Wilson disease: Treatment and prognosis

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INTRODUCTION

Wilson disease (hepatolenticular degeneration) is an autosomal recessive defect of cellular copper export. Reduced biliary excretion leads to accumulation of copper, initially in the liver and then in other tissues, particularly the brain. Tissue copper deposition causes a multitude of signs and symptoms that reflect hepatic, neurologic, hematologic, and renal impairment. The incorporation of copper into ceruloplasmin is also impaired.

Patients most often present with liver disease (which can range from asymptomatic elevations in the serum aminotransferase or bilirubin concentrations to fulminant hepatic failure to chronic hepatitis) or with neuropsychiatric disease [1]. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Clinical features'.)

This topic will review the treatment of Wilson disease. The epidemiology, pathogenesis, clinical manifestations, and diagnosis of Wilson disease are discussed separately. (See "Wilson disease: Epidemiology and pathogenesis" and "Wilson disease: Clinical manifestations, diagnosis, and natural history".)

MEDICATIONS

Lifetime therapy aimed primarily at treating copper overload is required in patients with Wilson disease, and treatment should be considered in two phases: removing or detoxifying the tissue copper that has accumulated and preventing reaccumulation.

Copper removal is achieved by the administration of potent chelators. The primary chelator that has been used is D-penicillamine. However, approximately 30 percent of patients do not tolerate long-term therapy because of side effects and it may not be the treatment of choice in patients with neurologic symptoms. Trientine has traditionally been used as a second-line agent for those intolerant of D-penicillamine, but it is also a reasonable option for primary therapy, and may be the preferred treatment because of its lower incidence of side effects. There are no controlled trials that have compared these agents to one another and thus recommendations for their use are based mainly on observational data and clinical experience [2].

Prevention of reaccumulation can be achieved with chelators or by use of zinc salts. Typically doses of chelation can be reduced by approximately 33 percent from that used for initial treatment and copper removal. Oral zinc acts by preventing copper absorption by increasing the endogenous chelator metallothionein in enteric cells, but may also increase the levels of metallothionein in the liver itself. A newer agent, tetrathiomolybdate (another chelating agent), was shown in a prospective trial to be an effective treatment for those presenting with neurologic signs and symptoms [3]. Tetrathiomolybdate is still being evaluated in a new clinical trial [4].

To further prevent accumulation or reaccumulation of copper, patients with Wilson disease should also be maintained on a low copper diet and avoid copper-rich foods. (See 'Dietary recommendations' below.)

Patients who may have been well treated but stop taking treatment may develop new neurologic abnormalities or rapidly progressive hepatic decompensation refractory to treatment and requiring liver transplantation. Monitoring of therapy is critical to detect non-adherence or failure of medical therapy.

Other aspects of treatment for patients with Wilson disease include pharmacologic or interventional treatment of complications of portal hypertension in those with ascites or esophageal or gastric varices, and treatment of hepatic encephalopathy if present. Additional treatment of neurologic symptoms such as tremor or parkinsonism and psychiatric symptoms independent of treatment of the copper overload may improve patients' quality of life and should be considered.

D-penicillamine — D-penicillamine contains a free sulfhydryl group that functions as a copper chelating moiety. Its major effect is to remove copper from less tightly bound sites on proteins, peptides, and membranes, and promote its urinary excretion, although it may also function by other mechanisms such as stimulation of endogenous metallothionein. It has also been used in the treatment of rheumatoid arthritis, cystinuria, and lead and mercury poisoning.

Pharmacokinetics — Penicillamine is absorbed rapidly from the gastrointestinal tract [5]. Its absorption is decreased by as much as 50 percent when taken with food. More than 80 percent is excreted by the kidneys. Its half-life is in the range of 1.7 to 7 hours, although there may be considerable individual variation [6].

Dosing — The drug should be introduced at a dose of 250 to 500 mg/day and then increased by 250 mg increments every four to seven days to a maximum of 1000 to 1500 mg daily in two to four divided doses. For children and adults who weigh less than 100 lb (45 kg), we recommend starting with 250 mg daily with a maximum total daily dose of 20 mg per kg (rounded to the nearest 250 mg) or approximately 1000 mg in two or three divided doses. This regimen may reduce the incidence of early adverse side effects such as fever and rash, but does not appear to reduce the incidence of late-onset toxicity, such as the nephrotic syndrome. (See 'Adverse effects and their management' below.)

A lower dose (750 to 1000 mg daily in two divided doses) is sufficient during the maintenance phase (usually after four to six months). The therapeutic response to changes in the maintenance dose usually will not become evident for four to six weeks.

Penicillamine should ideally be given one hour before or two hours after meals since food interferes with its absorption. However, some patients may require dosing closer to food intake, which is an acceptable compromise if the patient is shown to be stable, as it increases compliance.

Efficacy — Multiple studies have demonstrated the effectiveness of D-penicillamine in patients with Wilson disease [7-14]. Clinical improvement in patients with advanced liver disease is usually observed during the first two to six months of therapy, but can continue thereafter. Even advanced fibrosis or cirrhosis may show reversibility following prolonged treatment [15]. A repeat liver biopsy is not necessary to monitor tissue copper serially as long as there is a progressive improvement in symptoms and liver biochemical tests.

Adverse effects and their management — Penicillamine is associated with multiple side effects leading up to approximately 5 percent of patients to discontinue therapy. Other treatments should probably be used in patients who are at increased risk for toxicity including those with a history of renal disease, severe thrombocytopenia, or an autoimmune tendency. Crossreactivity to penicillin may occur. Thus the drug should be used cautiously in patients with known penicillin allergy.

- Early sensitivity reactions (occurring within one to three weeks of beginning therapy) are characterized by fever, cutaneous eruptions, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria. The drug should be discontinued immediately in such

patients and alternative treatment (principally trientine or zinc) begun. (See 'Trientine' below and 'Oral zinc' below.)

Prior to the availability of alternative treatments, patients could be desensitized to these reactions to D-penicillamine by stopping the medicine for one week, then restarting it at a dose of 25 mg per day, after which it was doubled at weekly intervals as long as it was tolerated. Some patients were also treated with prednisone during this desensitization period. Desensitization is now rarely required due to the availability of alternative oral therapies.

- Several side effects occurring months to years after initiating therapy have also been described. The appearance of proteinuria may herald the onset of nephrotic syndrome, which may occur early or years after treatment begins. The onset of nephrotic syndrome necessitates cessation of the drug. However, protein excretion of up to 2 g per day produces no symptoms and may not progress. Although cessation of therapy always leads to resolution of the proteinuria, the mean time required for this to occur is approximately one year and some patients take more than two years [16]. A much less common but more serious renal complication is the development of a crescentic glomerulonephritis.

  Other later reactions include Goodpasture syndrome, bone marrow toxicity including severe thrombocytopenia or total aplasia, myasthenia gravis, polymyositis, hepatotoxicity, loss of taste, and a lupus-like syndrome characterized by hematuria, proteinuria, and a positive antinuclear antibody.

- Skin changes have been described including elastosis perforans serpiginosa pemphigus, lichen planus, and aphthous stomatitis [17,18].

- Nausea, vomiting, and anorexia are dose-related signs of gastric irritation and improve if the dose is reduced.

- Aplastic anemia is rare but may not reverse with the cessation of therapy.

- The neurologic status of patients with predominantly neurologic symptoms may worsen with the initiation of treatment with D-penicillamine. Limited data suggest that approximately 10 percent of such patients will have neurologic deterioration after beginning treatment [19,20]. Furthermore, new neurologic symptoms may appear in some patients. These events may be caused by two potential mechanisms: mobilization of hepatic copper stores leading to increased brain copper exposure, or the development of intracellular copper complexes [21].

Although some patients recover with continued use, the manufacturer recommends that the drug should be stopped (and an alternative used) in patients who develop worsening neurologic symptoms (other than loss of taste). Although there are limited data, generally a switch to trientine or to zinc should be considered in these patients. For severely symptomatic patients and for those individuals whose symptoms worsen on D-penicillamine or trientine alone, we consider using combination therapy. Zinc may be added to the regimen of patients on D-penicillamine or trientine. While the use of combination therapy has not been established by randomized trials, the complementary actions of zinc and chelating agents (preventing copper absorption and removal of copper, respectively) has a theoretical advantage over either treatment alone. (See 'Oral zinc' below.)

Zinc should be given several hours apart from the D-penicillamine agent and needs to be given at least twice daily. The combination of D-penicillamine and zinc may increase the risk for development of sideroblastic anemia (an uncommon complication); thus, we monitor hemoglobin levels. Worsening of neurologic symptoms has been described with other copper chelators including trientine, although possibly less frequently than with D-penicillamine.

- Penicillamine inactivates pyridoxine. Thus, small doses of pyridoxine, 25 mg per day, should be given to patients treated with D-penicillamine to prevent pyridoxal phosphate deficiency.

Copper deficiency induced by D-penicillamine can lead to iron overload in the liver. Although the clinical significance is uncertain, excess iron may contribute to liver injury. This only occurs with high-dose therapy maintained for a long period of time.

Monitoring D-penicillamine therapy — Compliance is often a problem, particularly in children. It can be ascertained by measuring 24-hour urinary copper excretion or experimentally by determining the presence of D-penicillamine in urine by amino acid analysis. The binding of copper to D-penicillamine is stoichiometric. Thus, the amount of copper excreted in the urine will increase with increasing dosing of D-penicillamine. The presence of elevated serum aminotransferases does not necessarily indicate non-compliance since up to one-third of children continue to have mildly elevated aminotransferases despite adequate treatment [22].

The initial goal of therapy is increasing urinary copper excretion from baseline levels (often above 100 mcg per day in symptomatic patients). Copper excretion in the urine in previously untreated patients on D-penicillamine can reach levels of 2000 mcg/day (32 micromol/day). The rate of copper excretion falls as copper stores become depleted. Values usually fall to below 500

mcg/day (8 micromol/day) at approximately 6 to 12 months. Once the excess copper is removed, patients can be switched to maintenance therapy. Prior to switching to maintenance therapy, patients should be clinically well, have stable, normal, or near normal serum aminotransferases and hepatic synthetic function, have a normal nonceruloplasmin-bound copper concentration (<15 mcg/dL or 150 mcg/L), and have 24-hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromol) per day on treatment. Most patients require at least six months to a year of chelation therapy to achieve these goals.

We obtain a complete blood count, urinalysis, and serum creatinine after the first week and at every month during the first three months, at three-month intervals until stable target values are achieved, and twice per year thereafter. The manufacturer recommends that treatment should be withdrawn if the total white blood cell count falls below 3000 cells per mm^3, neutrophils fall below 2000 cells per mm^3, platelets fall below 120,000 per mm^3, or if a steady decline over three successive tests is observed, even though the counts remain above the values set for discontinuation. In patients with portal hypertension and hypersplenism, the platelet count and white blood cell count may be low prior to the initiation of D-penicillamine, and these patients can continue therapy with close monitoring. Patients on long-term treatment with this medication should be periodically monitored for proteinuria and for iron overload.

D-penicillamine should also be withheld (and trientine or zinc begun) if proteinuria exceeds 2+ on a dipstick, if red cell or white casts are observed at microscopic examination of the urine, or if more than 10 red cells are seen per high-power field. Our approach is to switch to trientine or zinc if there are any signs of renal toxicity given that there is significant experience with these drugs and it appears they have fewer side effects than D-penicillamine, though some authors would continue D-penicillamine if quantitative proteinuria does not exceed 1 g/day and is stable. D-penicillamine should be permanently discontinued if proteinuria exceeds 2 g/day or the glomerular filtration rate falls.

Dose adjustments prior to surgery — Treatment should **never** be discontinued altogether for any significant period of time without careful monitoring; patients who stop therapy for Wilson disease are at risk for the development of hepatic decompensation and acute liver failure [23,24]. It is reasonable to reduce the dose of D-penicillamine prior to surgery since laboratory and some human data suggest that it may impair wound healing [25]. Dose reductions during this time may be in the range of 25 to 50 percent of the presurgery dose, and full doses may be resumed after wound healing.

D-penicillamine and pregnancy — Clinical experience suggests that D-penicillamine is safe during pregnancy, though the drug is teratogenic in animal studies. Successful pregnancies

without teratogenicity have also been described in the published literature [26-30], though there are reports of women taking D-penicillamine giving birth to neonates with cutaneous abnormalities [31-33]. Stopping therapy is associated with a high risk of hemolytic episodes with hepatic insufficiency, including maternal fatality.

We agree with a guideline published by the American Association for the Study of Liver Diseases that suggests treatment be maintained during pregnancy [5]. In patients on maintenance therapy, the dose should be reduced by 25 to 50 percent of the pre-pregnancy dose to reduce fetal risk early in the pregnancy and to promote better wound healing should a cesarean section be required. Monitoring of liver function and clinical status should be done each trimester to assure safety of the reduced dosing levels of medication.

In addition, one authority made the following comments in an editorial regarding a study of zinc in pregnant patients with Wilson disease [34]:

- Mothers and infants tolerate pregnancy safely if they comply with prescribed regimens (750 mg to 1 g of either D-penicillamine or trientine in patients with well controlled Wilson disease during the first two trimesters and 0.5 g/day during the last trimester).
- Nursing mothers taking D-penicillamine report no ill effects on babies, although breast milk concentrations of zinc and copper may be reduced.
- The relatively low doses of D-penicillamine or trientine used to treat patients with Wilson disease have not been associated with teratogenicity. This is in contrast to patients with cystinuria who require larger doses.
- Interruption of therapy is associated with a high risk of hemolytic episodes with hepatic insufficiency including maternal fatality.

Trientine — Trientine, another copper chelator (available formulations: triethylene tetramine dihydrochloride; trientine tetrahydrochloride) [35], has been used successfully in patients unable to tolerate D-penicillamine as well as for primary therapy [23]. It differs from D-penicillamine by a lack of sulfhydryl groups and chelates copper by forming a stable complex with its four constituent nitrogens. Like D-penicillamine, it also functions principally by removing copper from less strongly bound sites on proteins and membranes, and it increases renal copper excretion. (See 'Dosing' below.)

On a mole for mole basis, more copper is bound by D-penicillamine than trientine; however, the amount of trientine used can be adjusted to achieve appropriate goals of therapy. Trientine seems to have fewer side effects than D-penicillamine when used as primary therapy.

Pharmacokinetics — The pharmacokinetics of trientine have not been well studied. It is poorly absorbed; only 1 percent of the ingested amount (and 8 percent of its principal metabolite, acetyltrien) is excreted in the urine. The amount of iron, zinc, and copper chelated correlates with the amount of trientine in the urine [36].

Dosing — The usual initial dose for triethylene tetramine dihydrochloride in children is 20 mg/kg per day, rounded to the nearest 250 mg, given in two or three divided doses. Similar dosing is used for adults (20 mg/kg), but the total dose should not exceed 1500 mg per day. Maintenance dosing is approximately 15 mg/kg given in two or three divided doses. However, a pilot study showed efficacy using 20 mg/kg given only once daily as maintenance therapy (to increase adherence and ease of dosing for patients) [37], but further study is needed before once-daily dosing is universally adopted. The drug should be taken ideally one hour before or two hours after meals. The drug is not stable at high temperatures and should be refrigerated for storage.

Another formulation, trientine tetrahydrochloride, has been approved by the US Food and Drug Administration (FDA) for treatment of adults with stable disease who are de-coppered and tolerant to D-penicillamine [38-40]. Doses of trientine formulations are generally not equivalent (except if expressed as trientine base), and local product labeling should be consulted.

Efficacy — Trientine has been available since 1969; thus, clinical experience has probably outpaced the published experience. The available data and clinical experience suggest that trientine is as effective for Wilson disease as D-penicillamine [14,23,41-43]. We use trientine for initial therapy in patients who developed side effects from D-penicillamine and for maintenance therapy.

Data summarized in the manufacturer's drug information for triethylene tetramine dihydrochloride focused on 41 patients between the ages of 6 and 54 years who did not tolerate D-penicillamine [44]. The average dose required to achieve an optimal clinical response ranged from 1000 to 2000 mg daily. After a mean of 49 months of follow-up, 34 of the 41 patients improved clinically, while four patients had no change in global response, one showed deterioration, and two were lost to follow-up. One patient who improved experienced a recurrence of lupus-like symptoms, which had prompted her to discontinue D-penicillamine and led to discontinuation of trientine.

Data from randomized trials suggested that trientine tetrahydrochloride was effective for preventing copper reaccumulation after initial chelation therapy. In an open-label trial including 53 patients with Wilson disease who were initially stabilized with penicillamine, there were no significant differences in serum levels of non-ceruloplasmin-bound copper or in clinical

response at 24 and 48 weeks for patients treated with trientine tetrahydrochloride compared with penicillamine [40]. In addition, trientine tetrahydrochloride was well tolerated with no serious adverse events.

Adverse effects — Trientine is associated with fewer adverse effects than D-penicillamine.

- Hypersensitivity reactions and pancytopenia are rare.
- Neurologic worsening is seen with trientine, but appears to be less common than with D-penicillamine [45].
- Hemorrhagic gastritis, loss of taste, and a rash have been reported in a patient treated with trientine for primary biliary cirrhosis [46]. Another case report described the development of colitis and duodenitis that improved after drug withdrawal [47].
- A reversible sideroblastic anemia has been described in case reports possibly because of the drug's effects on mitochondrial iron metabolism [48,49].
- Trientine chelates iron; coadministration of iron should be avoided since the trientine iron complex is nephrotoxic.
- Copper deficiency induced by trientine can lead to iron overload in the liver. Although the clinical significance is uncertain, excess iron may potentiate liver injury [50]. This only occurs with high-dose therapy maintained for a long period of time. Many patients with Wilson disease have iron overload in the liver unrelated to therapy [51].

Monitoring trientine therapy — The same clinical and laboratory monitoring described for D-penicillamine also apply to trientine. The adequacy of treatment should be determined by measuring 24-hour copper excretion, which should be in the range of 200 to 500 mcg (3 to 8 micromoles) daily. Normalization of nonceruloplasmin-bound copper to <15 mcg/dL (150 mcg/L), can also help document effective treatment. Patients should be monitored for iron deficiency. As noted above, if iron supplementation is needed, it should be given in short courses and at least two hours should elapse between administration of trientine and iron. Elevation of aminotransferases during treatment may signal noncompliance [52]. (See 'Monitoring D-penicillamine therapy' above.)

Trientine and pregnancy — The safety of trientine during pregnancy is unclear. Trientine has been administered during pregnancy with the delivery of normal infants, although chromosomal defects have been described [53,54]. The number of exposed infants is too small to demonstrate a clear causal relationship. Animal data suggest the potential for teratogenicity, possibly due to the induction of copper deficiency or zinc toxicity [55]. Whether the drug is

excreted in breast milk is unknown. According to the guideline from the American Association for the Study of Liver Diseases, trientine can be used during pregnancy, but the dose should be reduced as early as possible to approximately 500 to 750 mg daily and maintained during pregnancy because of the issues related to wound healing described above for D-penicillamine. As for D-penicillamine, reduced dosages necessitate more frequent monitoring, and following liver tests and clinical status each trimester is recommended.

Oral zinc — Oral zinc interferes with the absorption of copper, providing a rationale for its use in Wilson disease. Zinc induces metallothionein (an endogenous chelator of metals) in enterocytes, which has a greater affinity for copper than for zinc, causing it to bind luminal copper and thereby preventing its entry into the circulation [56,57]. The bound copper is excreted fecally during normal turnover of enterocytes. Copper secreted from saliva and gastric and intestinal secretions is also bound, thereby further enhancing a negative copper balance [58]. Zinc may also induce hepatic metallothionein [59,60].

Dosing — There are several forms of oral zinc salts, which probably have similar abilities to interfere with copper absorption, but differ in their tolerability and absorption. Zinc acetate has the best absorption. Zinc gluconate is an alternative zinc salt, which is more tolerable than zinc sulfate with respect to gastrointestinal side effects. In patients with severe side effects, alternative zinc salts or a change to chelation therapy may be warranted. (See 'Adverse effects' below.)

Dosing is in milligrams of elemental zinc. The dose of zinc acetate in adults and older children is a total of 150 mg zinc daily given in three divided doses. Twice daily dosing is also effective in patients who cannot comply with three times daily dosing [61], but once daily dosing is not effective. Smaller children (less than 50 kg body weight) should be given a total of 75 mg zinc daily in three divided doses [62]. The optimal dose for children younger than five is unknown. Dosing of zinc should be separated from food and beverages by at least one hour.

Efficacy — Most experience with zinc in the treatment of Wilson disease has been in the care of patients during maintenance phases following treatment with a chelator [63]. However, it has also been used as primary therapy, in patients who developed worsening neurologic symptoms with D-penicillamine, during pregnancy, and in young children [13,58,61,63-71]. One report of 17 symptomatic patients (mean age 18 years) treated exclusively with zinc and followed for a median of 14 years concluded that treatment was effective for neurologic disease, but less satisfactory for hepatic disease [72].

A study described in the manufacturer's prescribing information for zinc acetate focused on 60 patients who had been treated successfully with chelation therapy who were then treated with

varying doses of zinc acetate. Treatment was considered to be adequate if copper balance was maintained at less than +0.25 mg copper per day. Adequate copper balance was observed in 64 of 70 patients taking the 50 mg dose three times daily. A dose of 25 mg three times daily also seemed to produce adequate copper balance, but only 11 patients were studied.

A second study described in the manufacturer's information focused on 30 presymptomatic patients whose diagnosis was established based upon hepatic copper concentration. No patient developed symptoms of Wilson disease during ten years of follow-up. The manufacturer notes that the results have not been replicated.

A later retrospective series compared outcomes in a total of 288 patients who had been treated with zinc monotherapy or chelating agents [73]. Both approaches were effective, but chelating agents were more effective at preventing hepatic deterioration. The authors advised that liver biochemical tests be monitored in patients receiving zinc monotherapy and that consideration be given to adding a chelating agent in patients who have an increase in liver enzymes.

Most clinicians still rely on D-penicillamine or trientine as primary therapy for symptomatic patients. Zinc is an alternative for patients who cannot tolerate these treatments, who have neuropsychiatric disease that is not responding, or for maintenance in those who have achieved therapeutic goals on chelation therapy.

Adverse effects — The most common adverse effect of zinc is gastrointestinal upset. Approximately 20 percent of patients using zinc experience significant gastrointestinal side effects, including severe dyspepsia and gastritis, and alternative zinc salts or a change to chelation therapy may be warranted for these patients. Hepatic deterioration (including a fatality) has been described in case reports [74,75]. Neurologic deterioration is uncommon. Elevation in serum amylase and lipase without clinical evidence of pancreatitis has been observed.

Zinc and pregnancy — Studies in pregnant women have not demonstrated that zinc acetate or sulfate increases the risk of fetal abnormalities [76]. Furthermore, teratogenicity has not been observed in animal studies.

Ammonium tetrathiomolybdate — Ammonium tetrathiomolybdate given orally both interferes with copper absorption when the medication is given with meals, and binds plasma copper [3,77]. It has been proposed as a more effective treatment for patients with neurologic disease [78]. A controlled trial comparing it to trientine suggested that it may reduce the risk of neurologic deterioration [78]. It is not yet commercially available, but a new phase 2 clinical trial has been started for newly diagnosed patients using a stabilized form of tetrathiomolybdate [4].

Other agents — Other drugs, such as potassium sulfide and carbacrylamine resins, which bind copper in the gastrointestinal tract, are not recommended. Dimercaprol (BAL), the first drug that successfully treated Wilson disease, is rarely used as it requires intramuscular injection of 2 to 3 mL that are painful and lead to local sterile abscesses.

DIETARY RECOMMENDATIONS

During the initial phase of treatment, patients should avoid consuming food with high copper content, in particular shellfish, nuts, chocolate, mushrooms, and organ meats. Once therapy is ongoing and patients are doing well, moderating intake of copper can be acceptable. Dietary restriction is insufficient as sole therapy for Wilson disease. It may be prudent to test drinking water obtained from wells for copper content, or use appropriate filters that remove trace elements. Municipal water supplies usually do not require analysis. Patients who have copper pipes in the household should be advised to flush the system before using water for cooking or consumption. A detailed list of the mineral content of foods is available on the US Department of Agriculture website.

ACUTE LIVER FAILURE

It is useful to differentiate patients with acute liver failure due to Wilson disease from those with other causes of acute liver failure, as the therapeutic approach is different in patients with Wilson disease, and family screening can be performed on primary family members of the patient. Laboratory tests that suggest the acute liver failure is due to Wilson disease include an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio of >2.2, an alkaline phosphatase to bilirubin ratio of <4 (present together giving a sensitivity and specificity of 100 percent in adults with acute liver failure), a low hemoglobin due to non-immune mediated (Coombs negative) hemolytic anemia, and elevated serum copper above 200 mcg/dL [79]. Emergency liver transplantation must be considered early, and patients should immediately be referred to a transplant center urgently. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Determining the cause of acute liver failure' and "Acute liver failure in adults: Management and prognosis", section on 'General management'.)

Initial treatment must be aimed at the rapid removal of copper. Hemodialysis, peritoneal dialysis, and hemofiltration have been used to remove copper [80]. In addition, plasma pheresis [4] or plasma exchange with fresh frozen plasma replacement is an option, as it can remove relatively large amounts of copper in a short period of time [81,82]. Net copper removal is proportional to plasma concentration and can reach 12 mg per session. Most of these patients

also have hemolytic anemia. Copper ions leak from necrotic hepatocytes into the circulation and cause lysis of red blood cells [81]. Hemofiltration and albumin dialysis have also been described as temporizing measures, as well as the combination of these in the molecular absorbant recirculating system (MARS) device [83-87].

LIVER TRANSPLANTATION

Liver transplantation may be the only option for patients who present with acute liver failure and in those with decompensated liver disease who are unresponsive to drug therapy [88-92]. For those with advanced liver disease, a prognostic scoring system for children with Wilson disease presenting with failure was proposed by a group at Kings College and then later revised [93,94]. The revised system (based upon an index of serum bilirubin, the prothrombin time international normalized ratio [INR], aspartate aminotransferase level, and white blood cell count) had a sensitivity, specificity, and positive predictive value for determining the need for liver transplantation of 93, 98, and 88 percent, respectively [94]. This scoring system has been validated in pediatric and adult patients.

Liver transplantation is curative for Wilson disease, and patients do not require treatment for Wilson disease following transplantation. Outcomes for liver transplantation for Wilson disease are excellent for those transplanted for acute liver failure or for liver failure from chronic liver disease. A review of the United Network for Organ Sharing database showed that pediatric and adult outcomes were better than long-term outcomes for patients transplanted for other disorders [95]. The series looked at the outcomes of 170 children transplanted for Wilson disease between 2002 and 2008 and 400 adults transplanted between 1987 and 2008. The one- and five-year survival rates were similar for children and adults. They were 90 and 89 percent, respectively, for children and were 88 and 86 percent, respectively, for adults. Pediatric patients with Wilson disease were more often transplanted for acute liver failure, whereas adults with Wilson disease were more often transplanted for with chronic liver failure.

Whether or not liver transplantation is indicated in patients with predominantly neurologic manifestations is controversial [96,97]. This may be due in part to differences in the resolution of neurologic manifestations when the recipient also has extensive hepatic disease compared with those with neurologic manifestations as the principal indication for transplantation. Survival appears to be worse in patients with neurologic involvement.

- One series included 13 patients with Wilson disease who received a liver transplant, four of whom had intractable neurologic impairment as the only indication [91]. All required continuous nursing care prior to transplant and all showed improvement beginning four

to six weeks after transplant. One was asymptomatic after five years, two had noticeable improvement, and one showed only slight improvement.

- In another report of 55 transplants, seven with hepatic insufficiency had neurologic and/or psychiatric manifestations at the time of transplantation [90]. Four showed improvement. One patient given a transplant for intractable neurologic disease improved but died of a vascular complication.

- A third report included 37 patients of whom 32 percent had mixed hepatic and neuropsychiatric symptoms, while eight presented with acute failure [98]. Neurologic symptoms improved significantly after transplantation but overall survival was significantly worse among patients with mixed neurologic and hepatic involvement compared with those with liver disease alone.

PROGNOSIS

The prognosis in patients with Wilson disease is excellent in all but those with advanced disease and those who present with rapidly progressive liver failure and hemolysis. The neurologic, psychiatric, and hepatic abnormalities gradually improve with treatment, and liver biochemical tests results usually return to normal. Whether patients are at increased risk of hepatocellular carcinoma is not clear. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Risk of liver cancer'.)

SCREENING

Treatment is most effective when it is applied early in the course of the disease. As a result, it is mandatory to screen all siblings and children of patients with Wilson disease. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Asymptomatic first-degree relatives'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Inherited liver disease".)

SUMMARY AND RECOMMENDATIONS

Patients with Wilson disease require lifelong therapy. Discontinuation of therapy can lead to the development of acute liver failure or other symptoms. Treatment should be given in two phases: stabilizing the patient by removing tissue copper that has accumulated and then preventing reaccumulation (maintenance). The following will summarize our approach, which is consistent with recommendations proposed by the American Association for the Study of Liver Diseases (table 1):

- **Asymptomatic patients** – In asymptomatic patients identified through screening, we recommend treatment with a chelating agent (such as D-penicillamine or trientine) (**Grade 1B**). Zinc may be used in patients who are reluctant to use a chelating agent or who are intolerant of them, but liver biochemical test should be monitored at least every four months and a chelating agent added if these tests worsen (**Grade 1B**). Evolving consensus has been to use trientine because of its relatively favorable side-effect profile. Copper balance should be monitored regularly in such patients by obtaining a 24-hour urine collection and by estimating nonceruloplasmin bound copper.

- **Symptomatic patients** – Symptomatic patients should be treated with a chelating agent (D-penicillamine or trientine) until stable. As noted above, trientine may be preferred because it has fewer side effects than D-penicillamine and appears to be less likely to exacerbate neurologic symptoms. (See 'Adverse effects' above.)

  Patients typically require six months to five years of higher-dose treatment, after which they can be transitioned to maintenance therapy. Prior to the transition, patients should be clinically well, have normal serum aminotransferases, and hepatic synthetic function, non-ceruloplasmin-bound copper in the normal range (<15 mcg/dL or 150 mcg/L), and 24-hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromoles) per day. Maintenance therapy can be achieved with zinc or with lower doses of a chelator, and patients should be monitored regularly as described above.

- **Pregnancy** – Pregnancy appears to be safe in patients on D-penicillamine and trientine, but we suggest the dose be reduced to approximately 30 to 50 percent of the pre-pregnancy dose during the first trimester since both drugs are known to be teratogenic in animal models and continued to term as treatment with higher doses may impair wound healing should a cesarean section or episiotomy be required (**Grade 2C**). Case reports have suggested that zinc may be a safer and effective alternative, but experience is limited. (See 'D-penicillamine and pregnancy' above and 'Trientine and pregnancy' above and 'Zinc and pregnancy' above.)

- **Acute liver failure** – Patients presenting with acute liver failure due to Wilson disease require liver transplantation. Plasmapheresis, exchange transfusion, hemofiltration, molecular absorbant recirculating system (MARS), or dialysis may be performed while transplant is being awaited. Albumin dialysis may also be beneficial, but experience is limited. As noted above, recovery with supportive therapy has been described. (See 'Acute liver failure' above.)

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GRAPHICS

AASLD recommendations for treatment of Wilson disease (WD)

Initial treatment for symptomatic patients should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated.
Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment.
Treatment of presymptomatic patients or those on maintenance therapy can be accomplished with a chelating agent or with zinc. Trientine may be better tolerated.
Patients with acute liver failure due to WD should be referred for and treated with liver transplantation immediately.
Patients with decompensated cirrhosis unresponsive to chelation treatment should be evaluated promptly for liver transplantation.
Treatment for WD should be continued during pregnancy, but dosage reduction is advisable for D-penicillamine and trientine.
Treatment is lifelong and should not be discontinued, unless a liver transplant has been performed.
For routine monitoring, serum copper and ceruloplasmin, liver biochemistries and international normalized ratio, complete blood count and urinalysis (especially for those on chelation therapy), and physical examination should be performed regularly, at least twice annually. Patients receiving chelation therapy require a complete blood count and urinalysis regularly, no matter how long they have been on treatment.
The 24-hour urinary excretion of copper while on medication should be measured yearly, or more frequently if there are questions on compliance or if dosage of medications is adjusted. The estimated serum non-ceruloplasmin bound copper may be elevated in situations of nonadherence and extremely low in situations of overtreatment.

Data from: Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. Hepatology 2008; 47:2089.

Graphic 57105 Version 2.0

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