Acute loss of liver function is a devastating disease with a high mortality rate. It results in rapidly progressing multiorgan dysfunction, with circulatory instability, renal failure and sepsis as conspicuous clinical features. However, the most dramatic impact is on the brain. Hepatic encephalopathy (HE) in acute liver failure (ALF) is often associated with the development of intracranial hypertension (IH). A rise in intracranial pressure (ICP) is a unique and distinctive feature of acute liver failure, leading to intracranial hypertension (IH) development. IH is associated with systemic hemodynamic instability, alterations in the regulation of cerebral blood flow and the development of cerebral edema. This review focuses on the pathophysiology of IH with special emphasis on cerebral blood flow and the development of cerebral edema. Based on these considerations, both traditional and new treatments for the management of IH in the future are discussed.

**Key Words:** Ammonia; Brain; Cerebral blood flow; Cerebral edema; Fulminant hepatic failure; Intracranial pressure
feature of ALF, which is not seen in multiorgan failure caused by other critical illnesses.

The pathophysiology of circulatory instability is not fully understood but seems closely related to a decrease in systemic vascular resistance. The neurochemical mechanism responsible for HE is still controversial, but IH in ALF is closely related to the development of cerebral edema (1) and alterations in cerebral blood flow (CBF) (2).

This review first briefly defines ALF and describes the most important etiological causes. Then the focus turns to the pathophysiological changes in the systemic and cerebral circulation, with a special emphasis on the development of cerebral edema in ALF. Based on these considerations, hemodynamic treatment modalities are discussed.

DEFINITION
The fulminant form of liver failure was originally defined as a syndrome with the onset of HE occurring within eight weeks after the first clinical symptom of liver disease, eg, jaundice, malaise, nausea or right abdominal discomfort (3). This ambiguous definition distinguishes patients with acute liver injury from patients with HE as a complication of chronic liver disease. However, a subgroup of patients with liver failure and HE have a longer interval from the first sign of liver dysfunction to the development of HE without having chronic liver failure. This subgroup of patients have been termed to suffer from subacute liver failure (4) or late onset fulminant hepatic failure (5). Separating patients with ALF injury into subgroups of patients with hyperacute, acute and subacute liver failure has been proposed (6) to delineate a more appropriate management strategy, including liver-assist methods and liver transplantation (7). Thus, the current definition of ALF is dependent on the development of HE, even though it is associated with little prognostic and pathophysiological information. In fact, the extent of liver injury, as measured by liver function tests, is the single most important determinant of the outcome for patients with ALF (8).

INCIDENCE AND ETIOLOGY
It is estimated that there are about 2000 cases of ALF in the United States each year. Similarly, the incidence of ALF is approximately eight /1,000,000 in Denmark. Acetaminophen intoxication accounts for approximately 50% of the ALF patients in the United Kingdom (9) and Denmark (10). Acetaminophen overdose has also become the most common cause of ALF in American liver transplantation centres, and accounts for approximately 20% of ALF patients (11). Acute viral hepatitis (type A and B) is the predominant cause of ALF in central and southern Europe. Acute viral hepatitis E has been reported to be a frequent cause of subacute liver failure in pregnant women in India. Other causes of ALF may be mushroom intoxication, drug-induced hepatotoxicity (ecstasy halothan, valproate and disulfiram), autoimmune hepatitis, cardiac failure and inherited metabolic diseases (reviewed in 12).

PATHOPHYSIOLOGY

Systemic circulation
Lever failure induces cardiovascular dysfunction. Clinical examination reveals warm peripheries and bounding pulses. Using a dye-dilution technique in patients with chronic liver disease, Kowalski and Abelman (13) found that cardiac output and heart rate were increased while arterial pressure was reduced, ie, a hyperdynamic systemic circulation. Studies of patients with ALF have shown similar cardiovascular alterations (14-16). Trewby and Williams (14) reported that 82 of 94 patients with ALF had a systolic arterial pressure of less than 80 mm Hg for more than 1 h, and low systemic vascular resistance and cardiac filling pressures have also been demonstrated (17). With volume replacement, systolic arterial pressure above 80 mm Hg can be maintained in most patients with ALF, supporting the concept that ‘peripheral’ arteriolar dilation contributes to the development of arterial hypotension.

It is unlikely that low systemic vascular resistance is centrally induced, even though cerebral edema often develops in patients who exhibit a hyperdynamic state. This is because the systemic circulatory abnormalities are also present in patients with cirrhosis who rarely develop cerebral edema and IH.

Both patients with cirrhosis and patients with ALF develop portal hypertension. Leakage of endotoxins from the gut to the portal blood (translocation) and/or the lymph nodes may result in elevated systemic endotoxin levels because portal blood bypasses the liver via collaterals. In patients with ALF, it is also assumed that endotoxins are shunted through the failing liver without being cleared by Kupffer cells. Endotoxins induce the release of various cytokines (tumour necrosis factor-alpha [TNF-α], interleukin [IL]-1 and IL-6), which are potent stimulators of the inducible isoform of nitric oxide synthetase. The plasma concentration of TNF-α, IL-1β and IL-6 in the inflammatory host defense system are increased in patients with ALF (18,19). There is accumulating evidence that hyperdynamic circulation in both chronic liver failure and ALF, with high cardiac output and low systemic vascular resistance, may result from cytokine activation of the endothelium, which releases excessive amounts of endothelium-derived nitric oxide (20-22).

Patients with an increased, mixed venous lactate have a poor prognosis if it develops after adequate volume replacement (23). Mixed venous lactate concentration is inversely correlated to systemic vascular resistance (17). Arterial hypotension and low systemic vascular resistance may result from the development of arteriovenous shunts. Arteriovenous shunts and perfusion of non-nutritive capillaries have been considered main reasons for the development of tissue hypoxia, lactic acidosis and multiorgan failure (Table 1) (16,22,24). It has been suggested that systemic lactic acidosis results from insufficient blood flow, especially in the splanchnicus and brain (22). This concept of tissue hypoxia is supported by the observation that oxygen consumption increases during infusion of prostacyclin and N-acetylcysteine, ie, as oxygen extraction increases. However, recent studies of sys-
temic and regional circulation have failed to support this concept of ‘pathological supply dependency’. This may result from methodological problems, because the same techniques (ie, pulmonary artery catheter and Fick’s principle) were used to calculate both systemic oxygen delivery and consumption in the first studies (16, 22, 24). Walsh and co-workers (25) recently used two independent techniques to determine systemic oxygen delivery and consumption during N-acetylcysteine infusion into patients with ALF, and failed to demonstrate profound changes in systemic oxygen consumption. Also, Clemmesen et al (26) demonstrated that in patients with ALF, splanchnic blood flow is increased without demonstrating tissue hypoxia. On a similar note, the cerebral metabolic rate for oxygen remains constant despite the rise in CBF by noradrenaline (27). These results indicate that both the splanchnic organs and the brain are receiving sufficient perfusion for the maintenance of oxidative metabolism. Thus, it has not yet been proven that a critical reduction in oxygen extraction and consumption are of any pathophysiological importance in the development of multiorgan failure in ALF.

**CBF and cerebral edema**

One of the most common causes of death in ALF is IH, which develops in approximately 60% to 80% of patients (28). Its pathophysiology is not settled, but fruitful progress has recently been made in understanding some of the mechanisms involved.

In contrast to other organs, the combined brain volume, consisting of tissue, blood and extracellular fluid, submits to the physical limitations of the skull. The total volume must remain unchanged to avoid a rise in ICP (Figure 1). A primary rise in brain volume caused by cytotoxic edema leads to a compensated state, where a small increase in cerebral blood volume results in a serious rise in ICP. Thus, the gradual development of both cerebral hyperemia and cerebral edema will rapidly influence ICP.

**Cerebral edema:** Three explanations have to be considered for a pathophysiological explanation of cerebral edema in ALF. First, accumulation of osmolytes within astrocytes may be of importance (the glutamine hypothesis) (29). Second, CBF regulation may be altered (the hyperemia hypothesis) (2). Third, accumulation of compounds released from the necrotic liver may enter the brain and cause swelling.

**Glutamine hypothesis:** For decades, ammonia intoxication has been considered pathophysiologically important for the development of HE. Only recently has a study demonstrated that arterial ammonia concentration is related to cerebral edema and cerebral herniation in patients with ALF (30). This effect of ammonia is not fully understood, but could result from characteristics of ammonia metabolism in the brain, an organ that lacks a complete urea cycle. Cerebral detoxification of ammonia occurs by either the amination of alpha-ketoglutarate to glutamate or the ATP-dependent amidation of glutamate to glutamine by the enzyme glutamine synthase. Thus, glutamine concentration increases within astrocytes during ammonia intoxication both in vitro (31) and in vivo (32). Because glutamine is a quantitatively important osmolyte, water diffuses into the astrocytes and results in cell swelling, ie, cytotoxic edema. In chronic liver failure (ie, portacaval anastomosis in the rat), a compensatory decrease of other osmolytes, such as myo-inositol and taurine, restores normal osmolyte and water content in the astrocytes. This is in contrast to rats with ALF, in which the total osmolyte and water content increases (33). A reduction in cerebral blood volume, ie, CBF, in the setting of cerebral edema, may be the only way to avoid IH (Figure 1). The regulation of CBF is of vital importance to understanding IH in the setting of cerebral edema.

**Cerebral hyperemia:** Normally, CBF is closely regulated by brain metabolism (34). The coupling of CBF and metabolic requirements implies that reduced cerebral activity, eg, after sedation, is followed by a decrease in CBF. Seizures, on the other hand, increase CBF as metabolism is raised (35). Because the cerebral oxygen metabolism is inevitably reduced by approximately 50% in ALF, CBF would also be expected to decrease to a similar degree, ie, to approximately 20 to 25 mL 100 g⁻¹ min⁻¹. However, a wide intra- and interindividual CBF variation has been reported in ALF, ie, from 12 to 230 mL 100 g⁻¹ min⁻¹ (36). This variation has been shown to result, at least to some extent, from alterations in arterial pressure (37).

Normally, arterial pressure has no influence on CBF,
All other etiological causes:
- Edema, and should be avoided.
- ‘Extra-cerebral’ reasons may induce cerebral hyperemia and may result from luxury perfusion. Thus, pain, fever, in-
- Seizures, IH (41) and even hemorrhage can develop in ALF, ter movement into the brain (vasogenic edema). Agitation,
- Osmotic pressure and have a profound influence on wa-
- The vasodilatory response to hypercapnia be-
- Could explain the development of luxury perfusion CBF
- Lead to a critical increase in cerebral blood volume and ICP.
- Pathophysiologically involved in cerebral edema (27). Con-
- Conversely, arterial hypertension may result in an increase in CBF to an extent that exceeds the actual metabolic demands of the brain, ie, cerebral ‘luxury perfusion’ (2,36). This may lead to a critical increase in cerebral blood volume and ICP. Also, the hydrostatic capillary pressure may exceed the col-
- In ALF, CBF autoregulation is absent (27,37,39). As a result, circulatory instability with episodes of arterial hyper-
- In the initial stage of ALF, cerebral hypoxia seems less frequent, and it is not obvious that cerebral hypoxia is pathophysiologically involved in cerebral edema (27).
- Hyperemia and partially restored regulation of CBF in a pa-
- As a part of the explanation (47). Hypothermia normally in-
- Such substances may be intracellular components or membrane fragments (29). However, it may be worth noting that other conditions with massive cell lysis, such as necrotizing pancreatitis, rhab-
- In ALF, CBF autoregulation is absent (27,37,39). As a result, circulatory instability with episodes of arterial hyper-
- In most centres, the King’s College criteria for transplantation are used (48). But also, liver function tests such as galactose elimination capacity are used of value in selecting patients for emergency liver transplantation (Table 3) (8). However, a detailed discussion on the prognostic markers of ALF is be-
- It is not clear why these hemodynamic features improve after hepatectomy, but hypothermia may be a part of the explanation (47). Hypothermia normally in-
- Perform hepatectomy in patients with ALF, even if a do-
- Because approximately half of the patients with severe ALF survive without transplantation, it is important to determine the prognosis. In most centres, the King’s College criteria (Table 2) (23) or the Clichy criteria for transplantation are used (48).

### CRITICAL CARE MANAGEMENT

It is important to emphasize that the following proposal for the monitoring and management of systemic and cerebral hemodynamics should not delay efforts seeking to establish prognosis and regain liver capacity either by symptomatic support (and artificial liver-assist methods) or by liver trans-

#### Prognosis and basic handling

Because approximately half of the patients with severe ALF survive without transplantation, it is important to determine the prognosis. In most centres, the King’s College criteria (Table 2) (23) or the Clichy criteria for transplantation are used (48). But also, liver function tests such as galactose elimination capacity may be of value in selecting patients for emergency liver transplantation (Table 3) (8). However, a detailed discussion on the prognostic markers of ALF is be-

### Table 2

<table>
<thead>
<tr>
<th>King’s College criteria for liver transplantation in patients with acute liver failure</th>
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<tbody>
<tr>
<td><strong>Acetaminophen intoxication</strong></td>
</tr>
<tr>
<td>pH less than 7.30 after adequate volume expansion (irrespective of stage of hepatic encephalopathy (HE), or</td>
</tr>
<tr>
<td>International normalized ratio (INR) greater than 7 and serum creatinin greater than 300 µmol/L in a patient with stage 3 or 4 HE</td>
</tr>
<tr>
<td>All other etiological causes</td>
</tr>
<tr>
<td>INR greater than 7 (irrespective of stage of HE), or</td>
</tr>
<tr>
<td>Any of the three following variables (irrespective of stage of HE)</td>
</tr>
<tr>
<td>Age younger than 10 years</td>
</tr>
<tr>
<td>Age older than 40 years</td>
</tr>
<tr>
<td>Etiology: non-A, non-B hepatitis (ie, unknown etiology), idiosyncratic drug reactions</td>
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<tr>
<td>Duration of jaundice before onset of HE greater than seven days</td>
</tr>
<tr>
<td>INR greater than 3.5</td>
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<tr>
<td>Serum bilirubin greater than 300 µmol/L</td>
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</tbody>
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Data from reference 23

**Table 3**

Methods for evaluation of the prognosis in acute liver failure

<table>
<thead>
<tr>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>King’s College criteria</td>
<td>23</td>
</tr>
<tr>
<td>Factor V - Clichy criteria</td>
<td>66,67</td>
</tr>
<tr>
<td>Galactose elimination capacity</td>
<td>8,68</td>
</tr>
<tr>
<td>Arterial ketone body ratio</td>
<td>69</td>
</tr>
<tr>
<td>Japanese severity index</td>
<td>70</td>
</tr>
<tr>
<td>Computed tomography scan of liver volume</td>
<td>71</td>
</tr>
<tr>
<td>Transjugular liver biopsy</td>
<td>72</td>
</tr>
<tr>
<td>Plasma GC-globulin</td>
<td>73</td>
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</tbody>
</table>

...mean to be reduced by hepatectomy (45). Moreover, Ejlersen et al (46) reported that a hepatectomy ameliorated cerebral hyperemia and partially restored regulation of CBF in a patient with ALF. It is not clear why these hemodynamic features improve after hepatectomy, but hypothermia may be a part of the explanation (47). Hypothermia normally increases systemic vascular resistance (SVR) and decreases CBF in the experimental model of ALF (47). The idea for performing hepatectomy in patients with ALF, even if a do-

#### Toxins from the failing liver

There is some evidence that patients with ALF waiting for emergency liver transplantation may benefit from total hepatectomy as the systemic hemodynamics stabilize (7,44). Also, cerebral edema and IH...
TABLE 4
Previously proposed critical limits of systemic hemodynamic parameters in acute liver failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Limit</th>
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</thead>
<tbody>
<tr>
<td>Mean arterial pressure greater than 60 mmHg</td>
<td></td>
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<tr>
<td>Pulmonary capillary wedge pressure 10 to 18 mmHg</td>
<td></td>
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<tr>
<td>Oxygen delivery greater than 700 mL/min/m²</td>
<td></td>
</tr>
<tr>
<td>Oxygen consumption greater than 175 mL/min/m²</td>
<td></td>
</tr>
<tr>
<td>Oxygen extraction greater than 12%</td>
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</tbody>
</table>

Data from reference 22

Monitoring and treatment of systemic hemodynamic instability

Appropriate management, regardless of the decision to proceed with liver transplantation, should include the placement of arterial and central venous catheters. In patients with systemic hemodynamic instability who do not respond to volume expansion or achieve adequate cardiac filling pressures, the insertion of a pulmonary artery catheter is needed (Table 4). Central hemodynamics should be measured two or three times a day, following any change in inotropic support, or during any acute deterioration in arterial pressure.

Noradrenaline is the agent of choice if volume expansion is insufficient, and should be increased until the effect on arterial pressure is accomplished.

Low-dose dopamine, used to preserve or restore renal function, has not been demonstrated to be of any value for patients with ALF. Occasionally, patients may develop low cardiac output syndrome, which is associated with a poor prognosis. In these patients, low dose dopamine, dobutamine and adrenaline may be of value to increase cardiac output and arterial pressure. Transthoracic echocardiography should be performed to exclude pericardia effusion and/or hypokinesis. In addition, plasma magnesium and calcium ions, and phosphate levels should be determined and corrected.

Sudden deterioration in arterial pressure and/or SVR often results from the development of sepsis. In fact, sepsis should always be suspected in patients with ALF, because it is also a major cause of death (22).

According to the ‘intoxication concept’ that cytokines may be important for the development of low SVR, one strategy to maintain vascular tone would be to decrease the plasma levels of endotoxins and cytokines. In fact, clearance procedures such as high volume plasmapheresis re-establish normal systemic arteriole tone (26,49). Various hemodialysis procedures do not increase SVR, probably because the filter pore size does not allow TNF to be removed by the system (50). It remains to be established whether biological ‘liver assist devices’ influence cytokine status and systemic hemodynamics.

Monitoring cerebral hemodynamics

ICP: To preserve normal intracranial compliance, treatment has traditionally been based on the monitoring of ICP for the calculation of cerebral perfusion pressure (CPP) (mean arterial pressure minus ICP) of patients with ALF (51). Thus, the reliability of ICP monitoring becomes critically important for medical decisions with regard to the use of mannitol, sedation, hypothermia and liver transplantation. The accuracy of ICP monitoring depends on the method chosen, eg, epidural, subdural, parenchymous or intraventricular ICP catheters; epidural monitoring is the most safe but also the most unreliable method (52). Drift of the transducer, bend of catheters, wrong calibration or displacement during nursing or interventions may influence and change these parameters. Thus, aggressive and potentially dangerous treatments may be instituted on a false basis. ICP and CPP should always be interpreted critically, always in combination with a close evaluation of clinical condition before the escalation of medical treatment is instituted, and especially before liver transplantation is considered to be contraindicated (53). In a retrospective study, CPP has been demonstrated to have low predictive values in regard to brain death (54). Patients with CPP as low as 15 mmHg have survived without transplantation or neurological deficits (55), despite that the claimed critical limit of CPP is 40 mmHg (41). So, ICP monitoring and CPP calculation may be less important to the outcome in ALF patients than previously assumed.

Internal jugular vein oxygen saturation monitoring: Recently, it has been advocated that cerebral monitoring should focus on CPP in addition to ICP (Table 5). Relative changes in CBF can be monitored by internal jugular vein oxygen saturation (SvjO₂); SvjO₂ also gives direct information on brain oxygenation status (56).
SvjO₂ below approximately 55% is associated with cerebral symptoms both in those who are healthy and in patients with liver failure (57). A prolonged (period of minutes) decrease in SvjO₂ to below 55% may result in cerebral hypoxia and edema. Accordingly, mean arterial pressure should be increased instantaneously by volume expansion and/or noradrenaline. In some patients, CBF increases during the course of ALF, possibly due to gradual cerebral arteriolar vasodilation, and SvjO₂ may increase to above 75% (58). The prognosis for patients with uncorrected high SvjO₂ and cerebral edema is very poor (54,58). In such cases, SvjO₂ should be decreased by mechanical hyperventilation until SvjO₂ is maintained within the normal range, because acute hyperventilation induces precapillary hypocapnic arteriolar constriction (59).

Treatment of IH
Mannitol infusion is the main treatment for IH. Not only is ICP reduced, but CBF and the cerebral metabolic rates of oxygen and lactate increase (40,60). This effect is probably the result of an increase in colloid osmotic pressure in the cerebral capillaries and a reduction in interstitial water content.

Acute hyperventilation decreases CBF, SvjO₂ and ICP (61). Although hyperventilation has been considered inappropriate in intensive care units, hyperventilation is an indispensable and powerful part of the available treatment modalities for IH. Short term hyperventilation should be instituted to terminate IH episodes as long as the SvjO₂ level can be maintained above 55% (43).

Barbiturates are still used for the treatment of IH to reduce intracranial blood volume by precapillary hypometabolic arteriolar constriction. In a prospective study of ALF and IH, a significant reduction in ICP was demonstrated after the administration of thiopental, although the effect was only temporary (62). Although arterial pressure is decreased, CPP remains unchanged, and it has not been determined if the effect of thiopental results from a reduction in CBF. Furthermore, it is not known whether ICP can be reduced by other sedatives, ie, short acting benzodiazepines.

Future management
Hypothermia: Recently, mild hypothermia has been suggested as a new powerful treatment modality to reduce ICP in ALF (47). Mild hypothermia (33°C) reduces CBF and cerebral blood volume. It probably also restores the normal balance between the Starling forces, preventing edema. Although the rapid and dramatic effect of mild hypothermia on ICP seems promising, it awaits further study in controlled clinical trials (63).

Cyclo-oxygenase inhibition: In patients with ALF and severe IH, the injection of indomethacin decreases the ICP within a few minutes by reducing cerebral blood volume (64). Indomethacin is a very potent vasoconstrictor, inhibiting cyclo-oxygenase activity. Further experimental and clinical trials are needed to establish its indications and side effects.

Ornithine-aspartate: Specific pharmacological treatments, such as ornithine-L-aspartate, may prove useful in increasing the conversion of ammonia to glutamine in muscle, preventing cerebral edema development. A preliminary study has recently reported that ornithine-aspartate prevented brain edema formation in an anhepatic experimental model of ALF (65).

CONCLUSIONS
Treatment of neurological problems in ALF has mainly been symptomatic. Recent discoveries of distinct pathophysiological mechanisms responsible for cardiovascular instability, especially IH, may allow for the evaluation of specific treatments to prevent devastating complications of liver failure within the near future.


