

Questions and Answers on Alpha 1-Antitrypsin Liver Disease

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Following are Dr. Teckman's responses to questions asked on the Alpha 1 Liver Disease Online Mailing List.

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Phenotyping; Pre/Post-Transplant Vaccination for Hepatitis A & B

Phenotyping done only by blood test. Phenotyping from liver biopsy done only rarely within scientific research laboratory.

Phenotyping not done on cadavers before transplant.

If patient vaccinated pre-transplant for Hepatitis A and B; he will retain immunity post-transplant.

Q: Can phenotyping (at least differentiation of those homozygous to the “Z” allele versus those who are heterozygous) be accomplished via a liver biopsy?

A: Phenotyping, that is telling MM, from MZ, from ZZ is only possible as a blood test. This type of information cannot be gotten from a liver biopsy except under highly unusual circumstances within a scientific research laboratory.

Q: Do they phenotype or even do a biopsy on the liver before transplantation? I would think that related donors are very likely to be PI MZ. Is this acceptable? I assume a PI Z liver would be rejected as inappropriate.

A: During an evaluation of a prospective cadaveric (brain dead donor in hospital ICU) donor for liver transplantation no specific tests are done for Alpha 1 in our region. This is generally true nationwide. A wide variety of basic liver blood tests are done that look at general liver health and the presence of infectious diseases like viral hepatitis and AIDS. This is generally all the evaluation that there is time for. The family of the donor fills out a questionnaire about the person’s health, and if a close family history of Alpha 1 was uncovered, then changes might be made. There is generally no time for a liver biopsy of a cadaveric donor before the transplant. For a living related liver transplant, which is generally not done on an emergent basis, there is more time for thorough evaluation. All of the above tests, plus a lot more, are generally done if the questionnaire and patient’s personal history suggest that he/she would be an appropriate candidate. Liver biopsies of living related donors are usually not needed. In some centers, MZ relatives of ZZ patients needing liver transplants are never considered as living related donor candidates. In my opinion, I would consider MZ relatives as possible donors, but I would recommend that the prospective donor undergo a liver biopsy in addition to all of the other tests. If the biopsy, and the other tests, were normal I would go ahead.

Q: If pre-transplant patient has completed vaccination for Hepatitis A & B, after TX will he still have the Hep A&B antibodies from the vaccines or will he need to revaccinate?

A: If a patient was vaccinated against hepatitis A and B prior to liver transplantation, then they will still be immune after the transplant. This immune “memory” as it is called, is stored in blood and bone marrow cells even though the immunity is against a liver infection. In some cases, booster shots might be needed just as they might be needed in people who have not had transplants. However, when a person is on immunosuppressive medications after transplantation they might not respond as well (be as well protected from infection) to immunizations as they would before. This is highly variable between people and difficult to predict.

Liver Cell Transplant

*“Dead people” livers ethically need to be used for transplants.
Cell infusion has not been shown to save lives.
It will be a long time before infusion will be effective treatment.
Progenitor cells usually come from human fetuses.*

Dear List,

Unfortunately, this liver cell thing is beyond my typing ability and time resources to cover in an e-mail. Jack sent me some comments from you about studies in people with liver cell infusions purified from ADULTS. This has been done in a few patients over the last few years.

The problem is where to get the cells. You can't use “dead people” unless their livers are good enough for transplant and with people dying waiting for transplants it is not considered ethical to “throw away” a liver on an experiment (which is what cell infusions are) that may not work. That liver could be used as a transplant to save someone's life. Human livers or liver parts not suitable for transplantation but good enough for one of these experiments are very few and far between. The adult liver cell infusions haven't really been shown to save anyone's life as of yet. All the patients that got them so far either might have lived long enough to get a transplant anyway or might not have ever needed one and that's why they were on the list for the infusion experiment instead. It will be a long, long, long time before liver cell infusions purified from adult human livers will be a widespread, effective treatment.

That is why I commented on research that is looking at other sources of cells, like animals or fetuses. I threw away the previous description I was sent of the research on liver PROGENITOR cell transplants. That is work done by a specific company with some university involvement. I commented on it at Jack's request because the release made the research sound very exciting, which it is, but didn't say where the cells came from. If someone still has the release, please contact the company/researchers and find out where they are getting the liver progenitor cells. In common medical terminology, “progenitor cells” in that context usually means purified from human fetuses. However, I couldn't tell for sure based on the fax that I got from Jack.

Does A1AD Liver Disease Run In Families?

*Research being done that is promising to identify factor linked to liver injury.
Very preliminary, but may lead to treatment.
Most babies with jaundice and elevated liver tests get better, so the jaundice and elevated tests do not mean “liver disease family”.*

Q: Does A1AD associated liver disease run in families?

A: This question is perhaps the most unanswerable, or at least I should say we are working on it. That is, does A1AD associated liver disease run in families? Some people do believe that the tendency to have liver problems does seem to occur often in some families and not at all in others. In fact, in our laboratory here in St. Louis we are studying this question now by comparing tissue samples from patients with liver disease to tissue samples from other family members. In this way, we hope to find out what is different about A1AD people with liver disease compared to those with healthy livers. This is the first step to being able to predict ahead of time who might be at risk for liver injury and then to design and test a treatment. Many of you in the Alpha community have been very generous in donating blood or skin tissue to our lab so that this work can go on. Without this generous support we wouldn't be able to make any headway in this disease.

In a few individuals we have been able to identify factors that we think are linked to the development of liver injury. Factors that predispose to liver injury may be different among different families. It doesn't look like there is going to be "one" easy answer. We are now in the process of examining the tissue from these patients, and their families in greater detail. We have also done some VERY PRELIMINARY tests of substances in test tubes that might one day be part of some kind of treatment. Real treatments for A1AD liver in people though, are many years away.

In some of my previous postings I discussed the fact that most people with A1AD do not get liver disease. It is also true, although perhaps I have not spelled it out in detail in this forum, that most A1AD babies with jaundice or mild to moderate elevations of transaminases (LFT'S) will GET BETTER. The majority of these children DO NOT go on to have life threatening liver disease. Therefore, if a family has a baby who did have this type of mild to moderate liver dysfunction early in life, they will usually get better on their own and I'm not sure that such a situation would necessarily be considered a "liver disease family."

Compensated And Decompensated Liver Disease

Compensated is chronic liver disease.

Decompensated means patient is getting constantly worse.

Q: What is the difference between "compensated" and "decompensated" liver disease?

A: "Compensated" liver disease means that the patient has chronic liver disease, that may include cirrhosis (scar tissue in the liver), ascites (fluid build up in the abdomen), jaundice (yellow color), or difficulty digesting fats or certain vitamins but not getting worse. That is, the person has very few symptoms and with minimal medications goes about their daily life pretty much normally.

"Decompensated" liver disease means that the person is getting constantly worse which could mean that they might have repeated episodes of bleeding, abdominal infections, periods of mental confusion, frequent hospitalizations, etc. Fortunately, many patients with A1AD can remain "compensated" for many years and lead very normal lives.

Possibility of Lung Disease in ZZ Children; Genetic Liver Cells

Lung Disease in ZZ Children

Genetic liver cell replacement.

Dear Member List,

Hope everyone had a good holiday. I wanted to briefly follow up on a couple of questions.

First, several of you have shared information with me about the possibility of lung disease in ZZ children. Several people pointed out a group of medical journal articles published 20-30 years ago about ZZ kids with lung problems. I looked at most of them. All the kids I saw talked about had some additional problem, not just ZZ. For example, a premature birth or a rare infection (one was a nearly fatal case of measles) that evolved into lung damage. Likely the ZZ status of the children contributed to the problems, but these were rare situations not experienced by most people.

In addition, I've talked to the Swedish alpha 1 specialists who did a study on 125 ZZ kids from birth to age 20 years. None had any lung symptoms. Only a handful were smokers, but they had mild changes in PFT's already at age 20.

What does this mean? For me it means that some rare ZZ kids can have lung problems if they also have some other very major illness. However, the vast majority of ZZ kids are well from the lung standpoint and won't have problems until adulthood.

I would still be interest in helping with or referring for evaluation any ZZ child with lung problems because I'm sure there are rare kids out there that can be helped and who can teach the rest of us a lot.

Finally, I saw a post on genetic liver replacement cells. Replacing or transplanting liver cells has been a hot topic for several years since the cells can multiply in the body in a very unusual way. As many of you know, if you surgically remove part of the liver it will grow back, not exactly like normal, but pretty close. If you transplant a small liver into a big person it will grow to fit in just a couple of weeks and small person getting a big transplanted liver will have the liver shrink.

Taking all this into account, many people have wanted to give people with sick livers new doses of healthy cells, sort of like a blood transfusion that would multiply and fill the sick liver with good cells. Great idea! One problem: where do you get the cells?

You need a lot of cells. Probably too many to remove from another adult, anyway you would have rejection and then it's just another liver transplant. Many people had suggested using animal livers, maybe pigs. However, nobody knows how to get pig cells to live inside a person. One idea was outlined in a post that Jack copied me on. They want to use "liver progenitor cells." We don't know yet how to get any of these cells from an adult person, let alone enough to give to another person as treatment. In this context, I believe that "progenitor" could mean "fetal." In other words, using liver cells purified from aborted fetuses and given to patients as treatment. Clearly, one's feelings about abortion will make this either OK or an ethical dilemma. In any case, it will be technically difficult.

Evaluating all possible treatments at least intellectually is probably a good idea. However, for liver cell treatments the companies need to disclose completely where the cells come from so that people can make informed decisions.

Can someone find out what the cell source is for that company?

Premature Infants and Decreased A1AD Level; Respiratory Distress in Babies; Drug Treatment Triggering Jaundice in Babies

Little research exists re: premature babies and A1AD levels.

Only do the PI type and level if evidence of liver problems.

Illness at time of testing can result in low level.

No specific medical information about A1AD newborns and respiratory distress.

No specific medical information about drug treatment triggering jaundice or liver malfunction in an A1AD baby.

Q: Do all premature infants have a decreased level of alpha 1 antitrypsin?

A: This is a difficult question, partly because of the way it is worded, and it makes me wonder if it comes as a result of a specific unusual problem in a small baby, in which case I don't have enough information to really help very much, and would have to recommend a discussion with the patient's doctor, or perhaps a second opinion.

Let me cover a couple of issues that come to my mind about this and maybe that will help. I briefly reviewed some sources and I didn't find very much about alpha 1 antitrypsin levels in premature infants. That is, not very much is known about what the "normal" level should be, let alone the level in a sick child. Perhaps there is better information about this than I know, I just didn't find it yesterday.

I probably wouldn't get an alpha 1 level in a premature infant unless I got the pi-type too, and I wouldn't get that unless the child had some evidence of liver problems. If the pi-type was ZZ then that explains it. If the type was MM and the level was low then that could mean a couple of things. One is that the child could have one of the VERY RARE "m" types that reads like "m" on the test but leads to low blood levels. To figure this out, it takes some very special testing, and some of these patients are at risk of liver or lung disease.

Another possibility if the type was MM and the level low, is that the child was very ill at the time the test was done. Premature infants often have very immature lungs and often need to be put on ventilators (breathing machines) for a period of time. This type of patient is also at risk of some very severe types of lung infections. If any of these things were going on, then the alpha 1 blood level could be low temporarily because the alpha 1 in the blood was being soaked up by the lungs to help fight the acute problem. In these cases, when the patient improves, the level in the blood of alpha 1 returns to normal. If the type was other than MM or ZZ and the blood level was low, then the possibilities are too numerous for me to go into here.

I hope this helps the questioner, although my guess is that the situation that prompted the question is too complex to be answered unless one has full knowledge of the patient's condition and his test results. I recommend another conversation with the baby's doctor or a second opinion.

Dear Liver List:

I've looked over the posting about the baby with respirator distress immediately after birth and the subsequent questions. I must say that the situation is/was very complicated and that without reviewing in detail the patient's medical records and examining the child in person, it is impossible to say anything pertinent to this specific child's condition. Perhaps I can give some general comments, though.

The situation described is actually not uncommon in infants that are born prematurely or for infants who have serious infections soon after birth. The specific bacteria causing these infections are often difficult to detect. Could alpha 1 antitrypsin deficiency make such an affected baby worse? I would think that's not very likely, but I can't say it's impossible. To my knowledge, there is no specific medical information about A1AD in newborn respiratory distress.

Q: Could drug treatments or serious illness early in life "trigger" jaundice or some kind of liver malfunction in an A1AD baby?

A: Some experiments in test tubes suggest that high fevers or serious illness that affect the whole body might make A1AD liver disease worse. However, this has never been examined in people and, besides, other types of liver disease do sometimes get worse at times of disease stress. Therefore, many of us treat A1AD patients the same as those with other liver problems.

Symptoms Present To Justify Ordering A1AD Testing

Newborn jaundiced baby.

Unexplained liver enlargement.

Elevated LFTs or blood tests that measure inflammation.

Any young/middle-aged person with destructive lung disease.

First degree relative of newly diagnosed A1AD.

Q: What symptoms should be present for a physician to order testing of a patient for alpha 1 antitrypsin deficiency?

A: Several of my previous postings have touched on a number of the issues raised by this question. See my posting about the work up of newly diagnosed patients. Since testing for A1AD only involves a

simple blood test(s) that poses no physical risk to the patient, many physicians recommend testing any person who comes to medical attention with any unexplained problem that could possibly be undiagnosed A1AD. This means any newborn infant with “prolonged, obstructive jaundice.” This is NOT the common baby jaundice, or yellow color commonly treated with lights. Any infant, child or adult with unexplained liver enlargement, cirrhosis (fibrosis or scar tissue in the liver), elevated transaminases (LFTs, or blood tests that measure liver inflammation), or unexplained obstructive jaundice should be tested. In this context, “unexplained” means that there is no evidence of a physical injury to the liver, hepatitis virus infection, alcoholism, or other significant liver disease, although A1AD could occur along with one of these conditions in a single individual. It’s just that two liver diseases together is rare, but not impossible. Any adult with liver cancer, but without another major risk factor like alcoholism, should be tested. Many pediatricians, like me, who specialize in the evaluation of children with unexplained poor growth will often check for A1AD if other more common tests yield no explanation.

As far as lung disease is concerned, any young or middle aged person with “destructive” lung disease should be tested. This means lung disease that causes permanent scarring to the lungs, not merely asthma. Many lung specialists test all such patients regardless of age.

Finally, “first degree relatives” of newly diagnosed patients should be considered for testing. This means children, brothers, sisters, and parents. Any more distant relatives with symptoms or signs such as the ones mentioned above should also be tested.

To me, “tested” means an alpha 1 level and a “pi-type.” Although many authorities will just get the level and if normal go no further. However, this could miss some heterozygotes or “carriers” who themselves could have an affected child.

Risk Of Liver Disease For MZ/ZZ Alcoholic Consumption

Alcohol Consumption

MZ Risk

ZZ Risk

Q: Are MZ individuals at risk for liver disease?

A: Many of your questions are very insightful and cut right to the heart of what we DON'T KNOW about alpha 1 antitrypsin deficiency. You will notice that I am often unable to give a clear yes or no response, like many of the tough questions we face in life. The actual path any individual patient might take in diagnosis or treatment depends a lot on their specific, personal situation and discussions with their own physician.

The two bits below exemplify our uncertainty and could easily be answered differently by other physicians.

Q: What is the risk of liver disease from beverage alcohol consumption to a person with homozygous ZZ alpha 1 antitrypsin deficiency?

A: There is no specific information about the risk of alcohol consumption in a ZZ type person. However, we do know that excess alcohol use can cause serious liver damage in people with previously healthy livers. Therefore, it is probably prudent to recommend very low, infrequent, or even zero alcohol consumption in healthy ZZ type persons. If liver disease is present, from a ZZ A1AT state or from any other process, then it would be advisable to abstain from alcoholic beverages altogether.

Q: Are individuals who are heterozygous for alpha 1 antitrypsin (MZ or MS) at risk for developing liver disease?

A: In general, we do not consider individuals who have one normal A1AT gene, M, and one abnormal A1AT gene, S or Z, (so-called heterozygotes or “carriers”) to be at risk for developing liver disease. Liver disease usually only becomes an issue when a person has both abnormal z genes, termed homozygous ZZ. However, some controversial research studies have been done in the last few years which have raised the possibility of liver problems in the heterozygotes. These studies have had a number of flaws in that the heterozygous patients studied were found because they had problems. It was difficult to know these health problems began or many other heterozygous people were in good health and so never went to the doctor. In fact, several of these studies have included large numbers of heterozygous patients who also were infected with potentially serious viruses such as hepatitis B virus or hepatitis C virus. This confounded the understanding of any possible conclusion about the role of the A1AT heterozygous status.

While this does not rule out the possibility that in a rare instance a person’s heterozygous status, combined with some other factor such as a hepatitis viral infection, could lead to liver injury that would not otherwise occur; it would certainly be a very uncommon event. Moreover, in such a situation, it would be very difficult for a physician to say for sure what the cause was of any resulting liver dysfunction. This is especially true when one considers that approximately 1 in every 35 Americans is heterozygous, MZ, for alpha 1 antitrypsin. Clearly, the occurrence of liver disease in the U.S. is much less common than 1 in 35 persons. Not to mention that in most cases of liver disease a cause such as a toxin or infection can be easily identified leaving only a small minority of cases previously unexplained.

Therefore, heterozygous MZ or MS status for alpha 1 antitrypsin is usually not considered a risk for developing liver disease. If a person does develop liver disease, and it is discovered that he is heterozygous for A1AT, then this should not be readily accepted as the final explanation for the liver problems. An evaluation by a physician who specializes in liver problems should be performed to look for other causes of liver disease that would be much, much more likely, and possibly more treatable.

What About An A1AD Mother Breastfeeding

No reason for healthy woman with A1AD not to breastfeed.

Be careful of medication.

Mother’s nutritional status might impact breastfeeding mother’s health

Q: What is known about an A1AD mother breastfeeding her infant?

A: I know of no specific medical information that has looked at breastfeeding in A1AD. I can tell you, however, that I can think of no reason for a generally healthy woman with A1AD not to breastfeed. Generally, pediatricians like me believe that breast milk is the “best” food for infants, although certainly commercial infant formula has been a healthy alternative for hundreds of millions of infants over the years. Breastfeeding in the setting of maternal disease only generally becomes an issue with regard to a few specific situations. One is if the mother is taking certain medications. Most painkillers prescribed for women following childbirth are generally safe in usual dose for nursing mothers/ infants. However, many other medications are only used with caution during nursing and some have never been studied with breastfeeding in mind. A nursing mother should always consult her pediatrician or OB/GYN before taking any medication.

Another situation where breastfeeding is approached with caution or discouraged is where the mother has some specific infectious disease that could be potentially passed to the infant in breast milk. Some

examples of these would include AIDS and hepatitis virus infections. Most pregnant women are tested for these and other diseases by their OBs so that they can be advised properly or treated prior to delivery.

Perhaps the most pertinent issue for A1AD patients regarding breastfeeding is the mother's nutritional status. Both chronic lung disease and chronic liver disease can have a very severe impact on the patient's nutrition and fitness. As both types of disease progress, individuals can lose weight, appetite can decrease, in liver disease digestion of fats and certain vitamins can be impaired, and general energy level can drop dramatically. As any new mother knows, the demands of a new baby, whether nursing or not, can be very high. Moms need to eat a proper, healthy diet, drink plenty of fluids, and get enough rest. This can be hard to accomplish even without the burdens of a chronic disease. The fitness of any individual mother for childbirth or breastfeeding is best determined in discussions with her OB and pediatrician. However, if no special, specific medical reasons are found for an A1AD mom to breast feed, then I for one would encourage her to proceed with nursing.

MZ Health Issue

Most MZ's do not have liver disease; other causes explain most of the few MZ liver diseases that occur; a few rare individuals have no clear explanation of the liver disease and are MZ.

Cannot rule out MZ combined with some other as yet unknown factor can cause liver disease.

More research is needed.

Other genetic diseases may be involved simultaneously with MZ.

All family members could have an unknown virus or bacteria that causes liver damage.

There may be unknown toxins causing the disease.

Risk for MZ appears to be very low.

Dear Liver List:

I see there has been further discussion of the MZ health risk issue. This is not surprising since areas where there is insufficient scientific/medical knowledge such as this lend themselves to repeated discussions where neither "side" can convince the other. I prefer to try not to take a "side" but to simply state what is known, what is suspected, and offer a practical approach for my patients and me. There are probably more than 5 million people in the United States who are heterozygous, MZ for alpha 1 antitrypsin (A1AT). It is pretty clear that 99% of these people do not suffer from any kind of liver ailment, and the few who do are usually found to have a well understood explanation, such as a hepatitis C virus infection of the liver, which would make a person's liver sick if they were MM or MZ. However, it is also clear that there are a very few, rare individuals and families who are found to have liver problems with a clear explanation and who are also MZ. We must also acknowledge that at times doctors see patients with poorly understood liver problems who are MM type. What do all of these occurrences mean?

Can we rule out the possibility that in a few rare individuals and families that the MZ state, perhaps combined with some other genetic or environmental factor, has caused liver disease? No, we cannot rule that out. In fact, some theories support this idea even though it cannot yet be proven. When cases of unexplained liver disease in MZ persons come to light, should we study the patients carefully to try to understand the type of disease present? Yes, of course we should. If the MZ state is the cause of disease in a few, rare cases is there any testing or treatment, other than that given to any liver patient that could be used? No, with our present state of medical knowledge we would treat any liver disease the same way in an MM person or an MZ person. Therefore, is it worth making 5 million people worried, and giving them a label that could affect employment and insurability for an unexplained problem that arose in a rare few? I personally feel that we need a lot more solid information before taking such a big step.

Wait a minute! Aren't the rare occurrences of unexplained liver problems in MZ people solid enough information? It certainly is information that encourages those of us involved in A1AT research to keep on working. Although being involved in research means keeping a very open mind and considering all of

the possibilities until you have really solid evidence. Otherwise, the risk is that you could mislead 5 million people.

What are the other possibilities that ought to be considered as explanations for the rare occurrence of unexplained liver disease in MZ people? First, there are other genetic diseases. A1AT deficiency is only one of many genetic diseases, some of which are poorly understood, less well known than alpha 1, and VERY difficult to test for. With 5 million MZ people in the U.S. it would be expected that by chance alone some of them would also have other diseases. I personally know of 3 families, each of which has two genetic diseases. One has both cystic fibrosis and alpha 1, one has both cystic fibrosis and neurobiromatosis, and a third has Alpha 1 and another genetic liver disease.

Another possibility is that multiple family members could all have become infected with an infectious virus or bacteria, previously unknown to science, that causes liver damage. This is not so far fetched as it sounds. There are a lot of germs out there that doctors have not yet recognized. There are many recent examples of major infections that have gone unidentified for years.

“Legionnaire”’s disease, the deadly lung infection, was only discovered in 1976. The blood test that allowed the identification of the hepatitis C virus was only invented in 1989. HIV was discovered in 1981. Ebola virus was discovered in the 70’s/80’s. Lyme disease, an infection that can cause rash, joint problems, and sometimes liver problems was discovered in the 1980’s. The bacteria that causes “cat scratch fever” was grown in a lab for the first time only 3 years ago. Doctors usually like to appear pretty smart, but sometimes we wish we knew a lot more.

Exposure to toxins is also a well-known potential cause of injury to the liver that is notoriously difficult to figure out at a later date. Such exposures can occur to a worker in a chemical plant, for example, or a family living in a house on contaminated land. At times I have seen doctors completely stumped by a patient’s liver disease for years on end, until a toxin or drug ingestion is finally identified. It is for these reasons, and for others that are too long to cover now, that I stick by my general approach to this issue. If there is a health risk associated with the MZ status, that risk appears to be very, very low. Other risks we face every day, like driving without a seatbelt, are likely to be as high, if not higher.

Of course, if you or one of your family members has liver disease and believes an MZ status to be the cause, then this discussion provides little reassurance. I’m concerned about that. All I can do though, is give the best care possible to my individual patients and keep up my research to uncover the truth about this disease for the whole community.

Further MZ Discussions

No definite answer.

The majority of ZZ do not even get liver disease.

Perhaps other factors operate with MZ to cause damage.

Ascribing MZ to liver disease may cause unnecessary worry; increased insurance premiums

Dear Mailing List:

The issue of the risk of liver disease in MZ people is a hot item, both because people are generally interested and because the answer is controversial. Since there have been a number of interesting comments, let me expand a little on my previous posting.

First, as I mentioned previously, there really is no definite answer at this time. The medical research done to date is very preliminary and far from conclusive. Any two liver doctors questioned, who have really taken the time to look at the information available, could give different answers. Certainly there are rare individuals with liver disease who also are found to have an MZ phenotype. Many of these people have

had extensive testing for other diseases, although there are a lot of uncommon diseases out there which makes the phrase “extensive testing” mean different things to different people. Besides, just because two things occur in the same person (MZ and liver problems, for example) does not necessarily prove a cause and effect relationship. Sometimes things occur together by chance alone, although this too is nearly impossible to prove in any single individual.

Let’s review a couple of basic facts. It is well known that the majority of even homozygous ZZ A1AT deficient individuals DO NOT get liver disease, or at least not until old age. Actually, the best medical evidence to date would suggest that only 15% of ZZ children ever have any liver problem at all, and that many people in that 15% do not develop serious of life threatening problems. Studies in adults suggest that most ZZ people live well into old age without symptoms of liver disease. It is also clear to liver doctors in general from ongoing medical practice that MZ people with liver problems who do not have some other obvious health problem, like a liver infection with a virus such as hepatitis B are very, very uncommon. That is not to say that they NEVER turn up, but it is so uncommon that it makes people wonder if there isn’t some other factor operating that is still undiscovered by medical science.

For example, for decades doctors saw patients with what looked like viral infections of the liver, but in whom no viruses could be detected. Then, just a few years ago, new technology allowed the identification of a virus now called hepatitis C, which seemed to be responsible for many, but not all, of those previous cases. Such still unknown processes are possibly operating in the MZ/liver disease issue.

Finally, we are still in the unfortunate position of having no real treatment for A1AT associated liver disease, aside from the treatments that doctors give to liver disease patients in general.

This means that there is very little benefit to trying to ascribe an MZ status as the cause for a person’s liver problems, if they do occur. Actually, I feel that there are good incentives NOT to try to assign this cause and effect relationship with MZ and liver problems until more research is done for several reasons. One is that even if some relationship exists, as we have said, it is very rare. This means that literally hundreds of thousands of MZ people will be alarmed and worry unnecessarily. Remember, approximately 1 in 35 Americans is heterozygous for the MZ type. That’s a lot of people, and when you think about it, that’s a lot of healthy people. Lastly, in this day and age of insurance coverage concerns, I don’t think it is wise to assign a rare health risk to a very large group of people without good, solid medical evidence. We hardly need to give third party payors more excuses to raise rates on certain groups or to deny coverage altogether. I hope these thoughts have helped to clarify a very confusing issue. If people are concerned about their own, individual situation, then I recommend a consultation with their personal physicians, or perhaps a second opinion. Until more research is done, I will stick by my general answer that while I can’t rule out the rare possibility that some MZ people have a propensity for liver problems, I think that the vast majority of MZ people have nothing to worry about.

Cancer, Panniculitis and Transplant Medications

How should adults with Alpha 1 be monitored for liver cancer?

Can Panniculitis of the skin become cancerous?

Transplant medications and children.

Q: How should adults with Alpha-1 be monitored for liver cancer?

A: There are no specific recommendations for this. Children with Alpha 1 are not at risk for cancer, so this only applies to older people. Adults with Alpha 1 should be followed regularly by a physician who knows about the disease and who knows how to monitor the liver. Exactly what blood, ultrasound, or x-ray tests would be done depend on the patient and his/her history of previous test results. The important

thing to keep in mind is that Alpha 1 patients have (a probably small) increased risk of liver cancer and that doctors and patients should monitor as needed for that individual.

Q: Can Panniculitis of the skin in Alpha 1 become malignant?

A: Panniculitis is very rare. Therefore, it has not been studied very systematically. Medical books and journals basically only have collections of individual patient's stories. I have no knowledge that Panniculitis is a cancer risk. However, other physicians who care for adult patients (I'm only a pediatrician), may have personal experience with this that has not been published in medical journals.

Q: Transplant medications and children.

A: Pediatric transplant recipients are generally on the same drugs as adult recipients. All transplant recipients, with our current level of technology, will need to be on immunosuppressive drugs for the rest of their lives. There are only rare exceptions to this. Immunosuppressive drugs can have very serious, even sometimes fatal, side effects. Therefore, lots of research is underway to develop better transplant techniques and medications.

Medications; Transplant "Cure" of A1AD; Genetic Planning/ZZ Child

Over the counter medications

Will a transplant "cure" A1AD and prevent further lung damage.

Are there procedures that would help two MZ parents avoid having a ZZ child or that increase the likelihood of a MM child.

Dear Liver List:

I know that I have been somewhat lax in my duties in trying to cover many of your questions, although many of the queries in the most recent couple of lists have been rather personal and specific about individual patients. As you know, it would be unethical and reckless, not to mention illegal for me to give specific medical advice over the Internet with such limited information. So I will try to cover some of the issues in a general way, while encouraging individual patients to discuss specific questions with the physicians who know them best. When I say things like this, I know many of you respond that your doctors either don't know the answers or don't talk to you very much even if they do. Clearly, this would not be an optimal situation. I definitely think patients should be informed, however, with a serious, chronic medical problem you've got to find a doctor you can trust and generally take his/her advice. Constantly shopping from opinion to opinion is expensive, time consuming, exposes the patient to risk from repeated testing, and can lead to radical shifts in the plan of care. Try to find someone well versed in your problem, preferably at a larger medical center as Alpha 1 is often misunderstood, as you well know. If you are not near a large center, perhaps a visit to a distant specialist once a year or every other year could supplement visits to doctors close by, but who don't have experience in alpha 1. Anyway, just a suggestion.

Q: What over the counter medications should patients with liver disease avoid?

A: This is one of those things that is quite variable from patient to patient and doctor to doctor. Many medications give warnings on the label about taking in the setting of liver disease. These are usually general warnings added by the company without specific testing in liver disease patients, but simply stated to add caution and perhaps provide some protection from liability. The decision about whether or not any specific medication is safe for any specific patient can only be made by a doctor who is familiar with the patient's medical condition. Many times patients with SEVERE liver disease who have developed abnormal blood clotting are told not to take ibuprofen (Advil) or related, so called NSAIDS pain relievers (also called "non-steroidals") such as Aleve, or aspirin.

This is because this type of non-steroidal pain reliever can have a mild effect on blocking blood clotting, and if this is added to an already abnormal blood clotting situation from liver disease, the result can be very serious. In general, in my pediatric liver disease patients I do not restrict Tylenol for pain or fever in the usual safe doses. Tylenol does not effect blood clotting. It is true that too much Tylenol can be damaging to the liver, but in my opinion this is really only likely to happen in an overdose, even in a patient with liver disease. However, other doctors disagree with this, so anyone with liver disease should check with their personal physician before taking Tylenol. The real problem with medications and liver disease is in very sick patients who must take a wide variety of medications for multiple serious medical problems. This is especially true if the patient also has a seizure disorder because many so called “anti-convulsants” can have effects on the liver. Many patients on such medications have regularly scheduled blood tests to monitor for any effects of medications on the liver. As you know, this is a very complicated issue, and any more detailed discussion would need specific medical information about the drugs in question and the specific patient. Many of you have probably had conflicting advice on what type of over the counter medications you could take. This is because there isn’t very much actual medical information for doctors to go on, so many doctors will stay on the safe side and simply recommend that a patient not take many such medications.

Q: Will a liver transplant “cure” alpha-1-antitrypsin deficiency and prevent further lung damage?

A: The majority of the alpha-1-antitrypsin (A1AT) protein in the body is made in the liver. However, some is also made in certain blood cells and in a few other places. The A1AT made in the liver is released into the blood and delivered to the entire body, including the lungs. A few cells in the lung make A1AT, but this is likely to be only a small contribution to the total A1AT present in the lung.

However, I must admit that I don’t think that this has been totally worked out by scientists and that what I’m saying is what doctors are only “fairly sure” about. In A1AT deficiency, the liver makes A1AT protein, but is unable to release it into the blood, leaving the rest of the body, especially the lungs, mostly unprotected from damage. If a liver transplant is performed, and the new liver is normal with respect to A1AT (PiMM), that is, as is hopefully the case) then this new liver will make normal A1AT and release it into the blood. Most doctors believe that this will result in enough A1AT protein in the lungs to protect them from further A1AT deficiency-related damage. However, damage that has already occurred cannot be reversed. Therefore, it is probably reasonable to think of a person who has had a liver transplant with a PiMM liver to be “cured” of further injury from A1AT deficiency. Although, of course a liver transplant can bring a whole new set of problems. I must caution though, that to my knowledge there has never been a study of the lung disease of post-liver transplant patients. In general medical practice, progression of lung disease in liver transplant patients has not been observed, although I would be happy to hear from some lung doctors about this, too. Therefore, I think liver transplant patients can feel very reassured about a very low likelihood of future lung disease, but keep in mind that this is based on some theory and simple observation. No detailed medical study has been done to my knowledge.

Q: Are there procedures that would help two MZ parents avoid having a ZZ child, or increase the likelihood of a MM child?

A: At present, the simple answer is no. There are no generally available techniques to alter conception with respect to A1AT. As you know, a child gets one gene from each parent at the time of conception. At present there is no way to screen eggs or sperm to take out those that would carry the Z gene. Experimental techniques have been reported that might in the future make this possible. However, they are not available now. Once the child is conceived, so called prenatal diagnosis of the child’s A1AT status is theoretically possible, although it would be difficult. First, it would involve either amniocentesis or chorionic villus sampling, which are two techniques that allow a sample to be taken of fetal tissue. Taking a blood sample from the umbilical cord while the fetus is still in the uterus would also be a theoretical possibility. Once the information was obtained, then the hard part would be to know what to do with it. That is, simply be prepared for the birth of a ZZ child, or would one choose to abort a ZZ

child? If the conception were accomplished in a dish rather than in the mother (in-vitro fertilization) then again, theoretically a sample of cells could be taken from the embryo, and the A1AT status determined. Again, the ethical decision about what to do with the unwanted embryo would still remain. At present, none of these possibilities are generally available to patients, and I doubt very much that they will be anytime soon. Research will continue, and perhaps some of the future research will involve pregnant women, but results that could be applied to large numbers of patients are a long way off.

Organizations and Individuals Involved in Research

No comprehensive list of AIAD research organizations exists.

Alpha One Association currently funds research on lung afflicted, and more recently, liver afflicted alphas.

American Liver Foundation funds research on liver afflicted alphas.

American Lung Association funds research on lung afflicted alphas.

Names of individuals who are active in research.

Dear Friends:

I haven't communicated with you for a while because I've been busy trying to do that research you've been talking about. I also can't afford to let down my patients, so that doesn't leave a lot of time for the computer.

I can quickly comment though, on that question about research. I don't know of any all inclusive list of Alpha 1 research organizations/individuals. However, there aren't that many people involved at present so I can give you a partial list from memory.

The Alpha One Foundation has started an effort to support lung and more recently liver research. They are currently working with a number of researchers to provide much needed money for several ongoing projects. There has recently been an agreement between the American Liver Foundation (a not for profit liver awareness and research organization) and the Alpha One Foundation to pool money for Alpha 1 liver research. Contributions to either of these organizations, earmarked for Alpha 1 research or specifically Alpha 1 liver research will be well used.

The Alpha 1 Association has also made valuable monetary contributions to research in the past, and again money sent earmarked for research (liver or lung) will find a good home.

I suspect, but don't know for sure that money earmarked for Alpha 1 sent to the American Lung Association would also be fine. Of course, it would not go to the liver, though.

My collaborator, Dr. David Perlmutter and I are heavily involved in Alpha 1 liver research here in St. Louis, as well as patient care. A few other people around the country have at times worked on Alpha 1 and the liver. Some of the best known are Dr. Harvey Sharp (Minnesota), Dr. Sarah Jane Schwarzenberg (Minnesota), Dr. Harvey Lodish (MIT), Dr. Maureen Jonas (Harvard), Dr. Ardythe McCracken (Reno), Dr. Sten Eriksson (Malmo, Sweden), Dr. Tomas Sveger (Malmo, Sweden), Dr. Albert Probst (Austria), Dr. Mark Brantly (Florida), Dr. Jerry Brown (Colorado), Dr. Richard Sifers (Texas). I hope this helps.

Cause of A1AD Liver Disease and Relation to Lung

A1AT made in liver and released in blood to body.

ZZ makes abnormal A1AT.

Abnormal protein is stuck in liver.

Prolastin does not help liver disease.

Q. What is the cause of A1AT liver disease and how is it related to the lung?

A: No one is completely sure how the liver injury in A1AT deficiency occurs. However, I'll try to summarize for you the most widely accepted theory. The A1AT protein is mostly made in the liver, which then releases the protein into the blood to supply the rest of the body. In this way A1AT protein is delivered to the lung to protect the lung from inflammation and other insults. A person who is homozygous for Z (A1AT deficiency ZZ type), makes an abnormal form of the A1AT protein which when manufactured in the liver cannot be released into the blood. This leads to low levels of A1AT protein in the blood that are inadequate to protect the lung. This low level of lung protection can lead to emphysema. Prolastin is purified A1AT protein from normal people which is given to try to supplement the low level of A1AT protein in the blood of ZZ type persons.

However, in ZZ type persons the abnormal protein is still produced in the liver; it is stuck inside the liver cells unable to be released into the blood. In most people, the liver cells are able to break down and recycle the abnormal Z A1AT protein that gets stuck. It appears though, that people who get liver disease are not able to efficiently break down and recycle the abnormal z A1AT protein stuck inside their liver cells. This buildup of the abnormal z protein causes damage to the liver cells. In some infants with ZZ A1AT deficiency this damage may occur very rapidly while some people live well into adulthood before any liver injury becomes evident. In fact, most ZZ A1AT deficient people will NEVER get liver disease, or at least not until very late in life. Many patients with only blood test abnormalities in fact, will never progress to any more serious problems.

This is an important fact to keep in mind and can be very reassuring to the families of healthy appearing children whose only problem is a number on a blood test.

Since the liver injury seems NOT to be related to the low blood levels of A1AT protein, but to the buildup of the already manufactured protein in the liver, supplying extra blood protein in the form of Prolastin treatments would have no affect on the progression of liver disease. At present there is no drug or other treatment made specifically for A1AT deficiency associated liver disease. Much of the treatment involves managing complications and keeping the patients as healthy as possible in every other way. As mentioned above, many patients, even those with already significant liver injury, will go for years with very little change and leading very normal lives.

Tests Indicated For Newly Diagnosed A1AD ZZ Patients

Most ZZ patients do not develop liver disease, or at least not until very late in life.

Evaluation depends on age, previous illnesses, drug/alcohol use, viral hepatitis, etc.

Evaluation begins with liver function tests (LFT's)

Tests to measure liver's synthetic function

Other family members tested for phenotype.

Q: When a new patient with alpha 1 antitrypsin deficiency is diagnosed homozygous ZZ), what evaluation for liver disease should be done?

A: When considering the possibility of liver disease in a person with Z alpha 1 antitrypsin deficiency, it is important to remember that most people with the ZZ type DO NOT get liver disease, or at least not

until a very advanced age. Several lines of medical evidence suggest this, but the best study to date has been the prospective (patients identified at birth and followed as they grew) analysis by Dr. Thomas Sveger in Sweden. Dr. Sveger screened more than 200,000 newborn babies to find less than 200 with ZZ alpha 1 antitrypsin deficiency. He and his colleagues have followed these same children continuously for more than 18 years and fewer than 15% have ever had any sign of liver dysfunction. In fact, many of these 15% only had minor blood test abnormalities without the occurrence of any other health problems. Only a handful developed severe liver disease. Other studies in adults indicate that the chance of liver damage may increase with advancing age, but that it may not be medically significant until old age. Therefore, this evidence taken together with other medical studies allows physicians to be rather optimistic that most people with ZZ Alpha-1 antitrypsin deficiency will not develop severe liver disease until very late in life if at all.

The evaluation for the possible occurrence of liver disease in patients with A1AT deficiency depends on the patient's age, previous illnesses, and other factors such as any history of alcohol use or the presence of viral hepatitis infection. Usually the evaluation would begin with a series of blood tests that measure various aspects of liver function. One such series of tests, called serum transaminases or liver function tests (LFT's) is commonly elevated in A1AT liver disease and is a measure of injury to liver cells themselves. However, serum transaminases are also commonly elevated in other illnesses that involve the liver, or other organs, and so are not always related to the patient's alpha 1 ZZ status.

Other blood tests that may be commonly performed are designed to measure what is known as the liver's synthetic function. That is, the liver's ability to make things for the body such as blood proteins. A serum albumin level is one such blood protein measurement that is related to the liver's synthetic function and to the person's nutritional status. In addition, measurements of proteins that help the blood clot, called the prothrombin time, partial thromboplastin time, or the international normalized ratio (PT, PTT, INR) may also be used. These tests are also related to the patient's intake and digestion of vitamin K, which is adequate in healthy people but which can be disrupted in people with liver disease.

Sometimes, in more severe liver dysfunction, the ability of the liver to remove wastes and toxins from the body becomes impaired. This can be manifested by a yellow discoloration of the whites of the eyes or the skin known as jaundice. A waste product known as bilirubin is responsible for the yellow color and so blood measurements of bilirubin levels are also sometimes performed.

If abnormalities are detected on some of these blood tests, or if the physician is concerned about the health of the liver because of other elements of the patient's history or physical examination, then additional tests may be warranted. Some of these may focus on looking for other causes of liver problems such as viral hepatitis or other infections, exposure to medicines or toxins, or physical injuries to the liver. In some adult patients, multiple reasons for liver dysfunction may be found, including the alpha 1 AT ZZ type which can make it difficult to know for certain the origin of the patient's difficulties.

Often imaging studies such as an ultrasound examination of the abdomen or a CT (CAT) scan are used to make a picture of the liver and map its blood flow.

If more advanced liver dysfunction is suggested, then a liver biopsy may be recommended to obtain a sample of liver cells using a needle inserted into the side of the patient's body. In this way, the liver cells can be studied directly under a microscope, and other specific tests performed to gauge the severity of the injury to the liver. This may also assist in understanding the cause of liver injury in a case where multiple possibilities are under consideration. However, obtaining a liver biopsy carries with it a small but potentially serious risk of injury to the patient and so is reserved for situations where there are already serious indications of liver disease based on previous tests.

When a new patient with homozygous ZZ alpha 1 antitrypsin deficiency is diagnosed, then it is important to consider what, if any, other family members (brothers, sisters, children) might also be evaluated for the presence of the ZZ type. This is so they can be evaluated and treated for any complications of the disease already present, and urgently cautioned against smoking to prevent rapid deterioration of lung function.

Some families and medical professionals are concerned about testing other family members because of the possibility of genetic discrimination from insurance companies or employers. A careful discussion of the pros and cons of testing with the physician can help to reach an informed decision.

At the early stages, the evaluating physician may obtain some of the preliminary studies for liver disease mentioned above. As discussed, these will usually be normal and can be very reassuring to the patient and to the doctor. For a more detailed evaluation of the liver, it is generally recommended that the patient see a specialist gastroenterologist or hepatologist (liver specialist) who is familiar with alpha 1 antitrypsin deficiency. If the patient is under 18 years of age, then this is probably best done by a pediatric gastroenterologist/hepatologist.

Fortunately, liver disease in ZZ alpha 1 antitrypsin deficiency only occurs in a minority of patients.

However, when it does occur, the manifestations can be highly variable from severe disease in a newborn baby to only minor blood test abnormalities in an adult without other adverse health problems. Therefore, the plan for evaluation treatment is often different from person to person and can require the participation of a specialist experienced in the disease.

Will a Transplant “Cure” A1AD and Prevent Further Lung Damage?

How A1AD protein is made and how it affects the liver.

Transplant is “fairly certain” to cure A1AD.

Existing damage in lungs will not be reversed, but future damage controlled.

Transplant can cause a new set of problems.

More research is needed.

Q: Will a liver transplant “cure” alpha-1-antitrypsin deficiency and prevent further lung damage?

A: The majority of the alpha-1-antitrypsin (A1AT) protein in the body is made in the liver. However, some is also made in certain blood cells and in a few other places. The A1AT made in the liver is released into the blood and delivered to the entire body, including the lungs. A few cells in the lung make A1AT, but this is likely to be only a small contribution to the total A1AT present in the lung.

However, I must admit that I don't think that this has been totally worked out by scientists and that what I'm saying is what doctors are only “fairly sure” about. In A1AT deficiency, the liver makes A1AT protein, but is unable to release it into the blood, leaving the rest of the body, especially the lungs, mostly unprotected from damage. If a liver transplant is performed, and the new liver is normal with respect to A1AT (PiMM, that is, as is hopefully the case) then this new liver will make normal A1AT and release it into the blood. Most doctors believe that this will result in enough A1AT protein in the lungs to protect them from further A1AT deficiency-related damage. However, damage that has already occurred cannot be reversed. Therefore, it is probably reasonable to think of a person who has had a liver transplant with a PiMM liver to be “cured” of further injury from A1AT deficiency.

Although, of course a liver transplant can bring a whole new set of problems. I must caution though, that to my knowledge there has never been a study of the lung disease of post-liver transplant patients. In general medical practice, progression of lung disease in liver transplant patients has not been observed, although I would be happy to hear from some lung doctors about this, too. Therefore, I think liver transplant patients can feel very reassured about a very low likelihood of future lung disease, but keep in mind that this is based on some theory and simple observation. No detailed medical study has been done to my knowledge.

Research - PBA information

(PBA stands for 4-phenylbutyric acid. It is a chemical chaperone)

Researchers use fibroblast cells donated by AIAD patients.

AAT Z level in mice increased 5 times when PBA administered.

Evaluation in humans with AAT deficiency has started.

An adult dose is 40 large pills daily; a two-week supply costs \$1,000.00.

Trials on close by patients are being conducted at Washington University in St. Louis.

More work needed before widespread use of PBA.

Working together we can beat the disease.

Dear Jack and Liver List,

Yes, the PBA information is exciting, but we've still got a lot of work to do. Let me explain.

As you know, the Z form of AAT is abnormal and gets stuck inside of the liver cell after it is manufactured instead of being released into the blood as it is supposed to be normally. The result is low blood levels of AAT that leave the person at risk for emphysema, and a buildup of AAT Z in the liver that can damage liver cells. Interestingly, the AAT Z within the liver cells is nearly normal in its ability to protect the lungs from damage, if it could just get out of the liver and get up there.

We (my collaborators Dr. David Perlmutter, Dr. Jon Burrows, Dr. Lauren Willis, Dr. Nancy Marcus, and I) have found that a number of drugs can be used to affect how the liver cell handles the AAT Z. That is, increased breakdown of AAT Z stuck in the liver or increased release of the AAT Z stuck in the liver. One drug which has shown special promise is 4-phenylbutyrate (4-phenylbutyric acid, or PBA). This drug, known as a "chemical chaperone" helps "escort" the AAT Z out of the cell and into the blood. This drug has been extensively evaluated in cystic fibrosis where the CF molecule in one form of the disease also gets stuck inside the cells, similar to AAT Z. Studies in humans with CF showed that there was an effect, but that it was too small to change the course of the patient's disease. Several CF researchers are working madly to develop a new generation of PBA-like medicines that will do the same thing, only better.

Our group has been following the CF work with great interest. We have evaluated many drugs, including PBA, in the laboratory using several different experimental systems. Some of the experiments have indeed involved the fibroblast cell lines taken from the skin of Alpha 1 deficient patients that several of you have so generously donated. The results showed that AAT Z which we manufactured inside some of the human fibroblast cells was much more easily released from the cells when PBA was added.

Next, we used a genetically engineered mouse which mirrors human AAT deficiency disease. This mouse was given the human AAT Z gene (by other researchers, not us), makes AAT Z in the liver, develops liver damage as it ages, and has low, human-like blood levels of AAT Z. We gave the PBA orally to the mice. The AAT Z blood level increased five times under the influence of PBA. Wow! I outlined some of this work in my talk last fall at the Southwest Regional Education Conference that the Association put on. Some of you, I think, were there. A medical research paper describing the first part of this work was recently published by Drs. Burrows, Willis, and Perlmutter. It was the press release from this paper that many of you saw and are responding to.

Last year, I also started working on the logical next step, evaluating PBA in humans with AAT deficiency. Clearly, the idea is to give oral PBA to ZZ patients in order to increase the release of AAT Z from inside of the liver cells and therefore protect the patient from liver disease. At the same time, the blood level of AAT would increase, perhaps to the level where the patient would be protected from lung damage. PBA, or a medicine like it, could be an oral treatment of liver disease AND an oral replacement for ProLactin®! The medicine is already FDA approved for several other diseases, but it had never been tried before in AAT deficiency. It turns out to be very expensive, over \$1,000 for a two-week supply for an adult-size patient. Also, the adult dose is 40 (forty) pills a day, and they are rather large.

I (we) have treated a number of human patients in the last few months. I can't release the full results to you as yet. A few people on the list have participated, and to them I am very grateful. If I need more participants for this or other trials, I will post the information, but it has generally been easier so far to work with our patients who are close by, here in St. Louis. We are encouraged enough at present to keep working on PBA, and on a variety of other medications whose effects are also very promising. However, until more work is done, I do not recommend that patients go to their private physicians to get PBA. We still need more information on effectiveness, dosing, side effects, and how to monitor patients who are on the treatment.

As more information becomes available, I will keep you informed. I appreciate your support of our work. If we stick together we will eventually beat this disease.

Liver Tests And What They Mean

*Serum transaminases (also called liver enzymes, liver function tests, or LFT'S)
Chemical level tests SGOT (or AST), SGPT (or ALT), alkaline phosphatase (ALK Phos), and GGTP (or GTP or gamma GT)*

Dear mailing list:

A number of people have asked about various liver tests and what they mean. Let me briefly touch on some of these tests.

The liver is a very complicated organ that does many (dozens) of different jobs for the body, some of which are very poorly understood. There is no single test that could measure a person's total liver health. One set of blood tests that are commonly performed are so called "serum transaminases," (also called liver enzymes, liver function tests, or LFT's). These are a set of blood levels of chemicals that normally occur within liver cells, but leak out of liver cells into the blood at a slow rate. The specific levels measured are sometimes called SGOT (or AST), SGPT (or ALT), alkaline phosphatase (ALK Phos), and GGTP (or GTP or gamma GT). If liver cells are sick or injured, they can leak these chemicals at a faster rate causing the blood levels to rise. therefore, doctors use these blood levels as rough measure of ongoing irritation or injury to the liver.

The exact type of various serum transaminase elevations can vary with the patient's liver disease, other unrelated illnesses such as the flu which might be going on at the same time, or other problems in other areas of the body. These same chemicals that are made in liver cells can also be made by other cells in the body.

In alpha 1 antitrypsin (A1AT) deficiency associated liver disease, the serum transaminases are commonly elevated. Doctors often use these blood tests as a general measure of the presence or absence of ongoing liver problems. If the blood levels were very high and remained that way for some time, without evidence of some other ongoing process such as a viral infection of the liver, then that would be a cause for concern. However, we know that many patients will go years, if not decades with low levels of serum transaminase elevation and do not seem to go on to have any other measurable liver problem. In fact, many infants with A1AT deficiency will have elevated serum transaminases for the first few years of life, that will then return to normal later without any other problems.

Exactly what elevated serum transaminases mean for any individual patient is hard to say without specific information on that patient's history and medical status. As we have said, elevated serum transaminases are a REFLECTION of possible irritation/injury to the liver, not a cause of that irritation. Since, unfortunately, we have no specific treatment for A1AT associated liver disease, beyond vitamin supplements or other treatments that are used for liver disease patients in general, it is unlikely that measures of transaminase elevation could lead to some kind of action being taken for the patient. The exception would be that if enough concern were generated to see the patient more frequently or to

monitor more closely for treatable problems (like low vitamin levels) that might crop up. Therefore, we generally recommend that neither doctors nor patients get too fixated on specific numbers at any specific point in time. Rather, it is best to concentrate on the general trends in the patient's health and use tests like measures of the serum transaminases as only one piece in the puzzle of the patient's status.

I hope some of this information is of help to you. If you have specific questions about a specific patient's health, then of course that would be best dealt with by that patient's physician who has all of the relevant information at hand.

Large/Small Liver; Itching; Odors; Bad Breath

Difference between larger than normal and smaller than normal liver.

Itching, bad breath, unusual odors.

Q: What is the difference between a larger than normal or smaller than normal liver?

A: In various disease conditions the liver can become both enlarged and shrunken. In some diseases, excess fat accumulates in the liver, or the liver can be swollen from inflammation much like any other part of the body. Certain so called "storage diseases" lead to the accumulation of specific waste products in the liver. In Alpha 1 the liver can be enlarged from inflammation, fat, the accumulation of the abnormal Alpha-1 Z protein within the cells, or from other reasons. Some of the other causes of liver enlargement, also called "hepatomegaly," can be due to abnormal blood flow through the liver. The causes of a shrunken liver are probably less numerous, and the condition is more rare. Often, if a patient's liver is very sick, for example if a patient is waiting for a liver transplant, the liver will shrink as its function deteriorates.

However, there are other reasons that might apply in certain patients. In general, liver size is just one aspect of the physical examination that must be considered when trying to make sense of a patient's disease. To understand what liver size means for a specific person, a lot of detailed medical information is needed.

Q: What about itching, bad breath, and unusual odors in people with liver disease?

A: One of the liver's most important functions is the removal of waste products from the body. See one of my previous postings on the function(s) of the liver. Some wastes are removed in the bile that the liver makes and is then drained into the intestine where one part of the bile, known as bile acids, acts as an aide to fat digestion. If bile is not draining out of the liver normally, then many wastes, as well as normal constituents of bile can build up. Abnormal bile drainage from the liver can result from problems within the liver cells themselves (Alpha 1), or from problems in the bile ducts and gall bladder that conduct the bile from the liver to the intestine (gallstones, post-liver transplant problems, etc.). In this situation, bile acids can build up in the blood and become deposited in the skin in abnormal amounts. In many patients this leads to terrible episodes of itching that can be very difficult to treat. Itching, especially in young children, can be one of the most burdensome symptoms of serious liver disease. Various treatments can be tried. Talk to your doctor to find the best one.

Bad breath and unusual odors in patients with liver disease can result from the buildup of other waste products in the body that the diseased liver is unable to deal with. Also, some medications used in liver disease patients can cause skin changes, changes in body fluid colors, and changes in body odor. Interestingly, some childhood liver diseases (not Alpha 1) cause the children to have very specific odors as a result of changes in body chemistry. Sometimes in these cases a specific diagnosis can be made just by considering the patient's odor. There is usually no good treatment for unusual odors, except for

treating the underlying liver disease. If a liver transplant is needed, then the odors usually go away when the new liver is functioning well.

Hepatitis

Inflammation of the liver

Common Causes

Dear Liver List,

I've been handed a question about "hepatitis." Here goes.

"Hepatitis" literally means, "inflammation of the liver." You might recognize the root word "hepa" meaning liver, and the suffix "-itis" which means "inflammation" or "irritation." There are many possible causes of hepatitis; infections (viral infection of the liver itself, or even other types of infection in other areas of the body), toxins (beverage alcohol, industrial chemicals, poisons in contaminated food, etc.), so called "metabolic diseases" (alpha-1-antitrypsin deficiency, Galactosemia, Wilson's Disease, Cystic Fibrosis-sort of), auto immune disease (where the body's own immune system attacks the liver for unknown reasons), and many others. One of the main ways the signs of hepatitis are detected is through blood tests, especially blood measurements of the level of AST and ALT (also called SGPT/SGOT, LFT's, Liver function tests, or transaminases). These are chemicals normally found within liver cells that leak out into the blood normally at very low rates. However, if the liver is irritated or damaged, from hepatitis or being bruised in a car accident, or whatever, then these chemicals leak out at a faster rate and the blood levels go up. See my previous post on tests of the liver.

If a person has high AST/ALT and has not had recent trauma or surgery, then he is usually thought to have some kind of "hepatitis" and his doctor will usually do tests to look into some of the possibilities I've listed above.

Sometimes, people might have more than one reason to have blood tests suggestive of hepatitis. By far, the most common causes of hepatitis in the US are viral infections, either the hepatitis A, B or C viruses, and alcohol over-consumption. The confusion comes because sometimes we doctors, and other people, get sloppy and use the word "hepatitis" interchangeably with "viral hepatitis," because the viral causes are so much more common than the other causes.

Patients who are homozygous ZZ for Alpha 1 commonly have hepatitis, as defined by having elevated AST/ALT. Perhaps 15%-30% of ZZ children will have some period of time with these blood tests elevated between birth and age 18 years.

However, those blood tests often return to normal without any other health consequences. In adults, perhaps 50% of ZZ people will have elevated AST/ALT at some time or another, but those are rough numbers and very detailed medical studies have not been done. Sometimes these abnormal blood tests are a prelude to the development of more severe liver disease, but often they are not and additional tests and regular checkups are needed to follow-up on any individual patient. Sometimes, even if a patient is known to be ZZ, if elevated AST/ALT or other liver abnormalities are detected the doctor will do other tests to rule out common viruses, gallstones, or other problems to be sure nothing is missed. However, being ZZ by itself can easily be the cause of "hepatitis."

It is controversial if being MZ by itself is a cause of hepatitis. It probably can be in a few rare people, but it is safe to say the majority of the approximately 5 million MZ Americans don't have hepatitis. If an MZ person is found to have elevated AST or ALT then usually extensive testing is done to try to look for many of the much more common things listed above, especially the ones that are easily treatable.

Combined Lung/Liver Transplants; Hepatitis C; Prolastin and Liver Disease; Lung/Liver Disease Simultaneously Occurring

Combined lung/liver transplants are controversial.

Liver Transplants due to Hepatitis C performed at some transplant centers.

Prolastin could be contraindicated if liver disease is present.

Lungs and liver can both be affected in same person.

Dear Liver List.

Several interesting questions are raised here. If the patient would like to call me at my office, I'd be happy to go over them.

Basically, combined lung/liver transplants are controversial. Here at St. Louis Children's Hospital we've done three combined lung/liver in CF children. We have another child with a liver/heart, done at different times...long story. We've got a couple of other similarly complex patients that I can't go into right now. However, I am not personally aware of adult programs that are doing lung/liver in adults. They may exist, I'm just not aware of them. The patient's doctor should do some checking if the patient really wants to go that route.

The hepatitis C infection is a very big issue. It is a serious disease that by itself can cause fatal liver disease. Some adult transplant centers do perform liver transplants for liver failure due to hep C infection. Serious recurrence after liver transplantation is common. Other non-liver transplant programs do consider hep C infection to be a contraindication to successful transplantation of other organs. This issue is very complex and to be fully fair and satisfactory to the patient, he would have to go over it in detail with a transplant physician at the center of his choice.

The issue of Prolastin® and the liver is also complex. As you know, Alpha 1 Z is made and accumulates in the liver, causing liver damage in some, But not all ZZ people. When normal Alpha 1 M does its job of binding with neutrophil elastase, in the lung or elsewhere, a molecule is released that actually goes back to the liver and stimulates the manufacture of more Alpha 1 in the liver. This is a normal mechanism the body has to replace the Alpha 1 that has been used up. IN THEORY, THEREFORE, taking Prolastin® stimulates the liver of a ZZ person to make more Alpha 1 Z. IN THEORY, this could be bad for some people's liver. HOWEVER, this has never been tested in people. I discussed this issue once with a representative of Bayer (maker of Prolastin®) who insisted that there is no evidence that Prolastin® hurts the liver. In reality though, no study has ever been done that examined the liver SPECIFICALLY in patients on Prolastin®. It appears that in most people no liver effects of Prolastin® have been noted by doctors who care for large numbers of ZZ emphysema patients. Small, rare effects though have certainly not been ruled out.

Finally, the issue of lung and liver disease in the same person. Some doctors used to believe that lung and liver disease never occurred in the same patient. Now however, I think we all agree that both organs can be affected in the same person, but that it is unclear how often this really happens.

I hope this bit of information clears up some questions. Likely as not though, you now have even more questions than before. That's often the way it is with this disease.

ZZ Lung Affected Children Discussion

At present time no reported, medical proven lung afflicted ZZ children.

Knowledge constantly changing.

Possibly there are non-reported cases.

Scientific acceptance requires reviewed and published medical paper.

Dear Liver List,

I talked to Jack today and he mentioned some of your comments from yesterday. Let me make things clear as to exactly what I was trying to say. Covering topics that are very complicated is difficult in this kind of forum where there is not a chance for direct response to questions or visual aids. That is why I use a lot of caveats such as “ask your doctor” and “medically proven” because I can’t know every detail about every person and foresee every contingency. I try to provide the best and most accurate medical information I can to a large group of faceless people out in cyberspace. I try not to overstate ANYTHING. I try to stick to what people know for sure, AT THE PRESENT TIME. Knowledge is changing all the time. I’m certainly open to being updated. I have no agenda and no vested interest in any fact about MZ risk or ZZ lung disease. However, a lot of harm has been done over the years by doctors who overstated risks and causes of disease without solid PROOF.

I did not mean to suggest that lung and liver disease couldn’t occur in the same patient. They can. I did not mean to suggest that asthma is not related to Alpha 1, many reports have suggested that it is. I meant that, as far as I know, no ZZ CHILD has been reported in medical journals with emphysema (permanent damage to the structure of the lung that was medically significant during childhood) unless they had some kind of second problem, unrelated to ZZ that also damaged the lung. Clearly ZZ children have grown up to be ADULTS with emphysema.

Could there be someone out there not yet “reported.” Of course, and I’d love to meet them. However, when a person asks a doctor a question, they generally want to know proven facts, not just what a doctor has been told off the cuff.

For a moment, let me discuss with you the way doctors are trained to believe things. We generally don’t call something a fact without scientific proof. How is such proof established? In the case of a prospective ZZ child with emphysema a doctor with such a patient would do a number of tests to prove the emphysema. It might be seen on a chest x-ray, but more likely in this day and age a CT scan (CAT scan) of the chest would be needed. PFT’s alone would not be enough. In addition, a large number of other tests would be done to exclude infections and other unusual lung problems that could explain the damage to the lung and not be related to ZZ. This might include even a bronchoscopy. If all this were done and the doctor believed that all the results pointed to ZZ emphysema in a child with no other explanation, then he would write a medical paper about the patient that would detail all of the test results.

He/she would send the paper to a medical journal. The journal would send the paper to a panel of other doctors that are experts in that field. They would review the work for accuracy. Most of the time, this review panel requests that additional work be done to add additional proof. When the journal review panel is satisfied, then the medical paper is published. In this way, when other doctors read the paper they can be confident that the work is accurate and true. So far, to my knowledge, there has been no clear report about ZZ children with emphysema, unless they also had a second disease, published in a medical journal.

I could be wrong. I could have missed the paper. Please tell me if so. I have read several hundred papers about Alpha 1 and there are a handful that try to detail ZZ children with lung problems. However, they all seem to also have a second problem that also could have contributed to the lung damage. In fact, detailed, systematic medical studies of several hundred ZZ children that looked for lung disease have been published in medical journals and none of them were able to show a risk in CHILDHOOD as far as I’ve seen. Does that prove that such a child does not exist? No. However, it suggests that if those

children exist they are probably very rare or they would have been reported already. That is why I tried to say it using the phrase “reported” and “medically proven.”

Do you really want me to pass along on the Internet things I’ve been told offhandedly but that I don’t know personally are true? If you know of a ZZ child with emphysema, as I said before, I would be pleased to review their records, see the patient, or coordinate a referral to another physician. In this way, the patient can be reported and medical knowledge can advance.

Bone Problems, ZZ children and Associated Lung Disease, and Hepatitis A

Bone problems in kids with liver disease.

Do ZZ children get Alpha 1 lung disease.

What about Hepatitis A Vaccine

Q. Is there a relationship between bone problems and liver disease?

A: Liver disease can alter the bodies absorption and digestion of vitamin D, an important factor in healthy bone development. Therefore, some patients with severe liver disease will have serious bone damage, sometimes they can even develop rickets, a major disease of the bones. The general malnutrition that can sometimes occur with serious liver disease can compound the problems. However, with proper medical care, many of these bone problems can be avoided. However, remember that the same things that happen to healthy kids also happen to alpha kids, so that a simple accident or fall that leads to a minor fracture could happen to an alpha kid and be unrelated to the liver disease.

Q. Do ZZ children get ALPHA 1 ASSOCIATED lung disease?

A: Although I hear (through the grape vine) about ZZ children with lung disease, no such case has been medically proven and reported by doctors to my knowledge. I’ve discussed this with several prominent Alpha 1 lung specialists and they all said this same thing. Now that doesn’t mean that there aren’t ZZ kids with severe asthma or other lung problems. As many of you know, asthma can mimic Alpha 1, or other lung diseases and asthma is very common in children. Asthma can even be fatal. Usually when doctors talk about Alpha 1 lung disease they mean emphysema, that is, permanent destruction of the substance of the lung resulting from inadequate Alpha 1 in the blood to protect the lung from inflammation.

This type of damage takes decades to occur. Other lung problems in ZZ people are being researched, so in the future maybe ZZ will be found to cause more than emphysema, although this is still controversial. I suppose that if a ZZ child were exposed over a long period to a very harmful environment lung-wise, for example, work in a coal mine, dusty factory, or very intense smoke then damage in the teen years might be detectable. It might also be that a ZZ person might have some other health problem, for example a defect in the immune system, totally unrelated to Alpha 1, that would leave the person open to severe lung infections and also accelerated damage. In general though, PERMANENT, DESTRUCTIVE lung damage in CHILDREN resulting from their ZZ status has yet to be shown medically. That being said, I would be happy to assist in the evaluation of any ZZ child with a question of lung or liver problems. I work commonly with the pediatric lung specialists here in St. Louis on patients with other diseases. Perhaps there are rare ZZ children with Alpha 1 related lung problems who need to be evaluated and treated. Anyone interested in such a consultation can contact my office.

Q. What about hepatitis A vaccine?

A: There are many types of hepatitis virus infections. Hepatitis A is one particular virus that is a common infection in children and adults. At least 50-60% of all people in the U.S. have already had the infection, and most never knew it. Hepatitis A is passed through contaminated food and water or from the

stool of an infected person. It is commonly thought of as a type of “food poisoning.” The infection is often mild, but it can be severe in some cases. If a person has some other kind of liver disease, then hepatitis A can make them sicker than usual. Most authorities recommend that anyone with any type of chronic liver problem be vaccinated against hepatitis A. However, in reality this is followed rather loosely and depends a lot on the individual patient’s situation. Ask your doctor if it is right for you.

Pre and Post Transplant Anxiety

Make use of professionals

Make use of medications

Join support group

Accept help

Dear Mailing list:

Someone asked about how to deal with pre and post transplant anxiety related to facing such an uncertain future.

This is a very difficult issue, but also very common; you are NOT alone. In fact, as some of you may know, my wife is a lung transplant recipient although she does not have alpha-1. I can really understand what you mean by this concern.

I’ll give you two answers to this question; one as a physician, one as a person who’s been there and survived. As a physician I encourage you to talk to your transplant team, M.D., or perhaps your program has a nurse coordinator, social worker, chaplain, or psychologist who is specifically identified to help patients with these common issues. I’ll tell you personally, that we made liberal use of all of the professionals I’ve listed above during our ordeal, and that they really helped us a lot! In some circumstances medications, such as Prozac the common antidepressant, are very useful in helping people get through some of the crushing anxiety and depression. This doesn’t mean you’ve gone crazy, it just means that when you or your family are afraid someone is going to die, or worse yet suffer intensively, then it can TEMPORARILY make you pretty depressed.

Your transplant center may also have a support group. The best ones are usually led by a medical social worker and involve both pre and post transplant patients so that all aspects of the experience can be shared and discussed. It is especially great to have people who are doing well post transplant come back to the support group to tell their stories to bolster the spirits of those still waiting. The worst thing is feeling that you are alone and that you must be the only person to ever have felt so vulnerable. Hearing from other people with the same experiences can really help. However, it is best NOT to let support group sessions degenerate into “bitch sessions” where people start complaining about their doctors, the quality of care, their feelings that the transplant waiting list “isn’t fair,” etc. This sort of thing actually heightens anxiety and often the lay people who make such comments don’t really know what they are talking about or its pain and frustration just spilling over. The group needs to be built up not torn down, although I don’t necessarily mean that the discussion should avoid topics such as pain and death. That is why some kind of “official” leader of the support group with basic transplant medical knowledge is useful. If patients have concerns such as above they should be addressed privately with the nurse coordinator or the physician. Get involved in your medical care, but DO NOT be a pest. Try to find the middle ground.

On a personal note, I’ll tell you that life pre and post transplant can be fairly uncertain. That’s not to say that life isn’t good, long, or that the future isn’t fairly bright, it’s just that there is more uncertainty than in the usual person’s life.

This concept can be difficult for those of us who are control freaks. Too bad. Get on with life and enjoy what you've got. Pardon the expression, but "stuff happens" and sometimes it happens to you so you've just got to keep going. Don't be afraid to accept some help. It is not a sign of weakness. Those church ladies that want to bring you dinner are sincere and are not put out by helping someone in temporary need. Let them help you.

Finally, have faith and a sense of humor. Get back in touch with the clergy person of your choice. You have to believe that you will survive, even if intellectually you also must simultaneously acknowledge that the possibility exists that you (or your loved one) may die. Don't be surprised if some people seem sometimes to be avoiding you. They probably really care about you but have trouble seeing you so sick. Try to engage them on a non-medical level. Talk about the old, good times or make some good jokes (those Clinton/Monica ones are working pretty well these days). Just don't go on and on about the medical end of things all the time. Everyone will feel better if medicine isn't the topic of every single dinner table conversation. Try renting some funny movies, but don't watch anything too heavy.

I'm not sure how helpful all of this is. Lots of other people could have told you the same thing. Anyway, good luck.

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