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Strategies for Preventing or Reducing Parenteral Nutrition-Associated Liver Disease

by Susan Agrawal

Liver disease resulting from long-term parenteral nutrition (PN or IV nutrition) dependence is an unfortunately common side effect of this life-saving treatment, especially in babies and young children. While many cases of liver disease cannot be prevented with current medical techniques, there are many steps that can be taken to reduce the effects of parenteral nutrition on the liver.

We have just begun confronting these issues with our daughter Karuna, who has been 100% dependent on parenteral nutrition for the past two years, and whose liver function tests moved from normal to three times normal or greater over the past six months. While we are unsure of the magnitude of liver disease at this time, we have begun to research the options available to reduce or even reverse parenteral nutrition-associated liver disease. The following lists represents some of the suggestions currently recommended in the medical literature.

1. Try to obtain Omegaven, a fish-based lipid. Omegaven shows the greatest promise in preventing, stabilizing, and even reversing parenteral nutrition-associated liver disease. Two studies by Kathleen M. Gura, Mark Puder, and others associated with Children's Hospital Boston have shown amazing results, with a dramatic reduction in bilirubin, liver function tests, deaths, and the need for transplantation.[1]

Omegaven is fish-oil based and has a much greater percentage of omega 3 fatty acids as compared to plant-based lipids, which contain phytosterols and a high percentage of omega 6 fatty acids. Too high a percentage of omega 6 fatty acids (such as in the standard lipid solutions of soybean and safflower oil) can have a pro-inflammatory effect on the liver, and the phytosterols in soybean and safflower lipids may cause damage to the liver. Omegaven, on the other hand, is rich in omega 3 fatty acids, which are anti-inflammatory and seem to protect the liver.

Omegaven has been used in Europe and other countries around the world but is currently not available in the United States except in studies and compassionate use situations. It is considered very safe. Download this document [http://www.oley.org/documents/How_Physicians_Can_Obtain_Omegaven.pdf] from the Oley Foundation for more information on how to obtain Omegaven.

2. If Omegaven is unavailable, use a 100% soybean lipid instead of a soybean/safflower mixture. While the effect may be minimal, soy-based lipids contain a slightly higher percentage of omega 3 fatty acids as compared to safflower oils, which contain primarily omega 6 fatty acids. Omega 3 fatty acids seem to have a positive effect on the liver.

3. Run lipids only a few days a week or only for a short period of time each day (8-12 hours). Because standard lipid solutions (soybean or soybean and safflower oils) used in the United States contain phytosterols, they may contribute to liver inflammation or cholestasis.[2] Reducing the amount of lipids or the number of hours on lipids may decrease stress on the liver and limit the amount of potential exposure to damaging lipids. Children with metabolic problems and certain other conditions may not be able to run lipids this fast.

4. **Cycle the PN, aiming to run it for 10-18 hours.** Cycling the PN allows the liver to rest and recover during a portion of the day, which may reduce stress on the liver and mirrors a more typical circadian pattern of digestion and rest. While cycling is routinely recommended for healthy children, it may be metabolically stressful for those who are critically ill or have metabolic abnormalities.[3] These children should not cycle their PN.

In addition, if the PN is administered too fast, vitamins and minerals may be excreted rather than absorbed. Children with consistent deficiencies of these elements should run their PN over a longer period of time.

5. **Optimize the PN recipe, especially the balance of glucose with protein and fat.** While the connection between lipids and liver disease has taken center stage recently, high levels of glucose or dextrose can also cause liver diseases, particularly fatty liver, to develop.[4] Moreover, liver disease can be exacerbated by deficiencies in fatty acids, so completely eliminating lipids may be detrimental in the long run. The proper balance between glucose, protein, and fat must be maintained, and a skilled pharmacist and dietitian with many years of experience using PN is essential.

In addition, potentially toxic substances such as manganese or copper should be reduced or removed from the PN.

Make sure adequate fluids are given. Fluids keep the entire system working well and prevent dehydration, especially in children with large volume ostomy outputs or chronic diarrhea. See this article [http://www.articles.complexchild.com/00037.html] on Fluid Requirements.

Finally, make sure not to overfeed the body with excess calories as this stresses the body and liver. Many children find they can reduce calories as compared to oral intake, especially if they have had absorption problems with oral or enteral feeding.

6. **Monitor blood levels of vitamins and trace elements at least every six months since excess amounts of certain vitamins and minerals can be toxic to the liver.**

Iron in particular tends to accumulate in the liver, potentially causing both high blood levels of iron and ferritin and excessive iron in the liver.[5] While the mechanism for these actions is unknown at this time, a normal level of iron and other vitamins and trace elements is optimum.

Vitamin A is known to cause liver problems when it reaches toxic levels.[6] Other elements, such as manganese and copper, also have a tendency to build up in the liver or worsen liver function. While functional tests for all vitamins and trace elements are not available, those that can be quantified need to be measured to ensure an adequate amount while preventing toxic effects.[7] Measurements may not always be accurate, unfortunately, since blood levels often represent levels infused rather than the level in body tissues, especially for trace elements. Trace elements, including iron and selenium, should only be measured when the patient is well since illness can cause a change in distribution. The subject of trace elements will be the focus of the 2009 ASPEN conference, which will hopefully yield some more information on the subject.

Children on PN also tend to be deficient in a wide variety of vitamins and other trace elements. Individual levels must be monitored consistently and adjusted as needed. Trace minerals should be added one by one to the PN whenever possible to ensure adequate levels, and vitamins may also need to be administered separately (instead of as an IV multivitamin solution) if toxic levels or deficiencies of one or more vitamins occurs.

7. **Stop or reduce all medications that have liver side effects, such as Tylenol (acetaminophen) and many seizure medications.** Some of these include:[8]

- **Analgesics and Nonsteroidal Anti-Inflammatory Drugs**: ibuprofen (Motrin), acetaminophen (Tylenol)
- **Lipid-lowering agents**: statins, nicotinic acid (niacin; Nicolar)
- **Antidiabetic agents**: acarbose (Precose), pioglitazone (Actos), sulfonylureas
- **Antibiotics**: amoxicillin-clavulanate potassium (Augmentin), erythromycin, isoniazid (INH), nitrofurantoin (Furadantin), tetracycline
- **Antifungal agents**: fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral)
- **Retinoids**: etretinate (Tegison)
- **Anticonvulsant agents**: phenytoin (Dilantin), valproic acid (Depakene)
- **Psychotropic agents**: bupropion (Wellbutrin), chlorpromazine (Thorazine), tricyclic antidepressants
- **Hormones**: tamoxifen (Nolvadex), testosterone
- **Others**: halothane (Fluothane), methotrexate (Rheumatrex)
- **Herbs and Supplements**: Iron, Niacin, Vitamin A, Manganese, Copper, Comfrey, Echinacea, Niacin, Valerian, and many others

Please note that the risks and benefits of each drug must be weighed. In some cases, it may be necessary to remain on the medication, while in other cases, a different

medication may be more suitable. Never stop a medication without consulting your doctor. In addition, this is not a complete list. Other medications may also be problematic.

8. **Use the gut as much as possible.** When the gut is not used, a variety of negative consequences occur, including thinning of the mucosal barrier, bacterial overgrowth, lowered gut immunity, and decreased gall bladder function.[9] These can lead to increased episodes of sepsis if bacteria seeps from the gut into the bloodstream, as well as gallstones that may further impact liver function. Not using the gut also reduces gastrointestinal hormones, which can contribute to less gallbladder function and increased bacterial overgrowth.

While using the gut may be difficult for some children, the more the gut is used, the less likely PN-related liver disease is to occur. Even running water at 2ml per hour or only using the gut for meds may help. The ultimate cure for PN-associated liver problems that are caught early is to transition to oral or enteral (tube) feeds.

9**. Eliminate bacterial overgrowth.** Use of medications such as Flagyl to reduce bacterial overgrowth in the small bowel may help reduce episodes of sepsis from bacterial translocation (when gut bacteria seeps into the bloodstream) and other inflammatory responses that may impact the liver.[10] Breath testing may help to diagnose this problem, and treatment with antibiotics, which often must be rotated to prevent resistance, is usually helpful. Polymyxin B, another antibiotic that is particularly effective on gut bacteria, may be given through the gut to reduce bacterial overgrowth and reduce the severity of bacterial translocation, and has been shown to reduce steatosis in rats.[11]

Prebiotics and probiotics may also help to lessen bacterial overgrowth. In addition, reducing bacterial overgrowth may speed up the transition back to partial or full enteral feeds.[12]

10. **Prevent line infections and sepsis.** While the relationship between sepsis and liver function is not fully understood, sepsis can create an inflammatory effect in the liver, worsening function, and studies have shown a clear link between sepsis and liver failure.[13] Proper line care and aseptic technique to reduce line infections is an absolute must.

Use of needless systems, chlorhexidine, and other techniques may help prevent infections. Reducing bacterial overgrowth in the gut may also help to prevent sepsis from bacterial translocation, when bacteria seep out of the gut into the bloodstream.

11**. Add Carnitine to the PN.** Children with liver diseases tend to have low levels of carnitine in their blood, and some of the conditions that may lead to a child being placed on PN (such as mitochondrial disorder) are also associated with low levels of carnitine. Supplementation to normal levels is a must. In addition, at least one study in rats has demonstrated that carnitine may reduce hepatic steatosis (fatty liver).[14]

12. **Take Actigall (Ursodeoxycholic Acid or Ursodiol).** Ursodiol is a bile acid that may help improve bile flow and improve liver function. Typically used to treat gallbladder disease, Ursodiol may reduce gallstone formation or gallbladder sludge as well, leading to less blockage in the ducts connecting the gallbladder, liver, pancreas, and intestinal tract. A recent review article cites six studies on the topic, all of which found reductions in liver function tests and improvement of symptoms such as jaundice.[15] Ursodiol unfortunately only comes in oral forms, which may make treatment difficult in children with poor absorption or little gut function.

13. **Add Mucomyst (N-Acetyl Cysteine or NAC) to the PN or infuse it separately.** A recent article from the Hospital for Sick Children in Toronto includes the case histories of three children with liver cholestasis who were placed on NAC in an attempt to improve liver function.[16] Children on PN seem to be particularly lacking in cysteine, and adding NAC seems to compensate for this deficiency. The three children in the study showed dramatic reductions in liver biochemistries including bilirubin, AST, ALT, GGT, as well as Ferritin (iron stores), as compared to baseline before treatment with NAC.

14. **Add Choline to the PN.** Choline-deficiency is common in children on PN. While not much research has been done in this area, one study has demonstrated that choline deficiency increases steatosis (fatty liver), and supplementation with choline may improve the steatosis.[17]

15. **Add Glutamine or Taurine to the PN.** Glutamine, an amino acid, may reduce episodes of sepsis by improving gut function.[18] Along with other positive effects, Glutamine is thought to improve the intestinal barrier, preventing bacteria from seeping into the bloodstream and causing infections. Taurine, an organic acid, is often deficient in babies and children receiving TPN. One study showed that certain premature babies had improved liver function with taurine supplementation.[19]

For more information, contact the Oley Foundation [www.oley.org] or visit the Short Gut Wiki Omegaven page [http://grey.colorado.edu/shortgut/index.php/Omegaven].

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[4] Gura II, e200.

[5] Thomas R. Riley, *et al*. "Preventive Strategies in Chronic Liver Disease: Part I." *American Family Physician* 2001;64(9): 1558-9.

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[9] Deirdre A. Kelly. "Intestinal-Failure-Associated Liver Disease: What Do We Know Today?" *Gastroenterology* 2006;130:S71-2.
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[13] For a summary of these studies, see Kelly, S74; and Carter and Karpen, 252-3.
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