Acute liver failure: current management and future prospects

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Although the development of hepatic encephalopathy (HE) and the associated increase in intracranial pressure (ICP) in patients with acute liver injury is the key event that defines their prognosis [1–5], ALF is associated with dysfunction of multiple organ systems. The circulatory disturbance in ALF is an early manifestation that tends to worsen during the course of the illness and is characterized by generalized vasodilatation which results in increased cardiac output and, reduced systemic vascular resistance and mean arterial pressure [6,7]. These circulatory disturbances contribute to the occurrence of renal failure requiring renal support. ALF results in severe coagulopathy, which needs correction in cases of overt bleeding or for insertion of appropriate monitoring devices. Along with the increased susceptibility to infection this multiorgan failure often culminates in various degrees of adult respiratory distress syndrome requiring artificial ventilatory support [7]. In a study performed over a 7-year period in 315 patients with ALF, the immediate cause of death in those with evidence of severe liver injury was brain herniation from elevated ICP in 35% and most of the other deaths were the result of severe refractory hypotension resulting from supervening sepsis culminating in multiorgan failure. In the last 20 years, emergency liver transplantation has emerged as the ‘only’ therapeutic intervention of proven benefit for patients with advanced ALF [8].

The management of patients with acute liver injury must begin as soon as the patient presents and as was recently pointed out by Bernuau, early referral to the liver unit is imperative [9]. The rationale for this suggestion is the following: the etiological diagnosis of the acute liver disease, especially in cases with unusual clinical profile is often delayed and consequently, specific treatments targeting the liver, which is the key organ to be preserved and supported in patients with acute liver disease who still have no evidence of encephalopathy but with severe coagulopathy and thus threatened by ALF, may also be delayed. The clinical evolution of the condition is often so rapid that any chance of recovery may be lost. Classical examples of this issue include all the treatable acute liver diseases such as acetaminophen-induced hepatotoxicity, herpes simplex hepatitis, acute fatty liver of pregnancy, auto-immune hepatitis, hypoxic hepatitis, Budd-Chiari syndrome and the acute form of Wilson’s disease [10–13]. In addition, in the uninitiated environment, there is a risk of aggravation of either the destruction of liver tissue or the patient’s condition through the use of hepatotoxic, nephrotoxic or neurotoxic substances.

This review will focus upon the current strategies in the management of patients with ALF and focus upon (a) general issues and (b) specific management in relation to circulatory and renal dysfunction and HE. Detailed discussions surrounding liver transplantation and liver support in acute liver failure have been recently reviewed and will not be discussed [8,14].

1. General management

Time is of the essence in the management of patients with ALF because rapid deterioration is a particular feature and it is not unusual to find a patient with ALF and no neurologic or circulatory disturbance progressing to needing inotropic support for hypotension and ventilation, for Grade 3–4 HE. In the most unfortunate situations this rapid deterioration may culminate in a fatal outcome. Therefore, close clinical monitoring is important during the observation period and particularly when moving a patient either between hospitals or between different wards. Most of the patients with ALF will require liberal volume expansion. The choice of fluid is not crucial and usually a mixture of crystalloids and colloids is used. Close attention to acid–base balance and correction of hyperlactatemia is...
Acute liver failure (ALF) is hemodynamically characterized by a hyperdynamically perfused splanchnic circulation with high cardiac output, low mean arterial pressure (MAP), and low systemic vascular resistance (SVR) [31,32]. This reduction in MAP often requires intervention with vasoactive drugs and the dependence of the circulation on vasoactive drugs is a bad prognostic sign. In the fully developed syndrome the patients become refractory to inotropes and the immediate cause of death in up to 70% patients in ALF is severe circulatory failure [7].

There are very few studies that have systematically studied the hemodynamic and renal disturbances during the early phase of ALF. Unlike cirrhosis, the vasodilatation does not appear to be restricted to the splanchnic area and at least in the early phase of the illness (but when vasodilatation is already manifest) the vasodilatation is generalized.
including the muscle and the kidneys [33]. However, during the later stages of the disease, studies in a galactosamine rat model showed decreased renal blood flow and increased renal vascular resistance [34,35]. A hypothetical paradigm for the circulatory disturbance is that there is generalized vasodilatation at the initial phase, which produces profound activation of the neurohormonal system culminating in vasoconstriction of the regional vascular beds. This hypothesis will need to be tested in future studies. Also of importance is the observation from studies in animals that the renal dysfunction was manifest even when the renal blood flow was normal suggesting that other factors may be important in initiating the renal dysfunction in acute liver failure [33,36]. The pathophysiological mechanisms underlying these hemodynamic disturbances are unclear but increased nitric oxide production and cGMP has been demonstrated during the later stages of the disease [37]. Unlike cirrhosis, nitric oxide does not seem to be involved as a factor initiating the vascular disturbances. The differences in the pathophysiological factors underlying the development of the circulatory disturbances in ALF compared with cirrhosis suggests that therapeutic strategies that have been developed for the treatment of patients with cirrhosis cannot be directly applied to ALF patients (Fig. 1).

2.1.2. Aim of circulatory support

Given the fact that the patients have such markedly deranged circulation it is important to use monitoring devices which are able to provide information about changes in mean arterial pressure, the filling status of the patient, the cardiac output and the state of oxygenation. The 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 [38,39]. Unfortunately, it is not clear whether the goal of therapy in as far as the circulation is concerned should be (as is currently thought) to chase the cerebral perfusion pressure or whether some other end point such as oxygen utilization is more relevant.

2.1.3. Use of vasopressors

A particular problem in the management of hypotension in ALF is the fact that these patients have lost cerebral blood flow autoregulation [7,40]. The direct implication of this pathophysiological derangement is that an increase in mean arterial pressure results in an increase in cerebral perfusion pressure, which in turn would increase cerebral blood flow that has the potential to increase intracranial pressure. It is therefore important to have just ‘enough’ perfusion of the end-organs. There are no controlled studies addressing whether a given vasopressor is better than another but the management of patients will be critically dependent upon the need for expansion of the plasma volume on the one hand and vasopressor support on the other. As pathophysiological basis of the circulatory disturbance is one of vasodilatation and increased cardiac output, the preferred drug for vasopressor support is noradrenaline. There is at present no evidence for the use of adrenaline, dobutamine or dopamine.

Terlipressin (a vasopressin analogue) is widely used in patients with cirrhosis for the treatment of hepatorenal syndrome. Recently, it has been shown to be a powerful vasopressor agent for treating patients with hypotension from severe sepsis [41]. However, the role of terlipressin in the management of hypotension in ALF is not clear. Terlipressin acts through the V₁ and the V₂ receptors. V₁ receptors are distributed in the systemic circulation and mediate vasoconstriction. The V₂ receptors are distributed in the cerebral vasculature and in contrast mediate cerebral vasodilatation. Studies in an animal model of cerebral edema have revealed that administration of vasopressin results in worsening of cerebral hyperemia and consequently severity of brain swelling suggesting that terlipressin may accentuate intracranial hypertension in ALF [42]. In a pilot study, we evaluated cerebrovascular hemodynamic effect of administration of a small dose of a single bolus of terlipressin to patients with ALF and Grade IV HE. In this study, the low dose of terlipressin that was administered did not produce any significant changes in systemic hemodynamics but was associated with the increases in CBF and consequently ICP [6]. The mechanism of this apparent increase in CBF following administration of terlipressin may be the result of its action upon the V₂ receptors, which is known to modulate cerebral vasodilatation through a nitric oxide dependent mechanism. Until results of further studies in the more advanced stages are available, terlipressin should be used with extreme caution in patients with ALF.

2.1.4. Adrenocortical insufficiency

In septic shock, adrenal insufficiency, defined using the short synacthen test was shown to be associated with more
Recent literature has suggested that autoregulation is lost in patients with ALF resulting in cerebral hyperemia. In addition, continuous hemofiltration was associated with intermittent renal replacement therapy. The significantly higher cerebral perfusion pressures compared with significantly greater cardiovascular stability and G prior to treatment and this fell to 11.7.

Cerebral edema is possibly the first event. Ammonia related ALF is not entirely clear but a number of inter-related factors are thought to be responsible. Ammonia metabolism and its effects upon cellular bioenergetics increases brain lactate and alters reuptake mechanisms resulting in increases in extracellular glutamate which contribute to further brain swelling. The relative lack of randomized controlled clinical trial data makes it difficult to provide an evidence-based argument for the use of any particular form of therapy and Section 3 deals with the measures currently used. The main pathophysiologic targets of current therapies are summarized in Fig. 2.

Minimal intervention, and extreme care when moving or turning a patient underlie the general principles of management. Patients should be nursed head up by about 10–15%. There is ongoing discussion at present about how best to monitor patients with ALF from the neurologic point of view. Clearly, the most effective goal of management is control of ICP; therefore the use of ICP monitors seems logical. However, its routine use in ALF has to be balanced against the risk of bleeding. Having said this, the risks can be reduced to minimal levels by close attention to correction of coagulation and judicious use of recombinant factor VII.

We have recently suggested that it may be possible to select patients for insertion of ICP monitors based upon measurements using reverse jugular oxygen saturation. We showed that oxygen saturation of <65% or greater than 80% predicted a high likelihood of a high ICP. The complexity of monitoring using reverse jugular catheters, ICP monitors and, emerging new techniques such as continuous EEG monitors and microdialysis techniques supports the notion that such patients should be managed in experienced centers.

2.1.5. Renal support

In patients with advanced stages of ALF, renal failure is common and up to 70–80% will require some form of extracorporeal renal support in those who have circulatory disturbances and cerebral edema. Extracorporeal renal support also provides the opportunity to manage cerebral edema better allowing removal of fluid and reducing ammonia concentration. Several lines of investigation indicate that in patients with ALF complicated by oliguric renal failure it may be safer to use continuous hemofiltration rather than intermittent hemodialysis. In one of the early studies, intermittent therapy was associated with an increase in ICP from 8.4±1.5 mmHg prior to treatment to 12.6±1.8 mmHg on completion (P<0.05). However, during continuous therapy, the mean ICP was 15.6±5.2 mmHg prior to treatment and this fell to 11.7±2.3 mmHg at 4 h. In addition, continuous hemofiltration was associated with significantly greater cardiovascular stability and significantly higher cerebral perfusion pressures compared with intermittent renal replacement therapy.

The mechanism underlying the better neurologic tolerance of continuous hemofiltration compared with intermittent therapy is likely to be through the rapid water shifts that are encountered with intermittent haemodialysis.

2.2. Intracranial hypertension: pathophysiologic basis and management

The exact pathogenesis of intracranial hypertension in ALF is not entirely clear but a number of inter-related factors are thought to be responsible. Ammonia related brain edema is possibly the first event. CBF autoregulation is lost in patients with ALF resulting in cerebral hyperemia. Recent literature has suggested that the systemic inflammatory response may play an important modulating role. The alterations in ammonia metabolism and its effects upon cellular bioenergetics increases brain lactate and alters reuptake mechanisms resulting in increases in extracellular glutamate which contribute to further brain swelling. The relative lack of randomized controlled clinical trial data makes it difficult to provide an evidence-based argument for the use of any particular form of therapy and Section 3 deals with the measures currently used. The main pathophysiologic targets of current therapies are summarized in Fig. 2.

Ammonia reducing strategies. There are no randomized controlled clinical trials of lactulose in ALF. A recent retrospective study compared the outcome of 70 patients with ALF who received lactulose with data from 47 patients who did not receive the drug. There was no significant
difference between the groups in the severity of HE, stay in the intensive care unit, rate of infections, the percentage of patients that underwent OLT and the percentage of patients who died during follow up [57]. The routine use of lactulose cannot therefore be recommended.

L-ornithine L-aspartate is a mixture of two amino acids, which has been shown in controlled clinical trials to reduce blood ammonia concentrations by increasing ammonia detoxification in the muscle and the severity of HE in cirrhosis [58]. Although there are no data in humans with ALF, studies in experimental models of ALF suggests that the administration of this agent early in the course of illness may prevent the occurrence of brain edema [59]. Its further evaluation in ALF seems worthwhile.

Reduction of brain edema. The mainstay for the treatment of increased ICP in ALF is mannitol. Its use is associated with an increase in the osmolality of the capillaries in the brain and this results in movement of water according to Starling’s law. In patients with ALF, mannitol was shown to reduce episodes of cerebral edema significantly more frequently compared with those who did not receive this (P < 0.001). In those that received mannitol, the survival was significantly higher than those who did not receive it (47.1 and 5.9%, respectively, P 0.008) [60]. However, in patients with renal failure repeated administration results in an increase in plasma osmolality and loss of efficacy. Plasma osmolality needs to be measured if more than two doses are used to ensure 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. Although controlled data are lacking in the literature, reduction of blood volume (upto 500 ml) with hemofiltration is effective in reducing the ICP [7].

Hypertonic saline. Based upon principles similar to the use of mannitol, hypertonic saline has been evaluated in a small controlled clinical trial to try and prevent the occurrence of increases in ICP. Hypertonic saline (30%) via infusion to maintain serum sodium levels of 145–155 mmol/l was compared with a control group in 30 ALF patients. ICP decreased significantly relative to baseline over the first 24 h in the treatment group but not in the control group. The incidence of severe increases in ICP to values of 25 mmHg or greater, was significantly higher in the control group [61]. These results are provocative but before adoption into clinical practice, these results should be confirmed in another study. Importantly, as was pointed out in the accompanying editorial, some potential adverse effects of hypertonic saline should be considered such as multiple small hemorrhages, vein thromboses, brain shrinkage with obliteration of sulci, demyelination of the pons, induction of hypercholesemic acidosis, hematologic abnormalities, aggravation of coagulopathy and red cell lysis [62].

Sodium flux. Phenytoin acts upon the Na/K ATPase and this was used to test whether the frequency of subclinical fitting in ALF could be reduced. In a randomized study no significant differences in frequency of subclinical seizures (30 and 45%, respectively) were observed or the occurrence of increase in ICP was observed (25 and 50%, respectively). However, cerebral edema at autopsy was lower in the phenytoin-treated patients (P < 0.03) [63]. In another clinical trial from India, no benefit of using prophylactic phenytoin on the incidence of cerebral edema or in survival was observed suggesting that in the absence of new trial data, its use cannot be justified [64].

2.2.2. Cerebral blood flow and metabolism

Hyperventilation. The use of hyperventilation is based upon the observation that it restores CBF autoregulation [65]. In a controlled clinical evaluation of hyperventilation in ALF 20 patients were electively hyperventilated to maintain PaCO2 between 3.5 and 5 kPa. In 35 control patients, mechanical ventilation was instituted only if severe hypoxia or hypercapnia occurred. Cerebral edema, diagnosed clinically or by a rise in ICP to greater than 30 mmHg, occurred in 85% of hyperventilated patients and in 86% of controls. No significant reduction in the number of episodes of cerebral edema was observed in the hyperventilated patients (4.8 episodes/24 h) compared with the controls (5.3 episodes/24 h) [66]. Hyperventilation may reduce ICP acutely but should not be used over a prolonged period.

Thiopental sodium. Its administration results in cerebral vasoconstriction possibly by inhibition of nitric oxide synthase. No controlled trial data are available. Its use is mainly in patients who have increased ICP that is unresponsive to standard medical therapy. In 13 such patients, ICP was reduced by administration of 185–500 mg thiopental over 15 min. Five of the patients made complete recovery and there were only three deaths from intracranial hypertension [67]. However, thiopentone sodium administration to patients with ALF is associated with significant hemodynamic disturbances, which may require additional inotropes. Some of the benefit from reduction in ICP may be off-set by a reduction in mean arterial pressure and thereby cerebral perfusion pressure. Its use should be limited to episodes of catastrophic increases in ICP particularly in relation to OLT.

Indomethacin. Indomethacin induces cerebral vasoconstriction through inhibition of the endothelial cyclooxygenase pathway, alterations in extracellular pH and reduction in cerebral temperature [68]. Following initial positive results of its use in a patient with ALF and in an animal model [69], indomethacin has been tested in patients with ALF. In 12 patients with ALF and brain edema, indomethacin was administered at a dose of 25 mg intravenously. This was associated with a reduction in ICP from 30 (7–53) to 12 (4–33) mmHg (P < 0.05) without any deleterious effects on cerebral perfusion. Interestingly, the administration of indomethacin did not correct CBF autoregulation [70]. Although the results are interesting and may have some use in patients who do not respond to other forms of treatment, indomethacin is toxic for the kidneys, platelets and the gut.
and cannot be recommended for routine use in patients with ALF without more data.

Propofol. Propofol in a dose of 6 mg/kg/h 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/min of propofol. ICP was elevated in three of seven patients and remained controlled during the course of the illness in six of seven patients. One of the patients died from increased ICP and one during OLT [71]. Early data on the use of propofol in ALF are encouraging and support a fuller evaluation. The current literature supports its use as the sedative of first choice in ALF as it may also protect from intracranial hypertension.

2.2.3. Systemic inflammatory response

There is increasing evidence that systemic inflammatory response is important in the pathogenesis of increased ICP in ALF [7,23–25,55]. Hence, reduction in inflammatory response may be a strategy to prevent/treat intracranial hypertension in ALF.

Dexamethasone. There are no trials of steroids in ALF but in a relatively old study cerebral edema developed in 34 patients with similar frequency in those treated with and without dexamethasone (32 mg stat, 8 mg qds), (16 of 21 and 18 of 23, respectively). Survival was unaffected [60].

Hepatectomy. The use of hepatectomy in patients awaiting OLT is based upon the concept that the 'necrotic liver' is the source of unknown humoral substances that contribute to increased ICP. Ringe et al. performed hepatectomy with portacaval shunting in 32 patients. They observed stabilization of the cardiovascular and cerebrovascular state with 19 of 32 patients being successfully transplanted, 6–41 h afterwards [72]. In a single case, we have recently shown that the removal of the liver in an ALF patient resulted in improved ICP possibly through a reduction in CBF, nitric oxide and liver derived pro-inflammatory cytokines [24]. At present there is no role for this rather heroic intervention, except if there is a 'true' failure of every other approach.

2.2.4. Mild hypothermia

Mild-moderate hypothermia has been extensively studied in head injured patients and its use has been explored in a number of animal models of ALF. Peignoux et al. [73], Eguchi et al. [74] and Traber et al. [75] showed that hypothermic rats (32–33 °C) with ALF had significantly less brain water, reduced duration of encephalopathy and less clinical neurological deterioration compared with the euthermic rats. The proposed mechanisms impact upon all the major proposed pathogenic mechanisms of development of increased ICP in ALF. There are no controlled data of the use of hypothermia in ALF and most of the studies have been in ALF patients that have failed to respond to standard medical therapy.

The effect of moderate hypothermia (32–33 °C) in ALF patients is quite dramatic. Reduction in ICP in patients who have otherwise failed to respond to standard medical therapy is almost universal and recent data suggest that it may be effective in patients with established pupillary abnormalities and patients can be cooled for up to 5 days (median, 30 h). Rewarming a patient is associated with rebound increases in ICP, and therefore due care is necessary if this is to be undertaken [76]. Following our initial report on seven patients [76] providing proof of principle that hypothermia reduces ICP, we have recently reported a study on 14 patients who had ALF and uncontrolled increase in ICP and were awaiting OLT [77]. Thirteen were successfully bridged to OLT with a mean of about 32 h of cooling. Prior to cooling the ICP was elevated at a mean of 36 mmHg and this was reduced to a mean of 16 mmHg at 4 h, which was sustained at 24 h (P<0.001).

Table 1. During prolonged cooling, some patients do get increases in ICP, which has been shown in most patients to respond to further doses of mannitol. Although hypothermia can increase the risk of bleeding no such complication was encountered. Patients with ALF have a tendency to infection and theoretically hypothermia can increase that risk. Appropriate cultures and antibiotic therapy are essential. As stated above, hypothermia achieves its effect on ICP by impacting upon ammonia and its brain metabolism, cerebral blood flow and its autoregulation, reduction in inflammatory response and its markers such as nitric oxide, pro-inflammatory cytokines and markers of oxidative stress [77,78]. In addition to the neurologic effects hypothermia was associated with significant improvement in cardiovascular hemodynamics manifested by increased mean arterial pressure and systemic vascular resistance and reduced noradrenaline requirements (Table 1) [77]. Recently, we have shown that hypothermia (35 °C) can prevent the occurrence of increases in ICP in ALF patients who fulfilled criteria for poor prognosis and had Grade IV HE. Prior to

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<th>Pre-cooling</th>
<th>4 h</th>
<th>10–24 h</th>
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<tbody>
<tr>
<td>Intracranial pressure (mmHg)</td>
<td>36.5 (2.7)</td>
<td>16.3 (0.7)**</td>
<td>16.8 (1.5)**</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/100 g/min)</td>
<td>78.2 (9.7)</td>
<td>46.5 (3.8)**</td>
<td>44.0 (1.9)**</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>76.3 (3.6)</td>
<td>82.8 (2.2)**</td>
<td>84.9 (2.1)**</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s/cm−5)</td>
<td>503.8 (41)</td>
<td>671.4 (48.4)*</td>
<td>716.8 (43.3)**</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>11.3 (0.7)</td>
<td>9.2 (0.5)*</td>
<td>8.7 (0.5)**</td>
</tr>
<tr>
<td>Noradrenaline requirement (μg/kg/min)</td>
<td>0.5 (0.1)</td>
<td>0.2 (0.1)*</td>
<td>0.1 (0.0)**</td>
</tr>
<tr>
<td>Cerebral perfusion pressure (mmHg)</td>
<td>40.1 (2.9)</td>
<td>66.4 (2.8)**</td>
<td>67.2 (2.8)**</td>
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Note: The increase in mean arterial pressure and therefore the cerebral perfusion pressure is not associated with an increase in intracranial pressure indicating that hypothermia restores CBF autoregulation. [Data from Jalan et al. Gastroenterology 2004; 127: 1338–46]. Difference over time tested using one-way ANOVA with Bonferroni correction; *P<0.05, **P<0.01, ***P<0.001.
cooling, the ICP was elevated at a mean of 17.6 (2.7) mmHg and this was reduced to 15.2 (0.9) mmHg at 4 h, which was sustained at 24 h (15.9 (1.3) mmHg) ($P < 0.05$). There were no significant changes in CBF during the cooling period [unpublished data]. During the dissection and reperfusion phases of OLT in ALF patients, increases in ICP are inevitable and current therapies are limited to using barbiturates as treatment with its attendant difficulties. When the patients were maintained hypothermic during the transplantation procedure, the rises in ICP observed in the patients maintained normothermic during the dissection and the reperfusion phases was abolished. Furthermore, in this small study, we did not observe and major complications of hypothermia during the surgery [79].

The use of hypothermia in ALF is particularly promising and data for it strongly supports its use in patients with uncontrolled intracranial hypertension, particularly as a bridge to OLT. In patients, who have severe HE but do not have increased ICP, mild hypothermia reduces the risk of developing increases in ICP, but a lot more data are needed before recommendation for widespread usage can be made. A large clinical trial of hypothermia is being planned in the United States and selected centers in Europe.

3. Summary and future prospects

The multiorgan failure presented by patients with ALF is one of the most challenging management problems in clinical medicine and requires very close co-operation between the intensivist, the hepatologist, the neurologist and the surgeon. There are major issues regarding training of nurses and support networks from hematoloy, virology, biochemistry and radiology. Results can only be improved if there is a realization in the community hospitals that patients need to be referred early and the focus being shifted from responding to a patient in multiorgan failure to prevention of progression to multiorgan failure. Our knowledge about the pathophysiologic basis of the neurologic syndrome presented by a patient with ALF has advanced considerably and newer agents are aimed at drugs to reduce ammonia and its brain uptake, alter brain glutamine and glutamate metabolism and possibly use anti-inflammatory cytokine therapy. Our understanding of the pathophysiologic basis of hemodynamic disturbance, immune dysfunction and multiorgan failure is at a rudimentary stage and further understanding of the molecular basis of these circulatory disturbances is likely to improve our ability to manage these patients. Given the relatively small number of patients with ALF, it will be important in the future to organize ourselves in collaborative groups in order to explore the place of existing treatments and newer therapeutic modalities in appropriate multicenter studies.

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References


