J Gastroenterol 2002; 37[Suppl XIII]:78–81

Journal of Gastroenterology

Liver transplantation for fulminant hepatic failure

David H. Van Thiel[1], John Brems[2], Abdul Nadir[1], Ramazan Idilman[1], Alessandra Colantoni[1], David Holt[2], and Steven Edelstein[3]

Departments of [1] Medicine, [2] Surgery, and [3] Anesthesia, Loyola University of Chicago, Stritch School of Medicine, Bldg. 114, Room 54, Maywood, IL 60153, USA

The etiology and prognosis of individuals with various forms of fulminant hepatic failure are reviewed. Special techniques of clinical management and decision making as to when and to whom to transplant in cases of fulminant hepatic failure are reviewed.

Key words: fulminant hepatic failure, liver transplantation, acute hepatic failure

Introduction

Fulminant hepatic failure (FHF) was initially described by Trey as a syndrome wherein an individual without prior biochemical or clinical evidence of liver disease develops jaundice (the usual first overt sign of liver disease) that then progresses to hepatic coma (grade II–IV encephalopathy) within 2 weeks or less.[1] More recently, the syndrome has been redefined and amended by the French and British groups to include the concepts of acute and subacute hepatic failure, as well as hyperacute, acute, and late-onset hepatic failure, respectively.[2,3]

Etiology and prognosis

These later distinctions in nomenclature were created on the basis of etiology and prognosis. Individuals with hyperacute hepatic failure typically have either hepatitis A or hepatitis B (or possibly hepatitis E in parts of the world where hepatitis E is prevalent) as the principal cause of the condition, accounting for 60% of the total cases of fulminant hepatic failure. The principal causes of acute hepatic failure are also hepatitis A and B, but they also include acetaminophen hepatotoxicity. In contrast, cases of subacute hepatic failure and, to a greater degree, cases of late-onset hepatic failure present as cases of drug-induced hepatic failure other than acetaminophen hepatotoxicity and as cases of putative non-A, non-B, non-C hepatitis.[4]

The overall prognosis for survival for cases of fulminant hepatic failure is often cited as 30%–40%.[1–4] The prognosis for cases of hyperacute hepatic failure is the best, often as high as 50%, with maximal medical care.[4] In contrast, the prognosis for survival without liver transplantation for those with subacute and late-onset hepatic failure is poorest, often cited as low as zero. The prognosis for those with acute hepatic failure lies between these two extremes in prognosis for survival without liver transplantation and is intermediate in value at approximately 15%–20%.[4]

Clinical management

The medical management of fulminant hepatic failure requires aggressive attention to detail and invasive monitoring that necessitates admission to an intensive care unit. Accurate and frequent (often hourly) measures of intake, output, blood pressure, pulse, respiratory rare, and pH, as well as blood sugar, lactic acid, electrolytes (including calcium, phosphorus, and magnesium), renal functional measures, coagulation parameters, measures of intravascular fibrinolysis, and intracranial pressure monitoring (in adults).[5] In children, clinical measures of the level of consciousness and neurologic status are sufficient and usually are performed without placement of an intracranial pressure-monitoring device. This is because children typically have loose cranial sutures, and those under two years of age often have open fontanelles, allowing dissipation of any increase in intracranial pressure.[6]

Reprint requests to: D.H. Van Thiel

Part of this article was published in J Gastroenterol 2001;36: 1–4

Measures that can be used to maintain intracranial pressure within acceptable ranges include the infusion of 10% dextrose, mannitol, and large amounts of magnesium, phosphorus, and potassium, as well as evaluating the head of the bed. Every attempt should be made to maintain the cerebral perfusion pressure greater than 50 mmHg and the intracranial pressure less than 30 mmHg.[4,5,7] These pressures are defined by the following equation: the mean arterial pressure (MAP) minus the intracranial pressure (ICP) equals the cerebral perfusion pressure (CPP).[4,6,7] Elevating the head of the bed and mannitol infusions are the principal measures used to control ICP. The mean arterial pressure can be regulated with dopamine, often at renal doses. Higher doses may lead to cardiac arrhythmias, necessitating the use of adrenergic agents such as levophed (norepinephrine bitartrate). The requirement for levophed can lead to peripheral tissue hypoxia and lactic acidosis as a consequence of increased production of lactic acid rather than a failure to clear lactic acid by the liver. This scenario necessitates the use of large volumes of sodium bicarbonate or the use of artificial buffers such as THAM (trometamol; tris-hydroxymethyl aminomethane). Intracranial monitoring devices, when used, should be placed prospectively, as the patient becomes lethargic in stage II hepatic encephalopathy, and not urgently, when the patient is in stage IV coma.[6,7] This often necessitates placement of such a device at the time that the patient is admitted to the intensive care unit (ICU). A coagulopathy should not prohibit the placement of an extradural ICP-monitoring device unless the prothrombin time is more than 30 s.[4,6,7]

In order to maintain renal function, an infusion of dopamine (<10 μg/kg/min) is often required. To these attempts to maintain overall homeostasis in the face of severe liver injury can be added the use of ultrafiltration, hemodialysis, hemofiltration coupled with hemodialysis, and plasmapheresis in patients with advanced liver injury.[4,8] The administration of fresh frozen plasma solely for the purpose of correcting coagulation deficits is limited to individuals who have prothrombin times in excess of 50 s.

In addition to intracranial hypertension, infection and gastrointestinal bleeding are frequent lethal complications of fulminant hepatic failure.[2–4] Both require close monitoring and frequent cultures of blood, urine, sputum, and other fluids, as well as sites at which intravascular monitoring devices or infusion lines are located. Antibiotic prophylaxis with broad-spectrum antibiotics such as a third-generation cephalosporin and an antifungal agent (typically diflucan) is routine in such cases. Infections with either bacteria or fungi (often both) can occur in the absence of fever and/or leukocytosis in cases of fulminant hepatic failure. The use of an intravenous H_2 blacker or the oral administration of a proton pump inhibitor is also routine.

In our unit, we insist upon a transvenous liver biopsy within 24 h of admission to the ICU in all cases of fulminant hepatic failure. Moreover, in patients with biochemical evidence of renal failure or disease, we also obtain a simultaneous transvenous renal biopsy. The liver biopsy is used to gauge the severity of the hepatic injury as 60%, 70%, 80%, or 90% necrosis. It is also used to assess the liver for evidence of regeneration, as manifested by the presence of liver-cell mitosis. In general, patients with necrosis of 60% or less are likely to survive without the need for transplantation, whereas those with necrosis of 90% or more are not going to survive without transplantation.[2–4] Those patients with hepatic necrosis greater than 60% but less than 90% have a less clear prognosis and require the most aggressive care and attention. In rare cases, the liver biopsy can provide etiologic information that enables specific therapy to be instituted, as in the case of herpes, cytomegalovirus (CMV), adenovirus, and possibly paramyxovirus hepatitis infections. Because of the variable nature of liver biopsies in cases of fulminant hepatic failure, a minimum of three, and ideally six, biopsies of the hepatic parenchyma should be obtained for histologic evaluation. In addition, in cases in which Wilson's disease or hepatic iron toxicity is possible, a separate core of liver tissue should be obtained for hepatic iron and copper determinations.

The renal biopsies are useful in determining whether a liver and kidney transplant should be anticipated rather than an isolated liver transplant. Histologic evidence of preexisting glomerulonephritis or renal vascular disease would indicate combined transplantation, whereas the histologic absence of renal disease suggests that the renal dysfunction present is due to the hepatorenal syndrome or prerenal causes, and as a result there will be no need for renal transplantation.

Clearly not all cases of fulminant hepatic failure will require liver transplantation. Most of those with less than 60% necrosis certainly will not. For those with more than 60% but less than 90% necrosis, specific indications for liver transplantation have been developed empirically and have been shown to be very useful clinically.[2,3]

Transplantation decision making

Two major systems exist for the identification of those who will require liver transplantation.[2,3] The simpler is the French system (Table 1).[3] Only two measures are considered in this system: the patient's age and the factor V level in the plasma. The British system actually consists of two separate sets of criteria: one for patients

Table 1. French prognostic criteria for emergency liver transplantation for acute liver failure

Age (<30 years)
Factor V level (<20% of the normal level)
Confusion (present)
Coma (present)

Table 2. British prognostic criteria

Individuals with acetaminophen-induced hepatic failure
pH (<7.30)
Prothrombin time (>100 s)
Serum creatinine (>300 μmol/l)
Encephalopathy (grade III or IV)
Individuals with acute hepatic failure (any 3 of the following criteria)
Age (<10 or >40 years)
Etiology (halothane hepatitis)
Jaundice (onset >7 days before the onset of encephalopathy)
Prothrombin time (>50 s)
Serum bilirubin (>300 μmol/l)
Encephalopathy (grade III or IV)

Table 3. Liver transplantation options for individuals with fulminant hepatic failure

Cadaveric transplantation
Whole liver
Reduced-size liver
Split liver
Auxiliary partial liver
Orthotopic position
Heterotopic position
Auxiliary whole liver
Heterotopic position
Living related transplantation
Left lateral segment (segments 2 and 3)
Left lobe (segments 2, 3, and 4)
Extended left lobe (segments 2, 3, 4, and the left side if ↑)
Right lobe (segments 5, 6, 7, and 8)

with acute hepatic failure secondary to acetaminophen toxicity and a second for all other etiologies of acute hepatic failure (Table 2).[2] Unlike the French system, a variety of measures are taken into consideration in the British criteria for liver transplantation in cases of acute hepatic failure. Despite the considerable differences between these two systems, there is little or no difference between them in efficacy in terms of their positive and negative predictive values.[9] Both systems were developed to predict the need for liver transplantation on admission to the ICU and within 24 h. The reality, however, is that the decision whether or not to transplant dose not have to be made at the time of admission, but rather at the time a donor organ has been identified.[5] This is because the typical waiting time for a donor organ for a united network for organ sharing (UNOS) status 1 patient (those with fulminant hepatic failure) is 2 or 3 days or more.

Liver transplantation

Once the decision is made to transplant a liver into a given patient, the surgical options for transplantation come into play. These are shown in Table 3. The most frequently utilized procedure is cadaveric whole-organ transplantation, with the donor organ placed in the orthotopic position. Alternative procedures that are applicable to children with fulminant hepatic failure are a reduced-sized liver graft or split-liver transplant.[10,11] In the former cases, a whole cadaveric organ is reduced in size by the removal of segments 2 and 3 or segments 2, 3, and 4 from the whole liver, and the removed segments are transplanted in an orthotopic position in the recipient while the residual cadaveric cadaveric organ is discarded. In the second case, a whole cadaveric organ is split into its right and left halves, and the left lobe or its lateral segment is transplanted into a child while the right lobe is transplanted into an adolescent or adult, with both halves of the cadaveric donor organ being used. Thus, in the case of the split liver, two transplants are performed utilizing a single cadaveric organ. However, to accomplish this feat, as opposed to a reduced-size transplant, twice the facilities in terms of operating rooms, recovery rooms, and hospital beds are required. Moreover, twice as many staff are necessary, in terms of surgeons, anesthesiologists, and intensive care personnel. The additional staff must also have unique expertise in both pediatric and adult hepatic disease, liver transplantation, and post-transplant care.

The first type of auxiliary transplantation to be developed was whole-liver heterotopic transplantation. This procedure has fallen out of favor, both because it is technically difficult to do and because often insufficient space exists in the abdomen of the recipient for the donor liver. More recently, auxiliary partial liver transplantation has been developed.[12,13] In this scenario, a portion of the liver, usually the right lobe, is transplanted in the heterotopic position. Less often, a portion of the liver, typically the left lobe or the left lateral segment, is transplanted in the orthotopic position. The advantage of auxiliary liver transplantation, as opposed to orthotopic liver transplantation, is that with recovery of the native liver, immunosuppression can be discontinud.[12] This maneuver leads to rejection and involution of the graft. At times, surgical removal of the graft is accomplished, particularly, if the graft becomes a source of toxins with the cessation of immunosuppression or becomes infected.

In areas of the world such as Japan and the rest of Asia, where brain death has only recently been accepted and orthotopic liver transplantation has been limited by a lack of cadaveric donors, living related transplantation has been developed and refined as an acceptable alternative transplantation procedure.[5,14] The initial experience with living related liver transplantation was in children with biliary atresia, wherein the native liver is removed and is replaced by the left lateral segment of an adult donor, usually a parent. This procedure has little or no hazard for the donor and provides an adequate amount of donor organ for the recipient to recover immediately. After considerable experience with this initial procedure, transplantation of the left lobe into an adult or adolescent from an adult donor has slowly begun to be accomplished. Although the risk of this expanded resection to the donor is greater than that with donation of the left lateral segment, the procedure has sufficiently little risk in expert hands that it has become a widely practiced surgical procedure, particularly in Japan.[14]

Unfortunately, for living related liver transplantation to be successful, a minimum of 30% of the expected mass of the recipient must be removed from the donor and transplanted into the recipient.[14] Ideally, a mass equivalent to 40% or more of the recipient's expected normal liver mass is removed and transplanted. To accomplish this in an adult recipient, it is often necessary to resect the right lobe of the donor to provide sufficient hepatic tissue for the recipient to receive 30% to 40% of his or her expected hepatic mass. Because of a variety of anatomic issues, right lobe resection is a considerably greater surgical procedure than resection of the left lobe or the left lateral segment. As a result, right lobe resection carries a 1%–3% risk of mortality for the donor.[14] This level of risk for the donor of a living related transplant is considerable and has limited the willingness of many transplant surgeons to perform the procedure. Nonetheless, the experience with right lobe donation in adult-to-adult liver transplantation has slowly but steadily been expanded to involve more surgeons and more institutions. Because of the considerable Japanese experience with this procedure, the Western world has begun to investigate its use, in highly selected cases, by highly accomplished Western transplant surgeons.

Liver-cell transplantation

The use of liver-cell transplantation for the treatment of fulminant hepatic failure has not been particularly successful and may never reach its hoped-for potential, simply because of the number of cells that are required to be transplanted.[15] Therefore, this option was not included in Table 3. On the assumptions that a mass of available cells equal to a third of the expected liver mass is necessary for successful transplantation and that only a third of the cells harvested for transplantation will survive, the actual volume of cells required for success with liver-cell transplantation is equal to that contained in a whole liver. Harvesting such a large volume of cells and then infusing them is a logistic nightmare, and this procedure is likely to be a rare event capable of being performed at only a very few highly specialized institutions with a unique interest in its performance.

References

1. Trey C. The fulminant hepatic failure surveillance study. Brief review of the effects of presumed etiology and age of survival. Can Med Assoc J 1972;26:S525–7.
2. O'Grady JG, Alexander GJM, Haylaan KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–45.
3. Bernuau J, Samuel D, Durand F, Bismuth H. Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V below 50% of normal: a prospective study. Hepatology 1991;14:49A.
4. William L. Medical Progress: acute liver failure. N Engl J Med 1993;329:1862–72.
5. Van Thiel DH. When should a decision to proceed with transplantation actually be made in cases of fulminant or subfulminant hepatic failure: at admission to hospital or when a donor organ is made available? J Hepatol 1993;17:1–2.
6. Hattori H, Higuchi Y, Tsuji M, Inomata Y, Uemoto S, Asonuma K, et al. Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure. Transplantation 1998;15:686–92.
7. Detry O, Arkadopoulos N, Ting P, Kahaku E, Margulies J, Arnaout W, et al. Intracranial pressure during liver transplantation for fulminant hepatic failure. Transplantation 1999;67:767–70.
8. Moore K, Renal failure in acute liver failure. Eur J Gastroenterol Hepatol 1999;11:967–75.
9. Pauwels A, Mostefa-Kara N, Florent C, Levy VG. Emergency liver transplantation for acute live failure: evaluation of London and Clichy criteria. J Hepatol 1993;17:124–7.
10. Emre S, Schwartz ME, Shneider B, Hojsak J, Kim-Schluger L, Fishbein TM, et al. Living related liver transplantation for acute liver failure in children. Liver Transpl Surg 1999;5:161–5.
11. Sterneck M, Fischer L, Buggisch P, Malago M, Rogiers X, Burdelski M, et al. Transplantation of complete and split liver grafts for patients with fulminant hepatic failure. Z Gastroenterol 1996;34:795–800.
12. Van Hoek B, De Boer J, Boudjema K, Williams R, Corsmit O, Terpstra OT. Auxiliary versus orthotopic liver transplantation for acute liver failure. EURALT Study Group. European Auxiliary Liver Transplant Registry. J Hepatol 1999;30:699–705.
13. Neuhaus P, Bechstein WO. Split liver/auxiliary liver transplantation for fulminant hepatic failure. Liver Transpl Surg 1997;3:S55–61.
14. Miwa S, Hashikura Y, Mita A, Kubota T, Chisuwa H, Nakazawa Y, et al. Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure.
15. Riordan SM, Williams R. Acute liver failure: targeted artificial and hepatocyte-based support of liver regeneration and reversal of multiorgan failure. J Hepatol 2000;32:63–76.