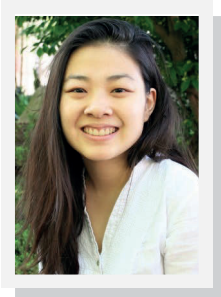


Winter 2018



CHANGING THE TREATMENT LANDSCAPE FOR ALPHA THALASSEMIA MAJOR

BY MEGHAN FOE,
OUTREACH COORDINATOR



AN EMERGENT
ISSUE IN
POPULATION
HEALTH

In 2016, the Northern California Comprehensive Thalassemia Center at UCSF Benioff Children's

Hospital Oakland and the UCSF Fetal Treatment Center partnered to establish the first multidisciplinary center for alpha thalassemia major. This partnership is part of a growing effort to raise awareness in the medical community about screening and management of alpha thalassemia major — an effort that reflects a key demographic shift in the thalassemia population in the United States.

Alpha thalassemias are highly prevalent in populations with ancestry from Asia, the Middle East, and the Pacific Islands. Immigration from these regions to the United States has increased significantly in the last decade, something that is mirrored by a significant rise in alpha thalassemia prevalence. A subset of this population is at high-risk for having a pregnancy diagnosed with alpha



Dr. Elliott Vichinsky with Elianna and her parents, Nichelle and Chris, in the clinic. Elianna was the first patient with alpha thalassemia major to receive intrauterine stem cell transplant. Read Elianna's story online: <https://nyti.ms/2LuBBQf>

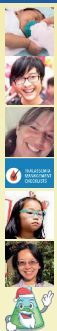
thalassemia major, concentrated mostly in Southern Chinese, Southeast Asian, and Filipino populations. In these regions, an estimated 5% of pregnancies are affected by alpha thalassemia major. By current population estimates, in California, 20-25 pregnancies with alpha thalassemia major occur each year.

WHAT IS ALPHA THALASSEMIA MAJOR?

Alpha thalassemia major is the most severe form of alpha thalassemia and results in the complete inability to produce alpha globin chains for the hemoglobin molecule. Alpha globin is necessary to produce both adult hemoglobin and fetal hemoglobin. When fetuses are unable to synthesize alpha globin, they develop severe anemia and produce a non-functional hemoglobin called hemoglobin Bart's, which has no capacity to transport oxygen from placenta to the fetal tissues. The resulting anemia leads to an enlarged heart, liver, and spleen, and eventually to generalized edema. This

(Continued on page 5)

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STARTING COLLEGE WITH VINH LUU

BY MEGHAN FOE, OUTREACH COORDINATOR

Vinh Luu is a 17 year old with thalassemia in his first year at the University of California, Berkeley. For someone studying at one of the most elite universities in the nation and who has ambitions to get a PhD in physics, Vinh is extremely easygoing. He describes himself as a “really go with the flow person,” and this attitude has carried him through the rigorous process of applying to and, now, starting college. Vinh is from the Bay Area, but is staying on-campus at UC Berkeley, which strikes a good balance between being close to home and allowing for some independence. In our interview, Vinh discusses this, the woes of procrastinating on his personal statement, and how to survive the first week of college when you’re bad with names.

HOW DID YOU DECIDE WHICH COLLEGES TO APPLY TO?

I only applied really to California schools, because I wanted to stay in the area. I liked San Jose, because that’s where I was born, raised. And this is close to the Children’s Hospital here. I applied to, like, eight different schools in-state. But I was really either going to go to San Jose State, or Berkeley.

WHAT WAS THE MOST CHALLENGING PART OF THE PROCESS?

Writing the personal statement. Because I left them until three hours before they were due. And I did them all in the last hour. Which is not a good thing, not a thing I should be telling everybody. It probably paints an image that you should do it last minute, but don’t do that. I’m just lazy.

MAYBE IT WAS GOOD THAT YOU DIDN’T PUT THAT MUCH PRESSURE ON YOURSELF.

Yeah, there wasn’t really that much pressure for me. I was like, “I’m going to apply to eight schools, and I’m going to one of them.” I had some friends who applied to a bunch of Ivy Leagues, and they were like, “I’m not gonna get in! I’m not gonna get in!” And I’m like, “Why do you care? Just go to whichever ones you let you in!” Because honestly, in the long run, it doesn’t really matter which college you go into. As long as you go, and you like learning, you’ll be fine. I think it’s more...like

“Honestly, in the long run, it doesn’t really matter which college you go into. As long as you go, and you like learning, you’ll be fine.”

how you make of it. Like, if you go to a good college but you didn’t take advantage of it or learn anything, it’s like you didn’t go to a good college, at that point.

SOME PEOPLE WITH THALASSEMIA WHO ARE THINKING ABOUT APPLYING TO COLLEGE MIGHT WONDER WHETHER THEY SHOULD WRITE ABOUT HAVING THALASSEMIA IN THEIR APPLICATION ESSAY. DID YOU?

I did! It was one of the easiest essays that I could have written, so I was like, “I’m going to go for it.” There was one about challenges I had faced, so I just did that.

WHAT ARE SOME EXAMPLES OF THINGS YOU DID TO HELP PREPARE TO MANAGE YOUR THALASSEMIA CARE ON YOUR OWN?

Well, for my transfusions, I took a look at the schedules, and none of the classes go later than 4, so I knew I could just come to the Day Hospital in the evening. The only difference is that instead of getting my labs in the morning [of the transfusion], I’ll just come here on the day before, because I have classes only from 9:30-11, and then 5-6:30.

DID YOU PURPOSELY SCHEDULE YOUR CLASSES AROUND TRANSFUSIONS?

Not really. I’m a really go with the flow person. So I kind of figured that I’d schedule my classes and work around it with the Day Hospital, especially because it’s so close.

Like, taking the bus only takes half an hour if it’s not delayed, which it was today.

WHAT ABOUT WITH YOUR CHELATION? ARE THERE ANY ADJUSTMENTS THERE NOW THAT YOU’VE STARTED COLLEGE?

In terms of ordering it, I have to keep track of how many I have left, but it’s pretty routine. In terms of taking it, I have missed a couple more times than normal because of going out, but I’ll usually remember to take it. The thing is, you’re in a whole new environment, you just have to get used to everything again.

WHAT IS SOME ADVICE YOU HAVE FOR PEOPLE TRYING TO MANAGE THEIR CARE ON THEIR OWN?

I guess, like, pay attention to what your parents are doing. And if you have any questions, ask them. Don’t go no-contact with your parents.

WHAT HAS BEEN THE MOST DIFFICULT PART OF THE TRANSITION INTO COLLEGE?

Meeting new people. Like, you meet so many new people in the first week, and it’s so hard to remember all of their names. I’m really bad with names. So now I default to saying “Hi” instead of “Hi” and their name. Other than that, it’s figuring out which buses to take. But after the first time, it was fine.

WHAT DO YOU FEEL LIKE HAS BEEN THE MOST HELPFUL IN THIS TRANSITION TO COLLEGE?

A big part of it is that I’m so close. Like, my dad is able to drive up here and get me stuff if I need it. Like last time, and this time actually, he’s going to bring me food and stuff that



I need from my house in San Jose. Also, keeping in contact with friends from high school. So if I really wanted to hang with them, I could just drive back on a weekend or take BART and then come back here. I guess some people reading this newsletter might go to a college nearby, maybe?

Because, like, if you go too far away, there might not be a specialty center for thalassemia? I actually don't know how that works. But honestly, going to a really close college has been really helpful.

WHAT DO YOUR PARENTS THINK ABOUT YOU GOING TO CAL?

My parents are like, "Oh, you're going to college...okay good. Keep studying." [LAUGHS] They're really hands off. I text them and call them every so often. They're always asking me, "What did you eat today?" or like, "Did you eat?", like every Asian parent. So I send them pictures of what I'm eating, and sometimes, they're like, "I don't like that." And I'm like, "Well, excuse me! You're not the one eating it!"

DO YOU TELL FRIENDS AND PROFESSORS THAT YOU HAVE THALASSEMIA?

"Now you have freedom! And you'll grow to love it eventually."

Not really. Like, I won't just straight up go up to someone and be like, "Hey, I have thalassemia." That's kind of weird. But if they ask, like, "Where are you going?" And I'll be like, "Oh, the hospital." And they're like, "Why?" And I'll say, "It's because I need a blood draw or a blood

transfusion." And they're like, "Oh, why?" And I'm like, "I have thalassemia." And they're like, "Oh what is it?" And I'm like, "Yada yada yada, it's a blood disorder. If you want more [information about thalassemia], you can look it up!" [LAUGHS] I'll just tell them, "Wikipedia it, it's fine."

DOES THE SCHOOL HAVE A CENTER FOR TO HELP STUDENTS WITH ACCOMMODATIONS, LIKE IF YOU'RE ABSENT A LOT FOR DOCTOR'S APPOINTMENTS?

Yeah, they do. But I'm not absent that much. There is a disability center that you can go to, DSP. I might be able to use the fact that I have it to stay on-campus for another year.

WHAT ARE YOU MOST EXCITED ABOUT AS YOU START COLLEGE?

Learning. Meeting new people.

Going to parties.

WHAT ARE YOU MOST NERVOUS ABOUT AS YOU START COLLEGE?

Classes, I guess? Mainly because I didn't know how college classes are going to be like. Because I know that my study habits are really garbage. Like, I'll study for a bit, and I'll be like, "I give up!" and play video games. I didn't really study in high school, so it's kind of bad transitioning to college, because I actually have to study and, like, manage my time. Which I'm, like, slowly learning. I've made some questionable decisions about time management.

IT'S CERTAINLY A LEARNED SKILL. WHAT ARE SOME FUTURE GOALS FOR YOU?

I want to study physics and go to grad school and get a PhD, if I can. I really want to do applied physics and go into computer science. I want to do quantum computing.

WHAT IS QUANTUM COMPUTING?

Basically, computers get smaller and smaller, like, over time. But it gets to a point where it can't get any smaller, because there's issues with...physics. So quantum physics is a branch of physics that deals with really, really small objects. So, in this case, I would help apply it to computers and be able to make them smaller and smaller, as well as faster, and store more memory.

THAT'S REALLY NEAT! ANYTHING ELSE YOU'D LIKE TO ADD?

Honestly, besides classes and meeting new people, college is not that big of a deal. You'll make friends. There are so many people in college. Now, you have freedom! And you'll grow to love it eventually.

ARE YOU LOVING COLLEGE SO FAR?

Heck yeah! I get to sleep in, if I want. It's great.



INTERVIEW WITH ANNE RISHON, PNP

BY MEGHAN FOE, OUTREACH COORDINATOR



Before Anne Rishon became the nurse practitioner at the thalassemia clinic, most of her work had been with vulnerable populations in women's and community clinics in the Bay Area. Most notably, Anne's love of working with adolescents led her to work for 10 years as a nurse practitioner in the Alameda County Juvenile Hall. Though her new role differs in some ways from her previous work, Anne maintains that there are some parts of nursing that stay the same and never cease to amaze her. In our interview with Anne, we spoke about this and more.

HOW DID YOU BECOME INTERESTED IN HEALTH CARE?

My mom's a nurse, and I was always fascinated by gross things and the body. I don't know why. In high school, I was a volunteer at the local hospital. Then, during my first quarter [of college], I didn't have a declared major, and I thought, "I don't know why I didn't think about doing nursing." But they didn't have a nursing program at my college. So, I contacted the UCLA School of Nursing and transferred to UCLA.

BEFORE YOU CAME HERE, WHAT FIELDS DID YOU WORK IN?

After I got my NP, I worked in community health clinics with predominantly the Latino immigrant population. I worked at La Clinica de la Raza for a long time, and then there was an opening at the Juvenile Hall Medical Unit. I really like interacting with adolescents; I do really well with them. So, I worked [at Juvenile Hall] for the last 10 years. Then it was time for me to move on, and here I am on the Thalassemia Team.

WHAT ARE THE SIMILARITIES AND DIFFERENCES BETWEEN WHAT YOU DID BEFORE AND WHAT YOU DO NOW?

The work is always going to be different with underlying similarities. Like here, in the thalassemia program, it's very detailed, very medical. But it's also very psychosocial, like my previous work with the kids in

the Hall. Making sure that everyone gets what they need is my end goal. That hasn't changed. But I'm learning a lot, because it is really different in the day to day business.

WHAT DO YOU FEEL LIKE IS THE MOST NOTABLE PART ABOUT WORKING WITH INDIVIDUALS WHO HAVE THALASSEMIA?

As always, it's the resilience of the patients; it's their ability to live with what's really a lifetime condition. And to see people go about living their lives in the midst of all this, it's pretty amazing.

WHAT IS YOUR DAY-TO-DAY LIKE?

I like to stay one step ahead of myself. The first thing I do is look at the labs for the patients we are going to see, to see how much blood volume is to be transfused, and to see what medical issues we need to address with each patient. And preparing for patient visits is super important; otherwise, you're constantly two steps behind yourself.



WHAT DO YOU DO AFTER THAT?

Then, I talk to the nurses in the infusion center, because communication in any field is really critical. So I make sure they see what orders I have for pre-transfusion, and that everything is set up before patients arrive. And then we see the patients – that's the fun part. Then, I go back and finish the notes, make calls, and return phone messages. It's kind of nice that there's a sort of rhythm to it, and there's always stuff that happens in between that might throw you off.

WHAT DO YOU LIKE TO DO WHEN YOU'RE NOT WORKING?

I watch a lot of TV [LAUGHS].

OH YEAH, ANY FAVORITES?

When I'm by myself, I'll just binge watch Criminal Minds or Law and Order. I love crime shows. Also, cooking shows! Me and the kid will watch cooking shows together. He likes Chopped and Bobby Flay because he likes the countdowns. My big kid (he's 19) watches cooking shows, too, so sometimes we all watch together.

ANYTHING ELSE TO ADD?

Nope! Thank you!

*(Alpha Thalassemia Major,
Continued from page 1)*

abnormal collection of fluid is formally known as hydrops fetalis, and such a fetus would not survive if left untreated.

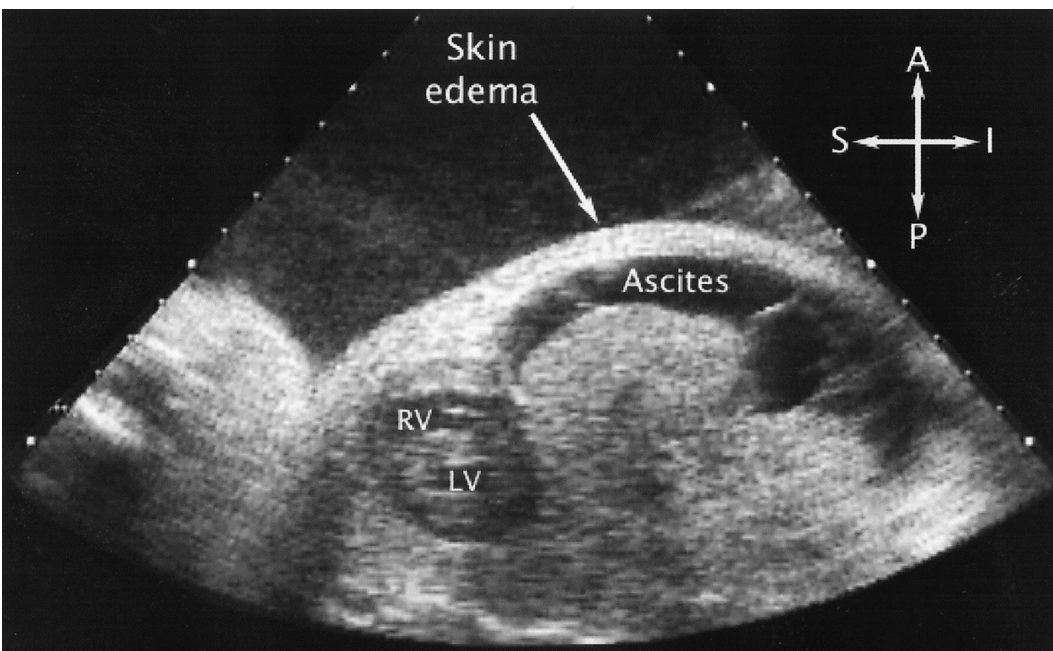
Hydrops fetalis can also be dangerous to the mother, who may develop mirror syndrome, named due to the similarity between the maternal and fetal symptoms. Mothers with mirror syndrome experience peripheral or pulmonary edema, placentomegaly, and pre-eclampsia.

CHANGING AWARENESS AND
SCREENING PRACTICES OF PRIMARY
CARE AND PRENATAL PROVIDERS

It is suspected that many pregnancies with alpha thalassemia major end in fetal loss without establishing a diagnosis. Even when the diagnosis is made, the dominant perception in medical communities that alpha thalassemia major is invariably fatal can discourage families from seeking treatment or delay the start of intrauterine transfusions.

Optimal outcomes for alpha thalassemia major are predicated on the providers' adherence to a complex pathway of screening, diagnosis, and counseling, which requires coordinated partnership between obstetricians, maternal-fetal medicine specialists, genetic counselors, and hematologists.

Fetal Ultrasound: Ultrasounds can detect signs of fetal hydrops, such as edema and ascites. Source: nurseszone.in

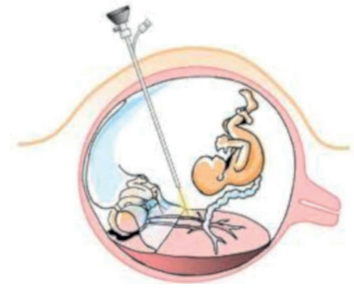


SCREENING PROSPECTIVE PARENTS
FOR THALASSEMIA TRAIT

Screening for thalassemia trait usually begins in the prenatal period with the mother's first complete blood count (CBC). If the mother is determined to have microcytic anemia, a hemoglobin electrophoresis is performed to identify different types of hemoglobin. This step represents a significant drop-off point in the screening process, since hemoglobin electrophoresis results come back normal for alpha thalassemia trait. Thus, it is essential to perform genetic analysis of the alpha globin gene to diagnose alpha thalassemia trait. Another significant gap in the screening process is the expeditious pursuit of paternal thalassemia trait testing, without which it is impossible to ascertain the fetal risk.

MONITORING AT-RISK PREGNANCIES
FOR ALPHA THALASSEMIA MAJOR

When a pregnancy is determined to be at risk for alpha thalassemia major, the family should be referred to a maternal-fetal medicine (MFM) specialist. The MFM specialist is responsible for performing chorionic villus sampling or amniocentesis to diagnose the fetus with alpha thalassemia major. They also screen the fetus regularly for anemia using Doppler ultrasounds of the middle cerebral artery (MCA). If fetal anemia is suspected, a blood sample from the umbilical cord using



Intrauterine Blood Transfusion (IUT)

percutaneous umbilical blood sampling (PUBS) is obtained for confirmation. The fetus is monitored for signs of placentomegaly, cardiomegaly, and hydrops with serial ultrasound, while the mother is monitored for mirror syndrome. Unfortunately, due to delay in the initial screening process or diagnosis, many affected pregnancies are not detected until this late stage.

COUNSELING AND MANAGEMENT

Following prenatal diagnosis of alpha thalassemia major, parents should be provided counseling to explain the diagnosis, its risks to the fetus and mother, and their options.

Termination of pregnancy remains an important option for many families, especially if the mother's health is being affected. The alternative option of intervening with intrauterine blood transfusions. IUT involves mitigating fetal anemia by delivering packed red blood cells into fetal circulation via the umbilical vein. IUT is a standard technique that has been used for many decades to treat fetal anemia due to Rh incompatibility, where it has a >90% success rate in allowing fetal survival to term. The application of IUTs to treat fetal anemia caused by alpha thalassemia major is more recent with variable standards in how they are performed. Regardless, there is strong evidence that full fetal development is possible with adequate prenatal intervention with IUTs.

Because an increasing number of fetuses are surviving to term with alpha thalassemia major, there is a significant need to understand long-term outcomes of children born with alpha thalassemia major. Similarly to those with beta thalassemia major, children with alpha thalassemia major

(Continued on page 8)

THALASSEMIA MANAGEMENT CHECKLISTS

Quick reference guides to reduce disparities in the care of patients with transfusion-dependent thalassemia

BY ASHUTOSH LAL, MD

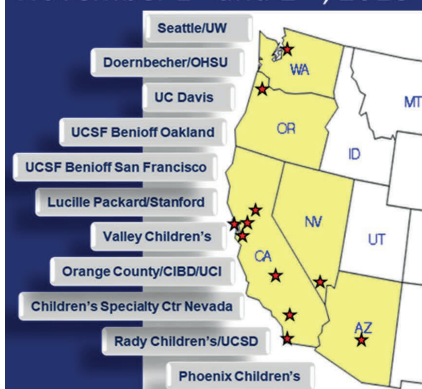
The prevalence of thalassemia in the United States is rising due to immigration, new births, adoptions, and improved survival. Advances in monitoring and treatment have significantly reduced morbidity and mortality in transfusion-dependent thalassemia (TDT).

Thalassemia Treatment Centers (TTCs) utilize a comprehensive care model to provide contemporary care. But, a majority of the patients with TDT are not managed at such centers owing to long travel distance and lack of insurance portability. Lack of access to specialized care increases the risk of complications, shortens survival, and reduces health-related quality of life.

Recently, there has been a national effort to standardize management of TDT and reduce disparities in access to and quality of care. This effort has been led in part by the multi-site Thalassemia Western Consortium, which held its fourth annual meeting in November 2018.

The backbone of the initiative to reduce disparities in quality of care for TDT has been the development of Thalassemia Management Checklists (TMCs), a set of quick reference

Thalassemia Western Consortium 2018 Annual Meeting November 1st and 2nd, 2018



Venue: Coast Ballroom
Wyndham San Diego Bayside
1355 North Harbor Drive, San Diego, CA 92101



guides that provide decision support to physicians managing TDT. Physicians are more likely to consult a quick reference guide — such as these — instead of textbooks, journals, or handbooks of comprehensive guidelines. TMCs cover most routine management of TDT while encouraging expert consultation for complex decisions.

The final product is in the form of three separate documents, each covering a single topic — thus allowing easy access to the summary information while displaying detailed information on demand. Over the next three years, adoption of TMCs and their impact on patient care will be formally evaluated in selected regions. Patient access to TMCs will increase knowledge and promote self-advocacy.

The Thalassemia Western Consortium is a regional network of 11 thalassemia centers across the West Coast. The Consortium aims to establish collaborative thalassemia standards of care, collect data on thalassemia services and outcomes, and reach hematologists outside of their group. The Consortium met in November 2018 for its fourth annual meeting in San Diego, CA.





Monitoring Deferasirox Therapy

Ashutosh Lal, MD, UCSF Benioff Children's Hospital Oakland

SIDE EFFECT	MONITORING	FREQUENCY	ACTION ¹
Reduced renal function	Serum creatinine	3-4 weeks	<ul style="list-style-type: none"> Lower dose by 25% if >33% increase over baseline at 2 consecutive visits Lower dose by 50% for 1 week if > upper limit of normal (ULN) Increase gradually to previous dose if tolerated. Interrupt therapy if creatinine >2x ULN
Renal tubular dysfunction	Serum potassium, phosphorus and bicarbonate	3-4 weeks	<ul style="list-style-type: none"> Lower dose by 25% if potassium, bicarbonate or phosphorus are < lower limit of normal on 2 consecutive visits Interrupt treatment for 1 week or more for severe deficits
Proteinuria	Urine protein: creatinine ratio (or albumin: creatinine)	3 months	<ul style="list-style-type: none"> Confirm any urine dipstick 2+ or higher with spot urine protein:creatinine or albumin:creatinine ratio If urine protein: creatinine ratio >0.5 g/g (or albumin:creatinine >300 mg/g) on 2 consecutive samples one month apart, lower dose by 50% and consider nephrology evaluation Explore alternative causes for proteinuria
Elevated transaminases, but normal at baseline	Alanine aminotransferase (ALT)	3-4 weeks	<ul style="list-style-type: none"> Lower dose by 25% if ALT>3x ULN on 2 consecutive visits Interrupt therapy if ALT>10x ULN or direct bilirubin >2x ULN Explore alternative causes for elevated ALT
Elevated transaminases at baseline	Alanine aminotransferase (ALT)	3-4 weeks	<ul style="list-style-type: none"> Lower dose by 50% in individuals with chronic viral hepatitis or marked liver iron burden if further elevation in ALT (>2x from baseline value and >5x ULN) on 2 consecutive visits (see literature review) If ALT does not improve after one month of holding DFX, the higher dose may be resumed
Retinopathy	Retinal examination	12 months	<ul style="list-style-type: none"> Specialty evaluation to rule out alternative etiology if abnormal
Drug interactions	Concomitant drugs	3-4 weeks	<ul style="list-style-type: none"> Evaluate potential interaction with initiation of any new drug (see literature review)

¹Action: Consultation with a comprehensive thalassemia center is recommended if a toxicity is recurrent or causes interruption of treatment

DESIGNING THE TMCs

Each checklist has three sections:

Summary table with essential information

Literature review and rationale for the recommendations

Bibliography of citations made available online with a link provided in the TMCs

2 Summary of Literature Review:

Jadenu contains the same active ingredient as Exjade, and the two are similar except that Jadenu has 36% greater bioavailability and 30% higher peak serum concentrations.¹ The dose of Jadenu is 70% of comparable Exjade dose, which is an important consideration when patients switch between formulations. The bioavailability and peak and trough serum concentration of DFX are increased when it is taken with fat-containing meal,² though this has not been observed to change the frequency of side effects.³

A common side effect of Exjade is gastrointestinal discomfort in up to one-third of individuals manifesting as nausea, abdominal pain or diarrhea.⁴⁻¹¹ These side effects appear to be less with Jadenu from experience and supported by patient-reported outcomes in a study.⁴ A serious side effect of deferasirox is occurrence of GI hemorrhage. GI bleeding is believed to be more common in elderly patients with thrombocytopenia secondary to malignancies, and its use in such cases is contra-indicated if platelet count is <50 x10⁹/L. Cases of bleeding from gastric or duodenal ulcer in individuals with thalassemia lacking these risk factors are rare but serious.⁵⁻⁸

A minority of patients experience elevation in transaminases during DFX treatment,^{6,9-11} although the true incidence is

unknown as severe iron overload also causes hepatic inflammation. Establishing baseline liver function is important (particularly when liver iron concentration exceeds 15 mg/g dry weight) to avoid unnecessary reductions in dose. The larger studies have reported persistent elevated alanine transaminase (ALT) in 1-6% of patients on DFX treatment. These elevations were usually mild, but 13% of patients experienced increase in serum ALT levels over ten times the upper limit.¹ Cholestasis is reported in an occasional patient,¹ but is very rare. Deferasirox is contraindicated in patients with severe liver disease (Child-Pugh C), and should be administered at a 50% reduced dose in those with moderate (Child-Pugh B) dysfunction.¹²

In clinical practice, the most frequently encountered toxicity of DFX is renal dysfunction. This can take various forms, including elevated creatinine, proteinuria and proximal tubular dysfunction. The use of DFX is contraindicated in patients with creatinine clearance <40 ml/min.¹² Increase in serum creatinine is relatively frequent and may require reduction in dose. The incidence of transient creatinine elevation is 32-38% in clinical trials^{13,14} with dose reduction in 13% of subjects.¹⁴ Acute renal failure can develop if the dose is not modified, though its incidence is <1%.¹³ Proteinuria occurs in 6% cases but the need for dose reduction due to persistent high-level proteinuria is rare.^{10,15} Tubular dysfunction or Fanconi's syndrome, manifesting as urinary electrolyte wasting and glycosuria, has been described in multiple case reports,¹⁶⁻²³ with an incidence of 8% in one clinical trial,²⁴ but rare in others.¹³ Tubular dysfunction is more common in pediatric patients with relatively low body iron.¹² The occurrence of febrile infection and dehydration, such as from diarrheal illness, can uncover or increase severity of acidosis that may require urgent attention. Low serum phosphorus and potassium are commonly described in this setting.^{21,22}

Skin rash can occur at the beginning of treatment with DFX in 4-17% of patients,^{14,25,26} but is transient in most cases, allowing continuation of therapy with or without a brief interruption. In post-marketing experience, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, anaphylactic reactions, vasculitis and angioedema have been reported.¹² Severe immune or cutaneous reactions preclude further therapy. Other rarely seen side effects are lenticular opacities and, possibly, hearing loss.^{27,28} Deferasirox is contraindicated during pregnancy and lactation. Deferasirox may interact with other drugs due to its effect on cytochrome P450 enzymes (such as induction of CYP3A4 and CYP2C8), and its metabolism by UDP-glucuronosyltransferase (UGT). A complete list of these agents is available with deferasirox prescribing information and through programs to analyze drug interactions.

References for this checklist can be found online at the Cooley's Anemia Foundation's website: www.thalassemia.org/checklists-references. The Cooley's Anemia Foundation encourages doctors to utilize this information in treating thalassemia patients.

This project was supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) under grant number U1AMC28550 (Thalassemia). This information or content and conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.

ACCESSING THE TMCs

There are currently three TMCs available, which discuss the following topics:

1. Managing Transfusion Therapy
2. Monitoring Deferasirox Therapy
3. Monitoring Iron Overload in TDT

Hematologists, patients, and families can access printed copies of the TMCs from Thalassemia Treatment Centers, such as ours. They can also download electronic copies from thalassemia websites like:

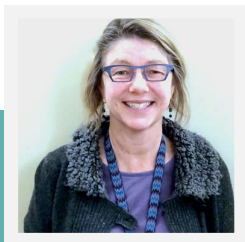
WWW.THALASSEMIA.COM/TMC

Thalassemia Management Checklists were developed in collaboration with the UCSF Benioff Children's Hospital Oakland, the Weill Cornell Medical Center, the Children's Hospital of Philadelphia, and the Cooley's Anemia Foundation.

6TH ANNUAL THALASSEMIA ADOPTION CLINIC

BY WENDY MURPHY, LCSW

For the past 6 years, we have organized a special clinic for families who have adopted a child with transfusion-dependent thalassemia. Most of these children have been adopted from China and live all across the United States. While many live in a community where their child may only know one or two other children with thalassemia, some live in a community where they do not know any other children with thalassemia.



Thalassemia Patients” (Gregory Kurio, MD), **“Renal Effects with Chelation”** (Christina Lo, MD), **Updates on Gene Therapy”** (Mark Walters, MD), and **“New Therapies in Thalassemia”** (Elliott Vichinsky, MD).

While the parents were attending the Dinner Talk, the children were being entertained with games, art activities and dancing. **Dancin Power**, a nonprofit organization that teaches interactive dance classes free of charge to hospitalized children, got the children pumped up with fun dance moves. We also received generous support from **AssetMark, Inc**, a local company, where several of their employees helped with the children’s program.

After all of the appointments, dinner talk — and fun and games, the annual clinic wrapped up with goodbyes to new and old friends. Before returning to their cities, many of the families stayed at a local hotel to continue socializing, as their children have become friends over the years and appreciate the chance to be together again, making the most of their opportunity to interact with others like them.

A special thank you to Heather Frandsen for her support and advice to our Thalassemia team in planning the Adoption Clinic. We really appreciate her guidance in addressing the needs of adoptive families.

On July 18th and 19th, 2018, the Northern California Comprehensive Thalassemia Center hosted our Sixth Annual Adoption Clinic. Families brought their child for a consultation in our clinic, obtained annual tests, and had appointments with other subspecialties.

On the evening of the 18th, our center held a Dinner Talk, a round-



table meeting where parents got to hear and speak with experts regarding the latest news in thalassemia care. Topics this year included **“Brief Overview about the Importance of Exercise”** (Ellen Fung, PhD, RD, CCD), **“Endocrine Issues with Thalassemia”** (Tariq Ahmad, MD), **“Cardiac Issues with**

Alpha Thalassemia Major,
Continued from Page 5

require regular blood transfusions and iron chelation therapy.

Depending on the availability of a suitable donor, some are treated with hematopoietic stem cell transplantation. In some important aspects, alpha thalassemia differs from its better-characterized beta thalassemia counterpart. For instance, neuro-developmental and congenital abnormalities can be prevalent in individuals with alpha thalassemia major and may require clinical support or intervention.

Over the course of first 4-6 months after birth, hemoglobin Bart’s is replaced by hemoglobin H, but the latter is equally incapable of transporting oxygen. Thus, suppressing hemoglobin H fraction in blood is an important goal of transfusion therapy in alpha thalassemia major.

Studies of long-term post-natal outcomes are sparse, and those that exist are limited by small sample sizes and variable management.

Currently, researchers at UCSF and BCHO have developed a registry for individuals with alpha thalassemia major. This, in addition to improved prenatal screening and management practices, may begin to remedy this dearth of information on the condition — fostering a deeper understanding of alpha thalassemia major and informing evidence-based guidelines for the care of those affected by it.



INTERVIEW WITH DR. LI ZHU

BY MEGHAN FOE, OUTREACH COORDINATOR

In November 2018, the news channel KTSF aired a segment about thalassemia on a Mandarin-language talk show featuring subject matter experts on a variety of topics. The segment featured Dr. Li Zhu, who began collaborating with the Northern California Thalassemia Center as part of an effort to raise awareness about thalassemia in at-risk communities. Dr. Zhu is a general pediatrician whose patient population is primarily Asian. In this interview, we talk to Dr. Zhu about the importance of providing culturally aware care and her perspectives on thalassemia as a community doctor.



TELL ME ABOUT YOUR PEDIATRIC PRACTICE. YOU ARE WORKING WITH THE ASIAN HEALTH SERVICES, RIGHT?

The private practice where I currently work, Pediatric Medical Associates, will merge with Asian Health Services next year. It's a very good fit, because most of my patients can continue to see me, and many are Chinese speaking. I'm excited to become a part of this large non-profit community health center that provides high quality, comprehensive care to the underserved Asian communities.

WHAT IS IMPORTANT ABOUT PROVIDING CARE THAT IS SPECIFIC FOR THE ASIAN COMMUNITY?

Families who, say, are Chinese-speaking are often relieved to find a doctor who speaks their language with whom they can comfortably communicate. Also, they are more comfortable with someone who actually understands their culture, who understands that there are other ways of approaching health and keeping healthy.

WHAT IS AN EXAMPLE OF BEING CULTURALLY AWARE IN MEDICINE?

Here's an example: drinking water. In general, most doctors tell people to drink a lot of water, right? People in America are used to ice water, but in Chinese culture, ice water is not so healthy, and a big no-no for post-partum moms. Nurses who are very culturally aware won't give a big pitcher of ice water to Chinese moms right after they have their baby, because in that first month,

they need to drink warm fluids and eat warming foods, such as foods cooked with ginger. Because they're still in the state of recuperation, they are very susceptible to damaging elements such as cold.

WHAT IS IMPORTANT TO COMMUNICATE ABOUT THALASSEMIA TO THE GENERAL OR AT-RISK POPULATION?

Not a lot of people are aware of how common it is. The carrier rate can be super high in some communities.

Also, it's really important for prospective parents to know about prenatal testing and pre-conception testing for thalassemia.

Lastly, I want people to understand how severe thalassemia can affect a person. For example, they need to have chronic transfusions, or they need to undergo some major, risky procedures like bone marrow transplantation. It's not an easy thing for a family or a child to take on those kinds of extra tasks in addition to living their regular life.

I WAS THINKING ABOUT HOW YOU TOLD ME THAT THALASSEMIA IN CHINESE MEANS "MEDITERRANEAN ANEMIA."

Yeah, the term we use is:

“地中海贫血 / 地中海贫血”
(di4 zhong1 hai3 pin2 xue4/
dei6 zung1 hoi2 pan4 hyut3)

or another term I heard was,

“海洋贫血 / 海洋贫血”
(hai3 yang2 pin2 xue4/
hoi2 joeng4 pan4 hyut3)

which means, “Mediterranean anemia” or “Oceanic anemia” because it occurs in the coastal regions. A lot of people may misunderstand it as something that occurs in the Mediterranean region and not in Asian regions.

WHEN YOU'RE NOT WORKING, WHAT DO YOU LIKE TO DO?

My husband and I like spending time with our three kids. We enjoy nature, so we like to take them hiking and camping. I started meditating regularly about a year ago. That was part of the reason I took on this TV interview. Meditation really opened me up as a person, helping me become aware of the connection between everything and everyone. I realized that whatever I can do to benefit others is worth undertaking. I welcomed this opportunity to serve the community, and it sure was a good learning experience.

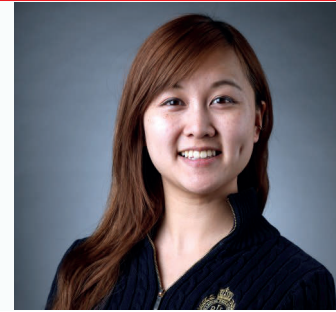


Read the full interview online:

<http://thalassemia.com/interview-dr-li-zhu.aspx>

THALASSEMIA RESEARCH STUDIES

BY LISA DU, STUDY COORDINATOR II



TITLE	ABSTRACT
<p>Natural History of Iron Burden and Risk of Organ Injury as Assessed and Predicted by Non-Invasive Measurement Techniques</p>	<p>Longitudinal assessment of whole body iron burden is essential for managing chelation and phlebotomy therapies — and may be effective in predicting risk of organ injury. Biomagnetic susceptibility measurement of liver iron concentration using SQUID technology. We will assess iron burden by biosusceptometry and serum ferritin at CHRCO and evaluate the clinical evidence of cardiac, hepatic, endocrine and orthopedic dysfunction, and relate it to total iron burden as assessed by biosusceptometry and other non-invasive techniques.</p>
<p>Evaluate the Efficacy and Safety of RBCs Derived from Mirasol-treated Whole Blood Compared with Conventional RBCs in Patients Requiring Chronic Transfusion Support (PRAISE Trial)</p>	<p>Thalassemia is the most transfused syndrome worldwide. The risk of transmitting pathogens is reduced by pre-screening of blood donors and testing of the blood. The Mirasol System offers a means to make transfusions significantly safer by targeting unscreened and undetected pathogens. This is a prospective, multi-center, randomized, crossover trial to evaluate the clinical effectiveness of RBCs derived from Mirasol-treated WB versus conventional RBCs in transfusion dependent thalassemia patients.</p>
<p>Towards the Development of a Noninvasive Prenatal Testing for Beta-Hemoglobinopathies</p>	<p>The goal of this project is to show proof of concept for a non-invasive prenatal test (NIPT) for beta-hemoglobinopathies utilizing a novel DNA probe capture assay and next generation sequencing (NGS). Our preliminary data have shown that our probe capture/ NGS system can overcome the challenges implicit in the analysis of cfDNA for NIPT: low DNA amount. The final proof of principle for this NIPT assay requires blood samples from pregnant couples, confirmed to have mutations in the beta-globin gene. For this work we are collaborating with our Indian colleagues at the Postgraduate Institute of Medical Education and Research, Chandigarh.</p>
<p>A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent -Thalassemia, who do not have 0/0 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral A-T87Q-Globin Vector in Subjects under 50 Years of Age</p>	<p>This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with β-thalassemia major. Patients must be less than 50 years of age with transfusion dependent β-thalassemia who do not have the $\beta 0/\beta 0$ mutation and are clinically stable to undergo transplantation but who lack a suitable matched family member donor.</p>
<p>A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects with Transfusion-dependent B-Thalassemia, who have a 0/00 Genotype, by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo with a Lentiviral Globin Vector in Subjects 12 - 50 Years of Age</p>	<p>This gene therapy study is a single-arm, multi-site, single dose, phase 3 study to evaluate the safety and efficacy of autologous hematopoietic stem cell transplantation (HSCT) using LentiGlobin® BB305 Drug Product in patients with transfusion dependent β-thalassemia. Patients must be at least 12 years of age with the $\beta 0/\beta 0$ mutation and be clinically stable to undergo transplantation but who lack a suitable matched family member donor.</p>

TITLE	ABSTRACT
<p>A Multi-center, Randomized, Open-Label, Parallel-Group Study with LJPC-401 for the Treatment of Myocardial Iron Overload in Adult Patients with Transfusion-Dependent Beta Thalassemia</p>	<p>This is a study of hepcidin (LJPC-401) in adults with transfusion-dependent beta-thalassemia and cardiac iron overload. This is an open-label study in which half of the participants will receive weekly subcutaneous injections of hepcidin in addition to their regular treatment for 52 weeks. The rest of the participants will receive regular standard of care for the first 26 weeks, and then will receive weekly hepcidin injections for the next 26 weeks in addition to their regular treatment. This study is designed to enroll 100 patients across multiple sites. BCHO plans to enroll up to 5 patients.</p> <p>Hepcidin is a substance produced by the liver to control the iron levels in plasma. Changing the amount of hepcidin allows control of iron released into the plasma from body stores and absorption of iron from food. As such, synthetic hepcidin may help in controlling iron excess. The aim of this protocol is to evaluate the effect of treatment with hepcidin on iron overload in the heart muscle. The study will also evaluate if the use of hepcidin safe and tolerable.</p>
<p>A Phase 2, Open-Label, Multicenter Study to Determine the Efficacy, Safety, Pharmacokinetic, and Pharmacodynamics of AG-348 in Adult Subjects with Non-Transfusion-Dependent Thalassemia (Pending)</p>	<p>This is an open-label multi-center study in patients with non-transfusion-dependent thalassemia, including patient with beta thalassemia and hemoglobin H constant spring disease. Approximately 17 patients will be enrolled at 3 sites in the United States. BCHO will enroll approximately 8 patients.</p> <p>Thalassemia is an inherited blood disease where the body cannot make enough hemoglobin. This produces anemia that can be severe enough to require blood transfusions for survival. Many patients do not require regular transfusions, but are at risk from the effects of severe anemia. The treatment options for such patients are very limited. In this study, we are evaluating whether the study drug, AG-348, which may improve the energy metabolism of red blood cells, will lead to improved overall fitness and survival of blood cells.</p> <p>The study will include patients with either beta thalassemia intermedia, or hemoglobin H Constant Spring disease. The primary objectives of this trial are to measure the improvement in hemoglobin level in response to treatment with AG-348. Secondary objectives are to evaluate the safety and pharmacokinetics or AG-348 and to determine the effect of the AG-348 on markers of hemolysis, erythropoietic activity and iron metabolism.</p>
<p>A Phase 2 Study of PTG-300 in Non-Transfusion Dependent (NTD) and Transfusion-Dependent (TD) β-thalassemia Subjects with Chronic Anemia (Pending)</p>	<p>This is an open-label study in which participants will receive weekly subcutaneous injections of PTG-300 in addition to their regular standard of care for 16 weeks. The study participants will receive the study drug at different dosage with the potential to titrate up in accordance with safety and efficacy evaluation. This study is designed to enroll 84 patients across multiple sites. BCHO plans to enroll up to 2 patients.</p> <p>Hepcidin is a substance produced by the liver to control the iron levels in plasma. Changing the amount of hepcidin with the hepcidin mimic allows control of iron released into the plasma from body stores and absorption of iron from food. Ineffective erythropoiesis is the hallmark of β-thalassemia that elicits a number of compensatory mechanisms resulting in erythroid marrow expansion, extramedullary hematopoiesis, splenomegaly, and increased gastrointestinal iron absorption. As such, a synthetic hepcidin mimic may result in iron redistribution in β-thalassemia subjects with potentially beneficial effects on erythropoiesis and consequently improvements in chronic anemia.</p>

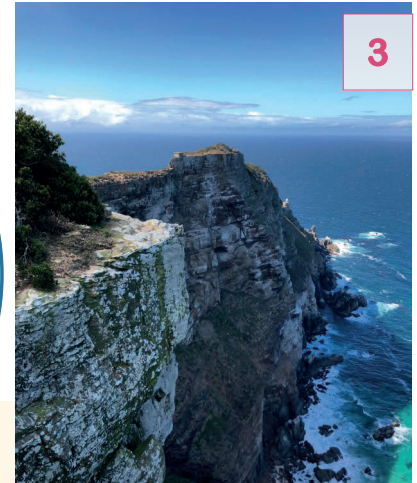




1



TRAVELS
 ABROAD:
 Photos from our Readers



3



2

1. Giza, Egypt (Tanou Chanhchaleun)
2. Crater Lake, Oregon (N. Ruparel)
3. Cape of Good Hope, So. Africa (Nimit Ruparel)
4. Petra, Jordan (T. Chanhchaleun)
5. Ha Long Bay, Vietnam (N. Ruparel)



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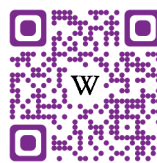
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If you no longer wish to receive our newsletter, please email info@thalassemia.com.