

Therapeutic hypothermia for acute liver failure

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Cerebral edema is a potentially life-threatening complication of acute liver failure, the syndrome of abrupt loss of liver function in a patient with a previously healthy liver. Although the prevalence of cerebral edema appears to be decreasing, patients with rapidly progressive (hyperacute) liver failure, such as after acetaminophen overdose, remain at highest risk. In severe cases of cerebral edema, intracranial hypertension develops and leads to brain death after brainstem herniation or to anoxic brain injury and permanent neurologic impairment. Intracranial hypertension in patients with acute liver failure often can be temporarily controlled by manipulating body position, increasing the degree of sedation, and increasing blood osmolarity through pharmacologic means. However, these maneuvers often postpone, but do not eliminate, the risk of brainstem herniation unless orthotopic liver transplantation or spontaneous liver regeneration follows in short order. To buy time, the induction of therapeutic hypothermia (core temperature 32°C–35°C) has been shown to effectively bridge patients to transplant. Similar to the experience in patients with

cerebral edema after other neurologic insults, hypothermia reduces cerebral edema and intracranial hypertension in patients with acute liver failure by decreasing splanchnic ammonia production, restoring normal regulation of cerebral hemodynamics, and lowering oxidative metabolism within the brain. Hypothermia may also ameliorate the degree of liver injury. Hypothermia has not been adequately studied for its safety and theoretically may increase the risk of infection, cardiac dysrhythmias, and bleeding, all complications independently associated with acute liver failure. Therefore, although an ample body of experimental and human data provides a rationale for the use of therapeutic hypothermia in patients with acute liver failure, multicenter, randomized, controlled clinical trials are needed to confirm that hypothermia secures brain viability and improves survival without causing harm. (Crit Care Med 2009; 37[Suppl.]:S258–S264)

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The syndrome of acute liver failure (ALF), the abrupt onset of coagulopathy and hepatic encephalopathy in a patient without preexisting liver disease, often leads to a multisystem illness that includes the development of brain dysfunction. The clinical expression of this dysfunction is hepatic encephalopathy, by definition a requisite for the diagnosis of ALF, and can evolve into cerebral edema and intracranial hypertension. The causes of ALF encompass a wide variety of toxic, viral, metabolic, and vascular insults to the liver, and the prevalence of any single etiology depends on the geographic and socioeconomic location of the patient. In areas of the developing

world, where orthotopic liver transplantation (OLT) is not widely available, fulminant viral hepatitis (principally hepatitis B and E) predominates, whereas drug-induced ALF (including acetaminophen overdose) is the principal cause in the United States and in many nations of Western Europe (1). Although the pathogenesis of ALF differs according to its cause, complications—including cerebral edema—are similar, suggesting that therapies aimed at treating complications should be applicable to all affected patients.

More than half of ALF patients develop spontaneously high intracranial pressure (ICP) as a consequence of brain edema, and one third die of cerebral herniation without critical care management in an experienced liver transplant center (2). Although the frequency of clinically overt brain edema in ALF patients has decreased over the last two decades, intracranial hypertension still accounts for 20%–25% of deaths (2, 3). To optimize neurologic recovery after ALF, a balance must be met between maintaining adequate cerebral blood flow to support aerobic metabolism and avoiding hyperperfusion, which contributes to intracranial hypertension. The optimal ICP and cere-

bral perfusion pressure (CPP) in patients with ALF have not been defined. Similar to recommendations in patients with severe traumatic brain injury (4, 5), interventions in ALF are usually considered when ICP exceeds 20–25 mm Hg or CPP declines to <50 mm Hg (6). Basic intensive care maneuvers to balance CPP and ICP include positioning the patient (head up 30°, neutral neck position), administering intravenous fluids, supporting mean arterial pressure with vasopressors, and treating hypo-osmolality (principally hyponatremia).

Patients who develop cerebral edema and intracranial hypertension despite these basic maneuvers have a poor prognosis and require emergent intervention. Although osmotically active agents, such as mannitol or hypertonic saline, and increased sedation with either barbiturates or propofol may initially control ICP, their benefits are often temporary and associated with potentially serious adverse events (7–10). The frequent recrudescence of intracranial hypertension after initial control of ICP emphasizes the need for alternative modalities to bridge these patients to OLT.

Therapeutic hypothermia has been shown to ameliorate neurologic deficits

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We dedicate this work to the memory our friend and colleague, Dr. Andres T. Blei.

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in other critical medical illnesses characterized by cerebral edema. In selected adults resuscitated from cardiac arrest, hypothermia has become standard medical practice because it improves neurologic outcome (11, 12). Furthermore, hypothermia has been shown to reduce ICP in patients with traumatic brain injury (13) and to minimize disability in neonates with hypoxic-ischemic encephalopathy (14). These clinical observations, together with studies in experimental models and preliminary data in humans with ALF, provide the rationale for the use of hypothermia in this highly life-threatening condition.

In the following synopsis, we first review experimental data that explore mechanisms by which therapeutic hypothermia modulates cerebral edema and intracranial hypertension in animal models of ALF. Subsequently, we review the small body of clinical experience in patients with ALF managed under hypothermic conditions, note potential serious adverse events of hypothermia in this patient population, and identify areas for further research.

Experimental Basis for Hypothermia in ALF

The pathogenesis of cerebral edema in ALF is multifactorial and incompletely understood. Simplistically, ammonia and anisotonic conditions increase the intracellular osmolarity of cortical astrocytes (15), inducing the passive movement of water from the intravascular space, resulting in brain swelling. Although previously controversial, blood-brain barrier permeability appears to remain intact (16), supporting the notion of a primary cytotoxic rather than vasogenic mechanism. Hyperammonemia is the single most important determinant of brain edema in ALF and parallels the risk of its development (17–19). In experimental animals and isolated astrocytes, the accumulation of glutamine, the product of ammonia and glutamate *via* glutamine synthetase, also parallels the development of brain edema (15). In addition to having an osmotic effect, the accumulation of glutamine in astrocytes triggers changes in mitochondrial function that affect cellular oxidative metabolism (20), leading to the accumulation of brain lactate (21, 22). The generation of oxidative stress also triggers cerebrovascular dilation and hyperperfusion, which contribute to intracranial hyper-

Table 1. Putative mechanisms of neuroprotection by therapeutic hypothermia in experimental models of acute liver failure

Target	Effect
Ammonia	↓ Arterial concentration → ↓ brain concentrations ↓ Production by intestinal bacteria ↓ renal release into blood ↓ Proteolysis
Brain osmolarity	Prevention of brain lactate and alanine accumulation Prevention of changes in brain organic osmolytes
Brain extracellular space	↓ Accumulation of glutamate → ↓ glutamate-induced astrocyte swelling
Cerebral hemodynamics	Normalization of ↑ cerebral blood flow → ↓ cerebral uptake of toxins (e.g., NH ₃)
Brain glucose metabolism	Restoration of cerebrovascular autoregulation ↓ Cerebral metabolic rate of glucose and oxygen ↓ <i>De novo</i> synthesis of lactate and alanine
Inflammation	↓ Arterial and brain production of cytokines Conversion from proinflammatory to anti-inflammatory cytokine profile

tension (23, 24). Indeed, even small increases of blood perfusion in the non-compliant cranium can raise ICP, which in turn can compromise cerebral oxidative metabolism. Cerebral hyperemia also increases hydrostatic pressure in brain capillaries, exacerbating osmotic disturbances by increasing ammonia delivery to astrocytes (25).

In experimental models of ALF, hypothermia reverses many of the pathophysiologic abnormalities leading to cerebral edema, including the production of ammonia, brain hyperosmolarity, and cerebral hyperperfusion (Table 1). The efficacy of hypothermia in preventing these abnormalities was first shown in experimental models of ammonia-induced brain edema, including mice receiving ammonia infusions (26), rats undergoing hepatic devascularization (27), and rats with portacaval shunt receiving ammonia infusion (28). Schenker and Warren (26) first noted that the dose of ammonia required to produce a 50% mortality rate in mice was almost twice as high in hypothermic animals compared with normothermic controls. Decreased concentrations of ammonia in the brain were detected as soon as 20 secs after ammonia injection in hypothermic animals, suggesting a reduction of blood-to-brain transfer. Later, Traber et al (27) reported that spontaneous hypothermia during ammonia infusion in rats with portacaval anastomosis ameliorated development of brain edema. Hypothermia also prevented development of brain edema in the rat with portacaval shunt that received ammonia infusion and reversed abnormalities in cerebral blood flow (28) and brain glucose metabolism (29).

Disturbed amino acid metabolism accompanies brain edema in experimental ALF (30, 31). As noted previously, the increase in extracellular brain glutamate seems particularly important in experimental ALF and causes astrocyte swelling *via* NMDA receptor activation, an effect prevented by cooling. The increase in brain amino acid concentrations includes aromatic amino acids, which have been incriminated in the pathogenesis of hepatic encephalopathy in cirrhosis and ALF (32). Although the increases of six of 11 (55%) amino acids can be attenuated (Ala, Phe), normalized (Glu, Asp, Gly, Trp), or maintained (Gln, Tau, Val, Tyr) by hypothermia, their exact pathophysiologic role in mediating brain edema in ALF remains poorly defined.

Experimental models also suggest that hypothermia attenuates liver injury in ALF. In mice with acetaminophen-induced ALF, cooling to 32°C not only increased survival but decreased alanine aminotransferase levels and lowered histologic evidence of apoptosis, compared with normothermic animals (33). Hypothermic animals also displayed evidence of impaired hepatic regeneration as assessed by lower bromodeoxyuridine incorporation, expression of cellular nuclear antigen, and mitotic activity, an observation supporting concern that hypothermia may delay hepatic regeneration in humans (discussed subsequently) (34). However, the retardation of bromodeoxyuridine incorporation strongly correlated with the degree of hepatocyte necrosis, leading the authors to conclude that hypothermia limits liver injury rather than retards liver regeneration. Another recent study in partially hepate-

ctomized mice found no difference in proliferative response in hypothermic vs. normothermic animals (35).

Clinical Application of Hypothermia for ALF

Within the spectrum of ALF in humans, the natural history of liver injury and the development of complications differ widely according to the cause of ALF (1). In particular, the risk of developing cerebral edema depends on the rapidity of the clinical evolution of liver failure (36). In the early 1990s, O'Grady et al (37), investigators from the King's College Liver Failure Unit in the United Kingdom, proposed a classification system for ALF based on the jaundice-to-encephalopathy interval. Patients with the most rapid evolution, so-called hyperacute liver failure, developed hepatic encephalopathy within 7 days of the onset of symptoms and more commonly developed cerebral edema than those with more slowly evolving liver failure. The most common causes of hyperacute liver failure in the United States and in some nations of western Europe are acetaminophen (paracetamol) overdose and acute viral hepatitis. The reason patients with rapidly progressive hepatic encephalopathy are more prone to develop cerebral edema probably involves the rapidity of developing hyperammonemia, which temporally overwhelms the ability of astrocytes to compensate for the osmotic stress of accumulating glutamine by exporting organic osmolytes (15). In addition to a short jaundice-encephalopathy interval, other risk factors for the development of cerebral edema include the degree of hyperammonemia, use of vasopressors, and presence of renal failure (18). In particular, a serum ammonia of $>150\text{--}200\ \mu\text{M}$ strongly predicts the development of intracranial hypertension (17). Considering their high risk of developing cerebral edema, such patients would be potential candidates for therapeutic hypothermia.

Standard Medical Therapy of Cerebral Edema in ALF. As noted previously, the medical management of cerebral edema in ALF usually postpones, but does not prevent, cerebral death unless followed closely by OLT or by spontaneous hepatic regeneration. Indeed, $>90\%$ of patients with ALF and intracranial hypertension die within 12 hrs if medical management fails to control ICP (36). The first line of therapy remains the administration of in-

Table 2. Criteria and management of patients with acute liver failure and uncontrolled intracranial hypertension treated with therapeutic hypothermia

King's College Criteria for Poor Prognosis	"Uncontrolled" Intracranial Hypertension
Acetaminophen etiology: arterial pH <7.30 or all of the following: (1) PT >100 secs (INR >6.5), (2) Creatinine >3.4 mg/dL, and (3) Grade 3–4 hepatic encephalopathy	Defining entry criteria: intracranial pressure >25 mm Hg for ≥ 1 hr despite mannitol boluses (1 g/kg over 20 mins $\times 2$) Withdrawal of 500 mL of fluid by continuous venovenous hemofiltration
Non-acetaminophen etiology: PT >100 secs (INR >6.5) or any three of the following: (1) Non-A, non-B viral hepatitis/drug/halothane etiology (2) Jaundice to encephalopathy >7 days (3) Age <10 or >40 yrs (4) PT >50 secs (INR >3.5) (5) Bilirubin >17.4 mg/dL	Methods Cooling blankets Norepinephrine to cerebral perfusion pressure >50 mm Hg \pm mean arterial pressure $>80\text{--}90$ mm Hg Intubated, mechanically ventilated Sedated (propofol) Paralyzed (atracurium) PaCO ₂ Prophylactic antibiotics and fluconazole Pulmonary artery occlusion pressure 8–14 mm Hg

PT, prothrombin time; INR, international normalized ratio.

Patients with acute liver failure reported by Jalan et al (42, 44, 45) were cooled based on fulfillment of the King's College criteria for poor prognosis (left column) (36) and a standard definition of uncontrolled intracranial hypertension (right column). Methods for managing patients with uncontrolled intracranial hypertension were also standardized by the methods indicated (right column).

travenous mannitol boluses, shown in the early 1980s to decrease ICP in ALF patients with intracranial hypertension (7). Unfortunately, the administration of mannitol is limited by hyperosmolality; additional mannitol boluses should not be given to patients with serum osmolality >320 mosm/L or a high osmole gap (38) or to patients who develop severe renal failure unless accompanied by continuous hemodiafiltration. In addition, mannitol does not reliably decrease ICP to safe levels (<25 mm Hg) in patients with severe intracranial hypertension (e.g., ICP >40 mm Hg), and rebound after a successful initial response occurs routinely (39). The administration of hypertonic saline has been shown in a randomized, placebo-controlled trial to prevent intracranial hypertension in high-risk ALF patients but has not been tested as treatment for existing intracranial hypertension (40). In cases refractory to osmotic agents, increased sedation (9) and intravenous boluses of indomethacin (41) have been used to lower ICP but are currently considered rescue interventions.

Use of Hypothermia in Humans with ALF. Drawing on the rationale and experimental data outlined previously, Jalan et al (42) reported their initial experience with therapeutic hypothermia in humans with ALF in 1999. In this and subsequent case series, these investigators studied subjects with poor-prognosis liver failure defined by King's College criteria (36)

and intracranial hypertension uncontrolled by conventional medical management, defined as an ICP >25 mm Hg for 1 hr despite two boluses of mannitol (1 g/kg body weight) and removal of 500 mL of blood volume via continuous venovenous hemofiltration (Table 2). All patients were mechanically ventilated, sedated, and paralyzed; all received prophylactic broad-spectrum antibiotics. Fiberoptic ICP monitors were placed in a subdural location, and norepinephrine was infused to maintain mean arterial pressure >90 mm Hg and CPP (CPP = mean arterial pressure – ICP) >50 mm Hg.

Patients meeting these criteria were cooled using external cooling blankets for various periods of time depending on whether they were candidates for OLT (Table 3). In the original series (42), three non-OLT candidates were cooled for 8 hrs to a core temperature of $32^\circ\text{C}\text{--}33^\circ\text{C}$, which was achieved within 1 hr. Hypothermia transiently improved ICP and CPP as well as cardiac index and allowed a decrease in the dose of norepinephrine required to maintain mean arterial pressure. All three patients promptly relapsed after rewarming and died. In contrast, four patients who met OLT criteria were successfully transplanted after 10–14 hrs of hypothermia, which was maintained intraoperatively with cooling blankets below the torso and on the legs. Although three transplanted patients had uneventful neurologic recovery, one succumbed to brain

Table 3. Characteristics and outcomes of patients with acute liver failure treated under hypothermic conditions

Author, Year	n	Acetaminophen, n	Duration of Cooling, hrs	Goal Temperature, °C	End Point	Outcome, n
Jalan, 1999 (42)	7	6	8–14	32–33	Intracranial pressure (n = 3) OLT (n = 4)	Survival non-OLT (zero of three patients) Survival OLT (three of four patients)
Jalan, 2001 (51)	9 ^a	7	4	32–33	Cerebral blood flow	Hypothermia restored cerebral blood flow autoregulation
Jalan, 2003 (44)	5	5	Not available	32–34	Intracranial pressure during OLT	Hypothermia prevented intracranial hypertension during OLT
Jalan, 2003 (65)	5	Not available	23–119	35	Prevention of intracranial hypertension	Survival to OLT (three of five patients) Spontaneous survival (one of five patients)
Jalan, 2004 (45)	14	13	10–118	32–33	OLT	Survival to OLT (13 of 14 patients) Survival at 3 mos (10 of 13)

OLT, orthotopic liver transplantation.

^aTwo patients were also reported by Jalan et al (42).

death. The effects of hypothermia on outcomes and cerebral hemodynamics in these patients and in those from subsequent case series are depicted in Table 3.

The initial series of patients treated with hypothermia emphasized the importance of OLT in rescuing patients with medically refractory intracranial hypertension. Indeed, not enough information exists at this time to support the use of long-term hypothermia to obviate the need for OLT. However, intracranial hypertension also represents a significant risk during OLT, even in patients with ALF who have normal pretransplant ICP (43). ICP most often spikes during dissection of the native liver and after reperfusion of the implanted allograft. To avoid intraoperative ICP spikes, five patients with uncontrolled intracranial hypertension, but in whom ICP was normalized by cooling, were transplanted under hypothermic (32°C–33°C) conditions (44). The strategy not only prevented ICP spikes during dissection and reperfusion but also prevented cerebral hyperemia. In contrast, in the same series, normothermic patients undergoing OLT experienced ICP spikes, cerebral hyperemia, and a decline in CPP, regardless of whether they required treatment for intracranial hypertension before transplant.

The efficacy of hypothermia in bridging patients to OLT was further demonstrated in 14 patients awaiting liver transplantation, in whom ICP remained uncontrolled despite the medical maneuvers outlined in Table 2 (45). Although ICP initially decreased to normal in all patients cooled to 32°C–33°C, six patients required intermittent boluses of mannitol for transient intracranial hypertension. Of these patients, five responded to mannitol and one died of cerebral herniation. Over-

all, 13 of 14 patients underwent successful OLT between 12 and 118 hrs after the induction of hypothermia (Table 3).

Other disease states characterized by hyperammonemia and cerebral edema, but in which classic ALF does not occur (other liver functions preserved), have been successfully managed with hypothermia. Children with cerebral edema in Reye's syndrome, a rare acquired syndrome of hyperammonemia ascribed to defective mitochondrial β -oxidation (46), have been cooled to 31°C–32°C with improvement (47–49). Similarly, mild hypothermia has been reported to ameliorate severe hyperammonemia in case reports of infants with urea cycle defects, with resolution of coma (50).

In the human studies discussed previously, hypothermia reduced arterial ammonia concentrations and the extraction of ammonia by the brain (42, 45). Hypothermia also prevented cerebral hyperemia (Table 4), possibly by restoring cerebral blood flow autoregulation (51). Concentrations of mediators of the systemic inflammatory response (tumor necrosis factor- α , interleukin-1 β , and interleukin-6), which may contribute to cerebral hyperemia and the loss of cerebral blood flow autoregulation (52), also decreased (45). Finally, markers of oxidative stress such as malonyldialdehyde, which are generated by proinflammatory cytokines, declined after cooling (45). There are no data in humans exploring a possible effect of hypothermia on ameliorating liver injury in patients with ALF, as have been described in experimental animal models and discussed previously in this article (33).

Safety of Hypothermia in ALF. The prevalence and severity of complications of therapeutic hypothermia in patients

with ALF have not been meticulously dissected. Although experience in non-ALF populations provides important lessons, the complications of ALF *per se* closely resemble those of hypothermia and may compromise an analysis of safety. In a comprehensive review, Polderman (53) emphasized several adverse effects of hypothermia, which may be particularly relevant to patients with ALF (Table 5). Generally, the most serious of these complications develop as core temperatures drop to <32°C, with less severe effects at temperatures <35°C. Perhaps the most important potential complications of hypothermia are those that occur independently as a consequence of ALF: bleeding, infection, and cardiovascular instability.

Core temperatures <35°C usually reduce platelet concentrations to 30,000–100,000/mm³ (54) and are associated with qualitative platelet dysfunction (55). Therapeutic hypothermia also inhibits the clotting cascade and increases the prothrombin time/international normalized ratio (56). Nevertheless, hypothermia has not been shown to increase the risk of bleeding in critically ill non-ALF patients. For example, hypothermia does not appear to extend intracranial bleeding in patients with traumatic brain injury or subarachnoid hemorrhage (53). Although an elevated prothrombin time/international normalized ratio comprises part of the definition of the syndrome of ALF, and hypothermia might be expected to exacerbate the coagulopathy, prolongation of the prothrombin time/international normalized ratio in patients with liver disease does not necessarily reflect abnormal hemostasis, because such patients have decreased anticoagulant as well as procoagulant factors (57–59). Therefore, it may not be surprising that

Table 4. Cerebral hemodynamics in patients with poor-prognosis acute liver failure and uncontrolled intracranial hypertension before and after institution of therapeutic hypothermia

Author, Year	Intracranial Pressure, mm Hg [range]		Cerebral Perfusion Pressure, mm Hg [range]		Cerebral Blood Flow, mL/100 g/min [range]	
	Before	After	Before	After	Before	After
Jalan, 1999 (42)	45 [25–49]	16 [13–17]	45 [37–56]	70 [60–78]	103 [25–134]	44 [24–75]
Jalan, 2001 (51)	46 [27–54]	19 [15–22]	48 [35–61]	66 [53–74]	111 [69–134]	56 [38–67]
Jalan, 2003 ^a (44)	16	17	56	57	47	51
Jalan, 2003 (65)	17.6	15.2	NA	NA	NA	NA
Jalan, 2004 (45)	36.5	16.3	40.1	66.4	335	252

NA, not available.

^aData are approximated from figures showing no significant change in intracranial pressure, cerebral perfusion pressure, or cerebral blood flow during orthotopic liver transplantation surgery in patients maintained at a median of 33.4°C compared with normothermic subjects, who experienced significant increases in intracranial pressure and cerebral blood flow and decreases in cerebral perfusion pressure during dissection of the native liver and reperfusion of the implanted allograft.

Table 5. Potential and observed adverse events in patients with liver failure managed under hypothermic conditions

Potential Adverse Effects ^a	Associated Temperature, ^b °C	Observed Effects in Hypothermic Patients With Acute Liver Failure
Infection	≤35	Non-OLT patients: sepsis (in one of five patients); OLT patients: catheter sepsis, pneumonia, and urinary tract infection (in nine of 13 patients; death in two of nine patients)
Bleeding	≤35	No difference in transfusion requirements at OLT compared with normothermic patients; no reports of spontaneous bleeding; no bleeding complications of intracranial pressure monitor placement
Cardiac dysrhythmias	≤32	No reported events; significant incidence of bradycardia requiring medical intervention in an ongoing, unpublished trial
Pancreatitis	≤35	No reported events
Renal dysfunction	≤35	No reported events
Drug intoxications	≤35	No reported events
Delayed hepatic regeneration	Not defined	No reported events

OLT, orthotopic liver transplantation.

^aPotential adverse effects of hypothermia have been observed in other disease states as described by Polderman (53); ^bpotential adverse effects are rarely observed until core temperatures drop below those noted in studies of patients without acute liver failure.

Jalan et al (42, 44, 45, 51) did not observe an increased prevalence of bleeding complications in ALF patients treated with mild hypothermia. Specifically, none of the patients rendered hypothermic experienced intracranial bleeding after ICP monitor placement, and mucosal bleeding, the most common source of spontaneous hemorrhage in ALF patients (54), was not mentioned as an adverse event. Furthermore, hypothermic patients undergoing OLT had similar blood, platelet, and plasma transfusion requirements compared with those transplanted under “normothermic” conditions, recognizing that core temperatures spontaneously

drop to 34°C–35°C during transplant surgery (44). Finally, there have been no instances of clinically significant bleeding in an ongoing randomized, controlled trial of hypothermia in human ALF (F. Larsen, J. Wendon, W. Bernal, and N. Murphy, unpublished observations).

Systemic inflammation and sepsis leading to multiorgan system failure comprise the single most common cause of death in patients with ALF (60). Consequently, potential adverse effects of hypothermia on immune function are particularly pertinent to the patient with ALF. Hypothermia impairs leukocyte function, reduces leukocyte number, in-

hibits inflammatory cytokine cascades, and results in an increased prevalence of pneumonia after 48 hrs of cooling in non-ALF patients (53). The prevalence of infection in patients with ALF managed under hypothermic conditions has not been directly compared with those managed under normothermic conditions. However, ALF patients cooled to 32°C–33°C experienced a significant prevalence of pneumonia and other infections after OLT despite prophylactic antibiotics: nine of 13 patients became infected after OLT, and two infections led to multiorgan system failure and death (45). In a different series, four of five hypothermic ALF patients developed post-OLT infections, but so did nine of 11 OLT recipients who were managed under normothermic conditions (44). As for the uncertainties regarding exacerbating coagulopathy, the possibility that hypothermia further impairs the immune dysfunction of ALF (61) requires further study.

Although sinus tachycardia followed by bradycardia occurs regularly in non-ALF patients cooled to ≤35°C, these rhythms do not signify clinical deterioration and do not usually require intervention (53). In an ongoing study of ALF patients at high risk of cerebral edema but with normal ICP, hypothermia frequently resulted in significant bradycardia and required dopamine infusion (F. Larsen, J. Wendon, W. Bernal, and N. Murphy, unpublished observations). In addition, myocardial irritability leading to atrial fibrillation and ventricular tachyarrhythmias may occur as core temperature drops to <32°C. Surprisingly, no reports of significant dysrhythmias appeared in the studies by Jalan et al (42, 44, 45, 51), even during OLT, when electrolyte shifts can lead to extreme cardiac irritability. In the same ongoing study of prophylactic hypothermia (noted previously), ventricular extrasystoles have occasionally required medical intervention. These observations emphasize the importance of close monitoring of the cardiac rhythm during hypothermia and rewarming as well as prevention of overshooting to temperatures <32°C.

Elevated amylase occurs frequently in ALF patients and may be a marker of multiorgan system failure and pancreatitis (62, 63). Hyperamylasemia also occurs regularly in non-ALF patients treated with hypothermia (53), but its clinical significance remains uncertain; clinically significant pancreatitis appears to be uncommon.

Whether hypothermia increases the prevalence of pancreatitis in patients with ALF remains unknown, although no reports from case series have appeared.

Hypothermia in patients with ALF may also have deleterious effects on liver regeneration and secondarily exacerbate the effects of liver failure on drug metabolism. A theoretical delay in hepatic regeneration by hypothermia was revived by Munoz in 2005 (34), who suggested that patients may not be bridged to OLT by hypothermia as much as they may be committed to OLT because of blunted regeneration. Although the notion merits further study, experimental data noted previously suggest that hypothermia limits hepatic injury and may thereby decrease the need for regeneration (33). Unfortunately, techniques do not exist to noninvasively evaluate the effects of hypothermia on hepatic regeneration in humans with ALF. Hypothermia may also delay drug metabolism, affect temperature-sensitive enzymatic reactions, and increase the risk of drug toxicity in patients with ALF, who already have delayed drug metabolism because of hepatocellular insufficiency. However, hypothermia affects drug metabolism by other unanticipated mechanisms, such as decreased affinity of drug for its receptor as well as changes in volumes of distribution (64). In the absence of studies in hypothermic patients with ALF, it would seem prudent to administer drugs sparingly, titrating doses to a desired effect whenever possible.

Conclusions and Perspective

In patients with intracranial hypertension from ALF, the clinical challenge remains to develop therapies as a bridge either to OLT or to spontaneous hepatic regeneration, while maximizing neurologic recovery. In the uncontrolled studies discussed here, the induction of hypothermia appears to effectively ameliorate brain edema and intracranial hypertension. Compared with other alternatives recently tested, such as bioartificial liver support devices, the induction of hypothermia is widely available and inexpensive. Both the pathophysiologic rationale and initial clinical experience support the use of hypothermia for the prevention and treatment of intracranial hypertension in ALF, recognizing that the effects of hypothermia on the complications of ALF and the extent of liver injury and liver regeneration remain undefined.

Based on experimental data and preliminary clinical experience, a growing rationale exists for the performance of a randomized clinical trial in ALF patients managed under hypothermic and normothermic conditions. Because ALF remains an uncommon syndrome even at large liver transplant centers, multiple sites will be required to ensure recruitment of an adequate sample size. The success of a randomized clinical trial of hypothermia in ALF will also hinge on standardization of a detailed management protocol to isolate the effects of hypothermia from the myriad of other interventions applied to these critically ill patients.

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