

Acute hepatic failure

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R WILLIAMS, J WENDON. *Acute hepatic failure*. *Can J Gastroenterol* 1993; 7(7):535-541. The etiology of acute liver failure in patients without pre-existing liver disease varies depending on geographical location. In the United Kingdom, acetaminophen toxicity remains the most common cause while worldwide, viral hepatitis B is the most prevalent cause. The management of patients with acute liver failure requires the application of good basic intensive care – recently, the advent of liver transplantation has widened the therapeutic options available. Careful attention to cardiovascular monitoring and manipulation of hemodynamic variables is required and mechanical ventilation is needed in patients who progress to grade III/IV encephalopathy. Renal replacement therapy is best achieved using a continuous hemodiafiltration system rather than hemodialysis in patients who present with acute liver failure. The development of cerebral edema is a common and frequently fatal complication, and requires meticulous care involving intracranial pressure monitoring. Patients are functionally immunosuppressed and require frequent bacteriological surveillance, the incidence of both bacterial and fungal sepsis being very high. In some patients, such as those with lymphoma presenting as acute liver failure, specific chemotherapeutic regimens may be available. The advent of liver transplantation has offered a great advance in the management of acute liver failure but requires stringent patient selection such that those patients with a good chance of spontaneous recovery do not undergo transplantation, while those with a poor prognosis can be considered.

Key Words: *Fulminant hepatic failure, Intensive care, Transplantation*

Insuffisance hépatique aiguë

RÉSUMÉ: L'étiologie de l'insuffisance hépatique aiguë chez les patients qui n'avaient eu aucune maladie hépatique auparavant, varie selon les lieux géographiques. Au Royaume-Uni, la toxicité liée à l'acétaminophène en demeure la plus fréquente cause, alors qu'ailleurs dans le monde, on l'attribue surtout au virus de l'hépatite B. Le traitement des patients en insuffisance hépatique aiguë exige de très bons soins intensifs, et récemment, la mise au point des transplantations hépatiques a diversifié les options thérapeutiques offertes. Une attention particulière doit être accordée à la surveillance cardiovasculaire et à la manipulation des

FULMINANT HEPATIC FAILURE (FHF) is the term used to describe patients with a very rapid progression of symptoms and signs of liver failure, with development of encephalopathy within eight weeks of symptom onset (1) in patients without preceding liver disease. A similar group of patients are those with late onset hepatic failure (LOHF), defined as the onset of encephalopathy within eight weeks to six months of the development of symptoms – again, in patients without preceding liver disease (2). The stratification of patients with respect to the speed of onset of encephalopathy is of great importance since this, in association with etiology, carries prognostic implications and is of special importance when transplantation is being considered as a therapeutic option. A number of alternative classifications based largely on time interval between onset of symptoms/jaundice and development of encephalopathy, and including such terms as 'subfulminant hepatic failure' have been described (3). Analysis of our data showed those with the most rapidly progressive disease who developed encephalopathy within seven days of the onset of jaundice had the best prognosis. On the basis of this analysis, we have proposed a new division and classification of hyperacute, acute and subacute hepatic failure to encompass the whole range of liver failure (Table 1).

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variables hémodynamiques, et une ventilation mécanique est souvent nécessaire chez les patients qui évoluent vers une encéphalopathie de classe III/IV. Le traitement substitutif rénal s'effectue mieux au moyen d'un système d'hémo-filtration continue qu'au moyen de l'hémodialyse chez les patients en insuffisance hépatique aiguë. L'installation d'œdème cérébral est une complication fréquente et souvent fatale pour laquelle il faut surveiller de près la pression intracrânienne. Les patients se trouvent fonctionnellement immunosupprimés et nécessitent aussi une surveillance bactériologique fréquente puisque les infections, tant fongiques que bactériennes sont fréquentes. Chez certains sujets atteints de lymphomes avec insuffisance hépatique aiguë, des schémas chimiothérapeutiques sont offerts. La mise au point de la transplantation hépatique a permis au traitement de l'insuffisance hépatique de faire de grands pas, mais requiert une sélection judicieuse des cas; en effet, les patients susceptibles de se remettre spontanément ne subiront pas la transplantation, qui est davantage indiquée dans les cas où le pronostic est sombre.

TABLE 1
Summary of rationale for proposed new terminology

Parameter	Hyperacute (0 to 7 days)	Acute (7 to 28 days)	Subacute (29 to 84 days)
Survival	Reasonable	Poor	Poor
Cerebral edema	High	High	Low

TABLE 2
Etiology of fulminant hepatic failure progressing to grade III and IV hepatic encephalopathy. Institute of Liver Studies, Kings College Hospital: 1973-93

Etiology	Number (%)
Acetaminophen	765 (60.9)
Viral hepatitis	329 (26.2)
Hepatitis A	60 (4.8)
Hepatitis B	94 (7.5)
Non-A, non-B	201 (16.0)
Others	6 (0.5)
Halothane	45 (3.6)
Drug reactions	32 (2.5)
Miscellaneous	86 (6.8)
Total	1257 (100)

ETIOLOGY

The etiology of FHF in the United Kingdom is most commonly acetaminophen overdose, taken with a suicidal or parasuicidal intent. Toxicity has, however, been reported following lower occasional (therapeutic) doses in patients concurrently taking enzyme-inducing drugs and in patients who are chronic consumers of alcohol (4). Halothane is seen much less frequently than previously among the drugs responsible for idiosyncratic drug reactions leading to FHF. Other agents include isoniazid,

monoamine oxidase inhibitors, gold, sodium valproate, cotrimoxazole, sulfonamides, disulphuram, ketoconazole, phenytoin and, most importantly, a number of the nonsteroidal anti-inflammatories.

Viral hepatitis A is an uncommon cause of FHF in the United Kingdom, although the increased incidence reported from some countries may relate to exposure to the virus later in life. Diagnosis depends on the finding of immunoglobulin (Ig) M antibody in the serum. FHF may occur following exposure to hepatitis B virus (HBV), and there is recent evidence showing that a mutant strain is associated particularly with a fulminant course (5). A fulminant course may also be seen in HBV surface antigen carriers at the time of a superinfection with hepatitis D virus (6). In HBV infection, viral replication has usually ceased by the time of presentation with FHF (2); since surface antigen is cleared more rapidly than in ordinary acute hepatitis, the presence of the IgM antibody to core antigen is required for diagnosis. Fulminant hepatitis may also present in patients with reactivation of HBV infection following immunosuppressive therapy (7). Non-A, non-B hepatitis has been implicated as the predomi-

nant cause of FHF and of late-onset FHF (8). Within this group, hepatitis C infection accounts for a very small number of cases only in the United Kingdom, USA and European series; in Japan, it accounts for the major percentage of non-A, non-B FHF and LOHF (9,10). Recent studies from the authors' unit have shown that hepatitis E virus accounts for about 10% of the sporadic cases of non-A, non-B hepatitis seen in patients in the United Kingdom and Europe (11). This virus is associated particularly with FHF in pregnancy, and this group carries a very high mortality (12). Other viral agents that can result in acute hepatitis are cytomegalovirus, Epstein-Barr, herpes simplex, coxsackie B and echovirus. Rare causes of FHF that should be considered are acute fatty liver of pregnancy, lymphoma, ischemic hepatitis from shock and other low output cardiac states, and acute Budd-Chiari syndrome. In a patient with all the signs of acute liver failure, with significant hemolysis in addition, fulminant Wilson's disease should always be considered. The Institute of Liver Studies' experience is summarized in Table 2.

Outcome from FHF has improved over the years with a number of important advances in intensive medical care, and the development of transplantation as a therapeutic option in patients with FHF has resulted in further increases in survival; this is relevant especially to patients with presumed non-A, non-B hepatitis. Improvements in overall survival for the authors' unit are given in Figure 1.

INTENSIVE LIVER SUPPORT

The management of patients with FHF involves critical attention to detail in assessment, aiming to optimize remaining function of the affected organs and prevent secondary damage. Although the classification of complications is separated into a variety of systems dysfunction, it is imperative to realize the interdependence of such systems with respect to critical care management.

CARDIOVASCULAR

The hemodynamic disturbances seen in patients with FHF are similar to those of patients with sepsis, that is, an elevated cardiac output and lowered systemic vascular resistance index.

Relative hypovolemia secondary to vasodilation is inevitable, and the use of a pulmonary artery flotation catheter is required to optimize fluid replacement. Colloid loading should be achieved with either 4.5% human albumin solutions or blood and crystalloid should be given in the form of dextrose only. Cardiac arrhythmias are rare and usually due to a definable precipitating event – hypo- or hyperkalemia, acidosis, hypoxia or cardiac irritation due to insertion of lines.

Work by Bihari and Gimson (13,14), who identified the pathological supply dependency for oxygen in patients with FHF, and significant differences in hemodynamics and oxygen transport variables can be seen between survivors and nonsurvivors who have lower systemic vascular resistance indices, oxygen consumption and oxygen extraction ratios, and higher blood lactates than surviving patients (13). The mixed venous lactate correlated inversely with systemic vascular resistance index, mean arterial pressure and oxygen extraction ratio, suggesting that in patients with FHF there is a disturbance of the microcirculation resulting in a tissue oxygen debt. The use of prostacyclin (a microcirculatory vasodilator) in such patients results in an increase in oxygen uptake, with the possibility of lessening or reversing the covert tissue oxygen debt (14). The development of hypotension in the face of adequate intravascular filling pressures is associated with a poor prognosis in patients with both FHF and chronic liver disease. Agents such as dobutamine are not effective in increasing mean arterial pressure. The most effective agents are either adrenaline or noradrenaline, commencing at a dosage of usually 0.1 µg/kg/min. Use of these agents may be detrimental with respect to oxygen consumption and extraction ratio (with the potential for worsening any existing tissue oxygen debt); the addition of vasodilators, such as pro-

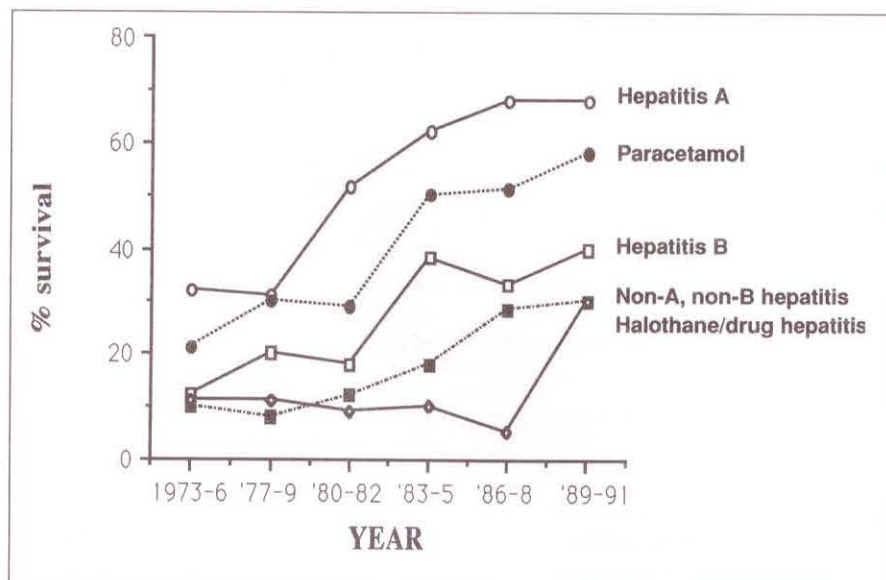


Figure 1) Percentage survival of patients with grade III and IV encephalopathy, Institute of Liver studies, Kings College Hospital, London, United Kingdom

stacyclin, may be advantageous, resulting in an apparent improvement in microcirculatory flow without impairing perfusion pressure (15).

The etiology of 'pathological supply dependency' for oxygen in patients with FHF and other forms of critical illness remains unclear (16). In sepsis and other inflammatory disorders, increased levels of inflammatory mediators are present, leading to changes in vascular tone (with the potential for the development of functional shunting) and increases in capillary permeability (leading to interstitial edema). Microemboli, as a consequence of cellular aggregates and fibrin, can also cause alterations in flow. In this situation of maldistribution of flow and increased diffusion distance from capillary to cell, increased oxygen delivery will be required to maintain oxygen uptake to cells at the same level as prior to any insult. In FHF there is platelet activation, fibrinolysis, generation of excess thromboxane A₂ and deposition of fibrin in the microcirculation, resulting in microemboli; this may be related to the underlying endotoxemia or to the release of thromboplastic material from the damaged liver. The normal liver, with its splanchnic circulation and extensively anastomosing sinusoidal microvasculature, allows ample opportunity for the clearance of toxins prior to

blood re-entering the systemic circulation. In the patient with FHF, marked impairment of Kupffer cell function occurs and clearance of endotoxin will be markedly impaired, allowing systemic endotoxemia and bacteremia. Endotoxemia results in activation of macrophages, with release of tumour necrosis factor (TNF) and interleukins, whose circulating half-life will also be increased in the face of hepatic dysfunction. The importance of endotoxin and cytokines in the development of multiple organ failure has been demonstrated by several elegant animal experiments. Infusion of endotoxin or TNF into experimental animals leads to a state of hypotension, acidosis and multiple organ failure (17), while pretreatment with TNF antibodies offers protection from a septicemic insult (18). Assessment of such treatments in the clinical setting is awaited. Recent work from this unit (unpublished data) has demonstrated elevated levels of cytokines in FHF. Levels of interleukin (IL)-6 (a marker of endothelial activation) were significantly higher in nonsurvivors than in survivors, while no differences were seen between levels of TNF and endotoxin. High levels of IL-6 were seen in association with hypotension and cerebral edema. Activation of cytokines in patients with FHF may result in high levels of inducible

endothelial-derived relaxant factor (EDRF), an agent that may result in disturbances in microcirculatory bloodflow and cytotoxic damage. The roles of inducible and constitutive EDRF in control of microcirculatory bloodflow, both in healthy and diseased states, remain to be elucidated, and much research is ongoing in this field.

USE OF N-ACETYLCYSTEINE

N-acetylcysteine will prevent acetaminophen-induced hepatotoxicity in most cases if given within 8 h of the overdose – but it is less efficacious if given after 8 h and fails to avert the development of severe hepatotoxicity if given more than 15 h after the overdose (19). It has always been assumed that once hepatic necrosis had developed, administration of N-acetylcysteine would confer no further benefit. However, recent work from the authors' unit has shown that patients who receive late N-acetylcysteine have a better prognosis than those who do not, with a lower incidence of renal failure and less progression to deeper levels of coma despite similar prolongation of prothrombin times (20). A prospective controlled trial has confirmed the beneficial role of N-acetylcysteine even when there is evidence of encephalopathy and coagulopathy; in treated patients there was less hypotension and less cerebral edema (21). Recent work has demonstrated that infusion of N-acetylcysteine results in an increase in cardiac output, oxygen delivery and oxygen consumption in patients with FHF (22), accounting for the reduced frequency of development of other organ failure. Several potential actions of N-acetylcysteine may be relevant here; it is a potent antioxidant and, as such, may stabilize the effects of EDRF and prevent endothelial damage by free radicals. In addition, it is possible that EDRF is important in maintaining tissue nutrient bloodflow in critically ill patients (but its full activity is not sustained because tissue sulphhydryl groups become depleted). N-acetylcysteine, by repleting tissue sulphhydryl groups either directly or by its action of increasing cysteine levels (23), could

restore full EDRF activity by a mechanism similar to its reversal of tolerance to nitrates (24).

CEREBRAL EDEMA AND ENCEPHALOPATHY

Once grade 3 to 4 encephalopathy develops, the patient is at high risk of developing cerebral edema and the overall mortality is high. In acetaminophen overdose, encephalopathy normally develops over the course of three to four days following drug ingestion and progresses rapidly through the different stages over a period of 24 to 48 h, while in viral hepatitis, the rapidity and rate of development is highly variable. The pathogenic mechanisms resulting in hepatic encephalopathy and brain edema in patients with FHF remain incompletely understood. Possible etiological mechanisms include the presence of benzodiazepine agonists, altered gamma-aminobutyric acid status, increased aromatic amines, ammonia and mercaptans. In conjunction with workers at National Institutes of Health, the authors recently demonstrated the presence of raised brain concentrations of 1,4-benzodiazepines in patients with FHF (25).

Cerebral edema develops in 80% of patients with FHF who go on to develop grade 4 encephalopathy, regardless of etiology, and is a major cause of death (26). It results from a combination of both vasogenic (extravasation of protein and extracellular edema in the presence of a damaged blood-brain barrier) and cytotoxic (intracellular edema) mechanisms when intracranial pressure (ICP) rises as a consequence of brain edema. The clinical signs are those of systemic hypertension: decerebrate posturing, abnormal pupillary reflexes and, ultimately, impairment of brain stem reflexes. Patients with FHF should be nursed at an angle of 20°C to maximize cerebral perfusion pressure (CPP) (27) and subjected to the minimum of tactile stimuli. Thus, mouth care and endotracheal suction should be minimized. New techniques for ICP monitoring are much safer, and the authors now use a fiberoptic system (Camino, California) inserted at the bedside. To allow optimal manage-

ment, an extradural catheter should be inserted in all patients with FHF ventilated in grade 4 encephalopathy to allow direct measurement of ICP and rapid treatment of rises in ICP before the onset of pupillary abnormalities. CPP should be maintained at greater than 50 mmHg. Work recently undertaken at the authors' unit have also confirmed that cerebral bloodflow (CBF) and cerebral metabolic rate (CMR) for oxygen is low in patients with FHF, and hyperventilation results in further falls in CBF and CMRO₂. First line management to treat rises in ICP is mannitol infusion – 0.5 gm/kg as a bolus over 10 mins. Plasma osmolarity should be checked and the patient can be redosed until a plasma osmolarity of 320 mOsm is reached. In patients who are not diuresing or those with incipient renal failure, ultrafiltration or arteriovenous hemodiafiltration should be commenced to allow for the removal of two to three times the volume of mannitol infused over the next 30 mins. Infusion of mannitol to patients with FHF results in an increase in both CBF and CMRO₂; infusion of N-acetylcysteine results in similar findings, and this may be related to the observed decrease in incidence of cerebral edema noted in the prospective trial (21). Recent evidence from this unit also suggests that thiopentone may be useful in patients who are resistant to therapy with mannitol (28). The prophylactic use of dexamethasone is not of benefit (29).

RESPIRATORY

As the level of encephalopathy deepens, artificial ventilation is needed both to protect the airway and to treat cerebral edema adequately. It is important that patients with FHF who are at risk of cerebral edema receive paralyzing agents in addition to sedative agents, to prevent coughing on the endotracheal tube, which can result in surges of raised ICP.

The arterial hypoxemia that frequently is seen in patients with both chronic liver disease and FHF is multifactorial. Aspiration of gastric contents, bacterial infection, intrapulmonary hemorrhage, atelectasis, V/Q mismatch and, more rarely, the devel-

opment of adult respiratory distress syndrome are contributory factors.

COAGULOPATHY

Prothrombin time is the most widely used indicator of the degree of liver damage, although factor V has the shortest half-life and is theoretically the more sensitive yardstick for assessing synthesis of coagulation factors. Recent work from the authors' unit has suggested that factor V and factor VIII:V ratio are useful in predicting outcome from FHF (30). In a study of 115 French patients with fulminant hepatitis B, factor V levels were lower in the 89 patients who died ($17 \pm 12\%$) than in the 26 survivors ($32 \pm 12\%$, $P < 0.001$), and multivariate analysis confirmed it to be the most powerful predictor of outcome (31). Circulating levels of antithrombin III are also reduced, which shortens the half-life of administered heparin. In addition to decreased synthesis of clotting factors, there is an increase in peripheral consumption and, in most patients, a degree of disseminated intravascular coagulation is present (32). Both quantitative and qualitative defects in platelet function have been described: thrombocytopenia, increased adhesiveness and impaired aggregation. Risk of bleeding appears to correlate not so much with prothrombin time, but with thrombocytopenia and the presence of overt disseminated intravascular coagulation. The prophylactic use of fresh frozen plasma in the absence of bleeding is not associated with a reduction in either morbidity or mortality and, hence, is not indicated (33).

Gastrointestinal hemorrhage normally is related to the development of gastric erosions, although work by Macdougall et al (34) has shown this to be much decreased since the use of prophylactic H_2 antagonists and agents such as sucralfate.

RENAL FAILURE

Renal failure (urine output of less than 300 mL per 24 h and serum creatinine of greater than 300 $\mu\text{mol/L}$) in the presence of adequate intravascular filling pressures occurs in about 70% of patients with acetaminophen overdose

TABLE 3

Criteria used at King's College Hospital for selection of patients with fulminant hepatic failure for liver transplantation

Acetaminophen-induced	Nonacetaminophen-induced
pH <7.30 (irrespective of grade of encephalopathy)	Prothrombin time >100 s (irrespective of grade of encephalopathy)
Prothrombin time >100 s and serum creatinine >300 $\mu\text{mol/L}$ in patients with grade III or IV encephalopathy	Any three of the following variables (irrespective of grade of encephalopathy): Age <10 or >40 years; etiology – non-A, non-B hepatitis, halothane hepatitis; idiosyncratic drug reactions
	Duration of jaundice before onset of encephalopathy >7 days
	Prothrombin time >50 s
	Serum bilirubin >300 $\mu\text{mol/L}$

and in about 30% of other cases (32). Renal replacement therapy should be instituted in patients with acidosis, hyperkalemia, fluid overload or creatinine greater than 400 $\mu\text{mol/L}$. Intermittent machine-driven hemodialysis should be avoided because hypotension is a frequent complication and this, in association with the rises in ICP that can be seen with machine-driven replacement therapy (27), can result in significant falls in cerebral perfusion pressure in patients with FHF. Anticoagulation normally is achieved with heparin, but in patients with a severe coagulopathy and disseminated intravascular coagulation, prostacyclin and low dose heparin may be preferable. In addition, the use of antithrombin II reduces heparin requirements (35).

Hypoglycemia is a consequence of increasing circulating insulin, impaired gluconeogenesis and an inability to mobilize glycogen stores. Blood glucose should be monitored hourly and 50 mL of 50% dextrose should be administered if blood glucose falls below 3.5 mmol/L. Frequently, normoglycemia is best achieved by use of a continuous infusion of either 10 or 20% glucose. Hypophosphatemia is a common occurrence in patients with liver failure who are passing urine, and should be treated with appropriate intravenous replacement.

INFECTION

Infection is a common occurrence in patients with FHF relating to compromised immune function, impaired neutrophil and Kupffer cell function, and a

deficiency of opsonins. In a series from the authors' unit, bacterial infection was identified in 80% of patients (36) and may result in surges of endotoxin and related cytokines into the systemic circulation. The infecting organisms were Gram-positive in 54% of cases, and over 50% of these were *Staphylococcus aureus*. Fungal infection, predominantly with candida species, is also a frequent occurrence in patients with FHF (37). Endotoxin activates the complement system by the alternate pathway and some of the products thus generated may have a role in causing the reported increased vascular permeability seen in endotoxemia. Impairment of the Kupffer cell function limits clearance of endotoxin and other toxins absorbed from the gut and may allow passage of bacteria translocated from the bowels into the systemic circulation.

The use of prophylactic antimicrobial decontamination of the nasopharynx and gut at the onset of liver failure might be effective in reducing the incidence of both bacterial and fungal infection. A recent controlled trial of selective antimicrobial regimen has demonstrated a decrease in incidence of infection in treated patients (38).

TRANSPLANTATION

Etiology, time from jaundice to encephalopathy, age, serum bilirubin and prothrombin time are important predictors of outcome in patients with nonacetaminophen-induced FHF, while in acetaminophen-induced FHF, pH, prothrombin time, level of

encephalopathy and creatinine are important predictors of outcome. On the basis of these prognostic features, a model for the selection of patients with FHF and LOHF for transplantation has been developed in the authors' unit (3) (Table 3). In patients with acetaminophen-induced FHF, indicators of a poor prognosis – and, hence, consideration for transplantation – are pH <7.3 or the presence of a prothrombin time >100 s, serum creatinine >300 µmol/L and coma grade at least IV. In patients with nonacetaminophen-induced FHF, the presence of any three of the following

would lead to a patient being listed for transplantation: etiology of non-A, non-B hepatitis or drug-induced FHF; age <10 or >40 years; serum bilirubin >300 µmol/L; time from onset of jaundice to encephalopathy more seven days; or a prothrombin time of >50 s.

Regardless of the decision to transplant, aggressive intensive care management is pivotal in the care of patients with liver failure, acute and chronic, and its sequelae. Patients who may be suitable for transplantation or the specialist care that liver units can provide should be considered for trans-

fer early, rather than late, in the course of their disease, before the development of hemodynamic instability and cerebral edema. In patients in whom transplantation is appropriate, support is needed to maintain other organ function and, thus, suitability for transplantation while awaiting a suitable donor. In patients in whom transplantation is not appropriate, optimal support of failing organs is required to promote as beneficial an environment as possible to optimize the potential for liver regeneration and to overcome sepsis.

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