

MS. GIRAND:

Thank you very much, Dr. Mauseth. Well we're going to go back to our Q A mode. Everybody remembers this. We ask you to come to the microphone and please give us your name before you speak and we will have some questions answered here and then I'm going to pop up again and then we will break for lunch. So come out if you have any questions; if you don't, I will --

MR. CRAWBUCK:

Hi, my name is Ken Crawbuck. First question I have one for Dr. Tarr. Earlier this morning there was -- we had a little bit of talk about preexisting factors for HUS. Do you have any comments on that. What do you know about that?

DR. TARR:

Is this preexisting, pre-infection?

MR. CRAWBUCK:

Correct.

DR. TARR:

Who is likely to get HUS?

MR. CRAWBUCK:

Correct.

DR. TARR:

When you think about HUS that results in a child getting HUS, there's multiple interacting factors that contribute to this event. So when a child ends up with HUS they have to have eaten the right vehicle. There are, perhaps, differences in terms of ethnic groups, in terms of geographic groups, in terms of access to the foods that are likely to contain the organism.

There are some data in adults in terms of developing symptomatic infection based on whether or not they are taking acid secretion-suppressing medications. So that's a step.

There are some data that we think are pretty good, now, that antibiotics given when a child becomes symptomatic affect the risk of getting HUS. And certainly age is a factor as to whether or not a child gets HUS. HUS is predominantly, but not exclusively, discovered in children under the age of 10. HUS can occur in any decade of life but the incidence goes way down after the age of 10.

Some genetic predispositions have been proposed but studies have been not very supportive. For example, a couple of studies suggested girls were at increased risk once an infection was established. Other studies say that there's a neutral sex ratio.

P1 blood group substance is a genetic factor that suggested the risk of getting HUS is reduced. Multiple studies suggest that's not the case. The factor that comes up time and time again is really only age.

MR. CRAWBUCK:

Great. Thank you.

DR. TARR:

Other things remain theory.

MR. CRAWBUCK:

And Dr. Mauseth, you refer to a normal islet cell reserve. What is that? We have this normal person, we have twice as many as we need or use?

DR. MAUSETH:

You have usually, in type one diabetes, you have about 20 times of what you need. And you can do a 95 percent pancreatectomy and that was that slide I showed before where you lost islet cells. But the problem arises on is with stress and with other illnesses your body needs more insulin.

And so in a normal healthy and active state maybe you only need five percent of what your pancreas can make but if you grow or you go through a rapid growth spurt or you have a major illness you usually need about 20 percent of what your total capacity will be.

MR. CRAWBUCK:

Okay. Great.

DR. MAUSETH:

So does that --

MR. CRAWBUCK:

Yes, I get it. Thanks.

SPEAKER:

This question is for Dr. Tarr. One of the slides, had shown emission and cholecystitis and I just wanted you to clarify that a little for me about E. coli 0157:H7. We had HUS resulted appendicitis.

DR. TARR:

Yes, rare, but it can.

SPEAKER:

Where would I go to find out more information about that?

DR. TARR:

It's really in the realm of case reports. I believe there's a series of reports from Canada that suggest that. I've heard of a couple of other cases. I don't know if they've appeared in literature, one from Japan, one from Europe, but the surgeons found the bloody diarrhea and the abdomen is so tender that the surgeon believed it was appropriate to at least take a quick look. And the appendix was just inflamed and the child had E. coli, but I am not certain how much has gone beyond that.

SPEAKER:

Would this occur while they were testing positive for 0157 or can it be both during and directly after with the appendicitis after a week or two? Does the appendicitis occur while you were testing positive for 0157 or is it possible that it would be occurring like directly after a week or two?

DR. TARR:

The cases I have discussed are just anecdotes, and again, these are just stories, I'm not aware of whether this was within hours or on the day of the first bloody stool. But it was in the midst of the acute infection. I don't quite know when the culture was obtained.

I am not aware of a somewhat delayed presentation of appendicitis. However, remember with appendectomies you really have to tolerate a certain false negative rate because it would be tragic to overlook something that's so treatable.

And even if that means there will be a number of children who undergo quick operations to make certain that it's not an appendix, the down side is that they would have an operation that is not necessary, but is probably not harmful. That's the down side. The upside is you would get an appendix out, potentially, that needs to be taken out.

SPEAKER:

Thank you.

SPEAKER:

I have two questions for Dr. Mauseth. The reports and studies that you did in relation to the incidence of diabetes following HUS, what were the respective lengths of the studies?

DR. MAUSETH:

How long did they run for? They were anywhere from two to four years, but that's -- that was one of my points. I think that the length of time we observed these and the other thing that may come out of this is that if you look at the longer term there may be more people that have problems three, six, ten, twelve years down the road

SPEAKER:

That goes into the second question I have which is how would one differentiate between diabetes onset normally or through general recognition as opposed to diabetes, which is relative to HUS? Can you distinguish between the two?

DR. MAUSETH:

Well, when we look at the antibody studies, it depends on how specifically we want to look at it. Most of the type one diabetes if you did a blood insulin level and you looked at blood usually in type two diabetes blood insulin level is very high. And in type one diabetes blood insulin level is very low.

So if you're trying to ask me is it secondary to HUS or normal type one or type two, if you were trying to differentiate a type one, say you had low insulin levels and it was -- and then you tried to say, okay, it's type one, there's usually genetic factors but not always. There's usually antibodies, but not always.

So if you ended up having genetic risk factors that can be measured and if you ended up having the antibodies being positive in patients with a significant period of time away from the HUS, then it's probably standard type one diabetes.

On the other hand, if you had a very high insulin level in a non-high risk group patient, say the non-Hispanic, Indian or black, and the patient was under a significant amount of stress, you might say it was type two related to that.

But in high risk populations, and some of it there's not going to be a clear-cut answer to that one, either. It's not going to be a hundred percent one way or the other.

SPEAKER:

Thank you.

MS. RIGERT:

Hi, I'm Jennifer Rigert. I have a question for Dr. Mauseth. Should someone who contracted HUS over 25 years ago be concerned about becoming diabetic and, if so, are there any preventive measures that can be taken?

DR. MAUSETH:

I think any -- I think the longer you're away from it the less likely, all right? And I think that the real risks, as far as preventing it, are the weight gain, lack of exercise. You see weight gain makes you insulin resistant. Exercise makes you more sensitive to insulin.

So that if you thought that you were at potential risk, the ideal thing would be to keep your weight down and exercise, and that's the prevention of type two diabetes. And that would be the main one you should worry about at that phase.

MR. HICKS:

My name is Randall Hicks. This question goes to either of you. My daughter had HUS and had, shortly after discharge from the hospital, we were informed that pregnancy could later in her life, of course she was only five when she contracted the disease, but now she's 13 and we're looking at our question is whether if she should get pregnant, will that increase the likelihood of complications such as diabetes or some of the other complications you've listed.

DR. MAUSETH:

Did she have sugar problems during the time of the HUS?

MR. HICKS:

She did have pancreatitis.

DR. MAUSETH:

Yes, but did she have specific elevated blood sugars, as you recall? There's no hard and fast rule. There really isn't. As far as diabetes goes and HUS we're really in the beginning part of understanding anything about it. But I think that I would -- I would say that probably needs to be monitored more carefully for diabetes. But as far as I would be concerned, we have patients who have frank diabetes and we don't tell them not to become pregnant as far as the diabetes portion. I wouldn't say that that was a contraindication of pregnancy.

DR. TARR:

I agree, that is to say, there is not enough data to reach a conclusion. Their obstetrician, your daughter's obstetrician, should be advised. But I would not hold off on pregnancy because of such a fear.

MR. HICKS:

Thank you.

MS. DONLEY:

I'm Nancy Donley. This question is for Dr. Tarr. You mentioned that, you know, that surgeons are routinely consulted with during the course of HUS. What role do you -- what role currently exists for hematologists in the consultative and diagnostic period? When -- how frequently do hematologists get consulted, is it something that - is there a trend to do more of this, and how much and what role do you see for plasma exchange in the role of HUS?

It seems to me, from Dr. Gail Rock's presentation earlier this morning, that in the case of TTP, that is something that is looked at almost immediately. And it gets really fuzzy here with HUS and TTP, and I'm wondering is there being any -- are we looking further into -- into this?

DR. TARR:

Yes. Let me answer the first question. The average child with post-diarrheal HUS has hematologic complications that almost always seem to be handled by the kidney specialists. And that would be addressed by them.

I have seen, over the years, a child with acute HUS being referred directly to the hematologist by a physician who obtains blood counts as the only test, doesn't detect a renal failure since they think that a child has perhaps

acute leukemia, and sent the child to a hematologist.

We get a broader range of tests, and it's usually the kidneys that are the acute concern. And the child is referred to a kidney specialist.

In terms of plasmapheresis, at least in the average form of HUS that we see where a child has bloody diarrhea caused by E. coli O157, there is no evidence of a lesion in von Willebrand factor system that would suggest that it would be remedied by plasmapheresis. There is no antibody to von Willebrand factor metalloprotease that needs to be removed.

There are never -- there has not been, to my knowledge, a report of the ultra large tissue form (which would be treated by plasmapheresis) of von Willebrand factor in what was certainly an E. coli O157:H7 infection. These are the molecules that are so pathogenic in TTP. So on the basis of that I can not say that plasmapheresis would help or hurt, but there's no theoretical justification for it.

MS. DONLEY:

I guess it sounds as if there are no -- I guess your answer, you anticipated my next question, is it contraindicated?

DR. TARR:

I am not sure. There are certainly risks from whatever procedure whatever is being administered to a child. Until recently, until 10 years ago, for example, there would have been a risk of hepatitis C by plasmapheresis, while blood is much safer now than it was then.

There's a theoretical concern, in my opinion, that, if a child has a somewhat diminished form of the physiologic form of the molecule we have, the average von Willebrand factor will circulate in everybody's blood and has platelet aggregating capabilities.

There are some reports that suggest that that level is actually decreased, probably to the benefit of the child in acute HUS, but those cases have been murky because the etiology of the HUS is unknown. It's not so certain they have post-diarrheal HUS.

If one then infuses plasma with the normal form of von Willebrand factor the theoretic concern then you are shifting back to the more aggregogenic form of this molecule. So there are some theoretical concerns with plasmapheresis.

MS. DONLEY:

In the cases where you had neurological involvement, would that be an indication that plasmapheresis would be -- should be called for or considered?

DR. TARR:

I would defer to the neurologist on that.

MS. DONLEY:

Thank you.

MS. GIRAND:

I have a question for Dr. Tarr. I had heard that there was a -- I have a daughter with gastrointestinal sequelae and I had heard that there was a test which sounded possibly less invasive than a sigmoidostomy, but maybe not, which involved putting a small probe into the -- into the colon that would study the motility of the colon, sort of. I don't understand that but maybe back and forth or something that that might help diagnose IBS. Could you comment on that?

DR. TARR:

Gastrointestinal motility is very specialized, very artful subbranch of gastroenterology. We are not doing that in Seattle. There are a few centers in the country that are doing it. And if a child is to undergo such a test, be absolutely certain that it's done in a center with large volume.

And may I ask the group a question related to abdominal pain in childhood HUS. How many people here have children who have syndromes similar to what I described. Is it very common? (Hands go up around the room) Wow.

MS. DONLEY:

With abdominal pain?

DR. TARR:

I'm not talking about the rare child suffering from abdominal pain. I'm talking about a child who at least once a week suffers from pain. (Hands go up around the room) That's extraordinary.

MR. GALLER:

Bob Galler. My question is: You talked a little bit about having surgical procedures done for appendicitis; it is my feeling that I lost my daughter because of a gangrenous bowel and a postmortem had not been done, so

that's not fact.

But as a parent who was first introduced to E. coli, I don't know "A" if I would have allowed a surgeon to go in there and possibly perform a laparoscopy prior to knowing the ability of this disease to take my daughter's life, and "B" how, as a surgeon, which I know you're not, but how would you talk to a parent and advise them to go forward with, although it might be a minor surgery, and a minor surgery is indicated as a surgery performed on someone else, but as a parent no surgery to a child is minor.

How do you get a parent acclimated to go forward into that and do you see in postmortem a lot of gangrenous bowels?

DR. TARR:

Regarding the postmortems where we have seen gangrenous bowel we knew that we had an idea that it was there pre-mortem from an immediately prior operation or an examination that strongly "suggested" it. It would never really come as a surprise.

In the sense of an acute ill child it's like any medical emergency where a procedure is contemplated. One has to sit down with the family, go through the risks and the benefits. Again, experience counts, and experienced pediatric surgeons in an active pediatric center are the crucial factor. It's a fuzzy sort of criterion to put on the decision to do something, but one on which I would place great weight.

MS. KENNE:

My name is Heather Kenne. My daughter had HUS in '96. In '98, she was treated for a strictured colon. I was wondering why the delay, you said normally it happens right after the HUS, and do you perceive any other GI problems?

DR. TARR:

I can't speak to the delay. Perhaps you can give me a little more information. Was she symptomatic immediately after the HUS and continued her symptoms and was diagnosed two years later?

MS. KENNE:

No, she was perfectly healthy, to our knowledge, healthy.

DR. TARR:

In a situation like that I would guess that the stricture had been there early on and that either because of her growth or just either continued fibrosis at that site it suddenly became critical. I don't know why suddenly it would show up at that point, that's unusual, very unusual so late.

MS. GIRAND:

Well, thank you -- oh, I'm sorry, go ahead.

MR. MARLER:

Bill Marler, a question for Dr. Tarr. You raised the issue of antibiotics being given to 0157 patients and given that there's been some recent literature on that I was wondering if you would sort of tell the group a little bit more about the pros and cons of antibiotics and where you see that going in the future.

DR. TARR:

Well, there was a paper recently published by Craig Wong, from our hospital, that looked at a number of children in a four state area in this region, and observed who developed HUS and who didn't.

And one of the factors that entered into his analysis was whether or not they received antibiotics, usually with presentation of medical care. And there did seem to be an unexplained increased risk of getting HUS following the administration of those antibiotics and could not be attributed solely to the child looked bad and therefore antibiotics were given. The concern has always been that a child was destined to get HUS, and got antibiotics coincidentally along the way.

This was not a perfect study, not a randomized controlled study where children would come in and received a placebo or antibiotics. So we can not state with certainty that the antibiotics actually increased the risk of developing HUS, but it seems highly plausible that they were associated with the deterioration.

However, about half the children in that series that did develop HUS, did not get antibiotics. And the last sentence in Craig's paper was the best way to prevent HUS is to prevent the primary infection.

MS. GIRAND:

We're going to actually have to call this, but you will have a chance, I'm sure, to speak with him at lunch as well. I apologize. Our lunch is actually out there waiting.

So that's why I would like to thank Dr. Mauseth and Dr. Tarr very much.

MS. GIRAND:

We need to -- I need to follow-up with a few details. Once again, if you're going to the dinner, and this is a tricky thing, if you have a short, little thing that's silver and you're going to the dinner, then look for people with

long, silver name things, they don't have a ride yet to dinner. Please take two or three people with you to dinner, that's for dinner, not lunch. Don't go anywhere yet.

In terms of lunch, the lunch is out here on the left. Your name tag has a number on it and that is indicative of the table at which you will be seated. And if you do not have any number on your name tag, please come and see me.

If you did not receive videotapes, please come and see me. Let me rephrase that. If your family did not receive videotapes, please come and see me.

And lastly, outside we're going to have some books for sale, an author who is a member of S.T.O.P. has written a book about her experience, and that's for sale. And there's also more information about S.T.O.P., itself, on our table outside. And I hope to see you back here at 12:50. Thank you very much. Actually 1:50.

(Whereupon, a recess was take at 1:06 p.m.)

MS. GIRAND:

We had two questions at lunch. The answer to the first is the little sticky dots on your badge relate to whether or not you returned your questionnaire. If you have no sticky dots that means you didn't return a questionnaire or I didn't get it in time.

If you have a sticky dot that is green on your badge that means your child, as you told us, that your child has renal issues. If your sticky dot is yellow your child has GI issues. If your sticky dot is blue you said that your child has some learning disabilities. And the last one, red, was a combination of two categories, one was increased allergies and the other was possibly diminished ability to fight infections. So that's what the red dot is.

The second question raised at the table that we were seated was how many children? How many people have children who have exhibited vision problems? And if you have, I would ask for a show of hands, please.

Okay. Vision problems would range from -- well, normal vision is normal vision, and vision problems would be really anything that deviates from normal in the age range that your child would be in.

So I suppose if your child was 20 and was wearing glasses that probably wouldn't really be categorized as a vision problem, whereas having cataracts in a three year old would probably be considered something unusual.

So one more time I will have everybody raise their hands if their child has exhibited vision problems. Raise your hands high. Great, thank you.