Acute Liver Failure - Current Management Strategies

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DEFINITION

ALF has been defined by three criteria: (1) rapid development of hepatocellular dysfunction (e.g., jaundice, coagulopathy), (2) encephalopathy, and (3) absence of a prior history of liver disease. Thus, ALF is a clinical syndrome that represents a final common pathway for a wide variety of diseases that rapidly produce severe liver injury.

The term "fulminant hepatic failure" was first introduced more than 30 years ago by Trey et al[1] to describe the onset of altered mental status (hepatic encephalopathy) within 8 weeks of initial symptoms in an otherwise healthy individual with no previous history of liver disease. The time course of the illness has etiologic, biologic, and prognostic significance, and the relationship between the time course of symptoms and the nature of the disease has led to the proposal for more restrictive definitions of FHF. Accordingly, various modifications to the original definition have been advocated by a number of investigators over the past two decades. Bernuau et al[2] 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 between 2 weeks and 3 months after the onset of jaundice. In contrast, Gimson et al[3] used the term "late-onset hepatic failure" to describe patients in whom hepatic encephalopathy occurred between 8 and 24 weeks after the onset of symptoms. O'Grady et al[4] proposed an umbrella term of "acute liver failure." Based on a retrospective analysis of 539 patients, they suggested a further subclassification comprising three distinct syndromes depending on the jaundice-to-encephalopathy time interval. Hyperacute liver failure denotes onset within 1 week, acute liver failure between 8 and 28 days, and subacute liver failure between 29 days to 12 weeks. This classification reflected differences in survival rate for these groups, the best prognosis paradoxically being in the hyperacute group. No universally accepted nomenclature has been adopted. For practical purposes, the definitions proposed by Bernuau et al and O'Grady et al, based on the time onset of jaundice, are easier to use because the presence of jaundice is usually more readily remembered or recognized by patients or their families than the onset of less specific symptoms, such as malaise and nausea.

CAUSES

The most common causes of ALF are drugs (notably acetaminophen), and hepatotropic viruses.

Causes of ALF in Eastern countries, particularly in developing countries, are predominantly due to the various hepatitis viruses.[5-11] All the published reports from the Indian subcontinent have identified hepatitis viruses as the etiological agent in 95-100% of patients with ALF (Table 1).[12] Other causes including paracetamol overdose, other drug-induced liver diseases, metabolic liver diseases like Wilson's disease, acute fatty liver of pregnancy, and toxicities such as Amanita poisoning, are extremely infrequent in Eastern countries.

In sharp contrast, the etiology of ALF in Western countries is heterogenous [Table2].[12] Hepatitis viruses cause ALF in 4-36% of the cases in various Western reports. In the UK, paracetamol overdose was the etiology of ALF in 60-75% of the ALF patients, whereas in the US, France and Denmark, paracetamol was the reported etiology of ALF in 20%, 2% and 19% cases, respectively.[4,13,14] In the latter countries NSAID-induced ALF is 12-17% of the cases.

Table 1: Etiology of acute hepatic failure—India[12]

Centers (Year)	Total no.	Hepatitis viruses	Drugs	Others
Delhi (2000)[Acharya][6]	458	95%	4.6%	0.4%
Chandigarh (1998)[Dhiman][7]	204	91%	7.4%	1.5%
Kashmir (1997)[Khuroo][11]	119	99%	1%	NR
Indore (1996)[Jaiswal][9]	95	100%	0%	NR

Table 2: Etiology of acute hepatic failure—West[12]

Centers (Years)	Total no.	Hepatitis viruses	Drugs	Others
KCH, UK (1990)[13]	943	36%	61%	3%
UK (1995)[14]	342	4%	75%	20%
USA (1999)[14]	295	33%	32%	45%
France (1990)[14]	502	36%	19%	45%
Denmark (1990)[14]	160	36%	36%	19%

Table 3 : Pathogenesis and Medical Management of the Major Complications of ALF

Major Complications	Pathogenesis	Management
Hypoglycemia	Diminished glucose synthesis	Blood glucose monitoring Intravenous glucose administration
Encephalopathy	Cerebral edema	CT scan (if advanced encephalopathy) ICP monitoring (if patient is in coma) Careful positioning of patient Consider osmotherapy (mannitol) or barbiturates
	Other common reversible factors (e.g., hypoglycemia, hypoxemia)	Standard therapy; avoid benzodiazepines and other sedative medications
Sepsis, pneumonia, other organ system infections	Bacterial or fungal infection	Aseptic medical/nursing care Surveillance cultures Antimicrobial agents
Hemorrhage (e.g., gastrointestinal, intracerebral)	Stress ulceration	H2 receptor antagonists, proton pump inhibitors, nasogastric aspiration
	Coagulopathy	Vitamin K Platelet or fresh-frozen plasma infusions
Hypotension	Hypovolemia	Hemodynamic monitoring of central pressures Volume repletion with blood or colloid
	Decreased vascular resistance	α-Adrenergic agents
Respiratory failure	ARDS	Hemodynamic monitoring of central pressures Mechanical ventilation
Renal failure	Hypovolemia	Hemodynamic monitoring of central pressures Volume repletion with blood or colloid
	Hepatorenal syndrome or acute tubular necrosis	Avoid nephrotoxic agents (e.g., aminoglycosides, aspirin, contrast dye) Hemofiltration/dialysis

CLINICAL PRESENTATION

The clinical features of ALF may result directly from loss of critical hepatocellular functions and from effects on distant organs (Table 3).

Hepatocellular Dysfunction

Hepatocellular injury or loss leads to impaired elimination of bilirubin; depressed synthesis of coagulation factors I, II, V, VII, IX, and X; diminished glucose synthesis; and decreased lactate uptake or increased generation of intracellular lactate as a result of anaerobic glycolysis. These derangements manifest clinically as jaundice, coagulopathy, hypoglycemia, and metabolic acidosis, respectively. Coagulopathy increases the risk of gastrointestinal and intracranial hemorrhage, hypoglycemia can contribute to brain injury, and acidosis can produce cardiovascular dysfunction.

Hepatic Encephalopathy and Cerebral Edema

Encephalopathy is a defining criterion for ALF. The severity of encephalopathy can range from subtle changes in affect, insomnia, and difficulties with concentration (stage 1); to drowsiness, disorientation, and confusion (stage 2); to marked somnolence and incoherence (stage 3); to frank coma (stage 4). The pathophysiologic mechanisms underlying ALF-associated encephalopathy are multifactorial. Many features of ALF, including hypoglycemia, sepsis, hypoxemia, occult seizures, and cerebral edema, can contribute to neurologic abnormalities. Neurologic conditions account for approximately 25% of patients with ALF who are excluded from liver transplantation and for more than 20% of postoperative deaths after liver transplantation.[15]

Continuous monitoring of cerebral activity by electroencephalogram (EEG) identifies subclinical seizures in almost 33% of ALF patients with at least stage 3 encephalopathy who are mechanically ventilated and paralyzed.[16] Cerebral edema is a common neurologic accompaniment of FHF and has been reported in 80% of cases that progress to stage 4 encephalopathy.[17] Progressive cerebral edema will produce intracranial hypertension, which results in cerebral hypoperfusion and irreversible neurologic damage. The pathogenesis of cerebral edema in ALF is poorly understood. It has been proposed to result from the actions of gut-derived neurotoxins that escape hepatic clearance and are released into the systemic circulation.[18] Two principal mechanisms contribute to the development of cerebral edema in this setting: brain cell swelling (cytotoxic edema) and disruption of the blood-brain barrier (vasogenic edema). In the cerebral tissue of patients who die of ALF, there is swelling in endothelial and astroglial cells, a phenomenon indicative of cytotoxic edema, as well as vacuolization in the basement membranes of capillaries, consistent with disruption of the blood-brain barrier and suggestive of vasogenic edema. Progressive cerebral edema can impair cerebral perfusion, which may lead to irreversible neurologic damage or even result in uncal herniation and death.

Infection

Infections develop in as many as 80% of patients with ALF, and bacteremia is present in 20% to 25%.[19,20] Uncontrolled infection accounts for approximately 25% of patients with ALF who are excluded from liver transplantation and approximately 40% of postoperative deaths.[15] Factors leading to increased risk of infection in FHF include: Gut-derived microorganisms entering the systemic circulation from portal venous blood as a result

of damage to hepatic macrophages (Kupffer cells), impaired neutrophil function resulting from reduced hepatocellular synthesis of acute-phase reactants, and various invasive procedures (e.g., intravascular and urethral catheterization, endotracheal intubation). The major sites of infection are the respiratory and urinary tracts.[19] The most common bacteria isolated are staphylococcal and streptococcal species and Gram-negative rods.

Fungal infections develop in up to one-third of patients with ALF,[21] the majority of these are caused by *Candida albicans* and aspergillosis. Aspergillosis may account for up to one-half of fatal infections in the period immediately following liver transplantation for ALF.[22] Risk factors for fungal infections are renal failure and prolonged antibiotic therapy for bacterial infections. Characteristically, fungal infection is associated with fever or leukocytosis refractory to broad-spectrum antibiotics.[21]

Gastrointestinal Bleeding

Patients with ALF have an increased risk of hemorrhage because of deficiencies in coagulation factors, thrombocytopenia and gastrointestinal stress ulceration.

Multiple Organ Failure Syndrome

A potential consequence of ALF is the syndrome of multiple organ failure. This syndrome manifests clinically as peripheral vasodilation with hypotension, pulmonary edema, acute tubular necrosis, and disseminated intravascular coagulation. Liver failure may trigger this syndrome by two mechanisms. First, polymerization of actin (released from dying hepatocytes) within the capillary lumen and platelet activation may produce endothelial injury.[23] Second, impaired hepatic clearance may lead to the accumulation of vasoactive substances in the systemic circulation.[24] Multiple organ failure is a significant contributor to patient mortality and a major contraindication to liver transplantation.

Hypotension is observed frequently in patients with ALF and can result from decreases in vascular resistance, which often accompany ALF, or intravascular volume depletion related to extravascular third spacing or frank blood loss.

Respiratory failure commonly is associated with ALF. In one series, 37% of patients with ALF had pulmonary edema.[25,26] Furthermore, ARDS is associated with intracranial hypertension, the requirement for vasopressive agents, and, most important, a higher rate of mortality.

Renal failure is seen in more than one-third of patients in ALF.[24] Causes include: hepatorenal syndrome, intravascular volume depletion, and acute renal tubular necrosis.

DIFFERENTIAL DIAGNOSIS

The diagnosis of ALF is made clinically on the basis of the physical examination (jaundice, altered mental status) and laboratory findings (hyperbilirubinemia, prolonged prothrombin time) that are consistent with hepatic dysfunction, in the absence of a history of liver disease. Infrequently, ALF may be confused with other clinical entities that manifest as jaundice, coagulopathy, and encephalopathy. The differential diagnosis includes sepsis, preeclampsia/eclampsia, and an acute decompensation of chronic liver disease.

In particular, both sepsis and ALF have similar hemodynamic pictures, with decreases in peripheral vascular resistance accompanied by high cardiac output. Encephalopathy also may be a manifestation of the sepsis syndrome. If the hepatic manifestations of sepsis are severe, the clinical picture can be mistaken for ALF. In this situation, jaundice and coagulopathy may result from the cholestasis of sepsis and disseminated intravascular coagulation, respectively. Measurement of levels of factor VIII, which is not synthesized by the liver, may be helpful in differentiating sepsis (low factor VIII level) from ALF (factor VIII level generally not suppressed).

In the pregnant patient, preeclampsia/eclampsia also can be difficult to differentiate from ALF, particularly ALF resulting from fatty liver of pregnancy. Differentiating between these two syndromes is of little practical concern, however, because delivery of the fetus is the management of choice in either situation and, if performed early enough, is almost always curative.

Finally, an acute exacerbation of liver dysfunction in patients with underlying chronic liver disease is occasionally confused with ALF. Examples include alcoholic hepatitis in patients with alcoholic cirrhosis and flares of chronic viral hepatitis.

PREDICTORS OF OUTCOME

Patients with ALF fall into two broad categories: (1) those in whom intensive medical care enables recovery of hepatic function and (2) those who require liver transplantation to survive. Thus, it is critical to determine rapidly the group into which a particular patient may belong. It is also critical to avoid the following two scenarios: (1) death of the patient despite intensive medical care without consideration of transplantation and (2) unnecessary liver transplantation when recovery would have occurred spontaneously. Clinical decision-making has been aided by the identification of prognostic markers.

In recent years, sophisticated multivariate analysis and prognostic modeling have been applied to static and dynamic variables to assess the relative importance and interaction in predicting outcome.[27]

Clichy criteria

In 1986, a French group of investigators assessed prognostic factors in a 115 patient cohort with hepatitis B virus-related FHF. Factor V level, patient age, absence of hepatitis B surface antigen, and serum alpha-fetoprotein level emerged as independent predictors of survival by multivariate analysis.[28]

King's College hospital criteria

Subsequently, in 1989 a landmark paper by O'Grady et al 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.[29] 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

Table 4 : King's College criteria for liver transplantation

Acetaminophen	Non-acetaminophen
pH<7.3 (irrespective of grade of encephalopathy)	PT > 100 s (INR > 6.5) (irrespective of grade of encephalopathy)
or all three of the following	or any three of the following
Grade III–IV encephalopathy	Age<10 or >40 y
PT > 100 s (INR > 6.5) Serum creatinine > 3.4 mg/dL	Etiology: non-A, non-B hepatitis; halothane; idiosyncratic drug reaction; Wilson's disease
	Period of jaundice to encephalopathy > 7 d
	PT > 50 s (INR > 3.5)
	Serum bilirubin > (17.5 mg/dL)

with other etiologies (Table 4). These criteria have 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.[30,31] Among patients with a cause of ALF other than acetaminophen toxicity, the presence of any single adverse prognostic characteristic was associated with a mortality rate of 80%, and the presence of three adverse characteristics was associated with a mortality rate of more than 95%. For patients with acetaminophen-induced liver failure, the presence of any one adverse characteristic was associated with a mortality rate of at least 55%, and severe acidosis was associated with a mortality rate of 95%. These mortality rates vastly exceed those associated with liver transplantation. Thus, the presence of any single indicator of a poor prognosis should prompt serious consideration of placing the patient immediate on a waiting list for liver transplantation. Although they were highly predictive of a poor outcome when fulfilled, but they have a low negative predictive value for poor outcome, in that lack of criteria fulfillment did not guarantee survival.[32]

Liver histology and liver volume

There is a significant risk of bleeding with biopsy and the potential for sampling error is considerable. Also liver histology does not predict outcome.[33]

A small or shrinking liver on radiologic assessment has been proposed by some to be a valuable prognostic marker.[34,35]

Miscellaneous prognostic variable

Several other parameters have been shown to have prognostic value in certain circumstances. Galactose elimination capacity,[36] the arterial ketone body ratio (reflecting the redox potential of hepatic mitochondria),[37] coagulation factors V and VIII, factor V ratio (in acetaminophen toxicity),[38] and plasma Gc protein concentration: group-specific component protein (an actin scavenger)[39] and the Acute Physiology and Chronic Health Evaluation-2 system and blood lactate level.[40,41]

MANAGEMENT

The initial approach to patient management includes intensive care support and prompt assessment for liver transplantation.

Initial Evaluation and Management

The initial management of ALF should include an attempt to identify the cause of ALF. A small number of causes of ALF can be treated specifically. For example, acetaminophen toxicity can be treated with N-acetylcysteine, and herpes-induced fulminant hepatitis has been reported to respond to intravenous acyclovir. Therapy of ALF caused by fatty liver of pregnancy is emergency delivery. Especially critical in the early evaluation of patients with ALF is the decision regarding the patient's candidacy for liver transplantation. Urgent transfer to a liver transplantation center is advisable for all potential liver transplantation candidates. Rapid clinical deterioration is common in patients with ALF, and transporting the patient may be dangerous later in the course.

Intensive medical care is warranted in all patients with ALF. Initial laboratory studies should include tests to determine the cause (e.g., viral serologic profiles, toxicology screening for acetaminophen and other drugs) and assess the severity of liver failure (e.g., liver, biochemical and renal function tests, arterial blood gas measurements).

Coagulopathy

The risk of upper gastrointestinal hemorrhage can be reduced by agents such as intravenous H2 receptor antagonists, sucralfate and proton pump inhibitors. Nasogastric tube to monitor bleeding and gastric pH should be put in intubated patients. A trial of subcutaneous vitamin K to treat coagulopathy possibly related to vitamin K deficiency is warranted. The decision to replace clotting factors in nonbleeding patients is difficult one: first, infusion of agents such as fresh-frozen plasma may normalize the prothrombin time and thereby reduce its accuracy with respect to assessing the patient's prognosis, and second, infusion of plasma can present a significant volume challenge. In patients with renal insufficiency, infusion of plasma can lead to volume overload and respiratory failure. Unless the patient is bleeding or an invasive procedure will be performed, the potential drawbacks of plasma infusions outweigh the potential benefits. Empiric administration of fresh-frozen plasma has not been shown to improve the clinical outcome of patients with ALF.

Hypoglycemia

Hypoglycemia commonly occurs in patients with ALF. It is thus critical to monitor blood glucose levels frequently. Hypoglycemia generally responds to parenteral administration of glucose (e.g., an intravenous bolus of 50% dextrose followed by continuous intravenous infusion of a dextrose solution).

Encephalopathy and Cerebral Edema

Unlike chronic hepatic encephalopathy, the encephalopathy associated with ALF tends to be progressive unless liver failure is reversed. Sedative-hypnotic drugs, which may exacerbate encephalopathy, should be avoided. Lactulose is of no proven benefit.[42] Reversible conditions associated with ALF that could contribute to altered mental status (e.g., hypoglycemia, hypoxemia) must be treated immediately. More difficult to diagnose and treat are subclinical seizures, cerebral edema, and intracranial hypertension.

Patients with profound encephalopathy (i.e., stage 3 and stage 4) should undergo endotracheal intubation and mechanical ventilation for airway protection. However, many mechanically ventilated patients are also deeply sedated or paralyzed, and evidence of generalized seizure activity may be concealed. Such seizure activity may worsen encephalopathy. Thus, it may be useful to monitor deeply sedated or paralyzed patients for subclinical seizures by EEG. Treatment of subclinical seizures with phenytoin or other antiepileptic medications is appropriate, but the efficacy of prophylactic therapy to prevent seizure activity has not been proved.[16]

Intracranial hypertension can be suspected noninvasively or detected directly. Noninvasive modalities such as physical examination and radiologic imaging have important limitations. Impaired pupillary responses, posturing, or seizures, which may suggest the presence of intracranial hypertension, are not sensitive, particularly when sedatives or neuromuscular blocking agents are used in mechanically ventilated patients. Computed tomographic (CT) scanning of the head is useful for identifying mass lesions, intracranial hemorrhage, and evidence of brainstem herniation,and should be obtained in all patients with advanced encephalopathy. But, the correlation between CT evidence of cerebral edema and measured intracranial pressure (ICP) is imperfect, ranging from 60% to 75%.[43,44] ICP monitoring is the most accurate way to detect intracranial hypertension. However, there are several limitations of ICP monitoring. First, placement of an ICP transducer requires correction of underlying coagulopathy . Second, the ICP transducer represents a potential portal of entry for infectious organisms. Third, placement of the transducer can precipitate intracranial hemorrhage, which can be fatal. The frequency of significant complications ranges from 4% to 20%.[45]

Elevation of the head of the bed (and avoidance of the head-down position) is a simple measure to reduce ICP. Blood pressure should be maintained within a narrow range to achieve a cerebral perfusion pressure of > 50 mmHg but < 65 mmHg to prevent cerebral hypoperfusion on the one hand and further cerebral hyperemia on the other.[46,47] Vasopressin and its analogues such as glypressin should be avoided because they may worsen hyperammonemia and also increase ICP through increases in CBF.[48,49] Hyperthermia should be prevented because it worsens intracranial hypertension.[50,51] Glucose levels need to be maintained to prevent cerebral and systemic effects of hypoglycemia. Hyperglycemia worsens cerebral edema in patients with ALF.[52] Hyponatremia can also worsen brain edema and should be prevented or corrected.[53] Hypercapnia should be avoided because it induces cerebral hyperemia and increases ICP.[54] Close attention to acid-base balance and correction of hyperlactatemia is important because it can worsen cerebral hyperemia.[55] Patients requiring renal support should have continuous venovenous hemofiltration rather than hemodialysis to prevent rapid fluid shifts.[56]

Osmotherapy with mannitol[in a dose of 1 to 2 mg/kg as a 20% solution] is effective in controlling intracranial hypertension in approximately 60% of cases but requires preserved renal function (or hemofiltration).[57] Plasma osmolality needs to be measured if more than two doses are used to ensure that it is less than 320 Osm/L. In order to be able to use mannitol repeatedly, fluid can be taken off with hemofiltration, which, by itself, reduces ICP. Intravenous thiopental has efficacy similar to that of mannitol.[58] Thiopental has advantages of rapid onset of action and not requiring preserved renal function. Potential drawbacks of thiopental are hypotension and, more importantly, masking of clinical indicators of neurologic recovery or deterioration. In general, it is reasonable to use mannitol as first-line therapy and to reserve barbiturates for patients with renal insufficiency or refractory intracranial hypertension. Glucocorticoids are of no benefit.[57]

Although there are no data in humans with ALF, studies in experimental models of ALF suggest that the administration of L-ornithine L-aspartate (an ammonia reducing agent) early in the course of illness may prevent the occurrence of brain edema.[59]

Phenytoin, which acts on the Na/K adenosine triphosphatase (ATPase) has undergone a randomized clinical trial in 42 ALF patients admitted with Grade III-IV HE. In addition to ICP monitoring, the patients underwent continuous EEG monitoring. Although there were no significant differences in frequency of subclinical seizure in the two groups (30 and 45%, respectively) or in the increase of ICP (25 and 50%, respectively), the autopsy examinations available in 19 patients showed signs of cerebral edema in only 22% of the phenytoin-treated patients compared with 70% of the controls (p < 0.03).[16] These data provide the rationale for the use of phenytoin in ALF as prophylaxis in those who have reached Grade III-IV HE.

Elective hyperventilation appears to delay the onset of coning, though there was no significant effect on number of episodes of raise ICP and cerebral edema.[60] Therefore, hyperventilation may reduce ICP acutely but cannot be recommended for prolonged use.

Propofol in a dose of 6 mg/kg per hour reduces CBF through metabolic suppression. Its use was investigated in seven patients with ALF. The patients were managed with an infusion rate of 50 μg/kg per minute of propofol. The ICP at insertion was elevated in three of seven patients, but remained within normal limits in six of seven patients. One of the patients died from increased ICP, and one died during OLT.[61] Propofol should be used as the sedative of first choice in ALF because it may also protect from intracranial hypertension.

The use of hepatectomy in patients awaiting OLT is a rather dramatic intervention but may be of value in desperate situations in which all the available treatments have been applied and the patient continues to deteriorate. It is based on the concept that the "necrotic liver" is the source of unknown humoral substances that contribute to increased ICP. In 32 patients with ALF who were likely to die while awaiting OLT, Ringe et al performed hepatectomy with portacaval shunting. They observed stabilization of the cardiovascular and cerebrovascular state, with 19 of 32 patients having successful transplants, 6 to 41 hours after.[62]

Mild to moderate hypothermia has been explored in a number of animal models of ALF. It has been shown that hypothermic rats (32 to 33°C) with ALF had significantly less brain water, reduced duration of encephalopathy, and less clinical neurological deterioration compared with euthermic rats. Brain edema was accompanied by an increase in CBF in the control rats, which

was not observed in the hypothermic animals, suggesting that the beneficial effects of hypothermia may be through a reduction in cerebral hyperemia, which is important in the pathogenesis of intracranial hypertension in ALF.[63-65]

Infection

Clinical recognition of infection may be difficult, because signs such as hypothermia, hypotension, leukocytosis, and acidosis may reflect the underlying liver failure. Therefore, surveillance cultures in patients with ALF are extremely helpful. The advisability of prophylactic antibiotics in the setting of ALF is debatable. On one hand, prophylactic antibiotics may offset the development of infections that limit the applicability of liver transplantation. On the other hand, they may increase the risk of superinfection with resistant bacteria or fungi. In a small randomized trial,[66] patients treated with prophylactic intravenous cefuroxime had a significant reduction in the rate of documented infections (from 61% to 32%) compared with those treated conservatively, and a modest (but statistically insignificant) increase in the rate of survival (from 45% to 67%). Therefore, a high level of suspicion for infection should be maintained in patients with ALF, as should a low threshold for administering antibiotics. If infection is suspected, the choice of antibiotics should be based on the spectrum of likely bacterial pathogens (e.g., *Staphylococcus*, Gram-negative aerobes) and local hospital microbial sensitivities. A reasonable empiric regimen is vancomycin and a third-generation cephalosporin.

Multiple Organ Failure Syndrome

The fundamental goals of management of multiple organ failure syndrome: to optimize arterial pressure and tissue oxygenation. Ideally, the mean arterial pressure (MAP) should be maintained above 60 mm Hg. If the MAP falls below this value, cerebral perfusion can drop precipitously.[67] Hemodynamic monitoring with a central venous or pulmonary arterial catheter may be useful for deducing the patient's intravascular volume status. Hypotension resulting from intravascular volume depletion should be corrected with blood or colloids. If hypotension is caused by reduced vascular resistance, administration of -adrenergic agonists may be useful. Although pressors can be used to maintain MAP within a physiologic range, they have the potential to further impair tissue oxygenation.[68]

Endotracheal intubation and mechanical ventilation frequently are necessary for patients with ALF. Hypoxemia can result from respiratory depression caused by coma or impaired gas exchange caused by ARDS or superimposed pneumonia. Endotracheal surveillance cultures are thus useful.

If renal failure is present, a major practical issue in management is whether the renal failure is caused by intravascular volume depletion (and is readily reversible) or other causes, such as acute tubular necrosis or hepatorenal syndrome. Nephrotoxic drugs, especially aminoglycosides and nonsteroidal anti-inflammatory agents, must be avoided, and care must be taken when contrast dye is used. Measurement of central venous (or pulmonary capillary wedge) pressure provides a direct guide to fluid therapy. Patients with ALF tolerate volume overload poorly, in light of their propensity to develop ARDS. Early measurement of central venous or pulmonary arterial pressure in oliguric

patients is preferable to empiric administration of fluid boluses. If oliguria persists in the face of adequate central filling pressures, continuous arteriovenous hemofiltration should be initiated. Continuous arteriovenous hemofiltration has been shown to be superior to intermittent machine hemofiltration with regard to hemodynamic stability and tissue oxygen delivery in oliguric patients with ALF.[69]

Liver Transplantation

Liver transplantation has transformed the management of patients with ALF. Before the era of liver transplantation, fewer than one half of patients with ALF survived. In contrast, survival rates for patients with ALF who undergo liver transplantation have been more than 70%.[43,70-75]

The decision to transplant a patient with ALF must balance the likelihood of spontaneous recovery with the risks of surgery and long-term immunosuppression. Furthermore, contraindications to transplantation, particularly irreversible brain damage, active extrahepatic infection, or multiple organ failure syndrome, must be considered. In countries, where cadaveric livers are not readily available for transplantation, living-related liver transplantation is performed with success.[76,77] The decision to place a patient list for transplantation must be made promptly, because a delay increases the likelihood that complications such as infection, multiple organ failure, and intracranial hypertension will develop. These complications can preclude liver transplantation, thereby virtually assuring death of the patient.

Experimental Therapy

Treatment strategies, such as charcoal hemoperfusion and administration of prostaglandin E1, have not been shown to be useful.[78,79] Plasmapheresis and hepatectomy have been suggested as possible "bridging" mechanisms to liver transplantation, but prospective trials have yet to be performed.[80,81] Additional forms of therapy may provide a bridge to liver transplantation or to regeneration of the native liver with spontaneous recovery: liver support devices, auxiliary liver transplantation nonhuman liver transplantation, and hepatocyte transplantation.

In spite of the best available intensive medical support, acute liver failure (ALF) still carries a substantial mortality. Orthotopic liver transplantation (LTx) is the treatment of choice for the severe cases but is limited by the shortage of cadaver organs. Living-related donor transplantation has proved to be encouraging,[77] yet a suitable donor is found in time in only 30% of cases (of living-related donor transplantation).[82] Consequently, there has been considerable interest regarding the development of liver support systems that can potentially help the patient through the crisis and provide more time to find an organ ("bridge" to LTx) or that allow the native liver to recover sufficiently so as to make transplantation unnecessary. The observation that end-organ dysfunctions can be reversed after LTx has led to the hypothesis that the hepatic dysfunction is central to their pathogenesis, with the accumulation of toxins as the immediately responsible mechanism.[83] A liver support system that can remove these toxins could potentially prevent or reverse end-organ failure and significantly improve outcome in ALF, particularly if these toxins also cause further damage to the liver.[84]
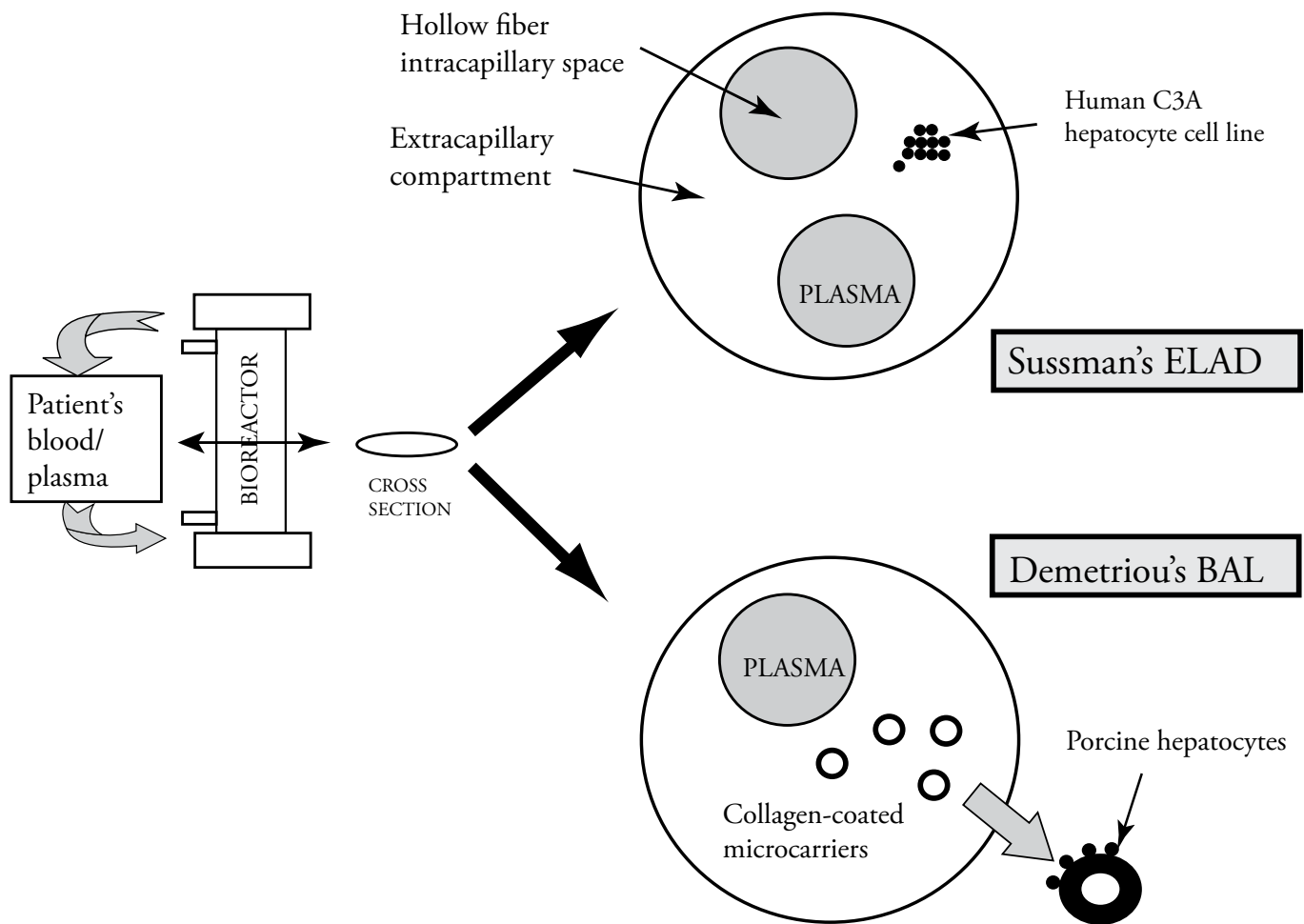
Fig. 1: Structure of bioartificial livers

The several liver support systems currently under investigation are considered under the two main categories of bioartificial and artificial.

Bioartificial System

By using viable hepatocytes, these systems should reproduce the synthetic, detoxifying, as well as the excretory, functions of the liver. Unfortunately, human liver cells, which would be the best to use, are not in ready supply and are difficult to grow in culture, becoming phenotypically unstable and rapidly losing liver-specific gene expression. The minimum quantity of cells required is not known, but based on the experience of hepatic resection in humans,[85] approximately 150 to 450 g of cells (or 10^{10} hepatocytes), providing the function of 10 to 30% of the normal liver mass, are required to support the failing liver.[86] Most of the current devices are based on the use of hepatocytes from other species particularly pigs [e.g. Demetriou BAL device]. A great advantage of porcine hepatocytes, unlike human liver cells, is that they can be satisfactorily cryopreserved, with cell isolation at a convenient time followed by storage at a clinical site prior to use, thereby avoiding the costs and contamination risks of long-term hepatocyte culture.[87] Another approach has

been with genetically engineered human hepatocytes to produce cells with the desired functional and survival capabilities. Thus, the C3A hepatocyte line, a subclone of the ubiquitous HepG2 hepatoblastoma cell line, has been used in one system (the Sussman device).[88] Another immortalized human hepatocyte cell line under investigation is HHY41, which retains many liver-specific functions, protein synthesis, gluconeogenesis, and cytochrome P450 activity.[89]

At the heart of the design for a BAL is the bioreactor (Fig. 1). The simplest type, and the one used most commonly, consists of a column containing hollow-fiber capillaries through which the patient's plasma flows. In the extracapillary space lie the hepatocytes.[88,90] Free exchange of molecules can occur between plasma or blood and hepatocytes in the bioreactor across a membrane with a cutoff selected to allow the movement of most toxins as well as transport proteins such as albumin (66 kD molecular weight) while preventing passage of immunoglobulins (100 to 900 kD), complements (> 200 kD), or viruses and cells. Most groups have used cutoffs between 50 and 150 kD.[91] The hepatocytes extract oxygen and nutrients and detoxify toxins from the plasma, and their metabolites are simultaneously passed
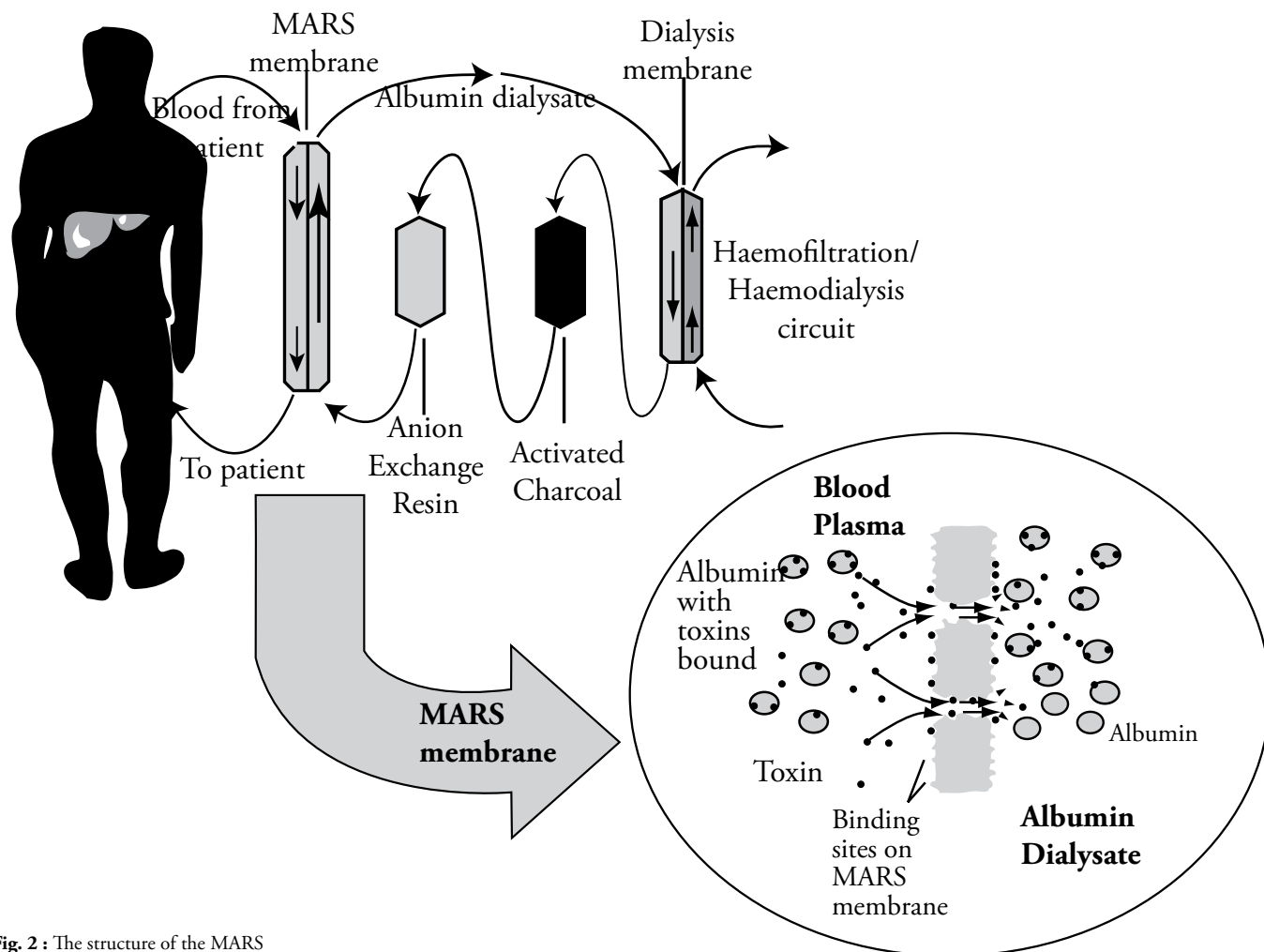
Fig. 2 : The structure of the MARS

back into the plasma. The Demetriou system also incorporates two charcoal columns in the circuit prior to the bioreactor for removal of toxins that could damage or impair the function of the pig hepatocytes.

The more sophisticated system developed by Gerlach et al[92] in Berlin (the Modular Extracorporeal Liver Support [MELS]) uses three sets of capillary tubes: one to provide oxygenation and two to carry inflowing and outflowing plasma. The hepatocytes (primary human hepatocytes from explanted livers found unsuitable for LTx) remain in the extracapillary space. A detoxification module allows single pass albumin dialysis to be performed, and continuous venovenous hemofiltration can be included. The AMC-BAL developed by Chamuleau et al incorporates a spirally wound polyester matrix sheet that includes an integral hollow-fiber compartment for oxygenation and uses porcine hepatocytes.[93] The published experience with such devices in patients with ALF is limited. Although case reports and small series suggest that bioartificial liver systems may improve encephalopathy and coagulopathy in patients with ALF, a survival benefit has not yet been demonstrated objectively.

Artificial Extracorporeal Systems
The main difference in the newer systems is an increased selectivity of the detoxifying capacity based on the use of albumin

dialysis with a membrane having a sufficiently small pore size. This makes the system specific for albumin-bound substances, which form most of the toxins accumulating in liver failure.[94] At the same time, larger molecules (immunoglobulins, growth factors) that might be physiologically important are prevented from crossing over.

The Molecular Adsorbents Recirculating System (MARS) (Teraklin AG, Rostock, Germany), which has been developed over the last decade, is currently under extensive investigation and clinical trial.[95] This uses a hollow-fiber dialysis module in which the patient's blood is dialyzed across an albumin-impregnated polysulfone membrane (with a cutoff of 50 kD) while maintaining a constant flow of 20% albumin as dialysate in the extracapillary compartment (Fig. 2). The premise is that toxins bound to albumin in the patient's blood will detach and bind to the binding sites on the membrane, because albumin, when attached to polymers, has a higher affinity for albumin-bound toxins. These then pass on to the albumin in the dialysate (where albumin is present at a concentration (200 g/L) five to seven times that in the plasma). The dialysate, carrying a quantity of toxins, is then cleansed by perfusing it over activated charcoal and anion-exchange resin. These take up most of the albumin-bound substances. Water-soluble toxins are removed by passage through a hemodialysis/hemofiltration module that is run in

conjunction with the albumin dialysis module. The dialysate is thus regenerated, and once more capable of taking up more toxins from the blood.

In the report of the International MARS Registry,[96] of the 38 cases of ALF treated up until September 2001, 19 (50%) have survived. Six of them were bridged to transplantation, and 4 others who were listed for transplant did not require one. Five of the 6 patients with paracetamol overdose recovered. Encephalopathy and serum bilirubin improved, although mean arterial pressure and serum creatinine did not. Thrombocytopenia was the only complication consistently observed.

Most of the benefits observed with liver support in the setting of ALF have been in the form of successful bridging to transplantation, rather than recovery of the native liver. The data supporting their use in ALF are encouraging, although in some of the instances in which the use of MARS was reported as making subsequent transplantation unnecessary, the treatment had been given early in the course of illness before any major clinical deterioration. Only when a carefully conducted controlled clinical trial has shown proven benefit, including survival, can we be certain of its value, whatever the efficacy of toxin removal.

Auxiliary liver transplantation as a temporary bridge to spontaneous recovery from ALF has also been investigated.[97] In this procedure, the donor graft is implanted orthotopically beside the native liver (after it has been surgically reduced) or heterotopically inferior to the native liver. The advantage of this procedure is that if spontaneous recovery of the native liver occurs, then immunosuppression can be stopped. The allograft can then be removed or permitted to atrophy. However, the utility of this operation is limited by the difficulty of predicting which patients with ALF are likely to recover spontaneously. Although early results are promising, the benefits of this procedure remain to be shown.

Transplantation of nonhuman livers (i.e., xenotransplantation) has been proposed as a solution to the shortage of human donor livers. If major problems with trans-species rejection can be solved, xenotransplantation, particularly utilizing porcine or nonhuman primate livers, offers the potential for developing a renewable source of donor livers. In the meantime, xenotransplantation has been suggested as a means to support patients with ALF until a human donor liver becomes available. In some case reports, porcine livers were used for extracorporeal perfusion or heterotopic transplantation to treat patients with ALF until human livers became available for transplantation.[98,99] Controlled studies remain to be conducted.

Hepatocyte transplantation represents an alternative approach. Its utility is likely to be similar to that of the bioartificial liver devices, that is, as a bridge to liver transplantation or regeneration. Preliminary reports suggest that hepatocyte transplantation may be useful in patients with ALF.[100,101]

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