

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of End-Stage Liver Disease

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G&H How do you define end-stage liver disease in clinical terms?

DH End-stage liver disease (ESLD) requires a relatively strict definition because it is a term that is used too loosely in the community. In my usage, ESLD is a complication of cirrhosis, no matter what the cause, that indicates a poor prognosis over the ensuing 1–2 years. This is usually indicated by significant ascites, variceal bleeding, locally advanced hepatocellular carcinoma, significant hepatic encephalopathy, or other similar complications brought on by cirrhosis.

G&H Could you describe the current epidemiology of ESLD in the United States?

DH The main disease states or risk factors leading to ESLD, or decompensated cirrhosis, include uncontrolled alcoholism and infection with hepatitis C virus (HCV; which is currently the leading indication for liver transplantation in the United States) and hepatitis B virus (HBV). Rapidly gaining ground, however, is the epidemic of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH), due to our society's growing problem with obesity. Currently, two thirds of our population is overweight or clinically obese and, as a result, the incidence of NASH is rapidly increasing. As more people develop NASH earlier in life, we see an increasing rate of cirrhosis from NASH, leading to the development of complications from liver disease, including liver cancer later in life.

Many of our ESLD patients do not have just one risk factor but rather combinations of two, three, or even four. In the recent past, we have learned that all of these factors interact and increase rates of scarring (fibrosis), cirrhosis, and, ultimately, ESLD. Obesity is an independent risk factor for progressive disease in cases of viral hepatitis, hemochromatosis, and alcoholic liver disease, and it is well established that alcohol use and abuse is a cofactor in hepatitis-related liver injury. Therefore, many of these risk factors interact to increase the likelihood of development of cirrhosis and its complications.

G&H How have recent advances in the treatment of viral hepatitis interacted with the rising incidence of hepatitis infection, in terms of rates of progression to ESLD?

DH Clearly, we have made tremendous strides in our ability to treat viral hepatitis, particularly HBV but also HCV. The number of patients requiring transplant due to hepatitis B has steadily declined with improved medical management through the antiviral agents developed in the last decade. Unfortunately, with regard to HCV, we have not yet seen the same phenomenon. This is partly due to the demographic maturation of the HCV epidemic. A steadily increasing proportion of patients have had the virus for longer than 20 years, which is long enough to lead to the development of cirrhosis. Thus, we have not seen a decline in the prevalence or incidence of cirrhosis, even though the rate of new HCV infections is steadily declining. This is despite the fact that we have improved

HCV therapy with the current combination of pegylated interferon and ribavirin.

G&H How have all of these factors affected the pool of available donor organs and wait list times?

DH The number of standard donors, those with so-called good livers, has remained relatively constant. We have made only small advances in recruiting more standard-criteria donors for transplant. Thus, we have been forced, because of the greater number of people waiting for transplant, to consider extended-criteria organs, where the donor may be a little bit older or the fatty changes on the donor organ may be more than was accepted 5–10 years ago. We are now using those types of organs in addition to organs that are donated after cardiac death (DCD), whereas 5–10 years ago, we rarely used them.

Further, as the proportion of our population with weight difficulties increases, more of those donors have fatty liver disease. We have learned through experience that fatty livers do not work as well for organ transplantation and this does limit our ability to obtain more donor organs. Many programs are using donors that have been exposed to HCV to obtain organs for those individuals who are already infected with HCV. This is a policy currently being explored throughout the United States.

These conditions particularly affect patients transplanted for HCV. We are learning that less-than-ideal donors may result in far-less-than-ideal results from transplant in our HCV patients, particularly the donation of organs from DCD donors and those where there are fatty changes in the donor liver.

G&H Do these less-than-ideal donor livers have a negative effect on the success of the procedure or on overall survival?

DH Success of the transplant procedure, in the immediate postoperative period, depends largely on the health of the recipient at the time of transplant. However, in hepatitis C patients, disease recurrence is often accelerated and much more aggressive in patients receiving suboptimal organs.

G&H What steps can be taken to optimize management of patients on the transplant waiting list?

DH For patients on the wait list, we provide primary or secondary prophylaxis to decrease the risk of variceal hemorrhage, following current guidelines for performing upper endoscopy and assessment of variceal bleeding risk and administration of either beta-blockers or variceal

band ligation. We also provide prophylactic antibiotics to selected individuals at high risk of infection in order to improve outcomes.

Patients and their families require thorough education regarding the signs of impending complications of liver disease. If they are alerted as to what to look for, they can seek immediate help. We educate patients about medications to avoid, such as aspirin and nonsteroidal anti-inflammatory drugs, as well as the limitation of acetaminophen use. We provide counseling regarding the cessation of alcohol, tobacco, and illicit drugs and the complications associated with these substances. We know that smoking increases the risk of vascular complications, post-transplant. Thus, one of our mantras is to advise patients to stop smoking. We actually screen them for tobacco use, as it affects their listing status.

Good nutrition is another important factor for successful transplant. A number of studies have shown that malnutrition, particularly in the extreme, negatively affects the result of transplant. We also want to make sure that patients are as active as possible, encouraging them to walk at least 30 minutes, 4 times per week. For patients with more advanced liver disease, we recommend physical therapy, either at home or while in the hospital awaiting transplant.

Finally, we surveil every 6 months for hepatocellular carcinoma with a liver imaging study (liver ultrasound, computed tomography, or magnetic resonance imaging), which is a better screening method than solely monitoring serum alpha-fetoprotein (AFP) measures.

G&H How do the findings of your screening methods affect a patient's prioritization for a transplant procedure?

DH Documentation of the development of a focal liver lesion in a patient with cirrhosis, who is on the wait list for transplant, can result in additional Model for End-stage Liver Disease (MELD) exception points, due to the presence of early-stage liver cancer. The diagnosis is based on imaging studies. AFP can be used to make a diagnosis, but the majority of tumors that we see meeting the early-stage Milan criteria are too small to affect AFP. Patients can qualify for additional MELD exception points with a high AFP that is continually increasing, even in the absence of a mass lesion. However, patients with that finding are quite rare.

G&H What future research is necessary to further optimize the care of patients with ESLD?

DH The most important question that needs to be answered through the utilization of high quality, ran-

domized clinical trials is the utility of both artificial and bioartificial liver-support devices. There is a population of patients who have compensated cirrhosis but develop a severe infection or a bleed that leads to acute-on-chronic liver failure. If these devices can be used to temporarily support these patients, the patients may be able to return to their compensated state. The application of these devices also needs to be investigated in patients who are candidates for transplant. They may have utility in maintaining patients to transplant and improving transplant success rates. Currently, more governmental research support is needed in order to investigate these devices. The identification of optimal patient populations, timing of administration, and the management of side effects from required anticoagulation are all key issues that need to be addressed.

Suggested Reading

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