About 50 individuals in each group. And what this table shows is the risk of infection in this group alright, so the risk of infection and the amount of infections and people with myeloma is much, much higher. Same with CLL compared to heart disease. So the point here is individuals with myeloma, CLL, lymphoma, have a much higher risk of infection compared to normal controls or their peer group. As you seen pneumonia here, 7354 compared to just 8.

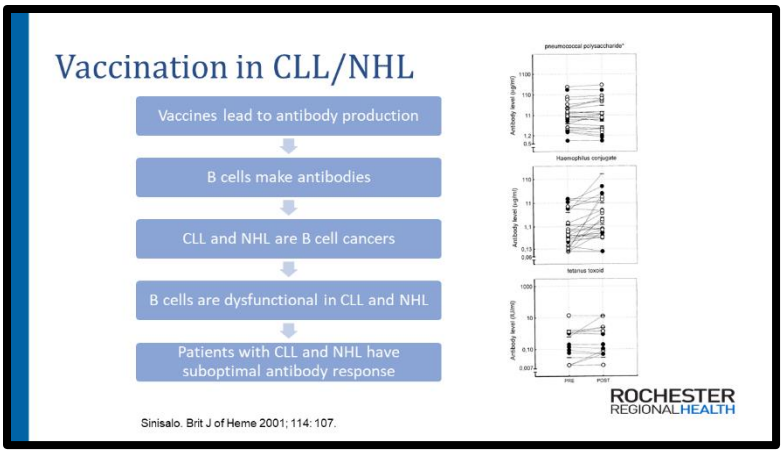
Importantly, as we get older, the risk for infection in this group gets even higher, alright. So under 50, it's much higher than individuals who have heart disease. It's much higher throughout, but it really gets pronounced as we get older over 70.



So, lots of infections, what are the most common? By far and away, the most common infections seen in individuals with blood cancer is sinopulmonary infections. Pneumonia is the most meaningful one, sinusitis is the other one. Lots of upper airway and airway inflammation. So these are very, very common and these can be a significant cause of actually dying from your cancer or certainly complications with your cancer.



So what are we doing about it? We've known this. We've known this for decades that infections remain a leading cause of complications and death in cancer. So we know about infections, we know which one right, we talked about. Pneumonia remains our biggest one. What's the bug? We know the bug also - streptococcus pneumoniae. We have vaccines against this right, maybe you guys ever received her Pneumovax® or your Prevnar®. This is what we are doing to prevent infections in individuals with B cell malignancy. What's happening, though? The number one cause of complications and death in individuals have blood cancer remains infection. Remains infection with pneumonia and strep pneumoniae despite our best efforts of vaccination against pneumonia. So clearly the current state, it's not working. We've got to do better.

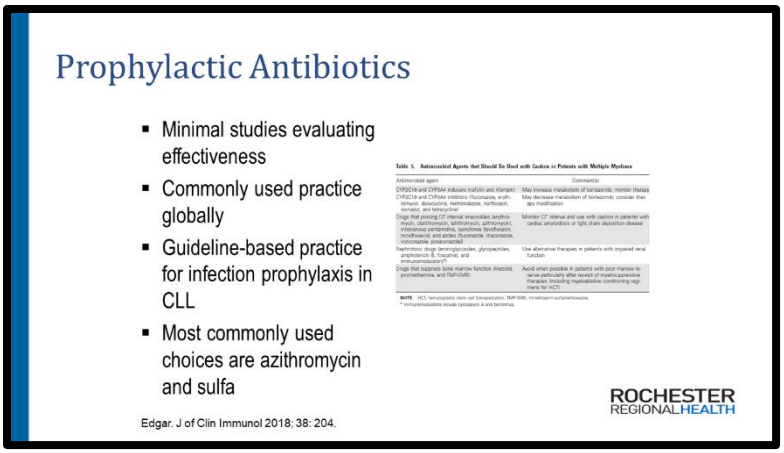


Why isn't it working, it makes sense if we stop and think about it. So what about vaccinations and blood cancers? What of vaccines do? When you get injected with a vaccine, your body builds antibodies. I think we all know a lot more about this today than we did two years ago with COVID. We've heard it constantly on mainstream media right? Antibody levels, antibody levels. The vaccines lead to antibody production.

How do we make antibodies? B cells in our immune system make antibodies, alright. T cells don't really make too many antibodies. B cells are the major part of the immune system, making antibodies. Well, what are CLL and lymphoma, or myeloma? These are actually B cell cancers. The B cells are abnormal, so we're asking abnormal B cells to make antibodies in response to vaccination. And they don't do a very good job of it. Unfortunately this is before COVID, We've known for a long time individuals with blood cancers like CLL, NHL, multiple myeloma, they respond suboptimally to vaccinations. They don't build antibodies like normal controls. This is very, very important.

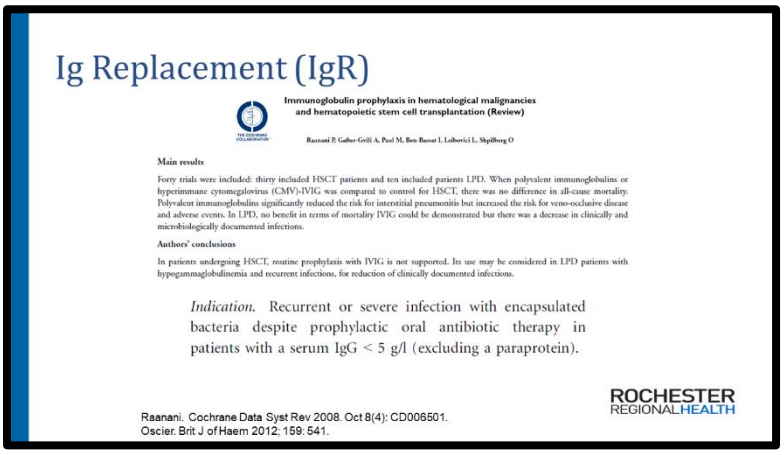
So vaccination, although recommended, and although I absolutely think everyone should be vaccinated for many reasons, which we'll talk about, the response is suboptimal. I'm just going to show you one study. This is a group of about 30 individuals with CLL, who we measured their antibodies to pneumonia here. Okay, this is pre vaccination and then we vaccinated them. Typically, would see these levels shoot up in individuals. they usually quadruple, at least double alright.

Look at this group of individuals with CLL. These levels are the same before and after. They never even like responded to the vaccine. What about for haemophilus, H flu? Some people here in this group of 30 pumped up. That's great, but most stayed pretty similar. Tetanus vaccine right. We all get our tetanus shot every 10 years. We bounce way up in our antibody levels, not individuals in this study was CLL. And unfortunately this study can be duplicated in lymphoma and myeloma and CLL over and over and over again, for years and years. Even this reference is from 20 years ago, so this is nothing new, we've known this for a very long time.



So if our primary means of preventing infection is vaccination but vaccination is not working, what other choices do we have, right? Well lots of people use prophylactic antibiotics, not treating the infection and putting someone on a low dose antibiotic. Maybe, azithromycin, like a Z-Pak, maybe two or three times a week, rather than a higher dose to prevent infection, this is commonly used. In fact, guidelines for CLL say this is usually the first step in individuals with CLL who have evidence of infections or who have evidence of abnormal antibody or immune deficiency. This is often the first step that you start with, prophylactic antibiotics. Azithromycin is commonly used in other individuals maybe Bactrim® or sulfa [sulfamethoxazole]

The problem is the studies about how effective this is are all over the place and they're not great. And we all know that being on antibiotics frequently, even low doses has downsides right. Get antibiotic resistance, you might get side effects. So it's not ideal, and in the world of infectious disease our ID colleagues, or even our immunology allergy crew we don't love the idea of individuals being on antibiotics chronically. But it is an option, it is approach and it's something I certainly use, and it is recommended by guidelines and certain individuals.



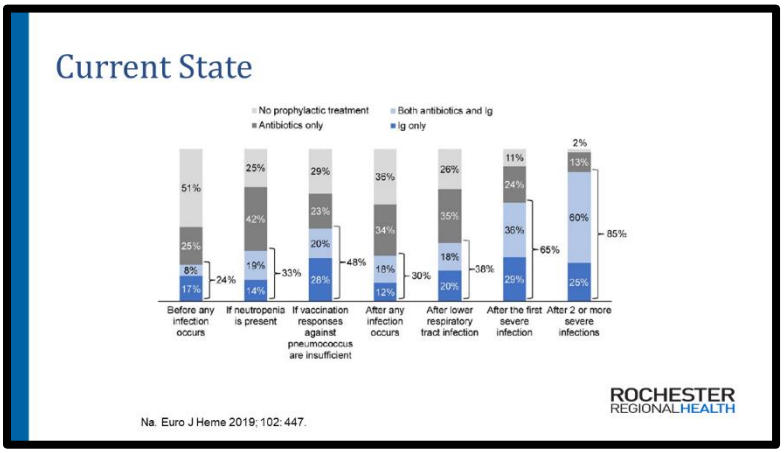
If you're not going to use prophylactic antibiotics and someone is having infections or someone's not making antibodies and have low antibody levels or immune problems, what else can you do? You can give them antibodies. You guys may have heard of immune globulin replacement, IVIg. People say IVIg, but there's other forms of Ig and we'll talk about that.

So, this actually comes from blood donors. Individuals donate blood, we collect their plasma, their plasma has antibodies in it, we refine it put it together and then give it to individuals. Just

like blood transfusions, this is instead antibodies only. So, there's all these guidelines on when and when not to use immune globulin replacement and individuals have blood cancer and the key here is certainly, if you're having recurring or severe infection and you're if your antibodies are low.

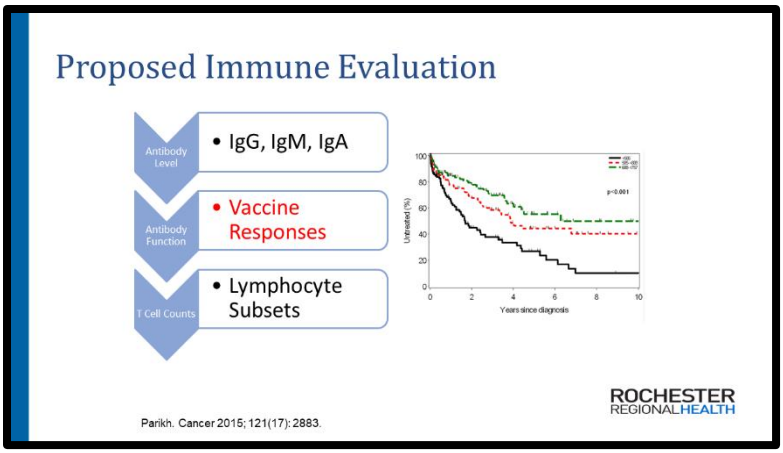
But I'm going to show you in the next few slides through a couple of studies we've actually done, the number of your end of it is not always the most important thing, and this recommendation is based on the number. What we care about is the function of your antibodies right. Think about it this way, if you have a big army, a huge army, but it's lazy, that doesn't do you any good. Conversely, you could have a small army, but it's great. I'd rather have a small army that's great than a big army that's lazy.

So the number is just telling you the size of the army. What we really want is function, alright, and we're going to talk about how to do that. And this, I will say, working with closely with my hematology colleagues, is something very different in the hematology world versus the immunology rather than this is why I think we should work together.



This is just a study that shows over Europe US, Canada, multiple regions globally, what are people doing? Some people are doing no treatment prophylactically, proactively, some people are doing a lot of antibiotics. Look at the gray, there's a lot antibiotic use proactively. Some are doing immune globulin; they're giving the blood products right. The blue. And then some are doing both.

But look at these, like it sounds, it seems like it's all over the place, some are doing it before infections, some are doing it after infection. To the point of this slide is there's a lot of differences and how we're practicing. And it makes me nervous when doctors, taking care of the same conditions are doing it a bunch of different ways, because that means we probably don't really know our way and we're guessing a little bit. So, this is a suboptimal management, a very heterogeneous management for similar conditions.



So, this is very important, this is a proposed immune evaluation, this is what we do for our patients here in Rochester, Rochester Regional Health and U of R. [University of Rochester] We have published data on it, but this is a proposed immune evaluation again, you need to take this back to your primary physician, your hematologist that you work with a clinical immunologist.

I think, checking antibody levels is not controversial and most individuals who have a blood cancer had antibody levels checked. You may be familiar with your IgG level or your IgM or your IgA. That again is the size of your army. It doesn't tell you anything about function. What I really care about is your function of your army and the key here is checking vaccine responses. This is something immunologists have been doing for decades, but it's less commonly done by our hematology oncology colleague.

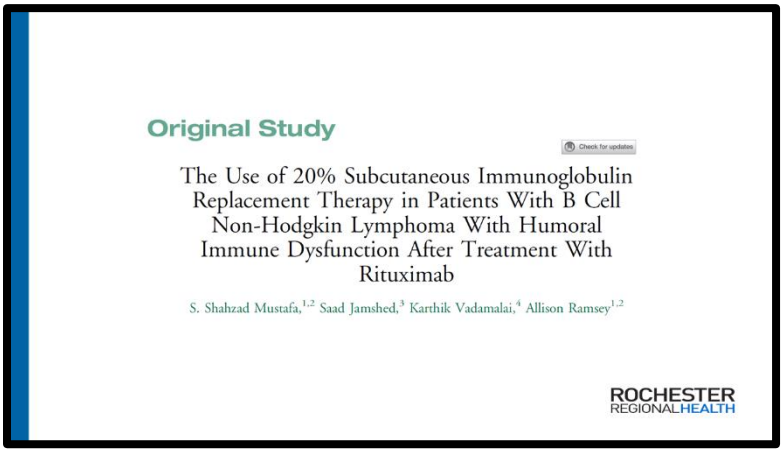
We don't just want the size of your army, but how does it work, so we will actually check your levels against something like pneumonia or tetanus or diphtheria, or meningitis, what have your hepatitis. Then we vaccinate you and then four weeks later, we check your levels again and what they should do is go way up. And that's great it tells us your antibodies are working, if your levels don't go up, but after vaccination that tells me, you have a glitch in your immune system and sometimes you can have very normal levels of antibodies, but they don't work that well.

And then there are T cells and I talked about earlier T cells and B cells work together. They work hand in hand, so we should check what we call lymphocyte subsets. This is something immunologists do, and I think many oncologists do as well. So, the question sometimes comes up from my colleagues is - this individual has CLL or lymphoma they're not having infections, why should I, why should I check all this stuff? Why do I even want to know?

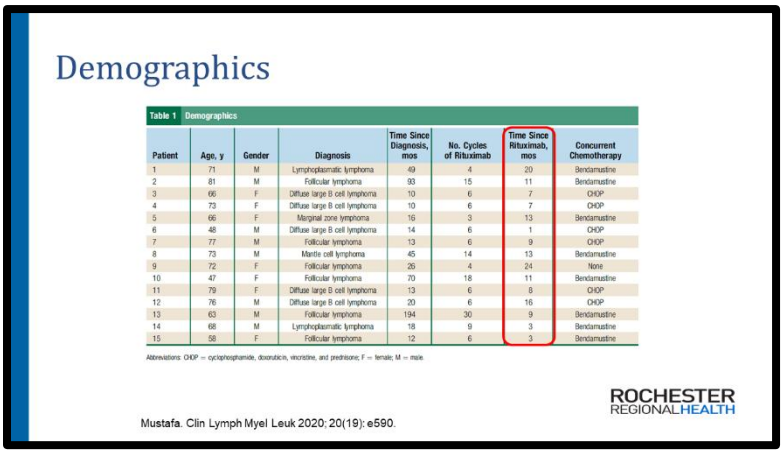
Well, I wanted the one of the reasons is even if someone's not having infections, these levels, these very simple levels that can be completed in any lab. I'm not asking for fancy labs here. These levels are part of helping predict prognosis in CLL and potentially in lymphoma and myeloma as well.

Anytime so when it gets diagnosed with cancer you guys know this better than me usually one of the first questions is what, "hey Doc what's my prognosis?" And these levels will help you predict prognosis this is for IgG. Individuals with CLL at the time of diagnosis, to have lower IgG levels, these lower levels compared to the higher levels tend to do worse and that's a very, very important. I think we shouldn't know that up front. But other than that, we can find out

tremendous information about your immune system, which is ever so important, which we've really, really come to appreciate in this world of COVID which I'm going to certainly touch upon.



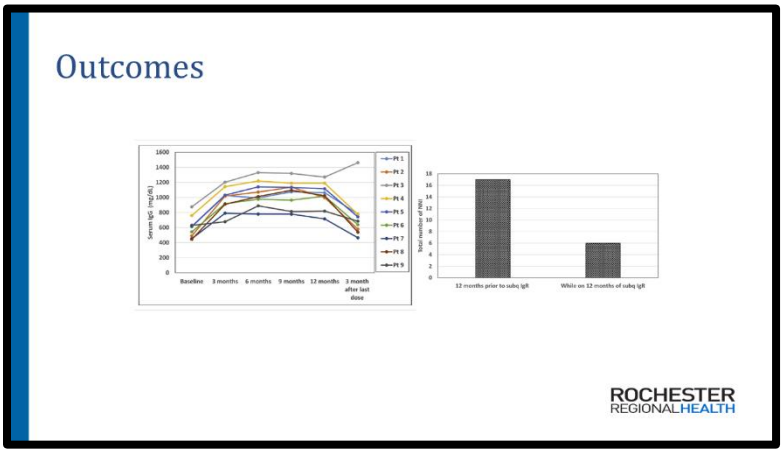
So, I'm going to show you two parallel studies that we did at our center. Very, very small studies. But they are proof of concept studies. I want to get the point across, and they'll hopefully lead to bigger studies. One is using immune globulin in individuals with lymphoma who have been treated with rituximab.



This is just 15 individuals, not a big study. Doing well. Their last cycle of protection, as you see, was anywhere from a month ago to almost two years ago alright, so the distance from their last cycles of rituximab is kind of all over the place. What we show, it is again, these are individual patients looking across the 15 patients right. Look at their IgG level, that's their antibody level right it's pretty good, some people are a little low, 300, 1100 is normal. Anywhere above 700 is normal, so we have some low numbers but they're pretty good. The average is 628, pretty good.

So, these individuals will look for my treated with rituximab. Their antibody levels, not bad at all little, low, nothing crazy, nothing that would catch my attention. There IgM an IgA is actually really good, but check out their function, despite normal levels, when you vaccinate him for diphtheria, check it out, only 20% respond to the vaccine, the rest don't bump their levels at all. Tetanus, one out of 15 of these individuals responded to the vaccine. Pneumonia, out of 15, 3 respond, it's at 20%.

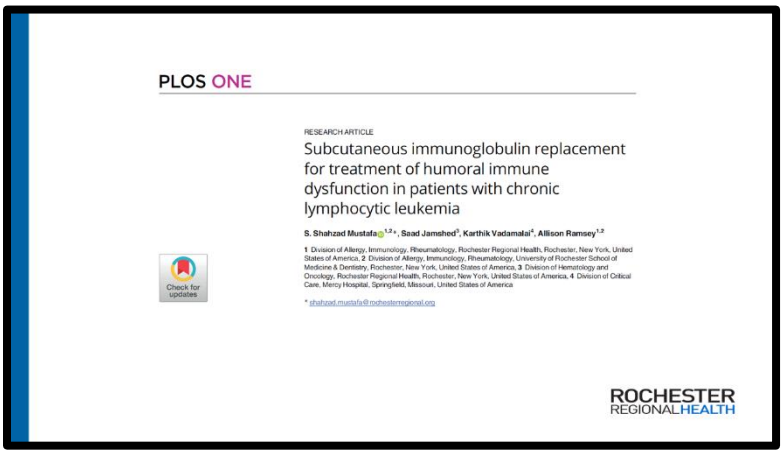
So, the point of this is in individuals who've been treated with rituximab, which is used commonly in oncology and rheumatology and neurology and other conditions for nephrology, your levels of your antibodies may not drop, but your function is really not so great.



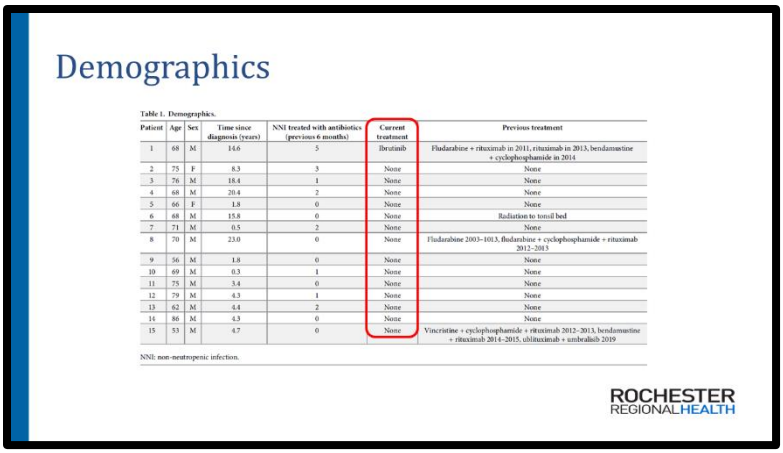
So, what are we doing with these individuals? We gave them immune globulin; we gave them antibody infusion. And not shockingly just in the 10 that I'm showing here, their levels their IgG levels went up. That's not surprising. We did it for a year and then we stopped. And then, most people when you stop came down one individual went up, so what that suggests is that a small percentage of people, as you get further away from your rituximab, your immune system may recover. But unfortunately for most people who are treated the rituximab, your immune system doesn't really recover as quickly as we'd like, six months a year, or even longer probably not so much immune recovery.

Alright, so we found that your immune system was a little sleepy, we gave it and have antibodies and improve the levels. Did that matter? Yeah, it cut down on infections in these 10 individuals. They cut their infections by half.

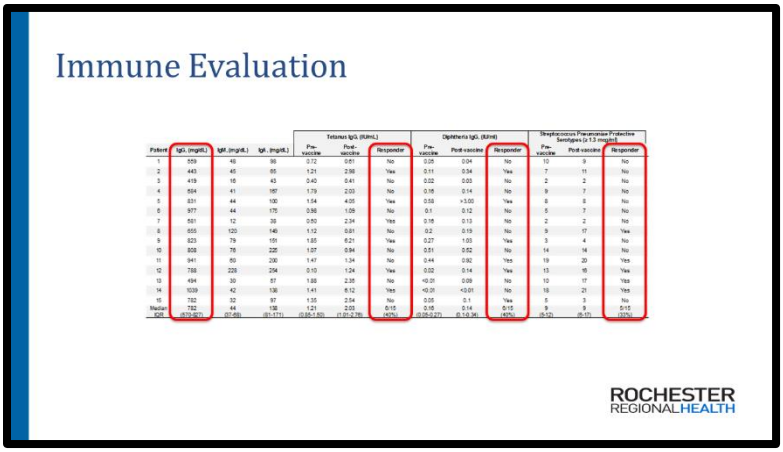
Now again, very small study. I'm not a statistician, but I know this study is not powered to say that this treatment will decrease infections, but just looking at it qualitatively, there's absolutely decrease on antibiotics, due to immune replacement in individuals whose levels are decent, but their function is not so good.



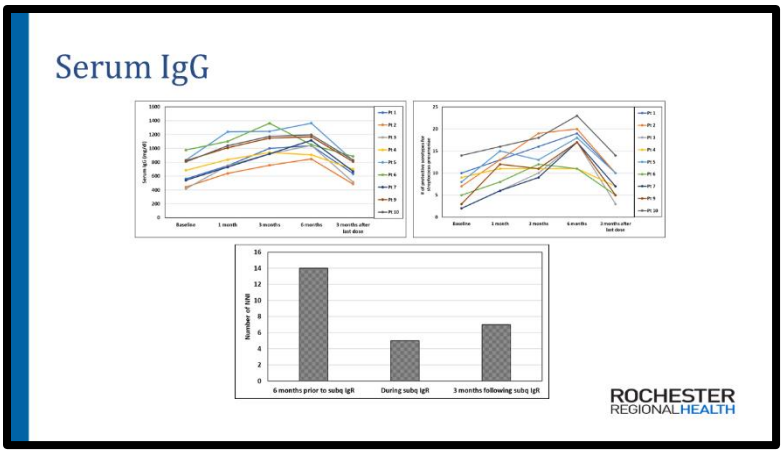
Same exact study in individuals with CLL just published this year in PLS One.



Same concept, 15 individuals, they have CLL. Check it out. This is pretty mild CLL, generally early watch and wait, which I hope many of you are in. Many individuals with CLL are in watch and wait. One individual was on ibrutinib, which is a common therapy. Even at the time of diagnosis for CLL, even watch and wait, many individuals have evidence of immune deficiency.



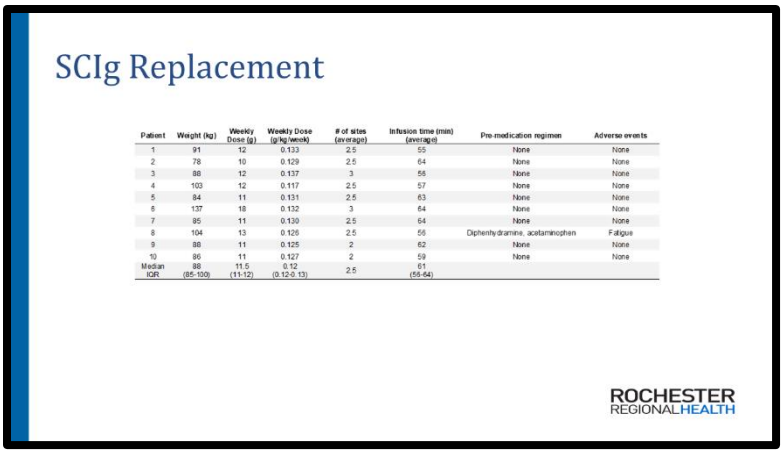
Same exact graph guys. Looks a little different. 15 individuals watch and wait for most. Ibrutinib for one. Their IgG average, 792. That's normal. Pretty normal levels. Did they respond to vaccines? Still not great. Less than half are responding the vaccines, so even in very early mild watch and wait, CLL with normal antibody levels, function's not great.



Same thing here, we did it for six months. We gave these individuals immune globulin. Levels went up just like we think. We're giving it to them, we're giving a diabetic insulin. And we're giving you know blood transfusions into someone who's anemic. Levels go up. We stop it at six months. Three months after levels come right back down. So again, the levels are going up because we're giving it, not because the disease is getting better, or the immune system is recovering on its own.

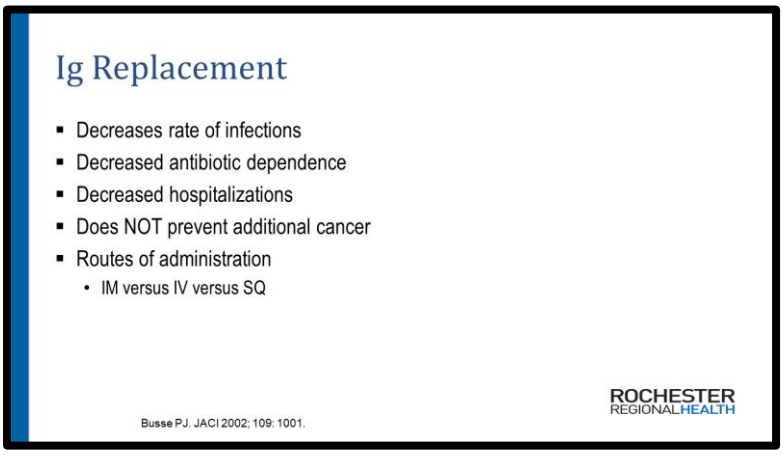
Here we even check levels against specifically pneumonia. And remember, I told you in the beginning, pneumonia is actually the most troublesome infection. So, we really care about your antibodies against pneumonia. Look at low some of these people started. Really low levels came way up with treatment and way down after treatment. So, clearly, we are improving antibody levels in general and, specifically, in this study to pneumonia too.

What happened here? Exact same thing that you saw on the rituximab study. We cut antibiotic reliance in less than half. This is before treatment; this is on treatment and this isn't the three months after treatment. So, antibiotics went down, we stopped treatment and antibiotics start going right back up. If we double this the six months here, it's going to get right back to here. So, again we're evaluating their immune system more than just the level with function. We're treating people proactively who are showing signs of immune deficiency and we're cutting down on antibiotics. This is a suggestion. I am by no means saying individuals who are not having infection should be treated with immune globulin across the board. I'm not saying that. Every individual is CLL, lymphoma, myeloma should not be an immune globulin. But these are proof of concept studies that even in the setting of normal antibody levels, there is dysfunction and there are things we may be able to do to improve outcomes.



Patient	Weight (kg)	Weekly Dose (g)	Weekly Dose (g/kg/week)	# of sites (average)	Infusion time (min) (average)	Pre-medication regimen	Adverse events
1	91	12	0.133	2.5	55	None	None
2	78	10	0.129	2.5	64	None	None
3	88	12	0.137	3	56	None	None
4	103	12	0.117	2.5	57	None	None
5	84	11	0.131	2.5	63	None	None
6	137	18	0.132	3	64	None	None
7	85	11	0.130	2.5	64	None	None
8	104	13	0.126	2.5	56	Diphenhydramine, acetaminophen	Fatigue
9	86	11	0.125	2	62	None	None
10	86	11	0.127	2	59	None	None
Median IQR	88 (85-100)	11.5 (11-12)	0.12 (0.12-0.13)	2.5	61 (56-64)		

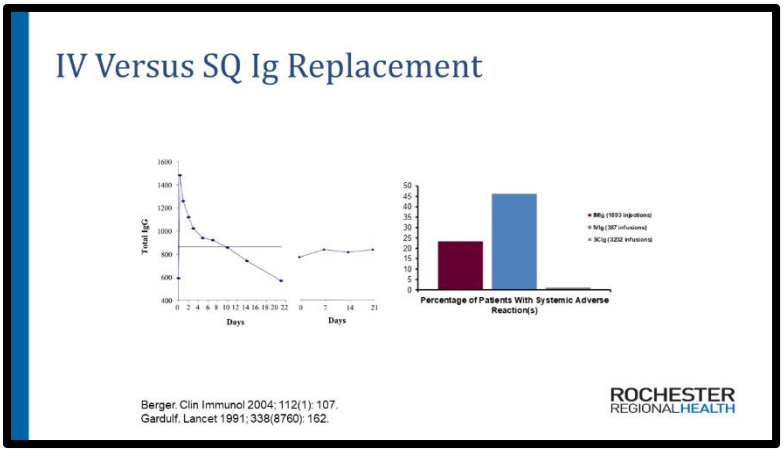
This is an important slide a lot of people are familiar with IVIg and maybe you guys are too, but are less familiar with subcutaneous IG and I'm going to show you some important considerations here.



The immune globulin is just giving someone antibodies right, plasma products. And there's many ways to do it and there's many things it does. It decreases your rate of infections and decreases antibiotic dependence. It decreases your risk of hospitalization. It does not prevent secondary cancers. Secondary cancers are actually a big complication with blood cancers, as well as additional cancer.

Immune globulin replacement does not affect that and there are different routes of administration. Years ago in the 70s, we used to inject it muscularly. It hurt a lot. And so, we don't do that anymore. The vast majority of individuals who get immune globulin, get it IV, intravenously. But I want to raise the awareness of subcutaneous kind of like almost an insulin pump.

So, what does subcutaneous look like? You put the immune globulin; you draw it up from a vial. You put in the syringe, and you put this syringe in this pump. Clean off a part of your skin. You put this tiny little needle it's kind of like an insulin injection. It's got tubing on it. You put this tiny little needle into your adipose tissue, most people do it in the abdomen. You can do it on your side, you can do it in your arm. And put some tape over it, you put the needles in there now you get this little tubing going to your pump. Push the drug in. This infuses it. You can put this in your pocket, you can walk around, you can certainly do it at home. Most individuals do this on their own after their part, it takes two or three times. They do it on their own, they can do it anytime they want at home to get rid of the needle. The deed is done.

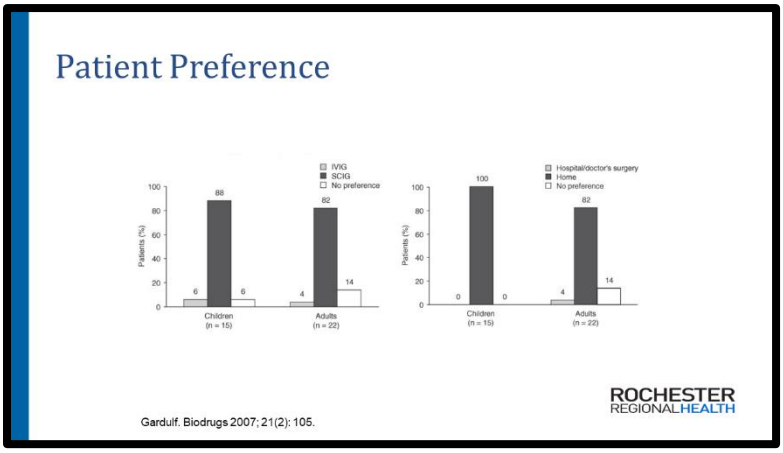


So, what are the differences? So, if you get IVIg, you get a whole slug of drug. And then the levels come down and then you get a whole slug of drugs, so you get the sawtooth pattern. IVIg is typically dosed every three to four weeks. The subcutaneous stuff is hugely affects flexible. You can do it daily, but most people do it once a week or you can do it twice, once every two weeks or even once every four weeks, you can do it. But because of the way it's administered, not into your veins, but into your subcutaneous tissue it's more like a depot of medicine. So, it releases slowly, so you get a much steadier level. You don't get these peaks and valleys that you see with IV, so that's a benefit actually.

This is the biggest reason I think subQ [subcutaneous], is the way to go. We don't do intramuscular, this is the percentage of meaningful side effects, real side effects. You can have infusion reaction, you have anaphylaxis, you can have even like forms of meningitis within IVIg.

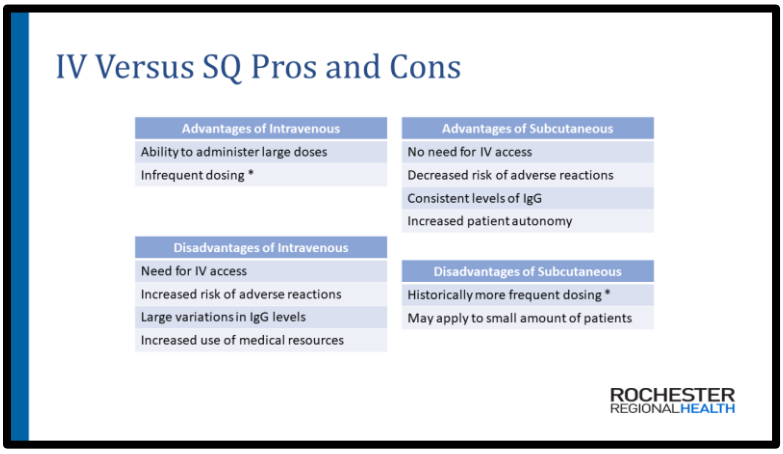
So, we don't do intramuscular. So, we'll take that out, but when you do IVIg, up to 50% of individuals getting the infusions have systemic side effects. Flu like symptoms are common, pains, fevers, people take off of work for the day or two after their IV.

Lots of side effects up to half the time. They can be managed, not a big deal. We do it all the time. But look at through frequency of side effects with the subQ. You can barely see it because it's rare. Sub Q rarely as systemic side effects.



So, again it's not right or wrong, but we need to know that these options exist. I think what's important in 2022 now is asking our patients what they want.

If you ask individuals on immune globulin, “do you prefer Ivy or subQ”, 80% will tell you they prefer subQ, if you've given them the option. Then, if you take a step further, “okay, you want subQ, you want to do it in my office you want to do it at home?” Almost everyone wants to do it at home because they can do it at home it's safe to do at home. It's well tolerated, it gives you patient autonomy. So again, patient preferences very important.

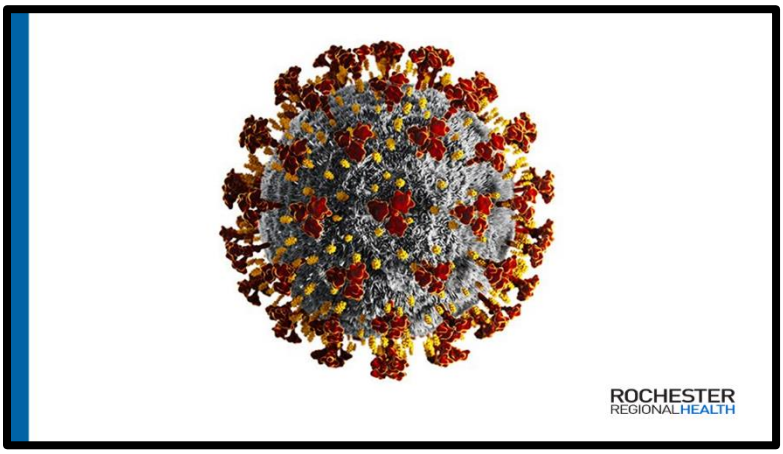


So, there's pros and cons to all of this right. What's IV pros? You can really give a big dose. Typically dosed once a month, so it's in frequent dosing. What's the disadvantages? You need IV access. You need a health care professional unless you're starting your own IV, which you’re not. There's a hugely increased risk of side effects. You get these peaks and valleys in your IgG level, and it requires medical resources, many people get IVIg in an infusion center.

That's never a bad idea, but particularly in the world of covert with social distancing and high-risk exposure, is that's not where you want to be. For subcutaneous, what are the advantages? You don't need IV access; you can self-administer it. It's much better tolerated and levels we talked about is much steadier. Patient autonomy. Individuals can be taught to do this in two to three sessions, it is pretty user friendly.

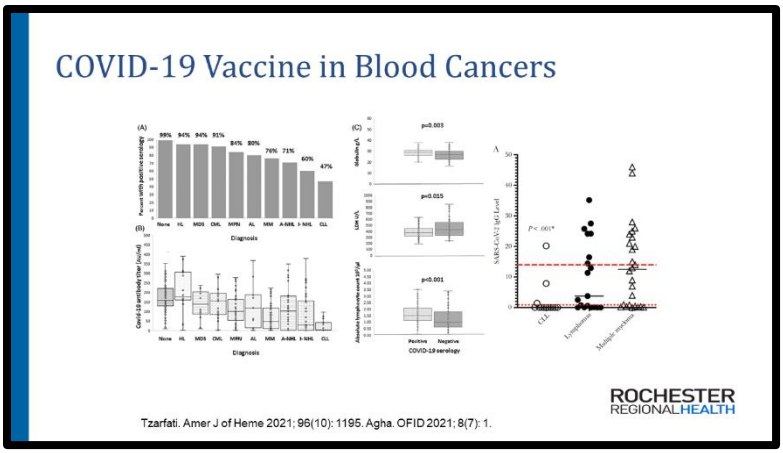
What's the downside? Let’s say historically, it's more frequent dosing rather than once every month. It's usually a weekly, but there are new products that can be those once a month. I will say when you do IV once a month, it's typical time for typical dose is three to four hours. When you do subQ weekly, the typical time is 45 minutes to an hour per week, so the total time it's similar just how you want to break it up.

Subcutaneous doesn't apply to everyone. Some patients may not want to do this. I have some individuals who want to come to our infusion center because our staff is amazing. They prefer that. But again, choices, choices, choices. I think choices are so so important.



That's a little background on thinking about how the immune system works, the components of the immune system, antibodies certainly, evaluating for your immune system, how it works, antibody levels, the antibody function, ways to intervene and individuals who may have immune deficiency, prophylactic antibiotics, immune globulin, ways of giving immune globulin, IV, subQ.

And now we're going to kind of put this into the context, and I wish I could spend an hour giving a talk these days without talking about COVID, but that is just not possible. So, we're going to talk about all of this stuff in the setting of COVID, which certainly impacts every one of us, and particularly our high risk individuals and individuals have blood cancer, they are high risk individuals.



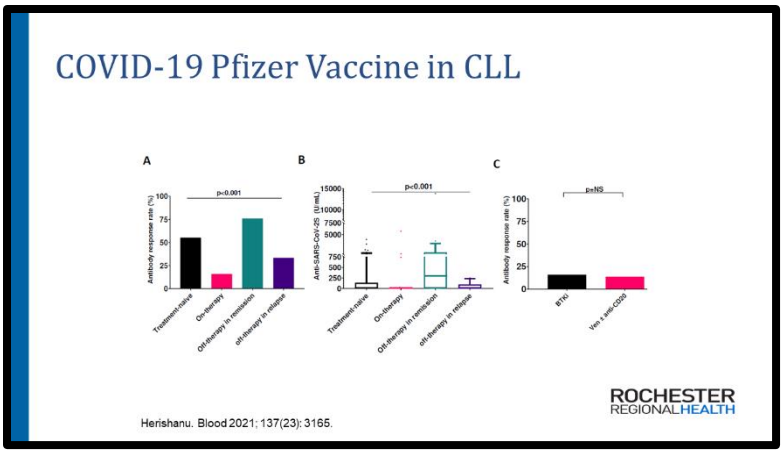
So, we started off way back when talking about people with blood cancer is not responding to vaccines. How did they do the COVID vaccine? You see this as normal control, 99% of normal individuals who are vaccinated with COVID will demonstrate antibodies against COVID. Now you see these abbreviations Hodgkin's lymphoma, myelodysplasia, CML, AL, multiple myeloma, non-Hodgkin lymphoma, and CLL.

So, look at the percentages after 2 mRNA vaccines. Only 47% of individuals with CLL demonstrated antibodies. You were able to find antibodies if you measured them. That was the worst. Lymphoma was better. Myeloma was better. Normal controls is 99%. This is after two doses. Stay with me there.

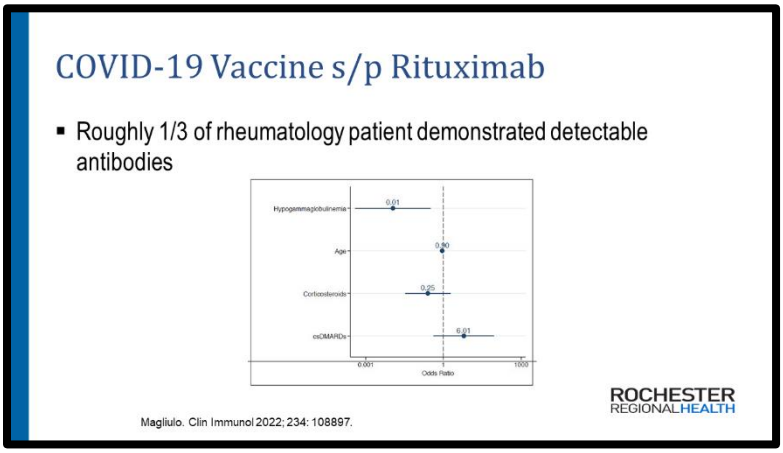
So only 50% were able to produce detectable antibodies for CLL, so 60% versus 70% for lymphoma. Of the individuals who produced antibodies, what were their levels? Not only that many not produce it, but when they did, their levels were lower than normal controls. So again, individuals with blood cancers not only don't respond to the vaccine, as well as we would like, but some don't respond to the antibodies at all. It does not mean that we shouldn't be vaccinating, doesn't mean the response is zero, it's just sub optimal.

Are there ways to predict who may respond to the vaccine or not? The best predictor is actually lymphocyte counts and your antibody levels. Your globulin, your IGg or IgA. The lower your level, the less likely, you are to respond to the vaccine. So even though we're not great at measuring antibodies to COVID, we can use this as a surrogate.

And this was a study literally just published last week of comparing just blood cancer, CLL, lymphoma and myeloma. Our patients with myeloma tend to have a much better response to two doses of mRNA vaccine compared to lymphoma and, unfortunately, again, our patients with CLL, even early CLL, tend to be the poorest responses to COVID vaccination. Very disappointing.



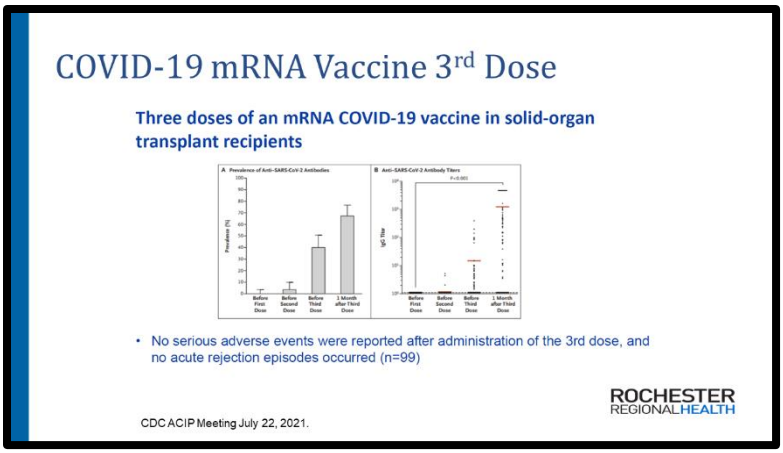
Does it matter if you're on therapy or not? Yes. If you're on therapy with CLL, your likelihood of responding to the vaccine is even lower than if you're not on therapy. So, therapy is kind of the double whammy. It doesn't matter what therapy. It doesn't matter if you're on ibrutinib or rituximab or other agents like venetoclax. But therapy is certainly a risk factor for poor response in the setting CLL.



You guys are familiar with rituximab. This is a study from rheumatology, but I just wanted to kind of bring out what it highlights about rituximab. Rituximab is anti-CD 20. I know I'm speaking to a sophisticated group, so anti-CD 20 is the marker for B cells. The rituximab knocks out B cells, so when you have B cell cancer, you have a lot of bad B cells making cancer cells. So, you want to knock out those B cells and you do with rituximab. The problem is, it takes good B cells with it, so you get lower antibodies.

So, in this rheumatology study, not oncology but rheumatology, if individuals had received a rituximab within the last year, only a third demonstrated antibodies to COVID vaccine, two doses. We're gonna get to more doses. Two doses.

What was the biggest predictor of not responding to the vaccine if you're on rituximab? Check it out. Same thing, low antibody levels, hypogammaglobulinemia. So many reasons that have these levels checked. Steroids, a little bit, but this was the biggest. So, blood cancers are a risk factor. Certain therapies, B cell depleting therapies, rituximab, risk factor. Problem is, sometimes we treat our blood cancers with these B cell depleting therapies and that's a double whammy.



So, we're talking about vaccination and we started with two doses, now it's three doses. Heck, there's some stuff floating around about four doses. Where did that come from? This was the one of the first studies published way back in the summer, which is eons ago in the world of COVID. It keeps changing week to week. This is individuals with solid organ transplants. They've had an organ transplant, they're on immunosuppression. And after two doses of the vaccine, you see that many have not responded to the vaccine okay.

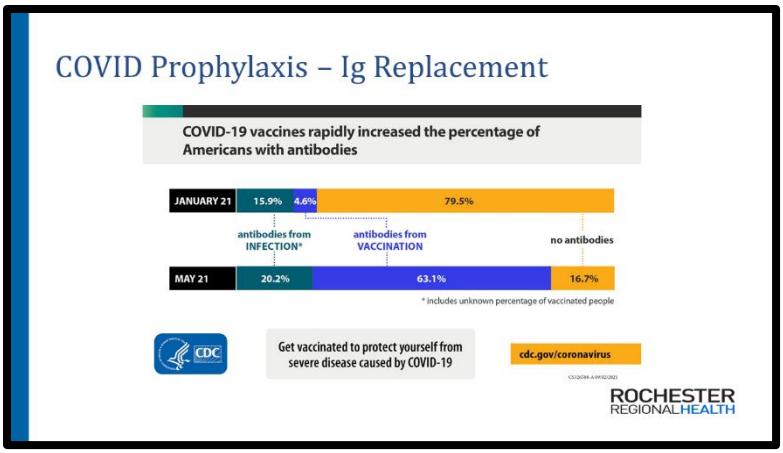
So, if you give them a third dose, about a quarter of individuals will respond to the vaccine. This is in solid organ transplant. So many don't respond to two doses, but a third dose, a quarter patients will respond and the levels will go way up and it's very well tolerated. This was the initial impetus to say individuals, high risk individuals remember should get a third dose of COVID vaccine, then brought into everyone.

This has since been looked at in CLL, as well. And what you see here is individuals with CLL who had two doses of vaccine have pretty low response rate. We talked about that. A third dose increases the likelihood of cranking up on your antibodies by about 25%. So again, people with CLL tend to do better with the antibody production from vaccine, with three doses into. They're both suboptimal. I'm going to be honest, but three is better than two.

And we predict who's going to respond to the third. Yeah, if you're not on therapy, active therapy, that's a good thing. Or if your antibody levels, we keep coming back to these antibody levels, are normal you tend to respond. So, this is why individuals, this is one of the reasons, with blood cancer should get three doses of vaccine, because you have a much better chance of responding to three doses then two.

Before I go forward, I want to mention one other thing that I want to because I noticed this is a sophisticated crowd. We're talking about antibodies here right, but remember that first graph with the four parts immune system? T cells are really important, and even in the absence of antibody response, we may be producing T cell responses and we're not great at measuring that.

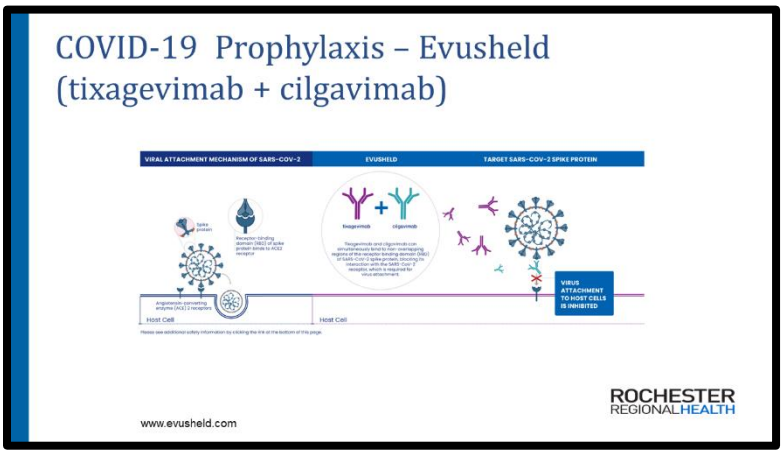
So, even in individuals who've been vaccinated with the three doses, maybe four doses and they know they don't have antibodies, they're worried about antibodies, it's very likely there is a T cell response. But please don't think the vaccines were useless. They're not useless, they're just suboptimal.



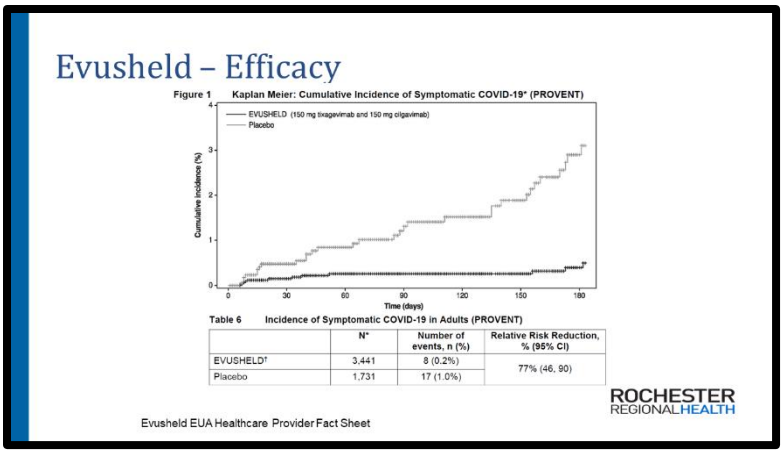
And because of that, we want to protect you from COVID, so what are some other ways? So do not start immune globulin replacement to protect yourself from COVID, but people should know who are on immune globulin replacement whether it's either IVIg or subQ Ig. As of now, you are probably depending on when you got your lot, where the lot came from, you're probably getting some COVID antibody in your immune gloublin.

From the time someone donates plasma to the time it gets to the product, it's about a 12 month delay, 9 to 12 months. So, people who are getting immune globulin today, their donor gave one in early 2021, which is when the vaccination campaign which starting right. So, in May blood donors for immune globulin, most had antibodies.

So, by this May, most immune globulin products will have some amount of antibody. Is it enough antibody to protect you sufficiently? I don't know that. But I want people to know, who are on immune globulin, you're probably, you're getting a lot of antibodies in your immune globulin, that's why you're on it. But some of those will probably include COVID antibodies as well.

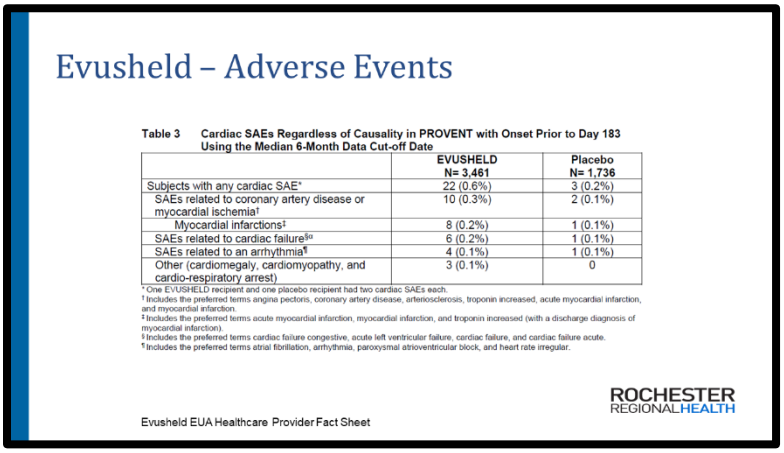


What's another way to protect against COVID? Prophylaxis. If you're not getting antibodies from your vaccines, guess what, we can just give you the antibodies. This product received emergency use authorization [EUA] just a couple of weeks ago and we just started ministering to our patients last week. Very, very exciting. It's called every Evusheld®. So, this is injection, two injections of COVID antibodies into you if you can't make them. They last at least six months, maybe longer.

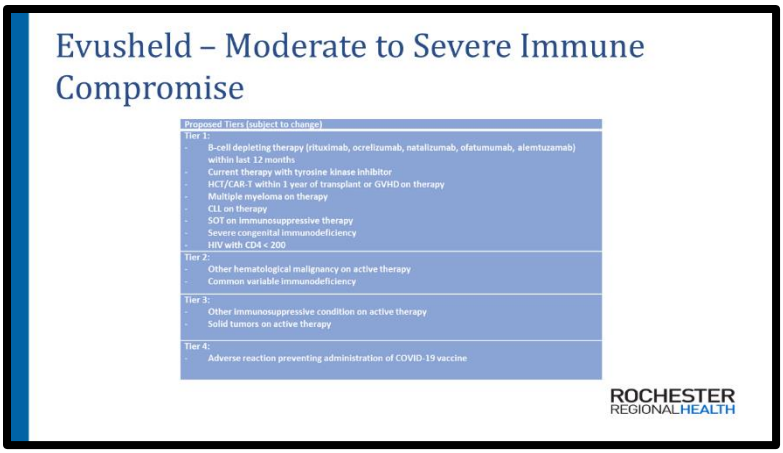


And what the study shows is individuals with Evusheld are very unlikely in this study to get COVID, whereas individuals on placebo had a much higher risk of getting COVID. So again, Evusheld is literally giving individuals who may not respond to vaccination - blood cancer, rituximab, chemotherapy, immunosuppression. If you can't make anybody from the vaccine, which is the whole point of being vaccinated, we're just going to give you the antibodies. Okay? And it works, really, really well.

The study was done in the time of Delta, we have this crazy thing called omicron now, which we all know, has some immune escape right, it's pretty different. Evusheld has adequate activity against omicron. important point.

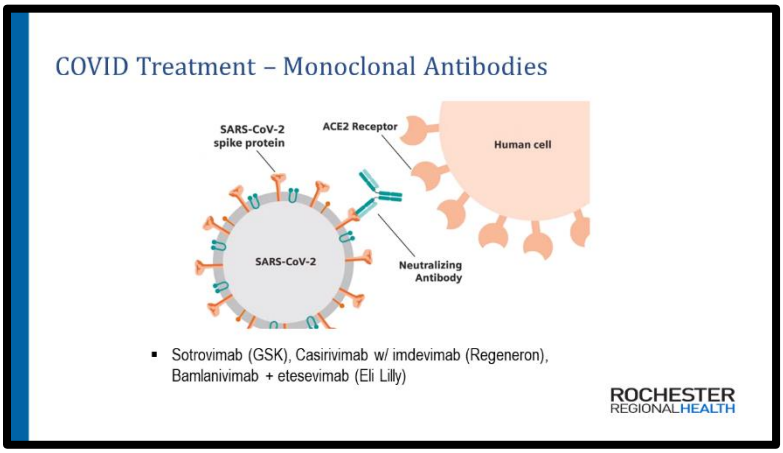


The beauty of this is it's fantastically safe. The side effects were not that different than placebo. So really, really, really safe, effective therapy. Very excited about it.



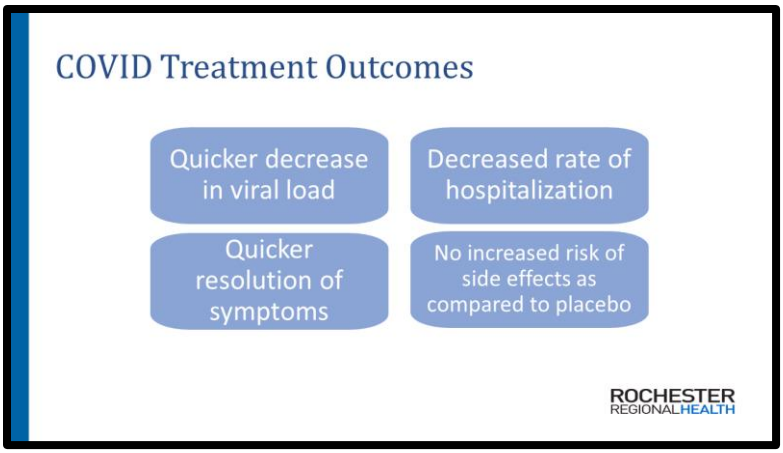
Here's the problem with a lot of our COVID therapies right now. Demand is huge. Lots of COVID running around. Supply is a really, really low. So, we are really starting. We just started last week here. Most systems started within the last two weeks with our highest risk individuals.

These are individuals on B cell depleting therapies within the last year, these are individuals with CLL on therapy, this is any individual with solid organ transplant. Where is that? This is my own list; I can't find it. Yeah, here we go, any individuals on transplant, solid organ transplant, and immunosuppression. So, we're really, really trying to pick the highest risk individuals we don't have as much drug as we want, as we get more drug, we can open it up the others. Multiple myeloma and maybe you know, there are things like that. But right now, we're really selecting out the highest risk individuals.

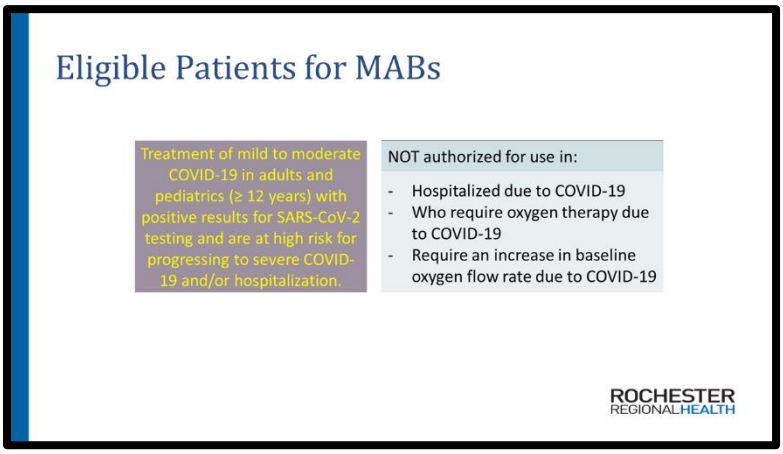


So, we're trying to prevent COVID with vaccination, three doses. Which maybe if you're on immune globulin, that's helping. Evusheld. But unfortunately, people still get COVID, so what happens if you still get COVID?

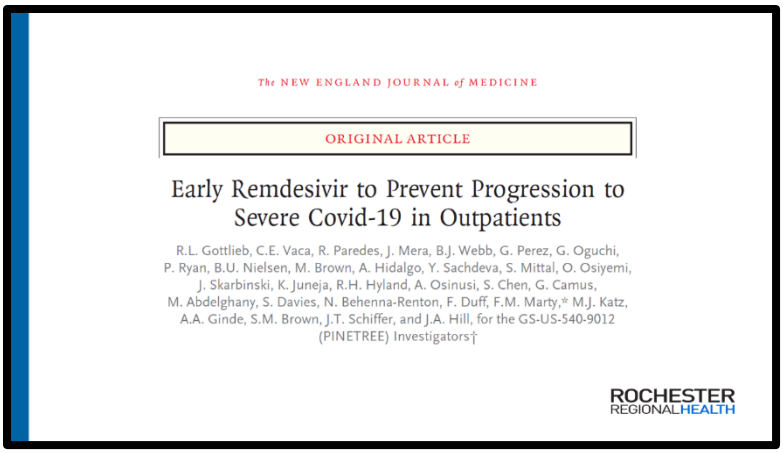
Now I'm going to stop and take questions, we do have monoclonal antibodies. So, this is different, this isn't giving you COVID antibodies, this is giving you an antibody injection that binds up COVID virus. There's three of them that, if you may have heard of. This is what a lot of the politicians getting you hear about in the media; they were treated with the Regeneron®. This is the medication. Unfortunately, these two medications don't have activity against omicron. What a punch in the gut. Using them for months and then I can't use because of omicron. Sotrovimab does still have activity against omicron.



What does it do when you treat individuals with these treatments when they have COVID? they're not get sick. They have COVID, but they're not really sick, they're not hospitalized, they're not hypoxic, they don't need oxygen, there don't have COVID pneumonia? These treatments decrease your viral load, which is great. It makes you feel better sooner, which is great. But the real reason we do them is it decreases your rate of hospitalizations. That's what we care about. It keeps you from getting super sick with COVID. And it's really, really, really well tolerated alright.

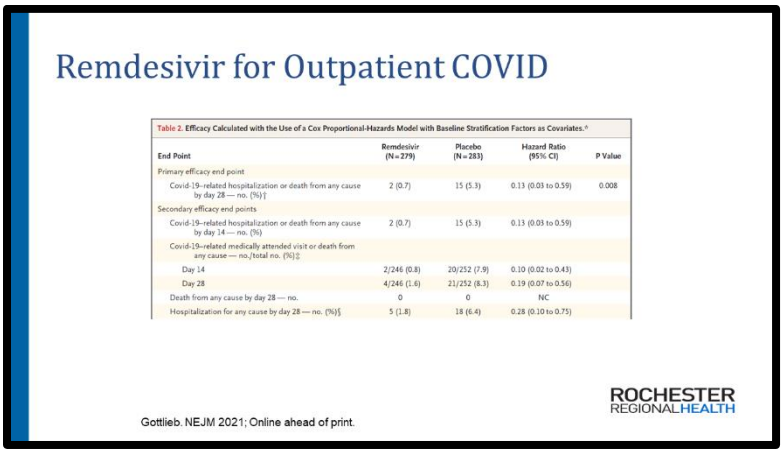


So, when do we do this? This is in individuals who have COVID as an outpatient, this is not if you're hospitalized. If you're hospitalized, these therapies don't work. There are studies that show these therapies don't work for hospitalized individuals. They work to prevent you from getting hospitalized, alright. So that's the key here. So, we're using this right now. Problem again I mentioned, drug supply, very low, demand very high.

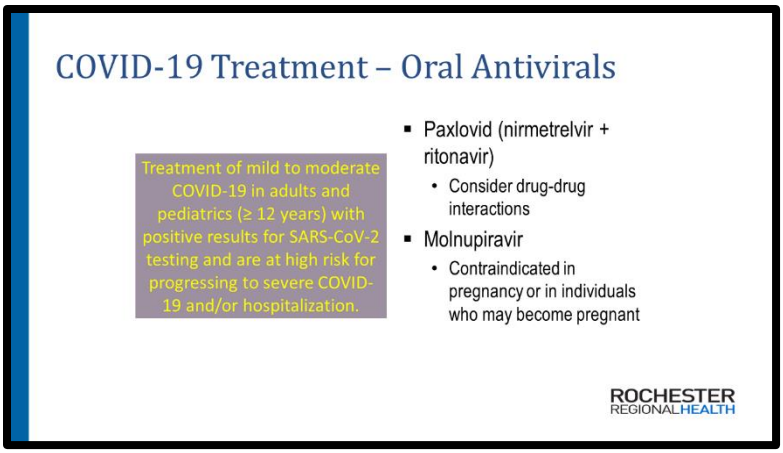


This is an exciting thing you guys may have heard of remdesivir. It's an antiviral. We've been using it to individuals hospitalized for COVID. There is great data that it works like these monoclonal antibodies. If you use it early in COVID disease as an outpatient, it prevents progression to severe COVID. The upside of remdesivir or over a monoclonal antibody, there will never be a drug shortage with readily available. That's great, why don't we just go to it? Because the other monoclonal antibodies are infusions that take about 30 minutes. It's hard to infuse someone who's COVID positive, where do you do it right?

You don't want to do an infusion center where there's a lot of oncology patients. You can't do it in emergency rooms. Emergency rooms are coming apart at the seams. It's hard to do, but you can do it. But those monoclonal antibodies are one time infusion. Guess remdesivir. It's three consecutive days or 30-minute infusion so it's logistically much more challenging but readily available, so our hospital system here is in the process of operationalizing it and I know other hospital systems are starting to operationalize outpatient remdesivir to prevent progression.

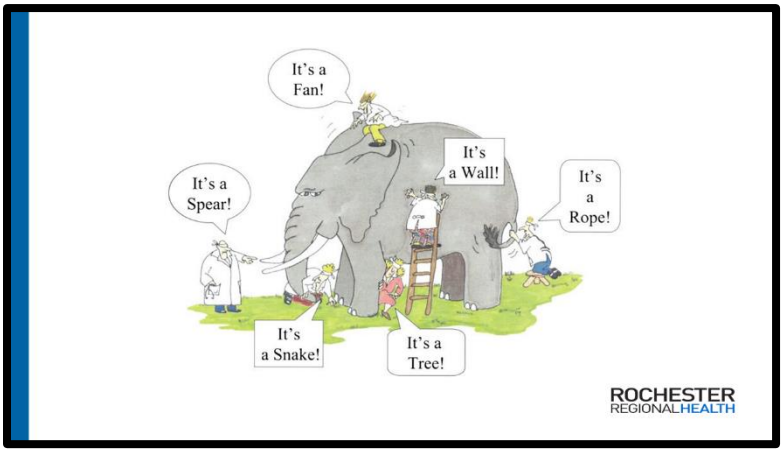


And again, what it shows here is individuals who are treated with remdesivir early in treatment and to get hospitalized 2 out of 79, much less often than individuals who have placebo. Really cuts down on your risk of hospitalization which is really the goal here.



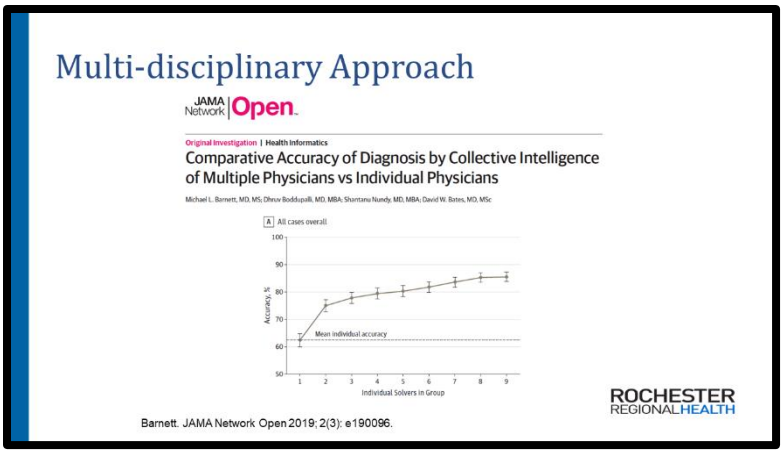
And then the last thing I'm going to end with is, there is now to oral antivirals. Um, same concept. This is for outpatient COVID. You've tested positive for COVID, you're symptomatic but you're not sick, yet you don't feel terrible, you're not hypoxic, you don't have pneumonia, and you don't need oxygen. And these treatments decrease a progression to severe illness.

Paxlovid™ and molnupravir. I can't even pronounce it very well. Paxlovid is absolutely the drug of choice. You want to start here, it's more effective than this one. Lots of drug interactions. This one has less drug interactions, but significant concerns in pregnancy or anyone who may become pregnant. You have to be careful, these are prescribed from pharmacies and the US again drugs supplies low. Demand is high, so again, a lot of this comes down to just availability. But there are options. There is a glimmer of hope. There are therapies for our patients with COVID, which is new. Wasn't like that months ago.



I shamelessly stole this slide from a real mentor at NIH [National Institute of Health], Steve Holland, and the concept here is, we all see things from our own prison. Oncologists are amazing at treating cancer, but sometimes they don't look around, you know. Sometimes, you know, there's other parts of cancer, their side effects, there's immune suppression. there's infection.

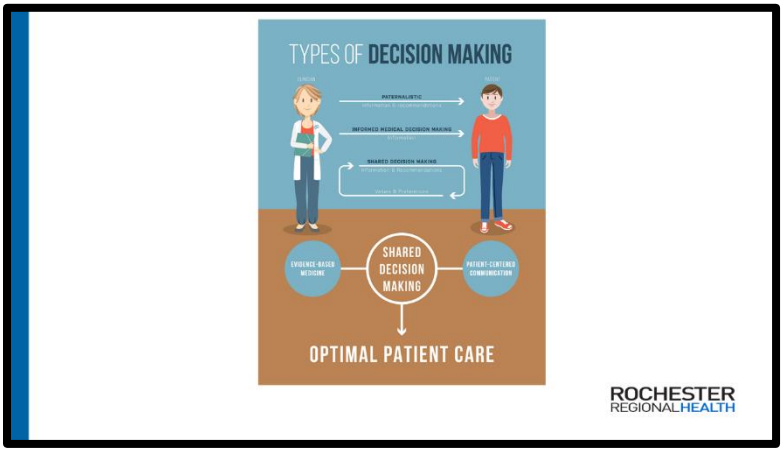
They're directed at treating cancer. I don't know how to treat cancer, if my life depended on it, but I'm really focused on immune effects of chemotherapy and the cancer itself. So we all see what we see. If you take a step back and do it as a team, you see the whole picture.



I love this study from JAMA [Journal of American Medical Association], and that Open Network, it says, if you treat someone alone, me by myself, I refuse to phone a friend, my chance of getting the accurate diagnosis is literally 60% if one provider does it. If I add just one more person to the team - I go from myself the two people, my chance of diagnostic accuracy goes up from 60% about 75%. And then, if we add team members, we get up to about 80%.

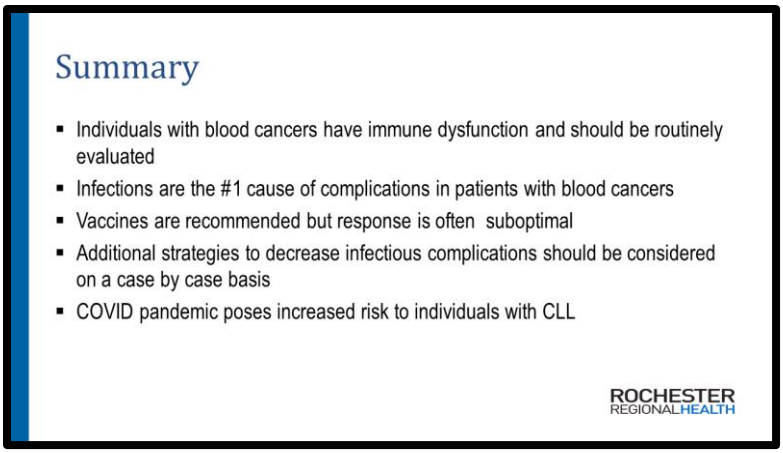
So if you have an oncologist managing your CLL, they're probably doing a great job for your CLL, but had they accurately diagnosed her immune deficiency. I don't know. If you have, you know, someone else managing your cancer, your bone marrow transplant, are they managing your infectious complications, are they managing your immune deficiency I don't know.

So I really, really am a big proponent of a team approach, a multidisciplinary approach. I am not around colleges or do I want to be nor am I trained to be. But doing it together as a team tends to lead to better patient outcomes.



And that's where this shared decision making comes in. Everyone has to be an advocate for themselves. I've grown up on the other side of healthcare. And we certainly have to advocate for our loved ones, our family members, our friends.

So it's really a shared decision. There's a provider, there's a patient, there's a family and we talked about it. We talked about the pros and cons, we talk about if you want IVIg or subQ Ig. We talk about what immune evaluation you deserve when you're diagnosed with blood cancer, and then we move forward and that's really what leads to optimal patient care.



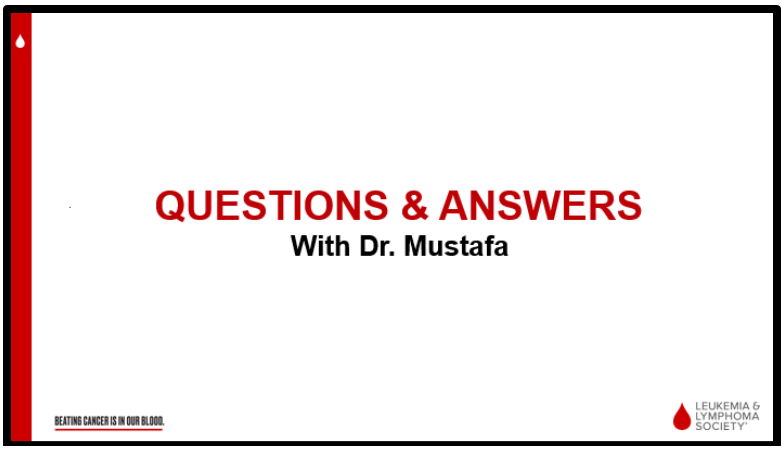
So I'm going to end with that and take some questions. I hope this has been helpful. Individuals we know with blood cancer, they have immune dysfunction and I think they should be routinely evaluated. Even in the absence of infections individuals with blood cancer had glitches in their immune system and checking these levels, checking these labs helps with prognosis.

Infections, not cancer, is the number one cause of complications in individuals with blood cancer. It is literally the number one cause of death. So it is our goal, it is our is our job to prevent infections. Vaccinations are absolutely first line therapy. They are not, not helpful, but they are their response is suboptimal and individuals with blood cancer and chemo certain chemotherapies like rituximab.

So we need additional strategies to decrease infectious complications and it has to be discussed on a case by case basis. Maybe you don't need to do anything, just watch and wait. That's fine. I have many patients to CLL, lymphoma, myeloma, so I just keep an eye on labs and clinical status and see how they do. We do use prophylactic antibiotics, we do use immune globulin in certain individuals.

And then COVID is really throwing a wrench into everything and it's really cranked the infection risk even higher in individuals with B cell malignancy and your response, the vaccination is certainly suboptimal in B cell malignancy and blood cancers. So we really have to think about protecting our most vulnerable with these other therapeutic options. Immune globulin may give you some protection. Certainly don't start immune globulin for that, I'm not suggesting that. I'm saying, if you're on it, you should know you're getting some antibodies probably.

Evusheld is very important, I think, and very exciting and then therapies, if you do catch COVID.



Angela Austin: Thank you, Dr Mustafa for your very informative presentation. It is time for the question and answer portion of our program. Our first question is: What are the side effects of Evusheld?

Dr. Shahzad Mustafa: Again very, very well tolerated. No significant side effect profile. I guess the one signal was people with active cardiac disease may have cardiac issues, cardiac outcomes, but again, it was not statistically more than placebo. Something to think about. Most people don't have active cardiac disease, active heart attacks happening, active atrial fibrillation.

Evusheld is fantastically well tolerated in the studies that had over 7500 individuals, which is pretty big. One study had 5000, one study had 2500. And certainly in our experience locally too.

Angela Austin: Thank you. Our next question is: if a person with leukemia didn't develop antibodies from the COVID vaccines, do they develop antibodies by actually having the illness?

Dr. Shahzad Mustafa: What a fantastic, sophisticated question and I don't know the answer. Maybe. In fact, likely. The problem is antibodies and T cells have memory. We know that, right. We've talked about these vaccines, they drop off over time. So even if you do build antibodies, I think there is probably some memory defect, so the protections not as good as we want, but I would suspect a natural infection's going to give you some antibodies, even if you don't have COVID vaccines, but maybe not as good as you want. If you do have COVID and you have B cell malignancy, you are still a candidate for Evusheld, by the way, for that exact reason.

Angela Austin: Our next question is how are leukemia patients responding to the Omicron variant despite being vaccinated and boosted? Are they requiring hospitalization?

Dr. Shahzad Mustafa: I don't have granular data on the leukemia patients. Great question. I think it's very important to note, omicron is much more contagious, but it does look to be much less severe compared to delta. It's much more of an upper airway condition than a lower airway condition, causing pneumonia.

Now of course that's not great for our hospitals, because of even small percentage of huge numbers, are a problem for our hospital, so we're still seeing lots of people hospitalized. But, in general, I don't want to get COVID, but if I was going to get COVID, I'd much rather sign up for Omicron than Delta, especially if you're vaccinated.

So I would say the rate of hospitalization in the general population is at least half of that of Delta, if not less. I don't know the specific numbers for leukemia, but again, we're having some better outcomes with individuals with blood cancer, because we have therapies now. These individuals are being treated sotrivamab and now they're getting Evusheld too and now there's some oral antivirals, so there is much promise.

Angela Austin: Thank you, doctor. The next question is: I have multiple myeloma and have low immunity. If I cannot produce my own antibodies to prevent infections, how can the covid vaccines trigger any antibodies for me as a myeloma patient?

Dr. Shahzad Mustafa: People with myeloma do respond to COVID vaccines, but it's certainly suboptimal. I can't speak this specific cases, but some individuals with myeloma certainly have significant defects. So again, I would definitely work with your oncologist to clinical immunologist, evaluate your immune system, check your antibody levels, check your pair of proteins, check your vaccine responses. So, so important.

Angela Austin: Our next question is: I have a 9.4 antibody test result, greater than 1 is reactive. Should I act like I have some protection from covid?

Dr. Shahzad Mustafa: So we have really great knowledge about evaluating immune levels to certain things, tetanus diphtheria, and pneumonia, meningitis, hepatitis. Our knowledge of a protective level of COVID is really crappy, not good. So we like seeing higher numbers of antibodies. That's fine, but we don't know if higher is better or if it lasts longer or if it's meaningful. So my example is for pneumonia, your level of IgG is over 1.3 for pneumonia, that's protective. We know that. We've studied it. I don't know what that number is for COVID. So yeah, I think people like seeing 70 or 80 or 90 more than 40 or 50.

But maybe it's all just as good. I have no idea, so that is why, at this moment, today we are not recommending individuals routinely check antibody levels decode it after vaccination. Because we don't know how to interpret it. Now don't get me wrong, I do order these levels and some of my patients and they are helpful, they're a guide. If we don't detect enough any antibodies, that's helpful. It's disappointing, but helpful to detect antibodies that's reassuring, but I can't tell you the quality of the antibodies. I can't tell you how long they'll last. There's a tremendous amount to learn in our COVID antibody levels.

Angela Austin: Thank you. Our next question is: I finished treatment for NHL with rituximab 8 years ago. Would you expect the immune system to respond normally yet? Or is it forever impacted?

Dr. Shahzad Mustafa: It is impossible to know. I was taught in fellowship that your immune response after rituximab should recover after one to two years. We know for a fact, your B cells go to sleep kind of B cell aplasia in many individuals for a much longer period of time, some people are forever impacted.

The beauty is we don't have to guess. Clinical immunologists can check blood work and figure this out. You can check B cell levels. You can check antibody levels, so I encourage that to be evaluated.

Angela Austin: Our final question for the program is: How often should cancer patients consult with immunologists or infectious disease doctors?

Dr. Shahzad Mustafa: This depends on where you're at with your oncologist is. Some oncologists are world's experts in clinical immunology, so you may not need it, okay. Certainly if you have an oncologist who's not that comfortable immunology, who's never checked immune globulin levels, it may help to have someone else on the team, a clinical immunologist or an infectious disease doctor with an interest in this space.

So talk to your immunologist. There's no right and wrong here. If you're happy with your team that seems to be taking great care of you, you have the information you need, kudos to you. But, again, I think this goes back to shared decision making. Blood cancers are complicated. They're complicated always. Treatments are changing. There's immune deficiency, infections are a problem now we have COVID. So I think a team approach, you know, I've never shied a phone a friend and asked for help, so I think this is an individual discussion, but I think your needs should be satisfied, and we all need to be advocates for ourselves. So if you have a blood cancer, you're just treating cancer, I think that's appropriate. But you should at least be cognizant of these immune defects and how they may play out and very straightforward ways to evaluate.

Angela Austin: Thank you so much, Dr. Mustafa for sharing your expertise with us, and for your continued dedication to cancer patients.

Dr. Shahzad Mustafa: And I really, really want to thank everyone, I know how busy everyone is, I know how busy the evenings are, certainly in my house, so thank you for taking an hour out of your busy busy schedules to spend with The LLS and myself, I hope this conversation was helpful you learn something. And I think, you know, I'm the eternal optimist and I do think there's a light at the end of the tunnel of COVID and moving out of it was not only therapies and knowledge, but hopefully with the virus kind of mutating and changing in form, so thank you so much. Angela thanks for having me.

Angela Austin: If we were not able to answer your question during this program, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9am to 9pm ET.

We also encourage you to please complete the program evaluation, which can be found at www.LLS.org/ImmunologyEval or by scanning the QR code on your screen with your smartphone. Completing the evaluation will help us to continue to provide the engaging and informative programming that would benefit you the most.

Dr. Mustafa, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for watching this program. Take good care.