MINIREVIEW

Recognition, Diagnosis, and Management of Wilson's Disease (44460)

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Abstract. **Wilson's disease is a relatively rare inherited disorder of copper accumulation and toxicity, caused by a defect in an enzyme that is part of the pathway of biliary excretion of excess copper. Clinically, patients usually present as older children or young adults with hepatic, neurologic, or psychiatric manifestations, or some combination of these. Wilson's disease is unusual among genetic diseases in that it can be very effectively treated. The prevention of severe permanent damage depends upon early recognition and diagnosis by the physician, followed by appropriate anticopper treatment. Anticopper treatments have evolved considerably since the days when the only drug available was penicillamine. Zinc is now the recommended therapy for long-term management of the disease.** [P.S.E.B.M. 2000, Vol 223]

Wilson's disease, an inherited, autosomal recessive disorder of copper accumulation and toxicity, occurs in about one of every 40,000 people (1–3). The responsible gene (*ATP7B*) codes for a membrane-bound, copper-binding protein, and is expressed primarily in the liver (4–6). The gene has considerable homology to *ATP7 A*, the gene responsible for another copper disorder called Menke's disease. There are numerous mutations in *ATP7B* accounting for Wilson's disease, and no one mutation is predominant (7).

Most diets provide about 1.0 mg/day of copper (1). Copper is an essential trace element required at about 0.75 mg/day. The liver is responsible for copper balance regulation by excretion of excess copper in the bile. The product of *ATP7B* is obviously required for that pathway to function because when it is knocked out by mutations, biliary excretion of this "regulatory" copper does not occur (8, 9). We have postulated that the liver "packages" copper for excretion in the bile in the form of ceruloplasmin, which is a copper-containing molecule that is protease-resistant (10). A role for the product of *ATP7B* in the maturation of ceruloplasmin could account for both low blood ceruloplasmin and failure of copper balance regulation in Wilson's disease. As a result of the positive copper balance, copper accumulates, first in the liver, where it eventually causes hepatitis and cirrhosis. Later, it accumulates elsewhere, and the next most sensitive organ is the brain, where damage to the basal ganglia and other structures related to movement coordination produces a movement disorder. Patients present, typically between the ages of 10 and 40 years, with liver, neurological, or psychiatric symptoms, sometimes with a combination of these (1). Additionally, some patients are discovered in a presymptomatic state as a result of family workup or accidental discovery.

Wilson's disease is an unusual genetic disease in that it is quite effectively treated, and there have been very good advances in anticopper therapy in recent times. This makes early recognition and diagnosis of the disease especially important because the less the damage caused by copper toxicity, the greater the recovery following therapy. In this review, we will briefly discuss the salient features of rec-

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ognition, diagnosis, management, and prognosis in Wilson's disease.

Recognition and Diagnosis

A major problem exists in that physicians of all types often fail to recognize the possibility of Wilson's disease when faced with patients who have this disorder. The presentation of Wilson's disease is sufficiently protean, and the disease is sufficiently rare, that the possibility that the patient might have Wilson's disease simply does not occur to the physician. Thus, a major purpose of a review such as this is to provide guidance on improved Wilson's disease recognition.

Hepatic Presentation. The disease may present with hepatitis, chronic cirrhosis, or liver failure (1–3). In the hepatitis presentation, there is nothing to distinguish Wilson's disease from viral hepatitis, except that the patient is often negative for viral tests. If the patient has had a brush with a hepatitis virus in the past, and is positive for one of the viral tests, the patient is almost certainly doomed to be misdiagnosed as having viral hepatitis, and if episodic bouts of hepatitis continue, as is common in Wilson's disease, the misdiagnosis becomes one of chronic active hepatitis. The hepatitic bouts in Wilson's disease can be mild, with primarily serum transaminase enzyme elevations or more severe, with jaundice and elevated bilirubin levels. With severe hepatitis, hemolysis may occur because of the release of stored copper from dying hepatocytes. Hemolysis in the presence of liver disease should always make the physician think of Wilson's disease because that is the most likely diagnosis.

The patient's liver disease may appear to be one of chronic cirrhosis when it first comes to medical attention. If the patient drinks alcoholic beverages, even modestly, the physician may assume that the patient is disguising his or her real alcohol intake, make a misdiagnosis of likely alcoholic cirrhosis, and then not think about it further. Alcoholic cirrhosis, like viral hepatitis, is common, and Wilson's disease is rare.

Some patients present with liver failure, which can run the gamut from mild to severe (fulminant). I classify patients with a lowered albumin and an elevated bilirubin as in liver failure, irrespective of whether they have edema, ascites, or encephalopathy. Later we will discuss triaging this group of patients to determine whether medical therapy or hepatic transplantation should be recommended. Here the issue is that the possible diagnosis of Wilson's disease should be considered in patients presenting with liver failure.

Guidelines to Prompt Recognition of Wilson's Disease in the Hepatic Presentation. Age is an important discriminator. Always think of Wilson's disease if the patient has liver disease and is less than 40 years old. Specifically, think of it with viral-negative hepatitis, and in patients under 40 with viral positive hepatitis, cirrhosis (even if the patient drinks), or liver failure.

Neurological Presentation. The areas of the brain involved with Wilson's disease are those that coordinate movement. Thus, it is classified as a movement disorder (11). Muscular strength is not involved, nor are there any sensory defects. Typically, speech is involved early, and results in a slurred, somewhat hypokinetic type of speech. Later in the course of the disease, more pronounced speech defects occur. Tremor is common, and is not characteristically different from tremors from many other causes. The physician should never think that he or she can distinguish Wilson's disease from other neurological disorders based on the type of tremor. Dystonia is also frequent and may lead to facial abnormalities, including difficulty with muscles of the mouth area, which often leads to drooling. Later dystonia in the neck, back, or extremities may lead to pain and abnormal positions. Incoordination is a frequent problem, and handwriting suffers, often leading to micrographia. Gait may be abnormal, and patients may be clumsy in walking, and have problems feeding themselves. Dysphagia is not uncommon. The patient may be very Parkinson-like in presentation. We have seen neurologically presenting patients most often misdiagnosed as having essential tremor, Parkinsonism, or multiple sclerosis.

Guidelines for Prompt Recognition of Wilson's Disease in the Neurologic Presentation. As with the liver presentation, age is an important discriminator. Always think of Wilson's disease when a patient 40 years or less presents with *any* type of movement disorder, be it tremor, a Parkinson-like picture, a multiple sclerosis–like picture, etc. Thus, every patient 40 or less, and most 50 or less, should be screened for Wilson's disease if the diagnosis being considered is essential tremor, Parkinsonism, multiple sclerosis (without sensory defect), or ataxia, and in every patient in this age group with unexplained tremor, dysarthria, or dystonia.

Psychiatric Presentation. Often, perhaps 2 or 3 years before any other clinical manifestation, the patient may develop behavioral abnormalities. These are quite diverse. Most common is loss of ability to focus on tasks, often leading to loss of a job, or failure in school. Also quite common are problems with temperament. This can be seen as temper tantrums, swings in emotionality such as frequent crying, depression, or sometimes manicky behavior. Occasionally, paranoia, hallucinations, delusions, or reduced sexual inhibitions can occur.

The occurrence of a distinct behavioral change in a previously psychiatrically "normal" young person often leads to suspicion of substance abuse, and indeed a significant number of the patients we've seen have been so misdiagnosed.

Guidelines for Prompt Recognition of Wilson's Disease in the Psychiatric Presentation. As before, age is an important discriminator. Thus, new behavioral abnormalities, or suspicion of substance abuse without definite evidence, in all patients 40 years or less, and in many 50 years or less, should lead to screening for Wilson's disease.

Screening

24-hr Urine Copper. This is the best single screening test because it is elevated to over 100 μg/24 hr in all symptomatic Wilson's disease patients (normal is 20–50) (1). Urine must be collected in containers free of copper contamination, and the assay must be done in a laboratory properly equipped, and with personnel experienced, in trace element assays. Urine copper may be falsely elevated in chronic liver disease with an obstructive component, and it may be only borderline elevated in presymptomatic patients (1). Presymptomatic patients are typically affected siblings of a previously diagnosed symptomatic patient, who have not yet developed symptoms of the disease. Urine copper values in these patients range from 65 on up. Since gene carriers have values from 75 down, urine copper values in the gray area of 50–100 need additional workup, such as a liver biopsy.

Kayser-Fleischer Ring Examination by Slit Lamp. These rings (12, 13) are due to copper deposits in the cornea, and can only be detected reliably by slit lamp examination, usually carried out by an ophthalmologist. They are present almost always (99% +) in patients with neurological or psychiatric symptoms from Wilson's disease so they are an excellent discriminatory test for that kind of patient (1, 2). They are often not present in the hepatic presentation and in presymptomatic patients, but if present, they are helpful in establishing the diagnosis.

Serum Ceruloplasmin (Cp) Assay. Serum Cp is usually abnormally low in Wilson's disease (1–3). The normal level is 20–35 mg/dl, and quite often, patients will have values below 5, although some patients will have intermediately low values ranging from 6 to 19, and some will have completely normal values. About 90% of neurologically presenting patients, about 75% of hepatically presenting patients, and about 90% of presymptomatic patients, have a low or intermediately low Cp value (1). However, it must be remembered that 10%–25% of patients have a Cp value in the normal range, so this is by no means a diagnostic test. To further complicate matters, heterozygous carriers of the Wilson's disease gene have an intermediately low Cp about 10% of the time. Since about 1% of the population are carriers, this means that about one in 1000 people have an intermediately low Cp because of being carriers. Thus, Cp values should only be used to shift the index of suspicion about the diagnosis, and not be used to make the diagnosis or exclude it.

Diagnosis

The above tests do double duty as being both useful in screening, and in the right situation, definitive for diagnosis. Thus, a patient with neurological or psychiatric symptoms typical of Wilson's disease, and positive for KF rings, requires no further workup. Similarly, a patient with hepatitis and an elevated urine copper (in this article we define "elevated" as more than 100 μg/24 hr), has Wilson's disease irrespective of whether KF rings are present.

In any patient in whom the diagnosis has any uncertainty, a liver biopsy and quantitative liver copper assay should be done (1). This is the gold standard of diagnosis, and the liver copper is always over 200 μg/g dry weight of tissue, (normal is 20–50), including in presymptomatic patients (1). False positives can occur in long-standing liver disease, particularly with an obstructive component. Carriers may have mildly elevated values up to about 125, but never reach 200. It is important to emphasize that the copper should be assayed quantitatively. Copper stains are not reliable for diagnosis. Generally the biopsy sample is split, and half sent for histologic examination. This allows confirmation that the tissue is liver, and gives some information on inflammation and scarring.

Anticopper Drugs for the Treatment of Wilson's Disease

The anticopper therapy of Wilson's disease has advanced considerably over the last few years. We divide the different stages of Wilson's disease therapy into initial and maintenance, and further subdivide those categories. That classification, and our recommended treatment of choice for each category is shown in Table I. Table II lists the anticopper drugs and briefly lists their main characteristics. With Tables I and II as an introduction, we will briefly review each of the four anticopper drugs, their mechanisms, toxicities, and recommended uses.

Zinc (Trade name Galzin, produced by Gate). Zinc acetate was approved by the U.S. Food and Drug Administration (FDA) in 1997 for the treatment of Wilson's disease and is rapidly becoming the treatment of choice for life-long maintenance therapy as well as other phases of the disease (Tables I and II). Most of the work in developing zinc as a safe and effective therapy has been done by our group (14–29) and unpublished (Brewer GJ, Dick RD, Johnson V, Fink JK, Kluin KJ, Daniels S, unpublished data). We became interested in zinc as a possible Wilson's disease treatment as a result of studies in sickle cell anemia (30). While using zinc as an antisickling agent in patients with sickle cell anemia, we produced copper deficiency (31, 32). We then tried the same dose and regimen of zinc in Wilson's disease and were able to produce a negative copper balance in these patients (14–16).

Table I. Anticopper Therapy for Different Categories of Wilson's Disease Patients

Category of patient	Treatment of choice
Initial presentation	
Neurological	Tetrathiomolybdate
Psychiatric	Tetrathiomolybdate
Hepatic	Trientine and zinc
Maintenance therapy	
Maintenance after initial therapy	Zinc
Presymptomatic	Zinc
Pregnant	Zinc
Pediatric	Zinc

Table II. Anticopper Drugs Used in Wilson's Disease Therapy

Drug	Trade name	Mechanism of action	Recommended use	Toxicity
Zinc acetate	Galzin (Gate)	Blockage of copper absorption	First choice Maintenance Presymptomatic from the beginning Pregnancy Pediatric Initial hepatic, with a chelator Second choice Initial neurologic	Mild abdominal discomfort in 10% of patients
Trientine	Syprine (Merck)	Chelator, urinary excretion of copper	First choice Initial hepatic, with zinc Second choice All other phases of Wilson's disease	Bone marrow suppression Proteinuria Autoimmune disorders Trientine toxicity not well studied yet
D-Penicillamine	Cuprimine (Merck)	Chelator, urinary excretion of copper	None	Neurological worsening in neurologically presenting patients Acute hypersensitivity Proteinuria Bone marrow suppression Effects on immune system Effects on collagen Effects on skin
Tetrathiomolybdate	None	Complexor of copper with protein, detoxifying copper, and blockage of copper absorption	First Choice Initial neurologic	Overtreatment produces reversible anemia

Although we were unaware of it at the time we did our initial work, Schouwink (33) had earlier given zinc to two Wilson's disease patients as part of his thesis work, but unfortunately these studies were never published. Hoogenraad later followed up his countryman's work in the Netherlands and also gave zinc to additional patients (34–36).

Zinc acts by inducing intestinal cell metallothionein, which has a high affinity for copper, and prevents the transfer of copper into the circulation (24, 37–39). Intestinal cells slough into the lumen of the bowel with about a 6-day turnover time, and in the process, take the bound copper with them for loss in the stool. Since there is substantial endogenous secretion of copper in saliva, gastric juice, and other GI secretions, the prevention of reabsorption of this copper by zinc (as well as blockade of absorption of food copper) puts the patient into a substantial negative copper balance.

Zinc has been shown to be fully effective in the treatment of Wilson's disease (29). In this sense zinc has no advantage over the earlier approved drugs, penicillamine and trientine, which are also fully effective. However, zinc does have a great advantage over these drugs because they have many side-effects (1), whereas zinc is essentially nontoxic. Alleged toxicities of zinc involving lipid metabolism (23), immune function (28), and pancreatitis (19), have been ruled out by specific studies. The only side effect of zinc is gastric discomfort in about 10% of patients. Zinc must be taken away from meals to be effective, and in patients who have discomfort, the first dose should be taken mid-morning rather than upon rising. An extensive report on our experience with zinc therapy gives many practical tips on how to use zinc, including dose, monitoring methods, and strategies for mitigating the problem with abdominal discomfort, when it occurs (29). Additional information on zinc (Galzin) therapy is provided in the Physician's Desk Reference.

Trientine (Trade name Syprine, produced by Merck). Walshe (40) developed trientine as a therapy for Wilson's disease, and it is approved by the FDA on rather narrow grounds, namely to use in penicillamine-intolerant patients. However, we see its application as potentially broader than that (Tables I and II). Trientine is a chelator that enhances the urinary excretion of copper. It does so in a less aggressive manner than penicillamine, which may be a factor in it being a somewhat less toxic drug than penicillamine.

As mentioned earlier, trientine is fully effective in the treatment of Wilson's disease. By virtue of the enhanced urinary excretion of copper, the patient is put into a negative copper balance. Toxicity during the first few weeks of trientine therapy may be exhibited by bone marrow suppression or proteinurea. Later, a variety of autoimmune disorders, such as systemic lupus erythematosis, or Goodpasture's syndrome, may occur. Trientine has teratogenic effects in animals (41). Because of its limited approval, a formal toxicity study has never been done with trientine. This, coupled with its limited use so far, should cause phy-

sicians to be cautious and observant in its use. The Physician's Desk Reference provides information on how to use trientine (Syprine).

D-Penicillamine (Trade name Cuprimine, produced by Merck). Penicillamine was actually the first orally effective drug developed for Wilson's disease, again by Walshe (42), and was the first drug approved for this purpose by the FDA. Penicillamine is a chelator that strongly enhances the urinary excretion of copper.

Penicillamine is fully effective in the treatment of Wilson's disease in terms of consistently producing a negative copper balance. However, it has a long list of problems and toxicities, and given that we now have much safer alternatives, we no longer recommend its use in Wilson's disease. The first problem is that if it is used in the initial therapy of neurologically presenting patients, it has a 50% risk of making them worse, neurologically (43). Of the patients who worsen, 50% never recover. In other words, there is an initial 25% risk with penicillamine that the patient will be permanently worsened, and the lives of many of these patients have been disastrously disabled. The mechanism of this worsening may be the aggressive mobilization of copper characteristic of penicillamine, temporarily further elevating brain copper.

About 25%–30% of patients treated with penicillamine show an acute hypersensitivity reaction, with rash, hives, fever, and other symptoms (2). This may be overcome with temporarily stopping or drastically reducing the dose, or using steroids (2). Subacute toxicities of penicillamine include bone marrow suppression and proteinuria (2). Chronic toxicities include effects on the skin, on collagen and the immune system (2). Effects on the skin include premature wrinkling, abnormal scar formation, and development of elastosis perforans serpiginosa. Additional effects on collagen include possible effects on weakening of blood vessels, as reported in animals (44, 45). Effects on the immune system include autoimmune diseases such as systemic lupus erythematosis, Goodpasture's syndrome, arthritis, and a decreased resistance to infections. Penicillamine is teratogenic in animals (41) and produces a teratogenic syndrome in human babies with a frequency of about 5% (46, 47).

Because of this extensive list of problems and toxicities, many of them common and some of them life-threatening, we do not recommend the use of penicillamine, given that now we have effective alternatives that are much safer.

Tetrathiomolybdate (TM). This drug is not yet commercially available and is being used under an IND (Investigational New Drug) approval of the FDA at the University of Michigan. TM acts by forming a very stable three-way complex between protein, copper, and itself (48–52). Given with food, it complexes copper and food protein and prevents the absorption of copper. Given between meals, it is absorbed into the blood and complexes the available copper of the blood with albumin. This copper is no longer available for cellular uptake, and is therefore rendered nontoxic. TM is extremely fast acting. We estimate that within 2 weeks of therapy initiation, copper toxicity is essentially halted.

At present, we use TM for 8 weeks of initial therapy of neurologically presenting patients, as indicated in Tables I and II (53–55). It is very effective in this setting as we will discuss later. The toxicity of TM appears to be limited to its dramatic effect on copper. If animals are not copper-supplemented, they exhibit toxicities, all related to copper deficiency (49–51). Copper supplementation prevents all the toxicities. The only human toxicity so far encountered is also related to copper deficiency. Over-treatment with TM can lead to a reversible anemia (55,56), related to copper depletion in the bone marrow, which can happen even in Wilson's disease patients.

Anticopper Treatments for Various Categories of Wilson's Disease Patients

Initial Therapy, Neurological and/or Psychiatric Presentation. As pointed out earlier, penicillamine is to be avoided in these patients because of the risk of neurological worsening. Zinc is rather slow-acting to be ideal, although the Hoogenraad group uses it routinely for their patients. Our concern is that during the 4–6 months it takes zinc to control copper toxicity, the disease may progress, following the course of its own natural history.

We have developed TM for just this purpose, and have had very good results with it (53–55). We use TM for 8 weeks, during which we carefully monitor neurological and speech functions with a quantitative score. Only two of 65 patients have reached our statistical criteria for worsening, and these two did not worsen severely. After 8 weeks of TM, we transition to zinc maintenance therapy.

Trientine is another option for treating these patients. It is gentler than penicillamine, and may not share penicillamine's propensity to make these patients worse. Since there has been no experience with initial use of trientine in neurologically presenting patients, we are carrying out a double-blind trial comparing TM and trientine in this type of patient. This study is being carried out in collaboration with Dr. Michael Schilsky of Mount Sinai Medical Center in New York.

Initial Therapy, Hepatic Presentation. It is important for physicians to recognize that some patients will present in such severe liver failure that the only thing that will save their lives is liver transplantation. On the other hand, patients presenting with mild to moderate liver failure may have a very good change to survive and retain their own liver, with medical therapy. There are, of course, many advantages for patients to retain their own livers, including not running the risk of ≈ 20% mortality during the first year after transplantation, not having to take antirejection drugs for the rest of their lives, and saving the expense and troubles that a major operation entails.

We have found the prognostic index of Nazer *et al.* (57) to be quite useful in the initial triaging of these patients. One

caution is that since bilirubin levels are used in the score, if the patient is hemolyzing, it will falsely elevate the score. Of course, this index should not be used slavishly, but simply as one tool to help in the decision-making. In borderline cases, if medical therapy is selected, the patient should be followed carefully. If he or she begins to deteriorate, transplantation should be reconsidered. Again, I find the Nazer index to be useful in following such patients, and helping in the continuing process of evaluating the transplantation option. One thing that physicians should be aware of is that decreasing serum transaminase levels are not always a good sign. If the patient's hepatic synthetic capacity is decreasing, the transaminase levels may fall for that reason and be an ominous sign. This can be evaluated by looking at other hepatic synthetic functions, such as coagulation factors. Falling synthetic functions in a patient with Nazer scores of seven or higher, keeping in mind the artificial effects of hemolysis on bilirubin levels, should probably dictate transplantation.

If medical therapy is opted for, we use a combination of trientine and zinc. Trientine is used to get a solid negative copper balance, and zinc is used to induce hepatic metallothionein, which has the potential to bind potentially toxic copper in the liver. We use trientine for 4–6 months, and then stop it, allowing the patient to continue on zinc maintenance therapy. We have not tried TM on patients in this setting, although theoretically, we would expect it to be quite effective.

Maintenance Therapy. After 2–6 months of initial therapy (the length of time depending on which drugs are being used initially), we use zinc as the maintenance therapy of choice. Because of their toxicities, trientine and penicillamine are poor second and third choices.

Therapy in the Presymptomatic Patient. These patients are viewed as comparable to maintenance therapy patients, and are treated with zinc alone right from the beginning (29).

Treatment of the Pregnant Patient. It is important for the pregnant Wilson's disease patient to continue on therapy during their pregnancy, or their disease may regress, sometimes fatally. Zinc is the clear choice here, because it is not teratogenic, whereas trientine and penicillamine both are teratogenic. We have treated women through 18 pregnancies with zinc therapy, with good results (29).

Treatment of the Pediatric Patient. Zinc is the recommended maintenance treatment for these patients. We use a reduced dose depending on age and body weight. We have successfully treated 30 pediatric patients (29) and unpublished (Brewer GJ, Dick RD, Johnson V, Fink JK, Kluin KJ, Daniels S, unpublished data).

Management Other than Anticopper Therapy

In patients presenting with acute disease, copper toxicity is controlled as discussed earlier. However, it takes about 6 months for the organ repair to be well enough established that clinical improvement is detectable. The window of improvement generally occurs between 6 and 24 months after therapy is initiated. After that, most disabilities are permanent.

It is important to emphasize that management of the whole patient, not just anticopper therapy, is an important component of achieving the best possible end result. This is true regardless of whether it is during the 2-year recovery period of initially presenting patients, or in patients with chronic disabilities. The various modalities to remember include speech therapy and communication devices, physical therapy, occupational therapy, symptomatic treatments for tremor, dystonia, chorea, appropriate treatment of liver disease, and psychiatric counseling, if indicated.

Low copper diets are no longer an important feature of the management of Wilson's disease. We restrict liver, which may have a very high copper content, for the first 6 months of therapy, and after that suggest the patient not take more than small amounts. We also restrict shellfish during the first 6 months, and after that restrict the patient to no more than one shellfish meal/week. We have measured the copper levels in other foods often restricted in low copper diets, such as chocolate, mushrooms, beans, etc., and find them not to be high enough in copper to be of concern (1). Thus, we restrict nothing but liver and shellfish. We do test the patients' major sources of drinking and cooking water, and if over one part per million, suggest they use alternative sources of water.

Prognosis

The degree of recovery to be expected in a newly diagnosed, symptomatic patient depends on, first, the severity of the disease at that point, and second, appropriate management. The more severe the abnormality at the start of treatment, the greater the likely eventual disability. That is why early diagnosis and treatment are so vital. Having said that, however, recovery during the first 2 years of treatment is usually substantial, and often dramatic. Thus, much of the neurological disability is likely to improve. Even in severely affected patients at the beginning, enough improvement is likely to occur to allow them to live some semblance of a productive life.

All patients have some liver damage at the time of diagnosis, even presymptomatic patients. Thus, there will be residual cirrhosis. However, with abatement of the destructive process in the liver, liver function will usually recover enough to provide normal liver function tests, even in patients who have exhibited hypoabuminemea and modestly elevated bilirubin values. Further, our evidence is that with zinc maintenance therapy, the liver disease is quite stable and nonprogressive.

Many, if not most, patients have sufficient portal hypertension from the cirrhosis to produce hypersplenism, usually manifested by a modest leukopenia, thrombocytopenia, or both. This is medically insignificant. However, some patients have esophageal and/or gastric varices, and these can pose a risk of bleeding. Patients who have already

exhibited bleeding from varices should be watched carefully because the risk of bleeding is highest in patients who have bled in the past, and variceal bleeding is the most important risk factor for death in this disease.

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