

Fulminant Hepatic Failure

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Fulminant hepatic failure (FHF), synonymous with acute liver failure, is a rare liver disorder that often leads to devastating consequences. It is one of the most challenging gastrointestinal emergencies encountered in clinical practice and encompasses a pattern of clinical symptoms and pathophysiological responses associated with the rapid arrest of normal hepatic function. The syndrome is defined by the sudden onset of hepatic encephalopathy in an otherwise healthy individual, often in association with coagulopathy, jaundice and multisystem organ failure. Until recently, FHF carried a very high mortality rate (widely reported to be in excess of 80%)¹; however, with an improved understanding and recognition of the syndrome, more aggressive medical therapy, intensive care monitoring, and the advent of orthotopic liver transplantation (OLT) as a treatment option, survival rates have improved considerably.²

This article reviews the topic of FHF in the form of a series of clinically relevant questions designed to allow the clinician to gain a comprehensive, up-to-date understanding of this important disease entity.

1. How Is “Fulminant Hepatic Failure” Defined?

The term fulminant hepatic failure (FHF) was first introduced more than 30 years ago by Trey and Davidson³ to describe the onset of altered mental status within 8 weeks of initial symptoms in an otherwise healthy individual with no previous history of liver disease. Various modifications to the original definition

have been advocated by a number of investigators over the past 2 decades, although to date, no universally accepted nomenclature has been adopted.

Bernuau et al.⁴ suggested that the term *fulminant* hepatic failure be reserved for cases in which encephalopathy developed within 2 weeks of the onset of jaundice and that *subfulminant* hepatic failure be applied to cases in which encephalopathy developed more insidiously, between 2 weeks and 3 months after the onset of jaundice. *Late-onset* hepatic failure has been used to describe patients in whom hepatic encephalopathy occurred between 8 and 24 weeks after the onset of symptoms.⁵ The “umbrella term” of *acute liver failure* was proposed by O’Grady et al.⁶ Based on a retrospective analysis of 539 patients, they suggested a further subclassification comprising 3 distinct syndromes depending on the jaundice-to-encephalopathy time interval. Thus categorizing liver failure as *hyperacute* (onset within 1 week), *acute* (between 8 and 28 days), and *subacute* (between 29 days and 12 weeks). This classification reflected differences in survival rate for these groups, the best prognosis paradoxically being in the hyperacute group.

2. How Common an Entity Is FHF?

The precise incidence of FHF has never been established. The International Classification of Diseases, Ninth Revision, has no specific code for FHF, thus limiting the availability of large databases from which to derive estimates.⁷ Currently, no comprehensive registry or population-based surveillance program exists. Estimates of incidence can, however, be gleaned from 1) liver transplantation programs, 2) population-based surveillance programs for acute liver disease, and 3) single hospital or county reports and suggest an incidence of FHF of 2,300 to 2,800 cases per year in the United States.⁷ In an FHF workshop convened in 1995, it was estimated that the syndrome represented 0.1% of all deaths in the United States and, perhaps, 6% of liver-related deaths.⁷ Moreover, it accounts for about 6% of liver transplants among adults.⁸

3. What Are the Causes of FHF?

FHF is the final common pathway for a variety of liver insults. The etiology of FHF varies widely depending

Abbreviations: FHF, fulminant hepatic failure; OLT, orthotopic liver transplantation; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; NAC, N-acetylcysteine.

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Table 1. Etiologies of FHF

<p>A. Viral HAV, HBV ± HDV, HEV, HSV, CMV, EBV, HVZ, adenovirus, hemorrhagic fever viruses</p> <p>B. Drugs and toxins</p> <ul style="list-style-type: none"> • Dose-dependent: acetaminophen, CCl₄, yellow phosphorus, <i>Amanita phalloides</i>, <i>Bacillus cereus toxin</i>, sulfonamides, tetracycline, Ecstasy (methylendioxyamphetamine), herbal remedies • Idiosyncratic: halothane, INH, rifampicin, valproic acid, NSAIDs, disulfiram <p>C. Vascular Right heart failure, Budd-Chiari syndrome, veno-occlusive disease, shock liver (ischemic hepatitis), heat stroke</p> <p>D. Metabolic Acute fatty liver of pregnancy, Wilson's disease, Reye's syndrome, galactosemia, hereditary fructose intolerance, tyrosinemia,</p> <p>E. Miscellaneous Malignant infiltration (liver metastases, lymphoma), autoimmune hepatitis, sepsis</p> <p>F. Indeterminate Includes primary graft non-function in liver transplanted patients</p>
<p>Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein Barr virus; HVZ, herpes varicella zoster virus; CCl₄, carbon tetrachloride; INH, isoniazid; NSAIDs, non-steroidal anti-inflammatory drugs.</p>

on geographic location, patient profile, and year of the report. Whereas in historical series from the 1980s, viral hepatitis was the most common etiology in the United States, the results of a recent multicenter prospective study of FHF has identified acetaminophen overdose (39% of cases) and idiosyncratic drug reactions (13% of cases) as the most frequent causes.² See Table 1 for a classification of the various etiologies.

The identification of the cause of FHF is critically important because the etiology influences prognosis and management. About 17% of cases remain indeterminate and this group likely includes patients with non-A–E viral hepatitis, unrecognized drug toxicity (including over-the-counter medications and herbal preparations), and possibly unrecognized metabolic or genetic diseases (more likely in the pediatric population).²

Acetaminophen is generally safe when used within recommended doses in otherwise healthy individuals. However, it has a narrow therapeutic range and is a dose-dependent hepatotoxic agent. Acetaminophen toxicity is the leading cause of FHF in the United States

(about 40% of cases) and the United Kingdom, where it is responsible for 50 to 70% of cases.^{9,10} The risk for acetaminophen toxicity is considerably higher among chronic alcohol abusers and patients on cytochrome P-450 enzyme-inducing agents in whom smaller doses for pain relief can accidentally cause FHF (the so-called “therapeutic misadventure”).¹¹ Malnutrition may also deplete glutathione stores and thus potentiate acetaminophen toxicity.¹¹

4. Describe the Clinical Features of FHF and Their Management

FHF often causes multisystem organ failure. Frequently the presenting symptoms are nonspecific, including fatigue, malaise, anorexia, nausea, abdominal pain, fever, and jaundice.¹² These symptoms progress to the development of encephalopathy (the hallmark feature of FHF) and / or coma, although the rates of progression are somewhat variable. Severe coagulopathy often precedes evolution of hepatic encephalopathy to coma.

Encephalopathy

Encephalopathy may vary from only subtle changes in affect, insomnia, and difficulties with concentration (stage 1) to deep coma (stage 4).¹³ This encephalopathy scale (see Table 2) has proven remarkably durable, and the prognosis of FHF is inversely correlated with the degree of encephalopathy. Cerebral edema is a common neurologic accompaniment of FHF, has been reported in the vast majority of cases that progress to stage 4 encephalopathy,¹⁴ and is the most commonly identifiable cause of death in FHF in autopsy studies.¹⁵ The pathogenesis remains unclear but both vasogenic and cytotoxic mechanisms have been invoked.¹⁶ Cerebral edema may be recognized clinically by the development of systemic hypertension and bradycardia (Cushing reflex), decerebrate rigidity, disconjugate eye movements, and a loss of pupillary reflexes, although these clinical signs are often unreliable.

Intracranial pressure (ICP) monitoring, although controversial, is the only means to detect intracranial hypertension.¹⁷ With the advancement to stage 3 encephalopathy, ICP monitoring by the placement of an epidural, subdural, or parenchymal catheter is recommended. The determination of cerebral oxygen consumption, measured by placing a catheter in the jugular bulb (to calculate the arterial jugular venous oxygen content difference), provides an indirect assessment of cerebral blood flow.¹⁸ An elevated ICP, >25 mm Hg, is a late event in the development of cerebral edema, and

Table 2. Stages of Hepatic Encephalopathy*

Stage	Mental Status	Tremor	EEG
I	Euphoria; occasionally depression; fluctuant mild confusion; slowness of mentation and affect; untidy; slurred speech; disorder in sleep rhythm	Slight	Usually normal
II	Accentuation of stage I; drowsiness; inappropriate behavior; able to maintain sphincter control	Present (easily elicited)	Abnormal; generalized slowing
III	Sleeps most of the time but is arousable; speech is incoherent; confusion is marked	Usually present if patient can cooperate	Always abnormal
IV	Not arousable; may or may not respond to painful stimuli	Usually absent	Always abnormal

*Adapted from Trey and Davidson.¹³

may in turn, cause a reduction in cerebral perfusion pressure (CPP). (CPP = mean arterial pressure – ICP). A sufficient CPP (>60 mm Hg) is crucial to maintain intact neurologic function, and some centers consider OLT contraindicated if the patient has had a CPP less than 40 mm Hg for 2 hours or more.⁷

Nursing and treatment interventions for controlling intracranial hypertension and minimizing cerebral edema include head elevation to 20–30°, minimizing patient suctioning and other noxious stimuli, treating fever and arterial hypertension, avoiding fluid overload, and correcting hypercapnia and hypoxemia. Osmotherapy with mannitol (1 gm/kg intravenously) is often employed, but the use of barbiturate infusions and hypothermia are controversial and there is currently no consensus statement regarding these treatment modalities.¹⁹ Mild hypothermia exerts potential beneficial effects at several levels in the chain of events that lead to brain edema in FHF.²⁰ One recent small study involving 13 patients evaluated mild to moderate hypothermia (32–33°C) as a bridge to OLT in patients with increased ICP resistant to standard medical therapy.²¹ This study, which was designed as a follow-up to the previously reported pilot observations,¹⁹ monitored mean arterial and cerebral perfusion pressures, inotrope requirements, arterial ammonia concentrations, and brain cytokine production. It showed promising results for induced hypothermia being an effective and safe treatment modality in FHF and this would seem to justify a large well-designed multicenter clinical trial. It should be noted that there are potential hazards to hypothermia induction, including development of infections, bleeding complications due to coagulopathy, and cardiac arrhythmias. There may also be challenges encountered with rewarming of patients. There is a distinct paucity of data regarding the optimal target temperature, the total permissible length of treatment, means of achieving and maintaining hypother-

mia, and whether it should be performed prophylactically or therapeutically. Because hypothermic therapy for increased ICP in FHF is by no means standard of care in the United States, well-designed prospective controlled trials should define its exact role as it appears to be a simple, relatively inexpensive approach to control the neurologic repercussions of this condition. The U.S. Acute Liver Failure Study Group plan to evaluate this treatment modality in acetaminophen-induced FHF patients.

Coagulopathy

The liver has a central role in the synthesis of almost all of the coagulation factors and some of the inhibitors of coagulation and fibrinolysis.²² The principal hematologic derangements seen in FHF include platelet dysfunction (with both quantitative and qualitative platelet defects) and reduced circulating levels of fibrinogen and the coagulation factors II, V, VII, IX, and X.²² This produces a prolongation in the prothrombin time, which is widely used as an indicator of the severity of hepatic injury. The levels of the coagulation inhibitors (antithrombin III, protein C, and protein S), although reduced, fail to have a corrective effect on the coagulopathy.²³ Overall, there is enhanced fibrinolysis (manifested by an increase in fibrin degradation products and poor clot formation) and disseminated intravascular coagulation (as measured by elevated levels of thrombin-antithrombin III complex).²⁴ Because the prothrombin time is an important prognostic variable, infusion of fresh frozen plasma is advocated only for control of bleeding or at the time of invasive procedures, e.g., with the insertion of intracranial pressure monitors. Platelet transfusions are, similarly, required for bleeding or at the time of invasive procedures if the count is <50 × 10⁹/L and prophylactically if <20 ×

$10^9/L$.²⁵ Preliminary experience with recombinant activated factor VII, an antihemophilic factor, showed that, in FHF patients, it is effective in transiently correcting laboratory parameters of coagulopathy so as to facilitate placement of ICP transducers.²⁶ Further studies to define the optimal dosing, safety, and efficacy of recombinant activated factor VII in FHF are still required.

Infection

Infection, particularly of the respiratory and urinary tracts, develops in as many as 80% of patients with FHF, and bacteremia is present in 20 to 25% overall.^{27,28} Patients with FHF are at substantial risk of sepsis caused by reticuloendothelial dysfunction and decreased opsonization.²⁹ Staphylococcal species, streptococcal species, and gram-negative rods being the most commonly encountered bacterial pathogens,²⁸ the clinician must maintain a high index of suspicion and obtain surveillance cultures if the patient experiences an unexpected deterioration in clinical status. General management should include infection control with careful attention to hand-washing, line changes, venipuncture sites, and wounds. Several centers now initiate broad-spectrum antimicrobial prophylaxis shortly after presentation (e.g., third-generation cephalosporin plus vancomycin). Selective gut decontamination does not seem to confer an additional advantage over systemic prophylaxis alone.³⁰ Fungal infections, particularly due to *Candida albicans*, occur in up to one-third of FHF patients with risk factors including renal failure and prolonged antibiotic therapy for existing bacterial infections.³¹ Fungal infection is a poor prognostic sign associated with a high mortality and often precludes transplantation.

Cardiorespiratory and Hemodynamic Complications

Cardiovascular, hemodynamic, and respiratory complications are notable clinical sequelae of the FHF patient characterized by systemic vasodilation, low systemic vascular resistance, hypotension, and a compensatory increase in cardiac output. There is also abnormal oxygen transport and utilization, in which, although delivery of oxygen to the tissues is adequate, there is a decrease in tissue oxygen uptake, resulting in tissue hypoxia and lactic acidosis ("tissue oxygen debt").³² Initial management of hypotension is directed toward optimizing volume status; however, with progressive renal failure and pulmonary edema, a Swan-Ganz catheter and full hemodynamic monitoring is required to

guide further management. The mortality in FHF escalates with the presence of noncardiogenic pulmonary edema or "adult respiratory distress syndrome,"³³ in part because it may contraindicate liver transplantation. Positive end expiratory pressure, commonly used to improve oxygenation, may actually compromise cardiac output and oxygen delivery and result in increased ICP and worse hepatic congestion.²⁵ Thus, treatment with increased FiO_2 is most appropriate.

Metabolic Abnormalities

Metabolic derangements in FHF include acute renal failure, electrolyte abnormalities, hypoglycemia, and pancreatitis. Renal failure complicates FHF in 40 to 50% of cases (70% of cases caused by acetaminophen) and denotes a poor prognosis.^{12,34} It is often multifactorial, with causes including prerenal azotemia, acute tubular necrosis, toxic renal effect from an ingested agent, a functional disturbance (hepatorenal syndrome) or a drug-induced toxicity, e.g., antibiotics and contrast agents.³⁵ Because of impaired hepatic urea production, blood urea nitrogen levels do not reflect the severity of renal dysfunction and serum creatinine levels are thus preferred as a more accurate guide for monitoring renal function. Initial management should ensure adequate intravascular volume status, treat complicating infection, and avoid nephrotoxic agents. Although therapeutic trials with low-dose dopamine and furosemide are often instituted, efficacy is not clearly established. When dialytic support is required, continuous renal replacement technique is preferable to standard hemodialysis as the latter may precipitate hypotension resulting in a fall in CPP and exacerbation of cerebral edema.³⁶ Hypoglycemia is a frequently encountered complication seen in up to 45% of FHF patients, as massive liver necrosis results in defective glycogenolysis, gluconeogenesis, and insulin metabolism.³⁷ It may be particularly refractory to intravenous dextrose. Acute pancreatitis, perhaps due to tissue hypoxia, is occasionally seen and in 1 study was found in 44% of patients dying from FHF.³⁸

5. How Are Patients With FHF Selected as Transplantation Candidates and What Mathematical Models Have Been Developed for Prognostication ?

The only therapeutic intervention of proven benefit for patients with FHF is that of emergency OLT. The prognosis of FHF varies greatly with the underlying etiology as well as a number of other factors. Accurately

Table 3. The King's College Criteria for Liver Transplantation*

Acetaminophen	Non-acetaminophen
<ul style="list-style-type: none"> • pH < 7.3 (irrespective of grade of encephalopathy) Or all 3 of the following <ul style="list-style-type: none"> • Grade III-IV encephalopathy • PT > 100 seconds (INR > 6.5) • Serum creatinine >300 $\mu\text{mol/L}$ (3.4 mg/dL) 	<ul style="list-style-type: none"> • PT > 100 seconds (INR > 6.5) (irrespective of grade of encephalopathy) Or any 3 of the following <ul style="list-style-type: none"> • Age <10 or >40 years • Etiology: (non-A, non-B hepatitis, halothane, idiosyncratic drug reaction, Wilson's disease) • Period of jaundice to encephalopathy >7 days • PT > 50 seconds (INR > 3.5) • Serum bilirubin >300 $\mu\text{mol/L}$ (17.5 mg/dL)
*From O'Grady et al. ¹⁰ Abbreviations: INR, international normalized ratio; PT, prothrombin time.	

predicting the outcome in FHF is critical to its effective management as determination of prognosis is required in establishing the need for referral to specialist centers and the indications for transplantation.¹² The risks of emergency transplantation in the context of evolving multisystem organ failure must be balanced against the possibility of survival with continued medical supportive care alone. With a mortality rate in excess of 80% without liver transplantation, it is vital that irreversible FHF be recognized early, in order that an organ may be procured and OLT be performed before complications of the disease contraindicate surgery. Equally pivotal is the realization that with the current organ scarcity, short-term risks of surgery, and long-term consequences of immunosuppression, physicians should be able to recognize reversible disease so as to prevent unnecessary transplantations.

A variety of selection criteria are in use worldwide. As with all diagnostic tests, the best evidence to support the use of particular criteria is from the confirmation of its performance in validation studies. However, the accurate assessment of these selection criteria in such studies is flawed by the methodologic quality of many of the reported series in which bias may be introduced, as studies include small numbers of patients and are usually unblinded and retrospective over periods of a decade or more.³⁹ Despite these limitations, sophisticated multivariate analysis and prognostic modeling have been applied to static and dynamic variables to assess the relative importance and interaction in predicting outcome in FHF.⁷

In 1986, a French group of investigators assessed prognostic factors in a 115-patient cohort with hepatitis B virus-related FHF.⁴ In these "Clichy Criteria," factor V level, patient age, absence of hepatitis B surface antigen, and serum alpha-fetoprotein (AFP) level emerged as independent predictors of survival by mul-

tivariate analysis. Transplantation is recommended in the presence of coma or confusion (grade 3 or 4 encephalopathy) with a factor V level <20% in patients under 30 years of age or <30% if over 30 years of age.⁴⁰ Validation studies for these criteria are scarce, yet they are in use in much of Northern Europe.³⁹ Their more widespread use has been limited by 2 main factors, namely, limited availability of factor V level measurement outside certain centers and the fact that the criteria were derived from a cohort of FHF patients with FHF resulting from a single etiology that may not be generalizable to non-hepatitis B virus-FHF.³⁹

Subsequently in 1989, a landmark article by O'Grady et al.¹⁰ from the King's College Hospital in London provided the most extensive retrospective multivariate analysis of clinical and biochemical variables and their relation to mortality in 588 patients with FHF (managed medically between 1973 and 1985). Importantly, they recognized the role of both etiology and mode of presentation in determining the possibility of recovery with medical supportive therapy alone. In these "King's College Criteria," the following variables were found to have prognostic significance: disease etiology, age of patient, duration of jaundice, bilirubin level, prothrombin time, arterial pH, and serum creatinine. In the analysis, a major distinction was made between patients with acetaminophen toxicity and those with other etiologies (see Table 3). These selection criteria are readily obtainable within a few minutes of the patient's arrival at the hospital and could thus expedite patient transfer to a transplantation center and facilitate early listing.⁴¹ The model has been remarkable in that it has withstood the test of time and has emerged as the standard to which other prognostic schemes are compared. The King's College criteria have been prospectively validated in separate cohorts as other investigators have examined their diagnostic accuracy.^{42,43}

More published data exist to support the use of acetaminophen than the nonacetaminophen criteria. Studies relating to acetaminophen have recently been scrutinized by a meta-analysis that confirmed that the criteria have a clinically acceptable specificity as they were highly predictive of a poor outcome when fulfilled.⁴⁴ Survival with medical management alone in this group is between 10 and 15% in most series.^{12,45} Although relatively effective in predicting death and the need for OLT, the criteria failed to identify patients at low risk of dying.^{9,43} In a retrospective analysis of 177 patients evaluated for FHF at the authors' institution over a 13-year period, the King's College criteria were found to have a low negative predictive value for poor outcome, in that lack of criteria fulfillment did not guarantee survival.¹²

The model for end-stage liver disease (MELD) score, originally derived to estimate short-term survival of patients undergoing transjugular intrahepatic portosystemic shunts,⁴⁶ is used nowadays to prioritize patients with chronic liver disease for OLT. Since February 27, 2002, the United Network for Organ Sharing implemented the MELD score for allocation of grafts to adult patients with cirrhosis awaiting transplantation in the United States as it was well validated in this group of patients.⁴⁷ MELD is a severity score derived from the transformation of 3 biochemical parameters in a logarithmic formula, i.e., total serum bilirubin, prothrombin time and creatinine. Kremers et al.⁴⁸ evaluated the MELD score at listing as a predictor of pretransplant and posttransplant survival in United Network for Organ Sharing Status 1 patients (listed at Status 1 between November 1999 and March 2002) and compared survival among 4 diagnostic groups within the Status 1 designation. The 4 groups were comprised of FHF due to acetaminophen, FHF without acetaminophen toxicity, primary graft nonfunction within 7 days of transplantation, and hepatic artery thrombosis within 7 days of transplantation. They found, using Cox regression methodology, that the FHF-nonacetaminophen group had the poorest survival probability while awaiting OLT. This was negatively correlated with MELD score ($P = 0.0001$), which translated into the best survival benefit associated with OLT. The authors concluded that liver allocation within the Status 1 designation may need to be further stratified by diagnosis and that MELD score may be useful in prioritizing the FHF-nonacetaminophen group. A further study out of Pittsburgh (which is presently only in abstract form) assessed the applicability of MELD in prognosticating patients with FHF using a database spanning the period 1983–1996.⁴⁹ It was found that

the mean MELD score on admission was significantly higher among nonsurvivors compared to survivors and transplanted patients. There was no significant difference between survivors and transplanted patients. The MELD score tended to remain high in patients who are likely to die compared with patients who are likely to recover. MELD was therefore felt to provide a complementary tool additional to other prognostic criteria.

6. What Nonmathematical Predictive Tools Have Been Evaluated for Use in FHF?

Other histologic, radiologic, and serologic prognostic markers have been proposed to improve the selection of transplant candidates. A liver biopsy may help to confirm the suspected etiology of FHF and may determine the degree of hepatocyte necrosis. Two limitations to its use as a prognostic indicator in FHF are, first, a significant risk of bleeding with biopsy and second, the potential for sampling error is considerable (especially if the needle samples an area of total collapse or a regenerating nodule).⁵⁰ Thus, most centers have not been reliant on liver histology as a key outcome predictor in FHF. A small or shrinking liver on radiologic assessment has been proposed by some to be a valuable prognostic marker, although measuring liver volume by CT also has limitations, as moving the patient to the scanner may worsen both the cerebral and hemodynamic instability.^{51,52} Several other parameters have been shown to have prognostic value in certain circumstances. Galactose elimination capacity,⁵³ the arterial ketone body ratio (reflecting the redox potential of hepatic mitochondria),⁵⁴ coagulation factor V and factor VIII : factor V ratio (in acetaminophen toxicity),⁵⁵ and plasma Gc protein concentration (an actin scavenger)⁵⁶ are a few such variables. Recently, the Acute Physiology and Chronic Health Evaluation–2 system and blood lactate level^{57,58} were found to have predictive efficacy similar to the King's College Hospital criteria in patients with acetaminophen toxicity. Similarly, hyperphosphatemia has recently been reported to be an accurate early predictor of poor outcome in severe acetaminophen-induced hepatotoxicity,⁵⁹ presumably reflecting both renal failure and poor hepatic regeneration. These findings were verified in a subsequent study evaluating both acetaminophen and non-acetaminophen etiologies of FHF.⁶⁰ The introduction of both lactate and phosphate measurements into selection criteria should, however, await confirmation of their performance in further appropriately conducted validation studies.³⁹

The prognostic value of serum AFP in patients with

FHF was first suggested almost 30 years ago,⁶¹ and a high or rising AFP, reflecting hepatic regeneration, was deemed a positive prognostic marker.⁶² A recent publication by Schmidt and Dalhoff⁶³ evaluated the prognostic value of serial AFP measurements in patients with severe acetaminophen-induced injury. The authors suggested that using a cutoff serum AFP level of 3.9 $\mu\text{g/L}$ 1 day after the peak alanine aminotransferase level was highly sensitive for identifying those who were likely to survive. In many instances, the increase in AFP preceded the decrease in International Normalized Ratio and thereby provided additional prognostic information. Clearly these observations will have to be further validated before being incorporated into widespread clinical use.

7. What Are the Key Factors that Determine Posttransplant Outcome?

The 2 key factors affecting post-OLT survival are the severity of the pretransplantation illness of the recipient and the nature of the graft used.³⁹ The more unwell a patient is, either in terms of the severity of encephalopathy at the time of surgery or overall multisystem organ failure, the less likely that the transplant will be performed and that the surgery will be successful. In a review of 100 transplants performed for FHF at the King's College Hospital, the severity of multisystem organ failure at the time of OLT was the single best predictor of patient survival.⁶⁴ In terms of etiology, acetaminophen toxicity tends to have a more favorable outcome than do viral hepatitis or drug reactions.⁶⁵ The main causes of death in the posttransplantation setting at the University of Pittsburgh⁶⁶ and other centers^{67,68} were sepsis and multiorgan failure.

In an effort to help improve estimation of patient survival following OLT for FHF and ensure optimal utilization of allografts, a group from Houston, TX, recently devised a risk stratification scoring system (which has been published in abstract form only).⁶⁹ Four risk factors identified in a multivariate analysis were 1) recipient age >50 years old; 2) body mass index >29; 3) history of life support; and 4) serum creatinine >2.0 mg/dL. The presence of all 4 risk factors was found to decrease 5-year post-OLT survival by 50%.

8. What Are the Principles in Managing Critically Ill Patients With FHF?

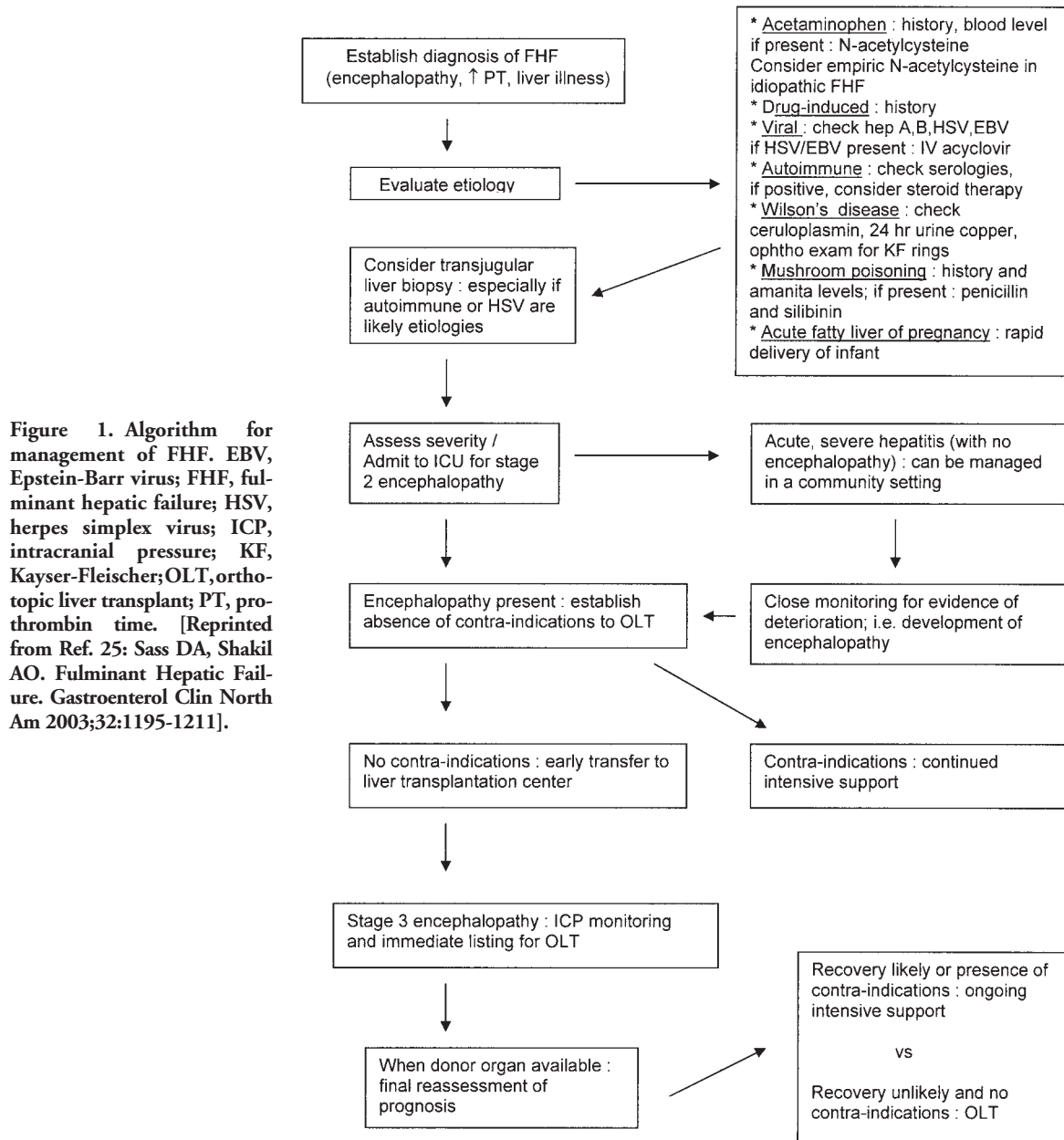
The liver has the unique ability to regenerate after acute, self-limited injury. Because there is no specific medical therapy for FHF, treatment is limited to supportive

measures that anticipate complications, allowing the liver time to regenerate. The management of patients with FHF poses formidable challenges to the clinician due to the rapidity, unpredictability and severity of its complications.²⁵ Very few therapies for FHF have been evaluated in a rigorously controlled fashion; however, in the era of liver transplantation, experience in the management of these critically ill patients has been accrued due to channelized referral to the transplant centers. The overall management strategy plan starts with identification of etiology and an initial assessment of prognosis. Especially critical in the early evaluation of patients with FHF, is the decision regarding the candidacy of the patient for liver transplantation. Early transfer to a transplantation center for all prospective candidates should be accomplished where a dedicated multidisciplinary team of experienced hepatologists, critical care intensivists and transplant surgeons can make the pivotal decisions regarding timing of transplantation and use of potential "bridges to transplantation."⁷⁰

A few etiologies of FHF demand immediate and specific treatment, including acetaminophen overdose (N-acetylcysteine, NAC), *Amanita* mushroom poisoning (penicillin and silibinin),⁷¹ herpes simplex infection (acyclovir), acute fatty liver of pregnancy (rapid delivery of the infant),⁷² and Wilson's disease. Other liver-focused specific therapies for FHF that have been directed at reducing tissue injury, removing accumulated toxins, and promoting hepatocyte regeneration have proven ineffective. These include corticosteroids,⁷³ interferon, insulin and glucagons,⁷⁴ prostaglandin E₁,⁷⁵ charcoal hemoperfusion,⁷⁶ exchange transfusion,⁷⁷ and hyper-immunoglobulin infusion, to name a few.

NAC has also been used for non-acetaminophen-induced FHF. To evaluate the effectiveness of intravenous NAC in this subgroup of patients, Sklar et. al. searched for studies in the MEDLINE (National Library of Medicine) bibliographic database, International Pharmaceutical Abstracts, and the Cochrane Library database.⁷⁸ All of the studies were found to be small and do not provide conclusive evidence that NAC benefits those with non-acetaminophen-induced FHF. Although microvascular regional benefits were seen, clinical outcomes were not studied satisfactorily. The NAC Study, a U.S. multicenter study of the safety and efficacy of NAC in the treatment of acute liver failure not caused by acetaminophen, is an important randomized study that will hopefully provide the necessary outcome (survival) data to answer this important clinical question.

Patients with milder degrees of hepatic injury are



generally well cared for in a community setting in which the focus of management should address maintenance of hydration, euglycemia, and correction of electrolyte imbalances.⁶⁶ Any evidence of early deterioration in clinical status with regard to progression of encephalopathy, worsening coagulopathy, development of infections, and respiratory compromise should expedite transfer to a transplant center for further management. Patients with FHF may deteriorate rapidly and unpredictably and require close monitoring in an intensive care unit setting. Aggressive intensive care serves to

stabilize the patient, allowing for improved morbidity and mortality rates posttransplantation. Figure 1 provides an algorithm for the management of FHF.

9. What Is the Role of Liver Transplantation for FHF?

Liver transplantation, the only proven therapy, has revolutionized the management of FHF.⁷⁹ The refinement in the procedure over the first 20 years following the first human liver transplantation in 1963 prompted the

National Institutes of Health Consensus Development Conference to recommend that OLT was not an experimental procedure, but an effective therapy that deserved broad application.⁸⁰ Although never subjected to a prospective controlled trial, OLT has become the standard of care in most centers. Before the era of liver transplantation, fewer than one-half of the patients with FHF survived. Nowadays, with the continued refinement in surgical techniques, introduction of better immunosuppressive agents, and improved comprehensive care of transplant recipients, OLT for FHF offers an overall survival of about 65%, with some series even quoting a survival of more than 80% (perhaps with more stringent selection criteria).⁸¹ However, the outcome remains worse than those transplanted for chronic liver disease.

All patients with FHF, meeting criteria for OLT, may be listed as United Network for Organ Sharing Status 1 immediately upon arrival to the transplant center. The decision to list someone must balance the likelihood of spontaneous recovery with the risks of surgery and long-term immunosuppression. A delay in placing a patient on the transplantation waiting list increases the probability of a complication developing that may preclude OLT. Contraindications to OLT include: extrahepatic malignancy, uncontrolled extrahepatic sepsis, multisystem organ failure, irreversible brain damage, or unresponsive cerebral edema with a sustained elevation of ICP (>50 mm Hg) and a decrease in CPP (<40 mm Hg).²⁵

Living donor liver transplantation is now an established part of elective transplantation and is being increasingly used in adults due to the scarcity of deceased donor organs.³⁹ A number of cases and case series have been reported in the FHF literature.^{82–85} In FHF, poorer patient and graft survival is seen in patients receiving “small for size grafts” with a graft to recipient weight ratio <0.8%; an optimal value of graft to recipient weight ratio would be closer to 1%.⁸² For this reason, most successful reported cases of living donor liver transplantation in FHF have utilized right lobe grafts,³⁹ although the complications are much more common in those donating a right rather than left lobe.⁸⁶ There are special concerns related to donor evaluation in the setting of FHF. The evaluation must be performed expeditiously because of the severity of illness in the recipient and the rapid clinical evolution of FHF; thus the potential for a rushed evaluation with suboptimal outcomes exists. The potential donor’s decision to donate must therefore occur during a very short interval; usually a few days. Some physicians have expressed concern that the expedited evaluation could

preclude the donor from making a careful reasoned decision about donation⁸⁷ and that there is a potential for coercion. It is thus uncertain whether this transplant technique will become popular in places where rapid availability to deceased donor organs is easily achieved.

10. What Alternative Therapeutic Strategies, Other than Standard OLT, Have Been Evaluated for FHF?

In patients with poor prognostic indicators and without potential for spontaneous recovery, OLT is the preferred therapeutic option. However, because of organ shortage and patient instability, other nontraditional approaches to liver replacement have been attempted and are currently the focus of investigation.²⁵

Auxiliary liver transplantation is a technique in which a partial liver graft is placed either heterotopically or orthotopically while leaving part of the native liver *in situ*. It has been pioneered for patients in whom there is anticipation of recovery of normal liver function and morphology. In theory, it combines the advantages of transplantation with the ability to withdraw immunosuppression when regeneration has been demonstrated in the native liver, occurring in 68% of patients at 3 months.⁸⁸ To date, no clear indications for auxiliary transplantation have been defined. Regeneration appears to occur best in young patients who have a hyperacute presentation and a viral or autoimmune etiology, i.e., the group in whom spontaneous survival is also most likely.^{88,89} If the host liver recovers, the donor liver can be removed or allowed to atrophy.

Total hepatectomy with porto-caval shunting is a temporizing measure that may be employed as a method of stabilizing a critical patient until a donor liver becomes available.⁹⁰ This is a controversial maneuver with successful outcomes reported only anecdotally.

Both mechanical devices and hybrid biologic-mechanical devices may serve as a “bridge to transplantation” when donor shortage makes organ procurement difficult within a useful time frame. A variety of extracorporeal liver-support devices such as hemodialysis, hemofiltration, charcoal hemoperfusion, plasmapheresis, and exchange transfusions have been advocated which essentially serve as toxin filters. Despite promising case reports and small series, no controlled studies have ever shown a long-term survival benefit.^{76,91–92} A “hybrid” system is an extracorporeal device that combines features of both artificial (plastic housing and semipermeable membrane) and biologic (hepatocytes) components in an effort to optimize metabolic and excretory hepatic-support functions.⁷⁰ The 2 hybrid

systems used in investigational studies are the extracorporeal liver assist device and the bioartificial liver. Despite initial promise in phase I and II trials in patients with FHF, the safety and efficacy of the bioartificial liver was recently evaluated in a prospective, randomized, controlled, multicenter trial. The results demonstrated acceptable safety but a distinct lack of efficacy.⁹³ Although theoretically attractive, no device has ever been shown to favorably impact outcomes.

Hepatocyte transplantation represents an alternative biologic approach attracting some interest as a method of augmenting liver function, but as yet no significant controlled clinical outcomes have been reported.⁹⁴

Use of a pig liver xenograft has also been proposed; however, a major problem with this therapeutic modality is that of transspecies rejection.⁹⁵

Conclusion

FHF, although resulting from a primary liver insult, is essentially a multiorgan disease with a myriad of systemic complications. It usually begins as jaundice with a rapid onset of encephalopathy. Early recognition of the disease and an expeditious transfer to a transplantation center is critical as a multidisciplinary approach and intense monitoring is required if a successful outcome is to be achieved. The mortality of patients with advanced FHF is high and the availability of liver transplantation has provided a means to rescue such patients. Survival prediction models, whether mathematic, serologic, or physiologic, have garnered much of the recent attention in the FHF literature. These prognostication tools are being designed to facilitate rapid clinical decision-making, which would allow transplant surgeons and hepatologists to make best use of the scarcely available donor livers. "Bridges" to transplantation (in the form of artificial liver support devices), hepatocyte transplantation, and xenografting are in dire need of controlled, multicenter trials before any conclusions can be made regarding their clinical utility in FHF. A better understanding of mechanisms responsible for liver cell death and multiorgan failure, and the development of strategies to enhance liver regeneration may, in the future, allow a more targeted approach to therapy.²⁵

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