
The Duct

Bringing you news on PSC



PSC PARTNERS
SEEKING A CURE

research, education, and Support

PSC Partners Seeking a Cure Foundation Summer 2012-II



PSC Partners' Million Dollar Milestone

As Fundraising Committee Co-Chair, I have the honor of announcing that PSC Partners has just accomplished a significant fundraising goal. Seven years of fundraising, followed by our 2012 Road to Research Campaign, led us to the one million dollars that have now been raised and committed to PSC research. These funds will be used exclusively to support research to help find a cure and better treatments for primary sclerosing cholangitis. Every dollar was the result of fundraising efforts and gifts to our foundation.

This milestone is evidence that PSC Partners Seeking a Cure continues to be committed to our mission. The achievement of this million-dollar milestone will allow us to continue to support research and demonstrates to the scientific and medical community that our foundation is credible and dedicated to achieving its mission: to raise funds with which to research the causes and a cure for PSC.

The Million Dollar Milestone is a huge success, but it is only a stepping-stone in our most critical mission to find a cure. Personal fundraising for PSC Partners Foundation is how we support our future and is the lifeblood of our hope. I am confident, with your support, that the next million dollars will come more easily.

We need your help! The cure for PSC will come through research. Research is expensive. Every dollar matters. There is work to be done. Please consider launching your own PSC fundraising effort

today and accept our invitation for assistance and mentoring. Together we will help make your vision a success.

We are here to help you in your fundraising efforts. If you have any questions, please do not hesitate to contact us at fundraising@pscpartners.org.

Thank you for supporting PSC Partners throughout the years. We are counting on your continued resources and talents in helping us move our cause forward.

With gratitude,

Ken Shepherd

Fundraiser Spotlight

Jordan Hannold

written by: Sandi Pearlman

Jordan Hannold Fast Facts: Age: 18

Location: Pennsylvania

Career Aspirations: E! News Correspondent or something in the medical field

Event: Fundraising Walk in honor of her cousin, Travis, to raise PSC awareness and funds.

Living in Pennsylvania with a mean cat and dreams of either being an E! News correspondent or doing something in the medical field, and citing Math and Gym as two of her favorite subjects, it would be easy to dismiss Jordan Hannold as just another pretty, brunette high school senior (now graduated) with self-diagnosed Bieber fever and an amateur celebrity stalker status. Except she's not. Eighteen-year-old Jordan turned a





graduation requirement into something remarkable, a chance to raise funds and awareness for PSC Partners Seeking a Cure and all of us living with the disease every single day.

Jordan was just sixteen years old when she learned her cousin Travis had PSC. She remembers her mother sitting her down and explaining it to her but it not quite sinking in. Travis and Jordan have

always been more like brother and sister (complete with sibling-style teasing) than cousins and Jordan just couldn't grasp what the words "primary sclerosing cholangitis" meant. Now, two years later, with a bit of time and age, she says this, "Travis and I were always close since we are the same age. [...] He picks on me and I pick on him. [...], However, it [the diagnosis] did make me appreciate Travis a little more and made me



realize he can handle

tough situations with a positive attitude and he doesn't let this disease change him." That inspiration and having participated in a walk for another cousin who was born with "severe physical damages" led Jordan to take that first step, pun intended, and hold a walk for Travis and for PSCers everywhere.



Her plan was simple, she knew she'd need a place to hold the event, an official go-ahead from Travis since it affected him, and a way to advertise her walk. Her local high school was more than willing to let her use their track. Travis, who had recently held a PSC fundraiser of his own, gave his enthusiastic okay and all that was left was advertising. Luckily for PSC Partners and PSCers everywhere, Jordan loves public speaking and isn't shy. But she says her plan would work for anyone. First step, she says, "Get the word out to as many people as possible. Tell all your friends to tell their friends and have your family tell their friends too. [...] Create a Facebook event with all the details for all the people you may not see everyday. It only takes a matter of minutes and hundreds of your friends can get all the details of your event. [...] Also, don't think that you need to hold the biggest most extravagant event to make a difference.

Any amount of involvement will make a difference in someone else's life." And a difference her walk did make. Despite the "coldest, ugliest day of March," and Jordan's fear that no one would come out in the rain and freezing temperatures, "everyone came out dressed in layers to help support PSC." The rain even magically stopped right when the walk started, leaving Jordan elated and convinced that the key to fundraising and raising awareness is to "just put your mind to it and you can do it. Don't give up and even if you think it might not be a success, it most likely will be."

Even after the walk was over, people remained and impromptu soccer and football games broke out, the sounds of laughter and accomplishment literally filling the field. And as for Jordan, it reconfirmed her faith that "every little thing can make a difference. If you can make just one more person aware of something, it could spread to many more people." It also made her more determined than ever to destroy the myth that "diseases like PSC only affect much older people." She says, "Travis is only seventeen years old and is very active and outgoing - not what I would normally think of as someone who has a potentially life-threatening disease."

So this reality "trash" TV show addict who loves to laugh, sing, and dance, and daydreams about moving to LA to live the Hollywood lifestyle is just your average teen right? Well, for the sake of all of us PSCers and caregivers all around the world, I hope so. Jordan, I hope all your dreams come true. Thank you for helping us to reach ours. As far as we're concerned, you're already a star.

SAVE the DAY

Join the ongoing local fundraisers all over the globe!
Special Fundraising Weekend October 12-14, '12.
Want to be a part of the action towards the cure?
Hold your local fundraiser and see your event
featured on our upcoming new webpage! Find out
how you can start a fundraiser by contacting us
today at fundraising@pscpartners.org.

A Dream Come True: PSC Partners Selected by ORDR To Create a Patient Registry



by Rachel Gomel

We are extremely excited and proud to share with you the great news that PSC Partners has been selected by the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), a branch of the National Institutes of Health (NIH), to participate in a two-year pilot project that will result in a PSC Partners patient registry and that will serve as a model for other rare disease organizations!

It is a dream come true for PSC Partners, especially because for the past two years, we have been solidly moving towards creating a patient registry. However, we would have been alone in this endeavor. Being selected to take place under the umbrella of the NIH and to serve as a model for other disease registries will be taking us to yet another level. Our registry will be guided and supported by the leading minds and national organizations that are currently focusing on advancing rare disease research and treatments.

ORDR has selected 34 organizations to participate in the GRDR pilot program: 19 organizations already having patient registries, and 15 organizations without registries, divided between organizations having under 2500 patients and over 2500 patients in their database. A review committee evaluated information provided by patient organizations according to specific selection criteria. To place the above in context, there are 7000 rare diseases!

The goal of the ORDR is to establish a Global Rare Diseases Patient Registry (GRDR) encompassing registries of the thousands of rare diseases. By standardizing each rare disease registry, researchers will be able to analyze data across many rare diseases, find commonalities, and facilitate clinical trials. Our registry will be PSC specific and will include medical information and family history of de-identified PSCers.

Though our registry will be under the GRDR umbrella, it will be the property of PSC Partners and of each participating patient. The information will be collected in a standardized and secure way. The aggregated data will be used for clinical and translational research, to recruit patients for clinical trials, to develop therapies, and to learn about population patterns and their association with disease development. Imagine a cure coming from within our own PSC Partners family!

Our guides will be the ORDR, and in collaboration with the ORDR, Patient Crossroads that will help to establish and host our registry; the Children's Hospital of Philadelphia that will recommend disease specific questions for patient data entry; WebMD that will provide input and recommendations on marketing and promotion for research and training programs. We are elated!

And to top it all, we are very excited about our own PSC Partners team. Dr. Chris Bowlus, hepatologist at University of California at Davis, is heading the registry project and will be working with our very own Dave Rhodes, Ricky Safer, Farla Kaufman and Rachel Gomel. With time, we will be looking for more experts among you.

However, this is not just an announcement bearing great news! It is an invitation, a plea, to each and every one of us to participate in this registry when we are ready to go! Remember, we each hold the key for a cure! Together in the fight . . . whatever it takes!



PSC Partners Grant Program Selections

by Richard Green, MD; Professor of Hepatology/
Gastroenterology, Feinberg School of Medicine, Chicago;
Co-Chair of PSC Partners Scientific/Medical Advisory
Committee (SMAC)

Editor's note: It was three years ago in January 2009 that PSC Partners awarded its first research grants selected on the basis that they supported research addressing an important and novel, basic or clinical research question related to PSC. For PSC Partners, this was an important milestone, an important step towards taking us closer to new treatments and to a cure. In three years, we have reached yet another momentous milestone of a magnitude we could have never imagined in the early days of the Grant Program. At our conference this year, PSC Partners announced that thanks to all of your donations, we had reached the first million dollars dedicated exclusively to PSC research. Dr. Green describes the three studies that were selected for a two-year grant for 2011. In September 2012, the SMAC will be announcing a second set of grants.

PSCPartners Seeking a Cure has recently funded three research studies on the pathogenesis and diagnosis of PSC and on potential therapeutic approaches for treating PSC. The recipients of the awards include Nicholas F. LaRusso, MD, the Charles H. Weinman Professor of Medicine at the Mayo Clinic in Rochester, Minnesota; Rinse K. Weersma MD, PhD, Associate Professor, the University of Groningen, The Netherlands; and Geoff Baldwin, PhD, Imperial College, London, UK.

These three investigators are of international renown and have proposed highly innovative studies to advance the diagnosis and therapy of Primary Sclerosing Cholangitis. Each has provided a summary for members of PSC Partners.

1. Dr. LaRusso's molecular and cellular biology study entitled *Potential role of cholangiocyte senescence in PSC* hypothesizes that the repeated exposure to injurious molecules promotes cholangiocyte (bile duct cells) deterioration which contributes to the onset and progression of PSC.

In Dr. LaRusso's words, "Primary sclerosing cholangitis (PSC) is a multifactorial disease with genetic, microbial, and environmental components. Emerging evidence suggests that cholangiocytes, i.e. the cells of the bile ducts, may not only be affected in PSC, but may actually participate in driving disease progression. Our recent data suggest that cholangiocytes, in response to biologically-relevant injurious stimuli, transition from a proliferative to a senescent phenotype, a metabolically active cellular state in which the cell is no longer capable of cell division. Furthermore, these cells secrete excess amounts of inflammatory mediators. Based on our recent work, we propose that chronic exposure to injurious molecules promotes cholangiocyte senescence and secretion of inflammatory molecules, thereby contributing to the development and progression of PSC. The proposed experiments will establish cholangiocyte senescence as a fundamental cholangiocyte response to persistent injury, address the mechanisms by which relevant injurious stimuli induce cellular senescence, and interrogate whether PSC-associated senescent cells are mediators of disease. This is a novel approach to understanding the development and progression of PSC that may have important implications for understanding disease initiation/progression and provide insights for the development of novel therapies."

2. Dr. Weersma's genetic study entitled *The Exome in PSC* uses novel genetic techniques to identify genetic factors responsible for Primary Sclerosing Cholangitis. Dr. Weersma summarizes his proposal: "PSC is a complex disease, with both environmental and genetic factors involved in its development and disease course. It is thought that changes in multiple genes in the human DNA explain part of the etiology of the disease. In recent years it became possible to screen the human genome by using 100,000s or even millions of markers spread around the genome. Several regions on the human genome have now been identified that contain genes that are associated with disease. Since PSC is a rare disease and large numbers of patients are required, this work has been performed by multiple centers throughout the world that have collaborated. It is expected that additional genetic regions will be identified in the near future.

By using these large numbers of genetic markers, we now know which broad regions on the human genome are associated with the disease, but we do not know which specific genetic variants within these regions are causing protein changes that lead to disease. Most of the associated variants are not causal, but merely markers for other functionally important, causative variants. Variants that reside in the so-called exons of the genes have direct implication in protein function and are therefore very interesting. Part of the heritability is thought to reside in these rare exomic variants with greater effect-sizes. Therefore, the primary aim of the study is the identification and confirmation of rare exomic variants involved in PSC pathogenesis.

This will be done by using a custom-made exome genotyping array including $\approx 250,000$ variants, to genotype a cohort of 1000 PSC patients and 6000 healthy controls. A second cohort of 1000 cases and 1000 healthy controls is available for replication of observed signals. Identified variants will give important insights in disease pathogenesis. The variants on the exome array will have direct functional implications and will therefore enable additional functional studies and hopefully targets for novel therapeutic interventions. In addition we might identify mutations with predictive value for disease occurrence or disease behavior."

3. Dr. Baldwin's study entitled *A Nano-Device for the Early Stage Detection of Cholangiocarcinoma* uses cutting-edge nano-technology that is currently revolutionizing diagnosis and therapeutics in many hepatic and other diseases. Its application to PSC may bring new perspectives. Dr. Baldwin describes his proposal: "Cholangiocarcinoma is a bile duct cancer that develops in up to 40 percent of individuals suffering from primary sclerosing cholangitis (PSC). If identified at an early stage, cholangiocarcinoma can be treated by resection of the liver. Unfortunately for individuals with PSC, the inadequacy of current screening technologies means that cholangiocarcinoma is frequently diagnosed at a late stage when palliative care is the only remaining option. By developing a tool for the early stage detection of cholangiocarcinoma, we aim to improve the prognosis of PSC. Protein nanocages (PN) are naturally occurring spherical structures. They are composed of multiple proteins that bind together in a specific pattern to create a spherical structure with a large internal cavity. We intend to re-engineer a PN such that the cavity can be loaded with an imaging agent and targeted to cholangiocarcinoma cells. Such a device could enable the early-stage detection of cholangiocarcinoma. Furthermore, a cholangiocarcinoma targeting nanocage constitutes a platform technology that could be adapted for the targeted delivery of chemotherapeutic molecules. PSC Partners has generously provided us with the resources required to test our nano-device in a *proof of principle* experiment. This study represents a first step towards a new generation of highly targeted therapies that have the potential to significantly improve PSC prognosis. The project will be implemented by an experienced team of engineers, scientists and clinicians. We expect to complete an *in vitro* proof of concept within 24 months. If successful, we will pursue additional funding to translate this technology into clinical practice where it could improve PSC prognosis."

The above proposals were among the numerous meritorious grant proposals submitted from around the world. Those selected utilize highly innovative molecular biology, genetic and nanotechnology techniques to provide research that could potentially have high impact on the search for a cure for PSC. At a time when government funding of research throughout the world is becoming extremely competitive, it is through the generosity of PSC Partners and their generous donors that progress towards a cure for PSC will continue.

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breaking news on
our community, new
research and
more...

Note to Readers:

Articles in this newsletter have been written by persons without formal medical training. Therefore, the information in this newsletter is not intended nor implied to be a substitute for professional medical advice.

PSC Partners Conference at Mayo Clinic Rochester Friday Afternoon Program



Stress Management and Resiliency Training (SMART): Program for PSCers and Caregivers

Amit Sood, MD, MSc, Associate Professor of Medicine, Director of Research and Practice, Integrative Medicine, Associate Director, General Internal Medicine Research, Chair

Reported by Rachel Gomel

In his two-and-a-half hour mini-training session, Dr. Amit Sood gave invaluable information on stress management and resiliency training for PSCers and caregivers. The impact of his presentation was felt throughout the weekend, as conference attendees talked about Dr. Sood's concepts in various contexts.

The Stress Management and Resiliency Program (SMART), as explained by Dr. Sood, consists of three components: 1. *Awareness* – how the brain and the mind work; 2. *Ascending* to a higher level; 3. *Actualizing* or transforming to one's highest potential. This process can be learned in spite of adversity, and can be helpful to anyone experiencing stress. SMART trains people to change their perspective and be in control of thoughts entering the brain.

Dr. Sood avoided defining "stress" and used the title of an old movie, "The Good, the Bad and the Ugly" to discuss stress. Among the *good* or healthy stresses, he named sports, eating a donut, traveling with a baby, taking an exam. Our stressometer better not read zero, he warned. The *bad stresses* include losing one's job or having no time to exercise. Even if these do not mean that there is something wrong with your life, how you carry the stress and for how long you live with this stress have an impact on your body.

When we eat emotionally, all our organs experience stress at the cellular level. With chronic stress, there is a *change in our chromosomes*, and our body becomes *physiologically* much older than a person of the same age experiencing lesser stress.

An example of *ugly stress* is having metastatic cancer and experiencing its repercussions, such as pain, the feelings of finiteness, and financial cost incurred by the disease. The uncertainty and lack of control create a “ring of stress” that can include anxiety, depression, obesity, diabetes, or memory loss. In confronting such stress, we see that some people are more resilient than others. What makes these people more resilient?

Dr. Sood identified the sources of stress as a *loss of control*, *loss of meaning*, and *loss of compassion*. He gave the example of a doctor seeing twenty-two patients a day and being stressed for not being able to show compassion. We experience loss of meaning in chronic illness. There is no meaning to pain, and this mental state permeates the mind and affects the body physiologically.



He contrasted the feelings evoked by watching little girls in a ballet performance versus watching soccer semifinals between Italy and Germany. In the latter case, adrenaline levels rise considerably. A study showed that in the 2006 games in Europe, the rate of heart attacks among males rose twofold. The impact is biological, affects sleep, behavior and general health.

To describe *resilience* Dr. Sood spoke about the willow tree that is flexible in high winds, has good roots and withstands and bounces back after a storm. The willow tree shows us that the first step towards resilience is *coping*; second, it is knowing how to return to balance – *rebalancing*. And the third step is *growing* from the experience.



As applied to human beings, resilience means resisting adversity. *Physical resilience* means the ability to maintain well-being. *Cognitive resilience* means maintaining focus in adversity. *Emotional resilience* allows us to continue with life the way Helen Keller, for example, continued being productive while being blind. And *spiritual resilience* makes us a spiritual black belt as we approach adversity with a realistic and flexible disposition.

Following this description of stress and resilience, Dr. Sood went on to provide a general background of the brain and how it runs our life. He spoke about the neuroplasticity of the brain that functions like an orchestra, each part and each of the hundred billion cells and trillion supporting cells collaborating with each other. The brain can be compared to playdough rather than to concrete. We have the power to revive and shape parts of the brain. The longer you exercise a part of the brain, the stronger that part will become. In a study, it was seen that taxi drivers had a well-developed posterior part of the brain though they had impaired memory and couldn't remember items they were told to buy for their home.

The higher and lower parts of the brain are separate networks we can actually activate in different circumstances. One is the **Task Positive Network** that gets activated when we see a caribou while crossing the street. The caribou is an unexpected novelty, and we focus on its exterior details because the scene is unusual and sudden. The second network is the **Default Network**. When our Default Network is active, all our files are open and we do nothing to activate any of them and let things happen. Some parts of the brain are activated as we mindlessly read or automatically drive to our destination.

These two networks are like traffic lights. The green light is the Task Positive Network, while the red light is the Default Network. Most of the day we are on default, and we shuttle between the two. We need to aim to be mostly on the Task Positive Network with some Default. The Default Network is important, as it is responsible for creativity; however, it should not be the dominant network. People with Alzheimer's have too much Default thinking and do not have control over the direction of their thoughts. They cannot consciously choose their thoughts. The Mayo SMART Program teaches ways of being *externally focused*.

The mind processes information in three stages. The first is *Attention* (input) during which we are on focus mode. The second is *Interpretation* and the third is *Action* (output). If tired, we will notice only that which is familiar to us – a Starbucks store or a clown. We are in *attention mode* when there is a threat, pleasure, or novelty. Threats function as black holes of the mind: They naturally lead us to rumination and start with a kernel of negative that can overwhelm us if we maintain our focus on naturally occurring black holes.

Q & A: A question from the audience turned Dr. Sood towards a PSC-specific issue, that of encephalopathy. Wouldn't encephalopathy necessarily lead to the predominance of default thinking? Dr. Sood said that letting the default network dominate predisposes a person to chronic pain and that the mind can still control the default network with encephalopathy.

Q & A: How does different sensory input affect the mind's networks? Dr. Sood said that we give most of our attention to vision. We must enhance engagement of the other senses to move to task positive thinking.

A discussion on the benefits of volunteer work on the mind ensued from the above questions. Volunteering helps stress because it helps the person attain higher meaning. Anti depressants enhance task positive network activity, but by volunteering or by performing activities that bring meaning to one's life, one can attain the same results naturally rather than artificially.

After discussing the *attention* component of focused thinking, Dr. Sood went on to the second component, which is *ascent to a higher level*. He provided simple but most effective training tools to rise above our natural instincts of letting our minds wander into black holes. The audience joined in these exercises. He explained that we would need to make our attention "joyful." And to accomplish *joyful attention*, one must withhold judgment and not allow the mind to wander into a black hole.

Exercise #1

The minute you wake up, make the first thought of your day that of *gratitude*. Think of five people to whom you feel grateful. Create a mental collage of these people you love. Place each at the center of an imaginary circle and express your gratitude. A tremendous shift takes place in the brain, and the person starts the day by activating the task positive network.



Exercise #2

Then continue bringing in pleasant sensory experience that you consciously choose. For example, try to feel and describe in detail the sensation of the soft carpet on the bottom of your feet. Unless you give your mind something to think about, it will move into a black hole. With chronic pain, the mind automatically would use the default network. It is important to fill the mind with positive thoughts. One must have a good wake-up plan. The key is to shift from one network to another.

Q & A: What if the black hole comes back? Dr. Sood said we should not push the black hole away but just start all over again with the gratitude and sensory exercises. The goal is to increase the mega pixel of our external sensory network and change the physiological make-up of our brain.



Exercise #3

Attention leads to interpretation, said Dr. Sood. The goal is to delay interpretation. One way is to focus on nature and be attentive to details. The audience had to focus on the details of the picture of a butterfly and a flower, and looked at the layers and layers of details in these beautiful specimens of Nature. This exercise makes you externally focused and pushes away default thinking. It makes us look at the flower not as a generic yellow daisy but as *this* yellow daisy. His advice was to spend more time in Nature.

Exercise #4

How do we spend time together with a loved one? Make your time together a micro-celebration by cooking together, having a healthy meal together. The option of being attentive to Nature is not often realized because of our hurried and busy lives. However, we can control our time with a loved one. Most often, as we are more apt to pay attention to novelty, we would rather give more attention to a long-lost high school friend than to our partner who offers us no novelty.



Practice being with your partner as if you haven't seen him/her in a week. Think of our *transience*. The feeling of transience anchors us in the moment and allows us to be kinder and more loving. Our first instinct is to find fault in others and in looking for what is wrong. Do not try to improve those you love. Accept them as they are. Be genuinely interested in the other. Find one good and authentic thing to say. This approach externalizes attention and creates changes in the brain.

In summary, practice joyful attention and gratitude for 15 minutes, four to eight times a day. For the rest of the day, pay attention and delay judgment.

Exercise #5

Have *scheduled worry time*. If you have too many open files, you postpone joys. Take half an hour a day to think of your worries. You can control your Default Network by writing in a diary when you feel worries coming. The goal is to close open files.

Exercise #6

Feel *kind attention*. Practice acceptance and forgiveness. Instant judgments are not helpful. Align your eyes and silently wish the person well, before you start judging him/her. Dr. Sood said that this is the way he starts with each of his patients. This approach of kindness and compassion prevents him from being irritated with a patient. Practice this "I wish you well" exercise many times a day.

Exercise #7

Integration of attention. Look at a person and see someone meaningful and spiritual and find a connection with the person. Dr. Sood started with a blank screen on which the picture of a woman's face very gradually appeared, and finally the audience could see that the face was Mona Lisa's. His message through this exercise was to be **mindful** and see people as important and unique.

It is important to note that our attention is guided by our preferences, and our preferences are guided by our prejudices. Prejudices create shortcuts. At the sight of "leaves of three," we generalize, and quickly tell ourselves, "let them be," thus using prejudice to consider all leaves of three as bad.

Exercise #8

Have a theme for each day. Focus on *gratitude* on Monday. If something bad happens to you, tell yourself, "I'm grateful I was never robbed; I'm grateful I wasn't the one who robbed." In other words, change your *threshold* to a good one. On Tuesday, focus on *compassion*, Wednesday on *acceptance*, Thursday on reaching a *higher meaning*. Make Friday about *forgiveness*, Saturday about *celebration*, and Sunday about *reflection*. It is easier to share sadness than to share someone's joy. Practice enjoying someone else's happiness.

Being compassionate is inherent to human beings, and we are compassionate to those we love and to those who are connected to us. So we need to create new connections with people to increase our compassion. Another way of creating positive energy is to be compassionate with oneself.



Practice *acceptance*, a concept lying somewhere between apathy and obsessive behavior. Acceptance is seeing things as they are and finding ways of engaging with that reality. Dr. Sood asked the question, "How broad is our sphere of control?" We cannot control our place of birth or falling in love. Through non-acceptance, we are fighting ourselves. Ask yourself, "Am I going to think about it five years from now?" Go to the extreme and find the worst-case scenario so you can see things in context and accept your situation.

Finding *higher meaning* requires *not personalizing* and believing that you can make the earth a better place. You ask yourself, "Who am I?" and you respond, "I am an agent of service and love." Why do I exist?" "I exist to make earth a little happier." "What is this world?" "It is a big school of learning." Nothing is personal in this perspective.

This exercise is about changing thresholds, having gratitude for big and little things in your life.

Q & A: Chronic illness consumes you. What do you do? One wastes four to five hours every day. You can change that by going through these exercises even when in pain.

Q & A: How can one teach all this to a child? Mayo has such a program directed to children. Children can be taught through gratitude exercises.

Dr. Sood and the conference participants could have gone on and on. At the end of the session, the audience surrounded Dr. Sood and continued with questions. You can purchase his book, *Train Your Brain, Engage Your Heart, Transform Your Life: A Course in Attention and Interpretation Therapy* by calling the Mayo Clinic Store, 507-284-9669 or 888-303-9354 (toll-free).

Breakout Session Summaries

Cancer Surveillance: Risks and Outcomes

Gregory J. Gores, MD, Chair of Gastroenterology and Hepatology
Mayo Clinic Rochester

Presentation slides available at [Cancer Surveillance: Risks and Outcomes](#)

Reported by Joanne Hatchett

Slide 3 – Dr. Gores worries more about cholangiocarcinoma (CCA) in those with newly diagnosed PSC. There is not as much risk with those who have had PSC longer.

Slide 4 – Surveillance: Blood Test Screenings are controversial. The blood test CA 19-9 is effective, yet it is still not clear why 1/3 of those with high CA 19-9 don't get cancer. Sometimes the numbers go up long before a tumor is found. Some people have high values and never get cancer. It is not known how sensitive the test is and how high the numbers need to soar.

Yet CA 19-9 is a simple test, and it is accessible. Dr. Gores likes to test, unlike other doctors who are more hesitant to test. The cost effectiveness of testing CA 19-9 is unknown.

Among imaging studies, ultrasound and CT scans are ineffective for cancer screening. MRCP is the best imaging tool.

Slides 5 and 6 – CCA is a slow growing cancer, and testing once a year is sufficient. Dr. Gores emphasized that CCAs occur within the first years of diagnosis. The treatment for CCA is liver transplantation which is life saving. Dr. Gores commented that if the disease develops slowly and the risk is high, it is important to monitor frequently. He recommends monitoring annually for most PSCers.

Q: Does the risk of CCA relate to the severity of PSC or to how long someone has had PSC?

A: The answers are not clear. He recommends annual CA 19-9 testing. He said most occurrences of CCA are in the first 5 years of disease.

Q: What about the range of CA 19-9 numbers?

A: Dr. Gores said that 25 to 50 is “OK”; for those with PSC; under 100 is OK, but he worries about numbers over 100. If CA 19-9 is over 100, he likes to get brushings for malignancy. If no cancer is found, then he would repeat testing in 3 to 4 months.

After CCA and liver transplantation, the chance of recurrent cancer in the new liver is very rare.

Slide 7 - Hepatocellular cancer (HCC) is relatively rare. In those with PSC and cirrhosis, he recommends an annual MRI which also monitors for developing hepatocellular cancer.

Slides 8, 9, 10 - Dr. Gores commented that he feels most people with PSC also have ulcerative colitis (UC). He thinks about 85% of those with PSC have UC .

He recommends annual colonoscopy for those with PSC and UC.

Slides 11, 12, 13 - Gallbladder cancer does occur in those with PSC, and Dr. Gores said, “Doctors may not think about this.” Thus, he recommends annual surveillance or MRI with MRCP. *He also said it helps for the radiologist to know that a patient has PSC and that s/he is being monitored for CCA and any gallbladder polyps.* Dr. Gores said that giving more information to radiologists helps in their interpretation of MRCP, ultrasound, etc.

If a gallbladder polyp is found in a PSC patient, he recommends the removal of the gallbladder.

Slide 14 – Should patients with PSC take ursodeoxycholic acid (Urso)? Urso does not prevent cancer, and high dose Urso may increase the risk of cancer.

Slide 15 – Take home points: PSCers should have MRI/MRCP and CA 19-9 annually to screen for CCA, gallbladder neoplasia and hepatocellular cancer (HCC).

He recommends reserving ERCP for abnormal MRI/MRCP. ERCP is more invasive, costly and risky than colonoscopy. During an endoscopy, brushings are important to look for abnormal cells. Dr. Gores does not believe in having an annual ERCP. He said that ERCP could be used as follow-up when there is an abnormal MRI/MRCP.

To screen for colorectal cancer, the patient should be given a complete colonoscopy with biopsies at the time of PSC diagnosis. An annual colonoscopy with multiple biopsies is recommended for those with PSC and UC.

Needed: *Volunteer letter writers to thank donors who make our conferences affordable and who fund PSC research.*
contactus@pscpartners.org



Inflammatory Bowel Disease and PSC

Edward Loftus, MD, Professor of Medicine
(replacing Dr. Sunanda Kane)
Mayo Clinic College of Medicine

Presentation slides available at [Inflammatory Bowel Disease and PSC](#)

Reported by Neil Dubrovsky

According to Dr. Loftus, 95 percent of patients with PSC have Inflammatory Bowel Disease (IBD), whereas only 5 percent of people with IBD have PSC. In fact, many PSC patients don't know that they have IBD until it is discovered during a colonoscopy.

Of the PSCers with IBD, 80 to 90 percent have ulcerative colitis (UC), while the rest have Crohn's Disease (CD). The PSCers' UC is characterized by diffuse and superficial inflammation of the mucosa in the bowel. In contrast, CD can be located anywhere in the GI tract, is patchy, and is penetrating (transmural).

Distinguishing between the two can be difficult, and the clinician needs to assemble all the available information to decide. PSC patients sometimes exhibit symptoms of both. For example, they may present as Crohn's but may actually be UC. Distinguishing between the two also has important surgical implications.

The cause of IBD is not known but likely involves a combination of genetic susceptibility and an environmental trigger. For example, while defects in the NOD2 gene are common (perhaps about 30 percent of the population), only a fraction of those with the defect develop CD. The intestinal microbiome is also important. Most treatments for IBD treat the symptoms without addressing the cause.

IBD in PSCers is often mild and only recognized after diagnosis of PSC. There seems to be two general classes of patients - those in which the liver disease presents first with very mild UC, and those that have active UC with PSC following UC. The course of IBD in patients with PSC is not necessarily different from the path followed by those who do not have PSC, and treatment is the same.

One important distinction is that patients with PSC have a greater risk of colon cancer than those with IBD without PSC. Average lifetime risk of colon cancer increases from 5 percent to 5–10 percent with UC, and to 25-30 percent with PSC and IBD. Due to this increased risk, an annual colonoscopy is recommended, even for pediatric patients. In addition, the use of indigo carmine dye during the colonoscopy has been shown to be more effective (three fold) at detecting flat, precancerous areas (precancerous dysplastic cells, or simply dysplasia). The increase in the rate of colon cancer in PSCers in the absence of IBD is not well defined.

There is no difference between the medications used in the treatment of IBD with or without PSC, but

this area is not well studied. There is anecdotal evidence that PSCers do not tolerate some medications. For example, it is Dr. Loftus' experience that PSCers often do not tolerate ASAs (acetylsalicylic acid, i.e. aspirin derivatives such as Asacol, Lialda, and Pentasa). Treatment of IBD usually starts with ASAs, temporary use of prednisone to "kick-start" remission, and progresses to the use of the immune-suppressants 6MP and azathioprine (Imuran), and biologics such as infliximab (Remicade). In general, the stronger the medication, the more side effects there will be. It is to be noted that removing the colon does not help the liver, and a liver transplant does not help the colon.

Q: There were a number of follow-up questions on how to reduce the number of pre-cancerous dysplastic cells.

A: Some studies have shown that if you suppress inflammation, you will reduce the number of dysplastic cells. Infliximab, however, has no apparent effect on occurrence of dysplasia. Similarly, Dr. Loftus was not familiar with any studies examining the effect of Vancomycin on the rate of dysplasia. He noted that Vancomycin is used to treat *C. difficile* infections, which often occur after the use of other antibiotics.

Q: Does low-dose naltrexone show any promise for PSC or UC?

A: Dr. Loftus said that yet unpublished studies recently concluded at Penn State were not well done, as they were not randomized. The IBD community therefore does not trust the data and discounts the findings.

Q: If you are asymptomatic, but an exam shows increasing inflammation, should you stay with your treatment or accelerate it?

A: In the past, the answer would have been not to change the medical treatment with an asymptomatic patient, but currently the focus has been on mucosal healing to reduce the likelihood of cancer.

Q: Should I be concerned about hepatic toxicity with ASAs?

A: "Don't worry – just monitor." The same holds true for azathioprine and 6MP.

Q: Is *clostridium difficile* (C diff) opportunistic?

A: Yes, it is, said Dr. Loftus. He first checks for C diff when a patient has an IBD flare. He noted that transmission of C diff is strictly by contact, and is not airborne.

Q: Is there a diagnostic antibody associated with IBD?

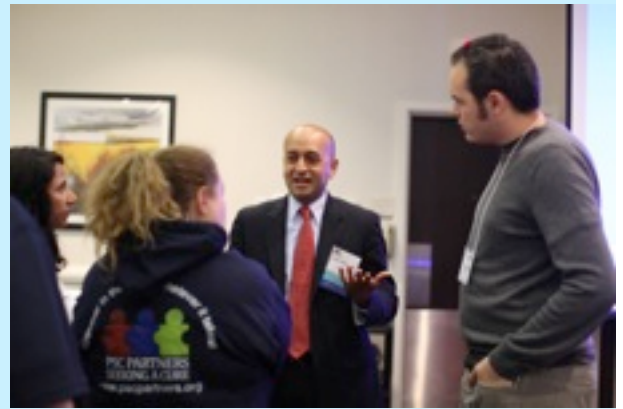
A: It was believed that the *saccharomyces cerevisiae* antibodies test (ASCA) held much promise in the diagnosis of CD. However, this test is nonspecific. If the colonoscopy is negative, the presence of ASCA does not point to CD. A PSC patient with diarrhea, however, makes him suspicious of IBD.

Q: Has premature failure of fertility been associated with IBS/PSC?

A: Some increased premature failure of fertility has been thought to be immune related. The answer may therefore be, yes, especially in PSC patients, but we're not sure.

Role of MRI & Advanced Endoscopic Techniques in PSC

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Presentation slides available at [Role of MRI and Advanced Endoscopic Techniques in PSC](#)

Reported by Arne Myrabo

Magnetic Resonance Cholangiography (MRCP)

MRCP was developed simultaneously in both Europe and the United States in the early 1990s. Neither group had knowledge of the other's efforts. MRCP uses magnetic principles to create a visual image of tissue and structures. The biggest advantage of the non-invasive MRCP procedure is that it can "see" the bile ducts, and there is no exposure to ionizing radiation.

Gadolinium is usually used as the intravenous (IV) contrast agent and can allow visualization of details of the blood supply. MRCP can also be performed without IV contrast. Images obtained with MRCP are considered to be as good as ERCP now, and ERCP is usually reserved for cases where therapeutic action is needed (e.g. balloon dilatation of bile duct). Due to technology sharing, MRCPs are usually acceptable regardless of where they are taken.

With respect to PSC diagnosis, MRCP studies show 86% sensitivity (if the test is positive, it will be correct 86% of the time) and 94% specificity (if the test is negative, 94% of the time it will be correct). Even if an ERCP is needed after an MRCP to address a stricture, studies still show MRCP to be cost effective, primarily because complications are avoided.

Image processing has greatly improved in just the last five years. Current images show outstanding detail due to changes such as magnet strength and breathing practices (to get a better "picture," data acquisition is performed while the patient is not breathing)..

Magnetic Resonance Elastography (MRE)

A fairly recent technology, MRE is often done at the end of an MRCP. A small plastic disk, or driver is placed above the liver. As it vibrates mechanically, waves are generated in the liver, much like a pebble tossed in a pond. Using computer analysis of the waves, a 3D image of the "stiffness" of the liver can be obtained. This can be used to establish areas that have more scarring and determine disease progression. Comparisons with liver biopsies show excellent correlation.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

Under sedation, a tube is passed through the stomach into the small intestine. The major papilla (bile duct drain into small intestine) is now accessible. A small tube can be inserted into the bile duct to

inject contrast media so the bile duct “tree” can be seen. Other instruments can also be inserted such as balloon catheter, cytology brush, stone removal forceps, etc.

Common features of PSC are a beaded look (beads on a string), consisting of narrow, scarred areas (string) and upstream dilation (bead). These narrow parts, or strictures can be expanded with a balloon-like device. Often, this mechanical dilatation will relieve cholangitis, fatigue and itching. Usually, the Mayo Clinic avoids using stents (straw-like plastic tubes), but when a stent is used, it is only left in between four to six weeks. Cell brushings are usually taken during an ERCP to check for abnormal cells. Antibiotics are taken post-ERCP to ward off possible infections. The most common complication is pancreatitis (inflammation of the pancreas), which is observed in 1-5% of ERCPs and that usually resolves within a few days.

Cholangioscopy (mother/daughter scope) allows direct visualization of the interior of the bile duct during an ERCP.

Intraductal US (direct ultrasound within ERCP scope) can be used to provide additional information on questionable areas.

Endoscopic ultrasound (EUS)

Main uses are for pancreatic disease, submucosal lesions, staging of GO malignancy and biliary tract evaluation. It is 90% effective for finding suspected gallstones. Its biggest role is in cholangiocarcinoma diagnosis. Lymph nodes can be sampled and blood vessel involvement visualized. These lymph nodes, even when they are bigger, are almost always benign. Their enlargement is just a reactive process in PSC. There is a trend with EUS to perform a needle biopsy on the bile duct to determine if it is cholangiocarcinoma. This is NOT recommended due to the possibility of “seeding” tumors.



Living Donor Liver Transplantation: A Guide

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Presentation slides available at [Living Donor Liver Transplantation: A Guide](#)

Reported by Nancy Reeves

Background

There are currently [about 2.5 times as many individuals waiting for a liver](#) as there were liver transplants in 2011. Of the 6342 liver transplants in 2011, 6095 received their liver from a deceased donor and 247 received a graft from a living donor. Since 2002, organ allocation is based on the [MELD](#) score, which is designed to predict who is most likely to die in the next three months, rather than being based on time on the list. No consideration is made for suffering, revolving door hospital stays, encephalopathy, frequent and debilitating cholangitis, or other factors which have a major impact on quality of life. As a result of this change in allocation, fewer people have died on the waiting list, but there are more people who are [“too well for transplantation, too sick for life.”](#)

Living donor liver transplant (LDLT) has become part of the solution to the organ shortage and an option for individuals who are sick, but not sick enough to be eligible for the few deceased donor livers which are available. LDLT has been available for pediatric patients since 1989, and [around 1998](#) for adults.

Making the Decision

Both the recipient and the liver graft survive better with LDLT than with a liver from a deceased donor (DDLT). [At 10 years](#) post transplant, the recipient and graft survival rates are 70.7% and 61.7%, respectively, compared to 58.7% and 52.9%, respectively, for the donor and graft with DDLT. Two multi-center studies, comparing the survival of all patients in the applicable populations in the [U.S](#) and [Canada](#), reached similar conclusions, even when adjusted for disease severity, age, and companion diseases.

In addition, using LDLT also comes with less tangible benefits. The “too sick for life” period can be shortened because it is possible to be transplanted sooner than a liver from a deceased donor would be available. A shorter time on the wait list also decreases the risks associated with becoming sicker while waiting for a liver. The transplant can be scheduled at a time that is convenient for all the parties, and the preservation of the liver graft in transit between donor and recipient is much simpler. In addition, the meticulous review process for a live donor typically results in an optimum graft (the portion of the liver donated). Some of these factors, including the likelihood that someone who has a living donor also has a very strong support system, probably contribute to the better survival rate with LDLT.

Although there are clear advantages to LDLT, there are also disadvantages. For the recipient, there is an increased risk of biliary strictures. Scarring, which can occur with any surgery, is more likely when the size of the bile ducts being joined are mismatched (as they are when using the right lobe of a liver,

rather than the entire liver). Strictures are generally manageable with stenting, and are not related to the risk of recurrent PSC. Earlier studies on the recurrence of PSC may have overestimated it because the strictures sometimes mimic PSC.

The primary disadvantage is that LDLT requires performing major surgery on someone who does not need it and who receives no medical benefit from it. A [number of studies](#) have [documented](#) the short-term risks to donors. Complications occur in around 35-40% of all donor surgeries. These include infection of the wound, abdominal complications (including intestinal blockage), clotting, pulmonary embolisms, fluid accumulating around the lungs, biliary or vascular injury, bleeding or a bile leak, and insufficiency of the remaining liver. In about 0.3% - 0.5% of the cases the donor dies or the remaining portion of the donor's liver fails (placing the donor at the top of the waiting list for a new liver). Virtually all short-term risks occur within the first year. The risks to the donor decrease with the experience of the center with live donation, and screening has been adjusted to better exclude donors who are at higher risk for post-surgical complications such as the risk for post-surgical clotting.

Less is known about the long-term risks. Living donors have only been used for adults since approximately 1998, and in the United States there is no long term tracking mechanism for donors. The Mayo Clinic has just completed a follow-up study on all of the ninety-eight donors who are more than a year past donation. Sixty-four of the donors returned for imaging, routine labs, a history, and physical exam. The donors who returned were an average of 5.4 years post donation. None of the donors had any complications with their own livers, other than asymptomatic changes that are normally associated with gall bladder removal (a part of the donation process). Common changes noted were weight gain (not necessarily related to donation), numbness around the incision, changes in bowel function, and moderately lowered platelet counts. One donor required treatment for depression.

All sixty-four donors were comfortable with their decision, including sixty-two of the donors who would make the same decision again, most citing the satisfaction of knowing they had saved or improved a life. The biggest challenges they noted were the surgical pain, more significant than expected recovery time and physical limitations, and the extended time away from home.

An unexpected finding was that donation impacted the ability of some five donors to obtain life or health insurance. The problems included higher premiums, longer time to qualify, more rigorous standards for proving they were in good health, denial of individual coverage, and the inability to switch plans.

The donor's medical costs are paid by the recipient's insurance or by the transplant center, from evaluation through transplant. Compensation for time off of work is not covered, but the [National Living Donor Assistance Center](#) may be able to provide assistance for lost wages and donation related travel costs. Treatment of other health problems, discovered as a result of the donor evaluation process, is not covered. The recipient's insurance covers any complications for the period immediately following the surgery and some transplant centers (Mayo, for example) will cover donation related medical and psychological care for the rest of the donor's life.

Even though short and long-term survival is equivalent or superior for LDLT, the decision to donate is not trivial. Being a live liver donor requires major surgery with the potential for serious complications and requires about 6-12 weeks off work. Some larger corporations offer paid time off, but most individuals

do not have the ability to take a three-month leave from work with or without compensation. Another non-medical factor in making the decision is the possibility that the transplant may not be entirely successful. The liver graft may be rejected or lost because of surgical complications. Even with a perfect surgical outcome, approximately twenty percent of individuals with PSC who are transplanted are eventually diagnosed with recurrent PSC (fewer than 5% need a second transplant). It is critical that both the donor and recipient prepare emotionally for the possibility that the donor's gift will not succeed in either the short or long term.

Overall, balancing the risk to donors and the benefit to the recipients, LDLT is an option which is best suited for individuals with a lower MELD score and significant symptoms, or for those at the highest risk for death if they are required to wait for DDLT (cholangiocarcinoma, a blood type that is compatible with fewer donors, or an area of the country where the demand for donors is high and the supply low, for example). Live donors can be used for patients with both PSC and PSC/AIH overlap. Waiting until the MELD score is extremely high, and the patient is extremely sick, may eliminate LDLT as an option because the right lobe may no longer be sufficient. On the other hand, when the MELD score is low and symptoms are minimal, risks of transplant to both donor and recipient outweigh the benefits.

[Becoming a Donor](#)

Living donors must generally be between 21 and 55 years old, and free from major chronic medical conditions, substance abuse, psychiatric issues, financial, or social constraints. The upper age protects both the donor and recipient because liver regrowth slows around age 55, a process needed for both donor and recipient. (Because the entire liver is used in DDLT older donors are acceptable). The donor blood type needs to be [compatible](#), but not a perfect match. A near-perfect match with a liver increases the risk for a rare and severe complication (graft v. host disease). The donor needs to be a similar weight or larger than the recipient.

A potential donor initiates the process by contacting the transplant center. Preliminary blood work and health screening, to rule out major barriers to donation, can be performed locally or by phone. A more thorough 3-4 day on site medical review includes evaluation for undiagnosed medical disorders with a special emphasis on undiagnosed liver disorders, hyper-coagulable (clotting) states, or cardiopulmonary disorders. An independent evaluation team is assigned to the donor, including a hepatologist, a live donor nurse coordinator, a psychiatrist, and a social worker/donor advocate. A complete psychosocial evaluation is performed including exploring the donor's motives (in order to rule out coercion or incentives), assessing health behavior, and screening for psychiatric, cognitive, and coping problems.

Once there are no medical or psycho-social barriers, the liver itself is evaluated. The liver must be able to be split into a graft which weighs more than about .8% of the recipient's weight and still leave the donor with 30-40% of the liver. Livers are not all identical, and there may be biliary or vascular variations which make splitting the liver impossible for the donor, the recipient, or both. Occasionally, a biopsy will be required to assess fat in the liver. In [one larger study](#), 40% of the donor candidates were accepted. Half of the disqualifications were medical in nature. The donor may withdraw from the process at any point, without revealing to the recipient the reasons for the withdrawal. The disqualifications in the study included both donor and recipient withdrawals.

The Donation

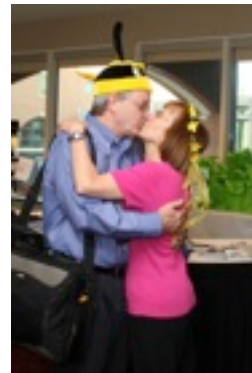
Either lobe can be used. If the left lobe is large enough, using that lobe is easier on the donor. Typically, the left lobe is used for children, but the right lobe is required for adults. When the right lobe is used, the donor retains the main biliary trunk and the branches on the left side. The donor graft, including the biliary structures in that graft, replaces the entire liver for the recipient.

Approximately one week after the surgery, the donor's liver is approximately 70% of its previous size, and by the end of second or third week it has regrown to a size sufficient to handle the donor's metabolic demand. Even though the liver regrows to its original size and is fully functional, the resulting biliary structure is different from the original structure. (It resembles the many small branches which grow when large tree branches are trimmed around power lines.) This new structure makes it unsuitable for a second living donation.

Less invasive surgical techniques are being developed. Columbia University Medical Center has developed a laparoscopic procedure which is used for adult to child donations. A number of small incisions are made to separate the graft. The graft is then removed through a slightly larger incision in the abdomen. The center hopes to expand the procedure for adult to adult donations later this year. This less invasive surgery reduces the recovery time to 2-3 weeks (rather than the more typical 4-8 weeks for the traditional surgery, as well as reduces the complication rate.



Our thanks to Arne Myrabo
for his dedication and tireless work as webmaster of the
PSC Partners Seeking a Cure website
www.pscpartners.org



Life After Liver Transplant

Jayant A. Talwalkar, MD, MPH, Associate Professor of Medicine

Mayo Clinic Rochester

Presentation slides available at [Life After Liver Transplant](#)

Reported by Rachel Gomel

Dr. Talwalkar's session was well attended by PSCers who were full of questions about life after liver transplant. He started by explaining that the Mayo Clinic was very involved with patients for the first few months after transplant and that he would be sharing his personal perspective as a Mayo Clinic transplant physician.

He gave the 2008 UNOS statistics on the indications for liver transplantation. PSC came fifth in the U.S. with 6 percent of all liver transplants, while PBC closely followed with 5 percent (PBC transplant rate is on the decline). PSC is therefore an important condition for liver transplant. When we look at patient survival by disease, PSC is seen to have the best survival rate. Living donor transplants started in 2000 and have become an important option. Prior to 2000, living donor transplant existed in Asia, primarily in Japan. A study shows that the live donor organ does as well as the deceased donor organ and that the five-year survival is similar in both. Hesitation to perform live donor transplants has been relieved by this study.

A typical operation at Mayo involves a 40-55 year old PSCer. Surgery takes 3-5 hours when there is no cirrhosis. It takes longer for live donor transplants. ICU stay is most often a day, and the hospital stay is between 7-9 days, depending on how sick the patient is before transplant. The patient is then followed for a month as an outpatient.

In the Mayo Protocol, a biopsy is performed on day seven to look for rejection. Dr. Talwalkar reminded the audience that the ominous connotation of rejection is unjustified, as rejection is a sign that the body is accepting the new organ, and in 99 percent of the time, rejection subsides with treatment. The first seven days have the highest rejection rates. Twice a week, the patient is given blood tests and immunosuppressants and is monitored carefully for rejection.

After a month, the patient is discharged and receives blood tests every week until four months, after which blood tests decrease to every other week. If the ultrasound looks fine, no biopsy is made for cancer, and if there had been cancer prior to the transplant, CT scans and biopsies are performed.

By six months, the immunosuppressants are decreased, and by one year, the dosage is at its minimal. After a year, patients have blood tests every three months and are only on Tacrolimus or Cyclosporine. Perhaps some will be kept on Immuran or prednisone to treat their IBD. At this point there are no restrictions in physical activity, travel, or occupation type. Though it is requested that exposure to infections be avoided, it is surprising how seldom transplanted patients catch a cold. After a year, medical appointments shift to "Tell me about your family."

The above is a rosy picture of when all works perfectly. There are, however, though rare in the most part, potential complications:

1. Acute cellular rejection (happens with over 20 percent of patients, mostly within the first seven days post-surgery). Liver enzymes are closely monitored and this complication can be resolved.
2. Chronic rejection (2percent). A biopsy is required to confirm the diagnosis. In this very rare complication, bile ducts disappear.
3. Hepatic artery thrombosis (5 percent) happens because the artery is sewn during surgery. Surgery resolves this problem.
4. Bile duct stricturing (10-15 percent) is resolved with a stent that is kept in for a short time.
5. Recurrent PSC (20-25 percent over ten years). Sometimes this rPSC starts as small duct PSC. Often it doesn't move and remains the same. In other cases, stenting may be needed. Second transplants are successful. Colitis can remain the same, or could get better or worse. The same risk of neoplasia exists. Regular surveillance colonoscopies are therefore required post-transplant.

Through experience, we have amassed much technical knowledge but little information on post-transplant quality of life. A study including 157 adult symptomatic PBC or PSC patients reported improved quality of life after a year post-transplant.

The results of a larger recent study show that after ten years, physical functioning is reduced; pruritis disappeared with transplant; fatigue does not always improve perhaps because patients are on immunosuppressants. There have been many studies on fatigue, and those show that many post-transplant PSCers forget they even had a transplant and are full of energy. There are more success stories than not. A transplanted member in the audience said that he had felt "fantastic" from the instant he woke up from surgery.

Q & A:

How often does PSC recur after transplant?

The new liver may or may not be susceptible to PSC. Though not the only factor, genetics are very important in transplant. The choice of donor can perhaps prevent PSC. With genetic studies, we will understand whether we may be replacing one PSC with another. The rate is not high.

Why isn't prednisone used for post-transplant patients in Canada and is current in the US?

At Mayo, prednisone is used to prevent rejection. We taper prednisone and discontinue its use at 4 ½ months post transplant. We taper faster than those who use prednisone. Some programs continue the small dose, and others are prednisone free.

Do you see PSC - autoimmune hepatitis (AIH) overlap patients who took prednisone prior to transplant and who are now prednisone free?

We keep the prednisone, though in low dose, because of the risk of recurring PSC and recurring AIH. The relapse rate is higher without prednisone which we taper quickly after two weeks. It is rare to have recurring PSC early on. It may happen years after transplant.

What are the risks of osteoporosis after transplant?

We monitor bone density closely. With cirrhosis, and post transplant, with immunosuppressants and prednisone, bone density declines. Some are helped with medication such as Fosamax. With time, bone density may rise and some even become normal.

How unusual is having multiple transplants?

It happens, though this is unusual. Sometimes the graft does not work, or a patient gets recurring PSC and needs another transplant. We have to remember that PSC is heterogeneous and people react differently.

What are your thoughts on Vancomycin?

The young pediatric PSCers may see some benefits. Improvement in biochemistry has been noted. Vanco works on bacterial infections, and a link between PSC and bacterial infections seems likely. We ask ourselves whether some types of PSC are bacterial while others may not be.

What is the likelihood of kidney failure caused by some of the medications?

If kidney function drops, immunosuppressants are quickly reduced. One can get side effects around four months post-transplant. We think long-term and change the medication. It is an art to balance medications.

How can you prevent cataracts and skin cancer when taking prednisone and Tacrolimus (Prograf)?

We check closely for changes and are aware of the risks.

Can we ever stop taking immunosuppressants?

We have seen some non-compliance. It is okay to skip a dose here and there, but not to stop taking the medication.

The most valuable part of the conference is the sense of connection, the sense of family. What I liked most was the friendship and support from all! Everything about this weekend was very emotional and difficult, yet also very rewarding and inspiring.

We are the best game in town for medical information, peer experiences and camaraderie.

Best weekend ever! Thank you so much for making this possible. I would not miss a future conference for the world!

Proactive Planning for Transplant

Lynn Pearson, RN, CCTC Moderator

Jane Kleist, LSW

Marilyn Salley, Patient Financial Services Representative, Transplant Programs
Mayo Clinic Rochester

Presentation slides available at [Proactive Planning for Transplant](#)

Reported by Chaim Boermeester

The three Mayo Clinic speakers were Lynn Pearson (Liver Transplant Coordinator), Jayne Kleist (Liver Transplant Social Services) and Marilyn Salley (Transplant Financial Coordinator).

Lynn Pearson, *Liver Transplant Coordinator*, started by commenting on the impressive and high caliber questions that had been asked at the lunch group breakout. She works mostly with pre-transplant patients, and also with children pre and post transplant.

A liver transplant may be far away in your future or it may be an option you need to seriously address right now. If a liver transplant is in the plans, you most probably already have a hepatologist.

Your first decision will be to select the location for your transplant. It may be the center where you receive medical care at the moment, or a center dictated by your insurance company. Other important considerations are travel time and survival statistics. The site www.ustransplant.org provides up to date information on survival statistics at various centers.

Evaluation:

At the point of transplant evaluation, you may just have been diagnosed with PSC, but most often, patients arrive with an established PSC diagnosis. The evaluation is meant to establish whether you need a transplant or whether it is still too early.

A typical transplant team includes the following specialists: a hepatologist, surgeon, social worker, financial advisor, dietician, pharmacist, researcher,* chaplains, nurses, lab technicians, radiologist, transplant nurse coordinator, endocrinologist (for Diabetes, IBD), cardiologist, pulmonologist (lungs), nephrologist (kidneys), operation room staff, infectious disease specialist, and educators.

**Note: Research is how transplant centers learn. It is an optional choice for you, but one should remember that this research provides an important self-improvement tool for transplant centers. Your care will not be affected whether you decide to participate in research or not.*

Transplant evaluation also serves to establish whether the patient has problems other than those arising from having PSC and whether these issues could be resolved or stabilized prior to transplant.

We need to educate the patient on risks and benefits, alternative treatments, survival rate, complications, medication side effects, and United Network for Organ Sharing (UNOS).

UNOS, the private, non-profit organization that manages the nation's organ transplant system under contract with the federal government, is the IRS of transplants. They set the rules for transplant and ensure that these rules are carefully followed. They face the huge challenge of making organ distribution as fair as possible.

The evaluation also entails an assessment of liver status and a determination of whether the liver disease is progressive, advanced, or incurable. The transplant team is the one to determine whether the patient can have a transplant or not.

Waiting List:

When approved for transplant, the patient is placed on the UNOS waiting list, a computerized list of all people in the US waiting for a solid organ transplant (heart, liver, kidney, pancreas, lung, bone marrow, bowel). People are listed according to blood type and body size.

Waiting time varies across the country and is based on the MELD Score which is dependent on lab values. The more abnormal the lab values, the higher the MELD Score will be. Children under twelve are rated by the PELD Score which also takes height and weight into account.

Financial Considerations:

When researching insurance coverage, the patient should consider the cost of transplant including insurance, medication coverage before and after transplant (medication can cost several thousand dollars a month after transplant and continue for a lifetime), travel and lodging, time away from work, post-transplant expenses.

Planning for a Transplant:

It is most important to take good care of oneself. One of the primary issues confronted by PSCers is fatigue. As the most common and devastating symptoms of liver disease, it must be remembered that only people with liver disease can know the intensity of this fatigue. And fatigue is a vicious circle. The more tired a person is, the less s/he does, and the worse the fatigue gets. The advice is to try to physically move, even if that would mean going to the mailbox and back several times a day.

Though PSCers have difficulties with sleep and often invert day and night, it is important to get adequate sleep, as sleep brings healing. Getting involved in hobbies, learning, work and games helps one to remain positive.

Nutrition:

People with liver disease tend to lose their appetite or their taste for certain foods. Though small amounts of protein should be eaten, it is important to make sure to get enough protein to build and maintain muscles. Small and frequent meals might be easier to handle than three large meals a day.

Vitamins should be taken as recommended. With liver disease, fat soluble Vitamins A, D, E and K, and the minerals Zinc and Calcium are not well absorbed. Vitamins A and C help with the immune system; Vitamin D helps bones and the immune system; Vitamin E is an anti-oxidant; Vitamin K helps clotting of blood; Zinc affects the cognitive system; and Calcium is important for healthy bones. When advised to take vitamin supplements, make sure to comply and to have vitamin levels monitored.

Medications:

To manage the various medications, using a pillbox and/or having a medication schedule have proven to be helpful.

Make a list of all your medications, dosage and side effects. Physical therapy helps to build strength. Some pre-transplant PSCers will continue to work as long as is possible. They prefer to stay busy and get out of the house. For some, being on disability means that they can take better care of themselves.

It is important to think of the wellbeing of caregivers. If family or friends offer to help, accept their desire to participate in your care.

Medical Care:

You will need to see your transplant team regularly. It is very important to have a local physician, and not necessarily a specialist. Do not assume that your specialist will inform the transplant center whenever needed. Make sure to keep the transplant center in the loop at all times.

Provide an authorization for the transplant center to share information with other healthcare professionals. You can indicate whom you want to include on your list and whom you would like to be excluded. A successful transplant team is the result of a concerted team effort.

Preparation for “The Call”

Make sure you have a plan to get to the transplant center within the eight to ten hours you are given. Some will have to relocate in preparation. Make plans on who will be taking care of bills, pets, or heating the house.

You will need to pack comfortable clothes, portable hobbies, laptops and books.

Be prepared for false alarms. The donor liver may not be adequate or you may have been called as a back up. Though patients face great disappointment when they get the call and do not get a transplant, they are better waiting for a good liver.

Other Considerations

The patient has the right to be listed in more than one transplant center. Each center has its own guidelines. If your insurance allows it, or you can afford it, you can be on more than one waiting list.

Some consider living donor transplantation; however most transplants are deceased donor transplantations. 10-20 percent of transplants are living donor transplants. The cost to the donor needs to be considered. It is your insurance that would cover travel, lodging, lost wages, and medical work-up.

Important Transplant Resources

www.ustransplant.org; www.unos.org; www.transplantliving.org

Jayne Kleist, *Liver Transplant Social Services, Mayo Clinic Rochester*, discussed practical planning, emotional reactions, social work evaluation, caregivers, and resources. It is important to be informed before going to a transplant center and inform others of your plans and your whereabouts. Find out about the climate of the location and pack appropriate clothes. Find a hotel that will accommodate your needs – oxygen, wheel chair accessibility are important to know ahead of time. Do not leave anything to the last minute. Bring a rolling suitcase to carry your medical files, your 24-hour urine jug, snacks, water, books and perhaps a laptop. The evaluation process moves on a tight schedule, so don't count on having time.

Make sure to bring your caregiver. At a time when emotions are running high, an extra set of eyes and ears helps to understand all instructions. Do not forget to bring your cellphone and laptop charger.

Inform yourself of your benefits at work, whether you are eligible for short or long-term disability, vacation time, and family medical leave. Make sure you get the paper work ahead of time. Find out whether your company accepts donated vacation time. Understand your insurance coverage and its limitations. Do you have travel, meal, lodging reimbursement for you and your caregiver? These considerations also apply to your caregiver who must also make sure to be informed.

It is important to save all receipts including parking, airfare, meals for yourself and your caregiver. Make sure you learn the medical assistance you are covered for in your state. Financial assistants will be present to help you in every transplant center.

Bring a copy of your advanced directive, if you have one. It will be placed in your file. It is a good idea to have a will, estate planning, and a financial power of attorney, documents you would not be able to complete if confused.

Expect emotional reactions to the transplant evaluation. From considering transplant as a distant option, suddenly the transplant becomes a reality. Relationships may change. Spouses may feel more like caregivers. The number of friends may decrease.

Identify the methods you like to use to deal with stress. It could be walking, talking to people, yoga or reading. Exercise and meditate as much as you can. Stay connected to all that gives strength – religions, organizations, or people. Be flexible. Nothing ever works exactly as planned.

Preparing for Social Work Evaluation

Jane Kleist explained that Medicaid and Medicare require this evaluation which is a discussion of who you are, where you come from, what you do, what your coping strategies are, what you understand about your diagnosis and about transplant. The social worker talks about your needs, habits, distances, finances, and support.

One of the most important topics is that of getting support. No one can have too much support. During evaluation, you must bring someone with you. It is of great importance that you identify who your support will be. It must be someone you get along with and not someone who will be waiting for you in the hotel while you go to your appointments.

You need a caregiver who may or may not be a spouse, a family member or a friend. You need someone from whom you have no secrets. Many personal questions will be asked. Your caregiver should not be afraid of medical issues, as descriptions may be quite graphic at times. It is also important that your caregiver have no addiction issues.

You will need a caregiver from evaluation through transplant. Having three and preferably five caregivers prevent burn out. Caregivers *do* burn out. If it is a spouse or a family member, your relationship will change. It is important to remember that the caregivers have their own families and problems.

Do not just accept help; also *ask* for help. People cannot guess your needs. Your cousin Joe might not be someone you would want with you for evaluation, but he might be great for mowing the lawn. Make a list of your needs, and select people who might be willing to help with those chores. When people say, "Let me know how I can help," do not give the usual response, "Oh, I'm fine; I don't need help." When you have your list, you can pick a chore and assign it. Be really specific. Ask for specific help from specific people.

Do not bring a child as caregiver. Someone under eighteen or twenty-one is not equipped to help, and there may be some legal repercussions.

Resources

Plan how you would want to spend your spare time. Find activities of interest to you in the city you are in. Many find services like www.caringbridge.org or www.carepages.com very helpful. These are free FaceBook type weblogs for people with medical needs. You can update daily what you did, what you need, in order to avoid giving your news each time you are asked. The site could be useful to the caregiver as well.

Marilyn Salley, Transplant Financial Coordinator

Before even calling for an appointment for your evaluation, the first thing you should do is to call your insurance company to make sure that a liver transplant is covered by the plan you purchased. Are there limits to the waiting time before transplant? Most plans have so called "centers of excellence" where they will direct you for your transplant. The pharmacy aspect of your insurance is as important as the transplant aspect.

The role of the transplant financial coordinator starts with a call to the patient prior to transplant evaluation. The financial coordinator will go over insurance information and make sure that everything is complete and accurate. We want to make sure that you have a plan we recognize and that you have the right referral for services at the transplant center. Some plans allow for only one transplant evaluation.

We ask many questions to avoid surprises. We are the ones who will follow up with your insurance, call for benefits, and determine whether there are any managed care requirements on your plan. We will address those requirements and make sure they are taken care of. We also ask whether the insurance company can assign a case manager. Many patients are wary of and nervous about having a case manager from their insurance company. We believe that they serve as your advocate and appreciate the presence of a case manager. We provide updated clinical information on your health status to the case manager and specify your position on the transplant list.

Though only the insurance company can quote your benefits, we can tell you about the information the insurance company gave us. And that includes your deductibles, your out-of-pocket maximum, a lifetime or an annual maximum, if you have one. Earlier in the day, there were questions on the changes made in health care with Obama. One of the initiatives had included the elimination of lifetime maximum; however, currently plans have shifted to an annual maximum. We make sure to inform you on such issues and policy changes as well.

One last piece of advice is to make sure you keep track of phone numbers of people (or their assistants) you spoke with during evaluation. You will be receiving so much information during evaluation that, inevitably, you will need to speak to some of these people again.

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Caregivers: Helping Us to Help Others

Mike Pearlman, JD, parent of a PSCer, Panel Moderator

Reported by Bill Bandy

Definition: By PSCer we mean a person with PSC. It is a term of efficiency, acknowledging that the person is much more than being defined by PSC.

Key points for caregivers from the panel members:

1. You will not be an effective caregiver if you don't take care of yourself.
2. Treat the PSCer as if he or she weren't having symptoms of PSC.
3. Don't let PSC define your relationship with the PSCer. Maintain a normal relationship.
4. Know when to offer advice and when to just listen.
5. Take care of yourself as a caregiver and maintain a normal life. Let the PSCer be a caregiver in return.
6. Don't overdo the caring. Don't make the PSCer feel like he or she has PSC.

Message to the PSCer: Let others help you because they *want* to help and will be grateful to you for letting them help you.

Questions with answers from the panel:

How to treat young adult PSCers when they are away from home, at school, traveling, or elsewhere: Trust the young adult's ability to take responsibility and to be able to figure things out, to lead a healthy lifestyle with proper diet and exercise, and abide by the medication regimen. Encourage your young PSCer to connect with fellow PSCers on FaceBook and other social networks. Let doctors know of their travel plans and whereabouts, and have the doctor's email address available for quick access in emergencies. Use all resources available to you before you need the information so as to be ready for any emergencies.

How to properly deal with your young adult children to insure they take their medications: Don't nag or try to micromanage them, but trust them, and let them take ownership of their medications. It is their responsibility to manage their medications. When possible, have their peers help them if help is needed.

How to find a balance in discussing medical issues when living away from your PSCer: Keep life normal for the person with the disease. Don't dwell on the topic, but instead, get the information and move on. Keep a positive attitude, but don't avoid the issue. Have an adult conversation, and consider using email if you can't have an open discussion. Make an agreement to withhold from asking about medical issues if they agree to inform you when they are having problems. Have a heart-to-heart conversation to communicate expectations and needs. Avoid trying to fix things; sometimes you just need to listen. You need to give the PSCer the opportunity to lead a normal life and to avoid being defined by the disease.

How to communicate with your spouse without having PSC define the relationship: As a caregiver, you have the right to feel tired without being told, “Welcome to my world.” In addition to verbal communication, try other techniques such as writing letters to one another.

How to help manage symptoms of itching for the PSCer: Try distraction. One approach is to provide an in-home “spa” space for a massage to relax the PSCer.

How to manage trips to the Emergency Room: Bring advanced directives, power of attorney documents, other documents providing you the authority to talk to the doctors, contact information for doctors, and lists of medications including dosages, allergies, and dietary restrictions. Discuss substance abuse issues. Be an advocate for the patient, but don’t be aggressive or intimidating with the nursing and medical staff.



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Interpreting Your Test Results

Andrea A. Gossard, RN, CNP Assistant Professor of Medicine Mayo Clinic Rochester

Presentation slides available at [Interpreting Your Test Results](#)

Reported by Steve Hatchett

Ms. Gossard has over twenty years of experience in nursing care of liver disease. It is important to understand that enzymes are markers of disease activity, not of liver function.

- AST is an enzyme inside many cells.
- ALT is more specific to the liver activity, but not one especially related to PSC.
- Alkaline Phosphatase (ALP) is an enzyme especially concentrated on the hepatocyte membrane.

Markers specific to liver function are,

- Prothrombin time indicates the clotting ability of blood (shorter time is better).
- Low Albumin level indicates poor liver function.
- Bilirubin level indicates narrowing and obstruction. High bilirubin indicates poor function.
- Ammonia level is higher when the liver isn't clearing toxins well and is thought to be related to confusion (encephalopathy), but the test has a relatively high level of error.

Defining some common terms:

- Hepatitis is inflammation of the liver, regardless of the reason for the inflammation.
- Cirrhosis occurs when normal liver tissue is replaced by permanent scarring (cirrhosis can be asymptomatic).
- Varices occur when impeded liver blood flow causes re-routing of flow through the veins around the esophagus.
- Portal hypertension is high blood pressure caused by restricted liver flow.
- Hepatic encephalopathy refers to liver-related confusion or impaired brain function. Can be triggered by medications such as sedatives or diuretics, by fever or infection, or by liver disease.

Cholangiogram slide:

- PSC shows narrowing and widening of bile ducts (called nodes or “pearl necklace” appearance).
- The narrowing and widening of bile ducts may only show up in small ducts or can extend to larger branches of the biliary tree.

Clinical presentation of PSC

- Elevated ALP
- Colitis/IBD
- Abnormal cholangiogram
- May be no other outward symptoms

Sometimes elastography, which is a test using sound/ pressure waves to assess rigidity/elasticity of liver, is used. This test is indicative of the extent of fibrosis.

Liver test results vary over time.

- A large percent of PSC patients will at some point revert to normal enzyme range for some period of time.
- Also, spikes in enzyme levels can occur, often with no other symptoms.

The tumor marker CA (cancer antigen) 19-9 is used as a marker, but is not a very sensitive or accurate test. There are high rates of false positives and false negatives.

An ERCP is indicated when dominant strictures are seen in a MRCP test.

Brushings are taken to test cholangiocarcinoma.

- Standard cytology diagnosis is subject to interpretation and judgment.
- FISH is a diagnostic protocol that reduces subjectivity.

Q: What is your recommendation on diet, lifestyle?

A: Have a healthy diet, adequate sleep, no alcohol, lower stress. Unfortunately, studies have not produced clear recommendations on specific diet factors. If you start using herbal supplements, tell your physician and have your blood tested in 4-8 weeks. Stress is believed to be related to PSC acuity, but rigorous studies and data are not yet available.

Q: What is rheumatoid factor?

A: It is a test for rheumatoid arthritis, which is also autoimmune in nature.

Q: What is ANA?

A: It is another autoimmune marker. It is not useful for PSC treatment unless there is suspicion of autoimmune hepatitis.

Q: Is immune-suppression being evaluated as a treatment?

A: There is little current interest in that approach. The old immune-suppression therapies have been abandoned as they are not effective. Anti-fibrotic agents appear to be more promising.

Q: What is recommended for PSC-related IBD?

A: PSC-related IBD does not appear to progress to full UC or Crohn's Disease.

Q: Does small-duct PSC lead to cancer?

A: Cancer appears to be less common in small-duct PSC, but the sample size is too small for us to know.

Q: What is the prognosis for the combination of PSC and sarcoidosis?

A: This is another overlap condition. It seems that the best approach is to quiet the sarcoidosis to have the best outcome on PSC.

Q: Are there any other important blood tests?

A: Platelet level indicates hepatic hypertension. Hemoglobin level indicates bleeding. Red or white blood cell count is not specific.

Q: Can Celiac disease be diagnosed on the basis of a blood test?

A: It could be a false positive. For an accurate diagnosis, one would need to have biopsy.

Q: When is stenting appropriate?

A: If the ERCP and balloon do not open the stricture, a stent that will not be kept any longer than eight weeks will often be added.

Q: Are there absorbable stents?

A: No, there aren't.

Q: What is the long-term prognosis if lab tests have been steady and good for a period of time?

A: It is unclear that the length of time with steady labs is an indication of a good prognosis. All that we can say is that the recent past is the best predictor of the near future.

Q: What are erythrocytes and sedimentation rate?

A: Erythrocytes are red blood cells. Sedimentation rate is another marker of inflammation.

Gluten Free Diet and Celiac Disease

Joseph A. Murray, MD, Professor of Medicine, Consultant, Division of Gastroenterology and Hepatology and Department of Immunology

Jacalyn A. See, MS, RD, Clinical Dietitian, Assistant Professor of Nutrition Mayo Clinic Rochester

Presentation slides available at [Celiac Disease](#) (J. Murray)

Presentation slides available at [Gluten Free Diet](#) (J. See)

Reported by Bill Bandy

Please make sure to consult the slides. A brief summary of points made outside the slides follows.

Celiac disease is an autoimmune disease triggered by exposure to gluten, which is pervasive in foods. About one percent of the population has celiac disease. This condition was first described in 150 AD. Celiac disease attacks the small intestine villi that reduce the normal nutrient absorption area from the size of a tennis court down to that of a ping-pong table.

Q & A: A gluten-free diet will not benefit PSCers unless they have celiac disease. Do not go on a gluten-free diet without being tested, as that in itself could cause problems if you do not have celiac disease. Testing is easy, and now includes capsule endoscopy, which is 90 percent effective in detecting Celiac disease. Celiac disease and Crohn's disease are not related and are separate diseases. If you have one set of genes, either DQ2 or DQ8 (see slide 5), you have a one in thirty chance of developing celiac disease. If you have both sets, your chance goes up to one in ten. Children can be tested for celiac disease at two to three years of age. They will need to have had gluten in their diet to be tested. Fifty percent of celiac patients are anemic with iron deficiency. Bone density in adults should be tested if they were diagnosed with celiac disease as children.



Dr. Jay Talwalkar was interviewed at our conference by the Mount Sinai Medical Center PSC Support group.

Please [click here](#) to listen to his audio lecture.

Understanding PSC Medications

Christine M. Formea, Pharm D., Manager of Pharmacy Research Service, Mayo Clinic
Rochester

Presentation slides available at [Understanding PSC Medications](#)

Reported by Stephen Harris

Christine Formea was trained in liver and kidney transplant research in Florida. Currently, she is involved in clinical trials at the Mayo Clinic. Her talk focused on themes rather than on specific medications. She was most interested in patient experiences and drug side effects. She was also interested in hearing about alternative therapy used by conference attendees.

She explained PSC as a scarring and subsequent narrowing of the bile ducts, during which bile acids both get stuck in the bile ducts and are displaced to other areas of the body. Since there are no proven therapies for PSC, only the symptoms are treated.

Generally, the symptoms include pruritis (itching) due to bile salt build up; liver damage for which ursodeoxycholic acid (Urso) has been used to increase bile flow; immune system involvement for which steroids are often used; and bacterial cholangitis which necessitate antibiotics.

There is much controversy about combination regimens; however, as trials continue, we have more information and can create more concrete regimens. Because the disease is so heterogeneous, treatment combinations are just as varied.

Christine Formea discussed Urso in detail. This medication stimulates bile flow from the liver. She explained that Urso keeps the “river flowing,” preventing bile salts from building up and hence protecting the liver. However, she said that indigestion drugs bind Urso and block its effects. Side effects of Urso include diarrhea and general gastrointestinal symptoms.

Cholestyramine is used for bile acid removal. Originally this medication was used to sequester cholesterol. It serves the same purpose for bile acids, binds them and then flushes them out. The session participants commented on the gritty powder and asked whether this medication existed in pill form. It does, but not in the U.S. Medications exist in different forms in different parts of the world.

The audience commented on taking Urso because it reduces itching. Christine Formea said that it was important to take Urso on an empty stomach, one hour before or 5-6 hours after taking other medications as there can be adverse cross-reactions. Participants named abdominal discomfort, flatulence, nausea, and vomiting as some of the uncommon side effects of Urso.

Used earlier for the treatment of tuberculosis, the antibiotic Rifampin is used for its bile acid processing effect. Rifampin, she said, “chews up bile acids,” and by increasing transport and processing, this antibiotic may reduce itching. One has to be careful with drug interactions when

taking Rifampin, especially with corticosteroids and immunosuppressants. She recommended that before taking Rifampin, the patient should consult with the physician and also with the pharmacist, as the dosage of Rifampin may need adjustment. Side effects of Rifampin include orange urine, saliva, sweat, stool, and tears that can even stain contact lenses. A member in the audience confirmed the bright orange urine while on Rifampin.

She then continued with medications taken for bacterial cholangitis (bile duct inflammation/infection). She urged the audience to seek immediate medical attention with symptoms like chills and fever. The antibiotics prescribed for cholangitis include Augmentin, Bactrim, Cipro, and Vancomycin which should be taken as directed. Like other antibiotics, patients must complete the full course, even when feeling better. Stopping antibiotics midway can of course result in recurrence.

Q: What does rotating antibiotics mean?

A: Bacteria get used to a drug and develop resistance to it. We use an ABC protocol. This keeps the germs confused as we switch between three types of drug (A, B and C). This rotation results in a better chance for long-term recovery.

Q: My husband is on A and B (rotating two drugs).

A: Two drugs are better than one. This choice depends upon the patient and the health care provider.

Q: Is there research on this? Which drugs are better?

A: There is no real optimal regimen, as each case, each infection is different.

To treat flares, we use the “immune system cool down.” We are not sure of how much of the immune system is involved in PSC. The immune system helps us fight infections and protects us, but in autoimmune diseases, that is not the case. During a flare up, the drugs that are available to us include corticosteroids, azathioprine, cyclosporine, tacrolimus, methotrexate, and intravenous immunoglobulin therapy (IVIG). The use of many of these drugs requires careful monitoring through regularly taken lab tests.

Q: There are different strengths of drugs. Do you prefer bottom-up or top-down treatments? In other words, do we first treat with weaker drugs that have less side effects and work up until we see relief of symptoms, or do we go for the “big guns” first?

A: It would make sense to use the big guns first to get a flare under control. She explained, however, that her expertise was in transplant and that physicians would know what option would work best for each individual case.

Regarding drug interactions, Christine Formea had several important recommendations:

1. With two or more drugs, interactions can occur.
2. Keep a list of all the medications you are taking and regularly update the list. Make sure

to write down any interactions you may have. Give a copy to your partner or caregiver. Talk to your pharmacist and health care provider to make sure your list is accurate and that you are all on the same page.

3. Try to fill all your prescriptions at the same pharmacy. By doing so, you will help identify any potential problems as they arise.

Comment: I'm a nurse. My son has PSC. I have lupus. We carry a flash drive with our medical information on a keychain.

Regarding side effects, she advised the audience to read the education material provided by the pharmacy, especially if the medication is to be used for the first time.

She spoke about complementary and alternative medications. She gave the example of echinacea which has both immunosuppressive and immune boosting effects. She explained that herbal medications are not distilled to provide one specific effect and are not directed towards one specific target. The FDA does not have much control over these types of substances, and many are not FDA approved. Therefore, **when we do not know the components of a compound, we cannot predict the effects.**

In general, and **ESPECIALLY FOR TRANSPLANT PATIENTS**, speak to your health care provider and pharmacist, as there are many potential issues with these types of substances.

Q: What about milk thistle?

A: It is believed to be protective of the liver according to some small studies.

Q: Are there alternative medicines relating to the peripheral nervous system? Are there any studies?

A: (From the audience) I use Sarna, an over the counter menthol cream. I use it for cooling the skin and have the approval of my doctor.

A: It acts as a counter-irritant, like Icy-Hot.

To follow what Christine Formea did not have the time to cover in this session, please see her PowerPoint presentation.



Relationships, Sexuality and Family Planning

Andrea A. Gossard, RN, CNP Assistant Professor of Medicine

Richa Sood, MD, Internal Medicine, Mayo Clinic Rochester

Presentation available at [Resilient Intimacy](#)

Reported by Stephanie McCarville

Dr. Richa Sood's practice focuses primarily on women's health. In this presentation, Dr. Sood tried to keep information relevant to both sexes. However, she advised that specific questions regarding male sexual dysfunction would be best directed to other resources.

Most people she sees ask general questions such as, "What is normal?" "How does normal sex life change with a problem or a medical illness?" "What can be done to maintain a normal and active sex life?" and "How do life stressors affect sex life?" These were the topics she focused on during her presentation.

The Traditional Linear Sex Response Model was proposed by Masters and Johnson in 1960. They performed experiments on human sexuality and suggested a four-stage model that starts with desire, continues with arousal, plateau, orgasm, and finally, resolution. This pattern is considered a linear model of sex response and seems to fit men more than it does women.

In 2001, Dr. Basson proposed a new model called the Intimacy or Connection Based Model that women seem to identify with more. This model has emotional intimacy at the center. In the presence of an emotional connection or relationship and presence of a sexual stimulus, women may notice arousal before they feel desire. Once desire kicks in, this feeds on the arousal and leads to emotional and physical satisfaction and further bonding.

A women's sexual process or drive can start at the desire level. This model tells us that libido has two parts - a spontaneous sex drive and a receptive desire. Both are normal means of female sexual expression. Factors that can affect the cycle negatively include biological factors such as physical health and medication that interfere with sex response and psychological factors such as stress and depression.

In the general population, 35-50 percent of people report sexual dysfunction. In those with a medical illness, the percentage is much higher.

Usually patients have a "Don't tell, don't ask" approach. They are often reluctant to discuss these types of problems with their doctor, either because they feel uncomfortable, or believe there are no available treatment options, or worry that the doctor will dismiss their concerns. Categories of sexual dysfunction include decline in libido, erectile or ejaculatory disorders for men, and sexual desire, arousal, orgasm or sexual pain disorders for women (see slide 9).

Typically problems for women overlap, and there may be co-existing problems. If there is a problem of sexuality, it is generally approached like a puzzle. Usually there isn't one fixable problem, as often, the problem is multi factorial.

Slide number 12 is a "cheat sheet" that lists the factors that may be contributing to sexual dysfunction. All of these elements should be explored to determine the underlying cause of the issue. With a medical illness, all of these may be affected.

To treat a sexual dysfunction, a thorough medical evaluation must be completed, preferably by a trained sex therapist and trained medical professional. In Dr. Sood's practice, there is a medical doctor and a sex therapist that both assess the patient to get the big picture. A sex therapist can be a very valuable resource as outlined on slide 16. It can be difficult to find a trained therapist in your area. The website www.aasect.org gives information about certified sex therapists that can be searched by entering your zip code.

Understanding normal sexual response is an important piece in managing sexual dysfunction. There are many myths around normal sexual function. Education about what is normal is where we start. For example, many women feel that if they can't achieve orgasm, it's a problem. However, one third of women can't achieve orgasm through penetration alone. Knowing this information alone can reduce stress on the partner.

When the body is in survival mode (fight/flight response), it will shut down activities that are not required in acute situations. The function of sexuality used to be that of procreation, but humans have adapted sexuality to pleasure. With the presence of stress, sexual desire is often reduced.

Sexuality can also be enhanced through illness because the body has sexual redundancy. For example, our brain has more than one pathway to achieve sexual function. If one pathway is damaged/injured due to a medical illness, the body has the ability to "build a new road" and to find a way to get around it. Someone with a spinal cord injury would be a good example.

Stress plays a big role on sexuality, both in general, and for those with a medical illness. It can tighten muscles, redirect blood flow, and inhibit relaxation, which is the exact opposite of what one would need in a good sexual experience. Some, however, find it beneficial to use sex as a stress reliever and work through the stressors.

The caregiver-partner relationship is very important and requires constant connection. Communication is essential. It is important not to assume that the other person knows how the

other is feeling. However, our brain has a negative bias, and our assumptions are generally negative. If someone is not nice to us, the first reaction is to assume that we are the cause. We do not consider that the other person could be having a bad day. It is always best to talk openly and understand the other person.

Sexual resilience is the ability to bounce back from adversity. In the case of a setback, can you spring back and even improve? Sexual resilience can be developed by understanding sexual response, exploring new ways of expressing sexuality and having flexibility. Sometimes there may be physical limitations, and it may be necessary to think of other options. Spontaneity isn't always an option when there is a physical problem or fatigue; therefore, some planning may be necessary to find a time of the day that works best for both parties.

Hormonal replacement has been used safely for both men and women with advanced liver disease with no adverse reaction. Please see the slides for reference and discuss this option with your practitioner if you are considering it.

There have been studies on Viagra and varices. The website information for Viagra asserts that people with serious liver problems can use this medication safely. In her practice, Andrea Gossard has seen male PSCers of all ages using Viagra on a regular basis without any side effects.

To improve vaginal health, vaginal estrogen is used in low doses without having any systemic effects on the liver and other organs.

Q. A patient has significant muscle wasting/atrophy as a result of PSC, has low testosterone on testing. How can she find a provider who will prescribe testosterone?

A. Andrea Gossard has had patients placed on testosterone. This hormone can often muddy the picture by elevating liver enzymes. There have been cases of elevated bilirubin or alkaline phosphatase resulting from testosterone injections. Such fluctuations make it difficult to determine whether the changes in LFTs are due to disease progression or to testosterone. Particularly if the disease is well established, providers hesitate to prescribe oral hormones because these make it difficult to determine whether the hormones are masking a complication of PSC.

Q. Are oral contraceptives effective and/or safe?

A. In general, if the disease is well established, it is not recommended to use oral contraceptives. We have two options for women: Oral or transdermal estrogen. Birth control pills have a much higher dose of hormones (4-6 times higher) compared to doses used for post-menopause hormone replacement. That is why there is hesitation in prescribing oral contraceptives. Transdermal or skin therapies are much less damaging to the liver than oral estrogen is. There are no known problems with using Depo-provera.

Comment. *A PSCer with overlapping AIH and UC explained that she had difficulties finding an oral contraceptive. She also had a bad case of acne. She was prescribed a non-estrogen 21-day birth*

control pill called Diane35 manufactured by Bayer. She said that Diane35 is commonly used in Canada, especially by people suffering from digestive diseases. Followed by the Cleveland Clinic and Mayo Clinic physicians, she said that both teams were comfortable with this medication that has had no effect on her liver enzymes. Neither Andrea Gossard nor Dr. Sood was familiar with this medication.

Q. Are there any studies on passing PSC or IBD to children?

A. The majority of people with PSC do not have a first degree relative with PSC. There does seem to be a link with autoimmune diseases within the family. There is a higher risk for children of PSCers of having an autoimmune disease. But it is highly unlikely that your children will develop PSC.

Q. What is your experience with pregnancy and PSC? Is it more likely for the mother to have a flare up after delivery?

A. She has seen around twenty-five pregnant PSCers, and the majority of these pregnancies displayed no problems. Those with more advanced liver disease (portal hypertension and cirrhosis) tend to have more complications during pregnancy. In a 2002 case report, a thirty-seven year-old woman with well-established PSC had an early delivery after she became increasingly symptomatic. She did go on to have a transplant, but this was likely due to the natural progression of her disease.

In the case of AIH as a separate entity and not as an overlap with PSC, the disease can sometimes become quiescent.

Regarding harvesting eggs or having fertility injections, Andrea Gossard advised to use caution when using hormonal injections. And for those who are planning to get pregnant, she advised close monitoring and supervision by a hepatologist. There is a wide spectrum of reactions to pregnancy depending on the PSCer's baseline prior to getting pregnant. The risks of pregnancy include fluid retention and risk of bleeding in the case of portal hypertension.

It is difficult to determine whether a correlation exists between a post-pregnancy cholangitis attack and pregnancy, or whether the flare is part of natural disease progression. In some cases, pregnancy may "stall" the process. In general, 30 percent of people will see an improvement in their symptoms throughout their pregnancy, 30 percent will remain unchanged, and 30 percent will worsen.

Q. Is it common for women with PSC to have no periods or irregular periods? Is there a link between PSC and premature ovarian failure (POV)?

A. Amenorrhea can be present in those with more advanced liver disease, but as a general rule, in the early stages, irregularity of periods is not specifically correlated with PSC. It may co-exist as a completely separate issue. It would be important to rule out thyroid problems, polycystic ovaries, life stressors, and other causes.

Male infertility in PSC can occur both early and later in the disease. Male infertility rate among PSCers may be similar to that of the general population. It may be related to the stress of having a chronic disease.

It is recommended that women with PSC be followed by a high-risk obstetrician/gynecologist, as the disease may progress during pregnancy. The physician needs to monitor liver enzymes regularly. The incidence of cesarean delivery is no different from that of the general population.

Q. Are there complications with PSCers who have a J-pouch or a colectomy?

A. Infertility may become a problem because anatomically or mechanically, the process may be obstructed. However, this is not a usual problem.

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How Do I Deal with Life and PSC

Philip Burke, PhD, Clinical Psychologist, Assistant Professor of Clinical Psychology,
Southern Illinois University at Carbondale, PSC Patient

Presentation available at [How Do I Deal with Life and PSC?](#)

Reported by Mike Pearlman

Dr. Philip Burke's session began by addressing two questions that were not answered during the morning session due to lack of time. The first question dealt with a discussion of the website he is developing - <http://www.morethanillness.org/>. The website is intended to help PSCers be "more than their illness," offering information to those dealing with chronic illness. The site applies both to PSCers and to caregivers. Dr. Burke commented on the deceptive perception of looking "okay" to others, when in reality, much is happening internally in the body.

The second question dealt with whether kidney and liver diseases are biological problems. Agreeing that they were, Dr. Burke said that a biosocial model exists where cause has no relevance. He explained that we needed to adapt to the sociological and psychological aspects of our environment. We need to manage our environment so we can better tolerate our setting. And for that, we need to develop coping mechanisms. For example, where excess noise may make it difficult for a person to concentrate, the person may choose to wear earplugs to weed out the extraneous noise. This process constructively deals with the situation. It also reduces the likelihood of getting upset and exhibiting behavior that may lead to unpleasantness.

Dr. Burke asked, "How do you describe illness to people who just don't get it?" This led to a discussion of Christine Miserandino's "SpoonTheory" (www.butyoudontlooksick.com). In trying to explain to her friend what it was like to have her illness (not PSC), Ms. Miserandino gathered spoons, saying that each spoon represented a task that needed to be accomplished. Each task had a cost attached to it – for example, a shower cost one spoon; washing hair would cost a second spoon; a third spoon would be used to take part in a conversation, and so on.

In other words, if we only had twelve spoons available to us each day and are not careful, half of the spoons could be used up before we even reached work. While we could borrow spoons from future days, this would mean that we would have fewer spoons at that later date. Dr. Burke noted that there are times when we may need more energy, so we push ourselves, and are successful in doing so; however, there are other days when the spoon "snaps," and we don't have sufficient energy. Even where friends offer to help out, making use of this assistance can result in the expenditure of several spoons.

In discussing this theory, Dr. Burke spoke about the “silver thieves,” the things that rob us of our energy. Dr. Burke spoke of the importance of finding ways to work within the illness.

In concluding his presentation, Dr. Burke made several key points. The first is that acceptance is not the same as “giving in.” One does not need to give in. Rather, acceptance refers to accepting reality for what it is, choosing to tolerate the moment, and a repeated commitment to accept. Focusing on the negative aspect of reality harms one’s ability to look at the positive aspects that come from such acceptance. It is important to shift away from willfulness to willingness, to respond with a smile, rather than having a more confrontative approach. Letting go of one’s sense of blame and judgment helps to avoid the feeling of bitterness. Dr. Burke encouraged the use of that time for more positive endeavors.

In his presentation, Dr. Burke stressed that we are more than our PSC. He encouraged an approach of working with PSC, life, and each other, instead of succumbing to a more confrontative approach. He stressed the importance of keeping PSC from being the center of one’s life, both for PSCers and caregivers. “Your life is more than one thing,” he said, and that something else also should exist so that life is not just centered around PSC.

The problem with making PSC “central” to one’s life is that the disease is unpredictable and largely uncontrollable. A better approach would be to look for that which is in our control. Examples include self-care (that is, getting dressed, sending messages to oneself); partnering with health care treatment in a positive way; pleasant activities; skill building; making social connections, building positive relationships; and focusing more on our positives (negatives don’t need special attention). He mentioned the importance of freeing time by using help from others. He stressed the importance of focusing on what is going to work, on pleasant activities, on something that meets the person’s higher need. Dr. Burke suggests that people will find ways to make their spoons last longer, will have greater tolerance and more energy when they are involved in activities they enjoy.

He believed that it was important to be completely honest, to answer questions truthfully. He also mentioned the importance of modeling behavior. Having the child become more involved in the assistance process was also perceived as being beneficial.

PSC Partners Patient Registry is Being Created!

PSC Partners was selected by the NIH Office for Rare Disease Research (ORDR) to participate in a two-year [pilot project](#) that will result in a PSC Partners patient registry. Please see page 5 in this issue of The Duct.

Be Informed: Disability Benefits and Employment Law Issues

Rebecca Long, JD

Jeremy Burke, ALHC, Learning Consultant

Tiffany Rotondo, PHR, Corporate Human Resources Generalist, The Jel Sert Company

Reported by Joanne Hatchett

Family and Medical Leave Act (FMLA) – You must request FMLA to make it happen.

Private Disability Insurance – Read the definition listed on the policy. It is recommended to take long-term disability if offered by your employer, even if it has an expensive co-payment or paycheck withdrawal. Most people don't want to be on disability. It is a difficult decision to make and difficult to explain to others, especially when dealing with issues like fatigue.

PSC is not an automatic eligibility for Social Security Disability Income (SSDI). Eligibility must be proven.

For approval, SSDI typically takes about two years from application time. There may be a gap in insurance coverage during this two-year time span. If you have to appeal SSDI, it is recommended to have an attorney at the hearing.

An excellent resource is Jennifer Jaff, who spoke at a prior PSC Conference. She has a non-profit legal service, Advocacy for Patients with Chronic Illness, with resources at: www.advocacyforpatients.org

It is important to keep all your medical records and any letters a physician writes for you.

Tiffany Rotondo spoke about Family and Medical Leave Act (FMLA), which provides job protection with the opportunity to take up to twelve weeks off for medical leave. This is unpaid leave from work, and it can be used for the patient or for the caregiver of a parent, spouse or child. This medical leave can take different shapes – It can be intermittent for doctor appointments, or can be a permission to arrive late to work or leave early for symptoms such as fatigue. Working less hours per week could be the preferred option. The leave can also be consecutive following a surgery or hospitalization.

The employee must request the FMLA form and must have worked 1,250 hours in the preceding six months to qualify for FMLA. It is important to give as much advance notice as possible or “as soon as practicable” when requesting FMLA. For example, it is advised to call as soon as possible when hospitalized.

The employer may follow FMLA hours on a twelve-month rolling calendar year (for example, May 1 to April 30th) or may follow the calendar year, as per company policy (Please see Notice of Eligibility and Rights and Responsibilities). The handouts included Glossary Terms Used in the FMLA, found at www.wagehour.dol.gov.

FMLA requires certification from the Healthcare Provider for the Employee with a Serious Health Condition. To get time off, it may help to attach a job description.

It is important that YOU track your time off work to be sure you know the exact time to the minute and also are aware of what the employer has documented. Keep copies of everything you give your employer.

Keep in touch with your employer when you are off work. Do not lose contact.

Jeremy Burke gave a snapshot of the key points for processing a claim. He said private Disability Insurance is complex, as the wording and interpretations vary.

The employer looks at claims from a risk management standpoint, to be sure to make the right decision for the right reason. Important review aspects include responses to the following questions:

When were you hired?

Were all premiums paid?

What was the job?

What are your functional limitations?

What is your diagnosis?

Words are important. The language used must adequately describe one's inability to perform a job as a result of a change in medical status.

Jeremy Burke noted that many people with chronic illness work too long and may actually lose their job because they are no longer able to perform the responsibilities required by their job. He said some people don't fully use FMLA and recommended that they should as the need arises.

When a claim is denied, the doctor needs to provide a detailed picture of the patient's functional limitations that hinder the individual's ability to perform his job. You can provide the doctor with the specific language you would want to have included. It is important to be specific. For example, in describing fatigue, it would be important to specify the limitations resulting from this fatigue.

The Future of PSC Research

Keith Lindor, MD, Moderator, Executive Vice Provost of Health Outcomes at ASU

Saul Karpen, MD, PhD, Professor of Pediatrics, Division Chief, Pediatric Gastroenterology, Hepatology and Nutrition, Emory University School of Medicine

Konstantinos Lazaridis, MD, Associate Professor of Medicine, Associate Chair Research, Division of Gastroenterology and Hepatology, Associate Director, Center for Individualized Medicine, Mayo Clinic Rochester

Jayant Talwalkar, MD, MPH, Associate Professor of Medicine, Mayo Clinic Rochester

Reported by Nancy Reeves

Pediatric PSC: What can we learn from it?

Pediatric PSC is in some sense, a “purer” entity than is adult PSC. For PSC to occur in childhood, it means that there is probably a genetic component. Why else would it happen early in life? What is going on in the bile ducts of a child with PSC is probably purer, and something we should be paying more attention to because it may give us better insight into the natural history and etiology of this disease which we might be missing when we look at adult PSC.

Many of the advances in adult medicine have actually taken place by paying attention to children that display more obvious aspects of the disease. Forty years ago very few people had heard of cholesterol, yet today, most people have not only heard of the word, but they also know their most recent cholesterol levels. These advances resulted from observing one child in Dallas who had a familial disease that gave him very high cholesterol. Doctors Brown and Goldstein developed an interest in the pathway and discovered receptors on the surface of cells that trap and absorb bloodstream particles that contain cholesterol. Subsequently, what was once considered a rare pediatric disease is now well understood and a daily issue in adult medicine.

Understanding childhood PSC may not give us tremendous new insights into all of PSC, but there is probably some low hanging fruit we can address, perhaps by looking at a pediatric issue more globally, as we have with adult PSC.

The other related issue is that there may be some other genetic disorders that look like PSC but that are not PSC. We can now detect and identify these disorders, whereas five years ago we could not. This makes it important for people with PSC and their caregivers to be up to date with new information.

If PSC is genetic, then why don't we see it from birth?

Damage to the bile ducts may be an injury response to an abnormal bile composition. By now, we know the molecular composition of bile and the way the bile is formed. Transporter proteins on the linings of cells move small molecules of cholesterol and bile acids across the cell membranes. Transporter genes represent the template for these transporter proteins. When the genes mutate in these regions, the resulting composition of the bile will be altered.

Traditionally we thought that all bodies were alike. We are finding that this is not the case. We have observed that disease progresses extremely slowly for some, whereas for others, the progression is extreme, and we see the disease early on. Sometimes disease is apparent on the first day of life.

Twenty-five percent of infants are jaundiced at birth. Usually the jaundice is the non-threatening kind. On the other hand, some of the jaundiced infants have an elevation of the direct bilirubin. Some of these infants may be predestined to bile duct diseases, and studying this may allow us to identify such children earlier in life, even if the disease does not manifest itself until the ages of forty to fifty.

PSC: A look at genetics

It is not always possible to look at a disease at the genetic level, but with PSC, we have the tools to assess the genomes, and we have the patients to provide specimens. Even though some patients will choose not to participate, we have been able to recruit patients over the years so we have enough specimens to evaluate PSC using Genome Wide Association Studies (GWAS). We are learning that there are likely to be variations among the different patients with PSC. The architecture of a few major pathways for different groups is emerging. The concurrence of PSC with IBD must also be a major part of the conversation. We are identifying the genes and the variants. We may not have individualized pathways in five years, but we are likely to identify perhaps five major pathways during the next few years.

Once we find these pathways, we will be able to try more selected therapies based on the pathway leading to the damage. If you are losing a protein or gene, for example, the therapeutic pathway could return the protein or gene to its original location. It is possible that more than one pathway needs to be addressed and that all will require treatment. The mixed responses we have observed to Urso, for example, may be because, in the past, classification of PSC was based on a few individuals only. If an additional pathway is deemed important, we could, for example, go back and add steroids to the treatment pathway and might achieve a different outcome.

Genome-wide association studies (GWAS) involve rapidly scanning markers across the complete sets of DNA, or genomes, of many people to find genetic variations associated with a particular disease. We correlate the differences with the genomic variants we have identified and try to associate the variants that are more frequent in people with disease. That doesn't mean that the variant is causing the disease. You will see the variant at a rate of perhaps 20 percent of the population, of which 10-15 percent are healthy. With PSC, there are many variants involving many genes. A single gene

or a single association will not explain disease. We expect to identify a number of variants so we can better define each pathway and the disease variation associated with it.

Exome sequencing selectively sequences the coding regions of the genome, the regions in the genes that are translated into proteins. These regions constitute most of the disease causing mutations. The cost of sequencing exomes will soon drop to a few hundred dollars. Currently the cost is around \$500. When this drop in cost occurs, people will go back and look more carefully at entire populations. All of the variants may have an effect on the gene clusters involved in bile formation, cholesterol formation, and hypertension. We will then be able to see where there is risk and follow those individuals more closely.

For every disease phenotype we develop, the impact of aging is significant. For some, the effects appear before we are born. For other phenotypes, the effects will appear later because of the interaction of genes over time. How many of these phenotypes will have clinical implication, only time will tell. And that is when we will be able to start addressing these phenotypes.

PSC: the environment

We know there are geographic influences on IBD because the distribution of IBD correlates with latitude above the equator. Why is that? Are we looking for similar variations with respect to South America and Africa?

Environment is equally important, but it is harder to study because environmental exposure is difficult to evaluate. People's descriptions of environmental exposure to alcohol, smoking, and coffee are difficult to quantify. Even evaluating the influence of antibiotic treatment, for example, would depend on the accuracy of memories over time. There are no biochemical markers that can determine how many antibiotics were used. In addition, responses to common exposures are not unique. For example, of all the people exposed to a toxic site, most will recover. Everyone is exposed to smoking, for example, but not everyone gets lung cancer. People with PSC lack the mechanism to return from a state of inflammation to a normal state. Consequently, inflammation for those individuals becomes a perpetual cycle. Some with the same exposure develop PSC, while others do not.

So the starting point is genetics because that is easier. As time goes by, we will try to combine environment and genes.

Clinical trials

People are realizing that there exists a disconnect between a small, short study and a larger more rigorous study. Some of the study designs we have used traditionally, especially with more complicated drugs, have followed a common trend. Studies signaling positive effects and potentially effective future therapies are rarely consequential after the trial has been expanded to a longer duration and a larger patient population. It is good to be a poster child, but being the poster child within this phenomenon has not been good for PSC researchers because this trend has been a great hurdle and has placed limitations on our research.

Before we invest time and resources, we need to look at study design to ensure that we can trust our results in moving forward. We cannot do single arm studies, and then say, “Yes, this works.” We still need a comparison group. Because the disease is heterogeneous, some of the surprises may be the result of studies that started off with a different mixture of variants prior to the expansion of the study.

For the smaller studies, we need to do a better job with the selection of a population with similarity of disease. Researchers are trying to identify subtypes of PSC and link the therapies to the subtypes with the greatest opportunity for successful treatment. One of the drugs that has been tested for treatment of PSC is docosahexaenoic acid (DHA). It was tested for a group of patients with cystic fibrosis. It was effective for the cystic fibrosis patients with receptor abnormalities. Some PSC patients have a transmitter and receptor deficiency. So DHA was tested for patients who have a CTR deficiency. In contrast, if the patient has a receptor deficiency, antibiotics would not be a good treatment choice. If we tried antibiotics for these patients, the possibility of success would be low. On the other hand, if the patient is enriched with bacteria, testing antibiotics as a treatment appears more promising.

We also need to redesign and rethink the endpoints we should be looking at to determine whether novel therapies are worth further investigation in a larger population. From the onset, we should look for novel endpoints that would have a relationship to some of the harder endpoints that we could have in a long-term clinical trial. The traditional endpoints of survival, progression of disease, development of complications, and need for transplant have been very successful endpoints in larger studies, but clearly, these are not the ones we can use in small studies that focus on understanding whether a treatment holds promise or is of no benefit to the patient. One option for a smaller and shorter study is to isolate a group of patient that is more likely to have rapidly advancing disease.

We also need to measure more. Elastography is one tool which can be used to explore the relationship between biochemistry and other markers. It might help us to get a stronger sense of whether a treatment not only makes us feel better, but also whether it brings about, for example, anatomical change. Biochemistries will still be important, but to strengthen our observations, we will use those in combination with other secondary evaluation tools.

Finally, it may be useful to test relatively well-known drugs, such as Urso, in combination with others for their potential synergistic effects.

Inflammation

Inflammation seems to be a central part of the disease process of PSC. Various therapeutic trials have tried to address it. It is challenging, however, because we don't know the source of inflammation. It may be a problem with the transporters in the bile ducts. And the source of inflammation could be a bacterial or viral infection, or a hyper responsive immune system. That makes it hard to target therapies. The process for moving forward is to identify a plausible mechanism for the inflammation and therapies that address that mechanism.

Collaboration

The International PSC Study Group (IPSCSG) was founded in Oslo in 2010 to coordinate PSC research among leading institutions in seventeen countries. The group meets during sessions of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) international liver congress. Currently, a number of groups worldwide have been maintaining databases, and these groups must ensure that their goals align in order to avoid competing for resources. The AASLD is trying to put together information from all cholestatic diseases, working from the doctors' point of view, in order to create a national enrollment effort. In Boston, in 2010, at the AASLD meeting, the group discussed the content and procedures for a shared database for PSC. The PSC Study Group has been searching for ways of collecting a common data set. All the details will have to be cleared through institutional review boards, so we know that this common database will not be available overnight. *(Editor's note: When our PSC Partners patient registry is ready, we, too, will be joining this collaborative effort.)*

Collaboration is also taking place at international centers for gene testing. There are subgroups working on itching. The Immunochip Consortium has developed the first immunochip for PSC and IBD, a genotyping platform that includes all of the inflammatory disease loci. It has been used with phenotype and biospecimens from 5000 patients with PSC internationally. The outcome of these efforts will soon become available. It is promising that the international collaborative efforts are increasing, and the number of members is growing at every meeting.

The Children's PSC Foundation group (www.childrenspsc.org) focuses on pediatric PSC. There is no multi-center research opportunity for pediatric PSC yet, but there is an opportunity to partner with 16 sites in North America, and that opportunity expands to 25 sites world-wide.

Imaging

The trend in imaging has been to move from invasive imaging to non-invasive imaging. For example, the ERCP has been replaced by magnetic resonance imaging (MRI). Biopsies are being replaced by transient elastography (FibroScan® imaging).

The MRI imaging technology will hit a limit at some point. We are using these tests to look at qualitative and descriptive features of the condition. We still cannot image inflammation with current technology. In the future, we may be able to use molecular imaging to characterize inflammation.

One of the limitations of cholangiography is that this technology allows only the imaging of the bile duct fluids rather than the bile ducts themselves. Consequently, the inflammation cannot be imaged. Progress in imaging the biliary tree has been slower because the tests have been invasive, thus limiting the ability to repeatedly measure or directly look at the bile ducts.

Colon cancer surveillance has presented similar challenges, but by changing the way we build endoscopes, we can now create ways of looking at the lining of the colon using a variety of different techniques. Currently, the images are almost like those a pathologist would see under a

microscope. The idea definitely has applicability to the biliary system. Image resolution has been improving with the improved tools. Now we can see the lining of bile ducts in such detail that the results are close to those we have with pathology. We would like to be able to see inflammation, but we cannot do that yet. We expect that developments occurring in other areas of imaging will also move into cholangiography, but the move from invasive to non-invasive tests will take time.

Imaging and treatment evaluation

We have not typically looked at MRCP images to evaluate the effects of an intervention. We give a drug, check at baseline, then twelve months later, the tests may or may not show improvement. We do not always check to see whether there has been improvement in the actual bile ducts. That is where imaging will play an increasingly larger role. We aim to have more of a functional and quantitative approach.

Trends in monitoring and treating cholangiocarcinoma (CCA)

In clinical oncology practice, positron emission tomography (PET scan) is used more and more in combination with computed tomography (CT scan) for staging cancer. Unfortunately so far, PET scan evaluation of CCA has been variable and more disappointing than helpful. These scans do not pick up small areas of change. Improvements in such scans may give us an idea of who is at risk for CCA, or might suggest the presence of other significant non-cancerous changes.

Currently breast cancer studies involve the injection of breast cancer cells into an animal. The animal is then used to study the pathogenesis of the disease and therapeutic treatments. We envision that to happen with CCA.



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Thanks to the generosity of our PSC Partners members and special friends, we have reached our goal of ONE MILLION DOLLARS dedicated exclusively to PSC research! The presenters at our conferences are together with us wanting to find a cure for PSC. Let's continue to support the [Road To Research](#) and give researchers the opportunity to explore the promising studies they propose.

Together in the fight . . . whatever it takes!



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Compiled by Meegan Carey, Development Director

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Another successful conference! Can I nap until Pittsburgh 2013?