Review Article

wiener klinische wochenschrift
the middle european journal of medicine
Printed in Austria

Wien Klin Wochenschr (2004) 116/3: 67–81
© Springer-Verlag 2004

Acute liver failure

Ludwig Kramer

Department of Medicine IV, University of Vienna, Vienna, Austria

Akutes Leberversagen

Zusammenfassung. Das akute Leberversagen ist ein seltenes und lebensbedrohliches Krankheitsbild, welches infolge einer schweren Leberschädigung bei bisher gesunden oder asymptomatischen Patienten auftreten kann. Die hohe Mortalität der Erkrankung ist vor allem auf zwei Komplikationen zurückzuführen, deren Entstehung von der zeitlichen Entwicklung der Leberschädigung abhängt. Das hyperakute Leberversagen kann aufgrund erhöhter arterieller Ammoniakkonzentrationen innerhalb weniger Tage zur Entwicklung eines Hirnödems und zu einer oft letalen Hirnstammeinklemmung führen, welche durch frühzeitige Lebertransplantation verhindert werden kann. Bei Patienten, welche das initiale Hirnödem überleben, wird häufig eine spontane Regeneration mit völliger Gesundung beobachtet. Entwickelt sich eine Leberschädigung hingegegen langsamer (akutes oder subakutes Leberversagen), so kann die zerebrale Osmoregulation eine Einkemmung meist verhindern. Diese Patienten haben jedoch eine schlechte Regenerationsfähigkeit und benötigen die Lebertransplantation vor dem Auftreten lebensbedrohlicher Komplikationen wie Sepsis, Nierenversagen oder Multiorganversagen. Einige Zentren versuchen, die Progression der Erkrankung durch den Einsatz extrakorporaler Entgiftungsverfahren zu verhindern, zumal erhöhte Ammoniakkonzentrationen durch Hämodialyse abgesenkt werden können. Pharmakologische Interventionen, welche die massive Apoptose in der Leber reduzieren und die Regeneration unterstützen könnten, befinden sich in Entwicklung.

Schlüsselwörter: Akutes Leberversagen, Ammoniak, Enzephalopathie, fulminant, Glutamin, Hirnödem, Leberunterstützung, Transplantation.

Summary. Acute liver failure is a rare and life-threatening clinical syndrome following severe hepatic injury. Depending on the rapidity of its development, two distinct complications contribute to a high mortality: in hyperacute liver failure, rapid development of massive hepatic necrosis and apoptosis gives rise to severe hyperammonemia, hepatic encephalopathy and life-threatening cerebral edema. The high risk of cerebral herniation requires early listing for emergency liver transplantation. Patients with hyperacute liver failure surviving the initial episode of cerebral edema have a substantial potential for hepatic recovery. If progressive hepatic failure develops more slowly, astrocytic osmoregulation prevents cerebral herniation in most instances. Unfortunately, these patients have a small potential of hepatic regeneration and transplantation should be performed before renal failure, sepsis or multiorgan failure emerge. Experimental treatment methods including detoxification by artificial or bioartificial liver support or by stimulating hepatic regeneration are currently evaluated. Recognition of ammonia toxicity has stimulated the search for early ammonia-lowering strategies and strongly renewed the interest in dialytic therapies. Anti-apoptotic interventions are among the most promising pharmacological options for the near future.

Key words: Acute liver failure, ammonia, bioartificial, cerebral herniation, encephalopathy, fulminant, glutamine, liver support, transplantation.

Introduction

Acute liver failure (ALF) is a life-threatening multisystem disturbance following severe hepatic injury in the absence of pre-existing symptomatic liver disease [1]. With an incidence of 1–10/10^6, ALF is a rare disease in western countries but occurs considerably more frequently in Africa and Asia, due to a higher prevalence of hepatotropic viruses [2]. The rapid sequence of jaundice, coma, multiorgan failure and death is among the most dramatic events in medicine and has fascinated physicians since ancient times. Mortality of patients progressing to advanced (grade III/IV) encephalopathy and cerebral edema approaches 80% despite intensive care therapy and can be currently reduced only by timely orthotopic liver transplantation. As hepatic encephalopathy is the most characteristic clinical feature of ALF, its temporal evolution is used to define different clinical variants of the disease. Until the recent advent of orthotopic liver transplantation, therapeutic measures have been largely unsuccessful. Progress in pathophysiology of cerebral edema has established a rationale for various medical and extracorporeal treatment methods, which are currently investigated in patients awaiting transplantation.

A multidisciplinary approach to patients with ALF is important to a) identify patients who need rapid referral to transplant centers, b) provide specialized intensive care including the possibility for extracorporeal detoxification, and c) allow early individual decision for emergency

transplantation on the basis of prognostic criteria. Due to increasing shortage of donor organs, many patients may develop cerebral herniation and progress to irreversible neurological damage before an organ becomes available. Thus, alternatives to orthotopic liver transplantation and specific measures to sustain life by prevention of cerebral herniation are currently investigated. Nonetheless, lack of unequivocal clinical benefit of such strategies advocates maximal physiologic support by dedicated intensive care medicine, aiming to prevent or delay complications and facilitate hepatic regeneration.

Definition

Trey and Davison (1970) have defined *fulminant hepatic failure* as "a potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within eight weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease" [3]. Bernuau's subsequent discrimination between *fulminant* and *subfulminant* hepatic failure was based on the different clinical presentation of patients according to the latency between jaundice and encephalopathy (0–2 weeks versus >2–10 weeks) [4]. Analyzing the largest single-center experience at King's College Hospital, London, O'Grady et al. further discriminated *hyperacute, acute and subacute* liver failure, which is currently the most frequently used classification (Table 1) [5].

The obligatory role of hepatic encephalopathy in the definition of ALF has been criticized [6] and probably reflects the high incidence of hyperacute liver failure in the UK. Both coagulopathy and increased intracranial pressure are reliable prognostic parameters as well. Many patients with subacute hepatic failure develop encephalopathy only as they progress to septic multiorgan failure (where transplantation is not feasible anymore) and require listing for transplantation before fulfillment of O'Grady criteria. Acknowledging different clinical characteristics of ALF in most parts of the world and difficulties in assessing jaundice in dark-skinned patients, the International Association for the Study of the Liver (IASL) has proposed a modified definition differentiating *acute hepatic failure* ("encephalopathy occurring within 4 weeks from onset of symptoms") and *subacute hepatic failure* ("encephalopathy *or ascites* developing between 4 weeks and 6 months from onset of symptoms"). The IASL also recommended that acute and subacute hepatic failure be viewed as distinct clinical entities and not as subgroups of a common syndrome [7].

Table 1. Acute liver failure – definition of subtypes according to O'Grady et al.

Subtype of liver failure	Hyperacute	Acute	Subacute
Encephalopathy	yes	yes	yes
Jaundice to encephalopathy (days)	0–7	8–28	29–72
Cerebral edema	frequent	frequent	rare
Prothrombin time	+++	+++	+
Bilirubin	+	++	+++
Prognosis without transplantation	moderate	poor	poor

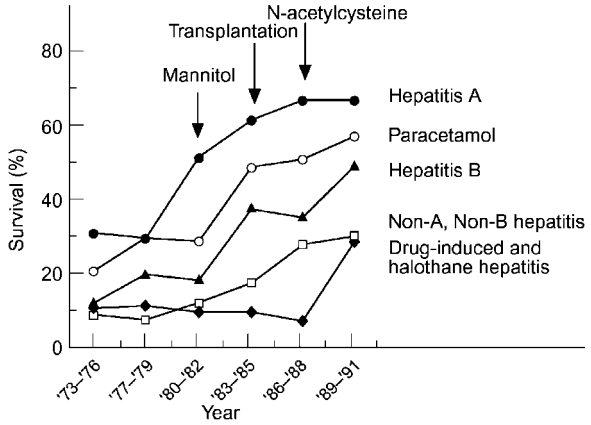

Fig. 1. Survival rates according to etiology and therapeutic interventions in patients with acute liver failure at King's College Hospital, 1973 to 1991. Reprinted with permission from O'Grady [13]

Etiology and pathogenesis

Etiology of ALF is among the most important determinants of prognosis (Fig. 1) but varies according to geographic region. Viral infections, intoxications and drug side effects account for approximately 80% of known etiologies. Despite a thorough diagnostic evaluation, no specific cause of hepatic failure can be found in up to 50% of patients (Table 2).

A detailed review of the pathogenesis of hepatocyte injury is beyond the scope of this article. Hepatic damage may occur due to predominating necrosis (such as in paracetamol intoxication), apoptosis (viral hepatitis, Wilson disease), both mechanisms (ischemic hepatitis), viral cytotoxicity (herpes simplex virus, HBV) or a massive immune-mediated host response (HAV, HBV, idiosyncratic drug reaction). Many studies have investigated the role of pro-and anti-inflammatory cytokines, both in development of acute hepatic failure and in regeneration [8]. TNF-α plays a prominent role in apoptosis and its blockade prevented development of experimental ALF [9]. Infiltrating mononuclear cells express high amounts of TNF-α and hepatocytes overexpress TNF-receptor-1. TNF-initiated signaling pathways result in a direct apoptotic response as well as potent activation of proinflammatory gene expression via activation of the transcription factor nuclear factor-kappa B. Blockade of TNF-α downstream signals by nuclear factor kappa B decoy oligodeoxynucleotides prevented endotoxin-induced fatal liver failure in a murine model [9]. In contrast, NF-kappa B activation in hepatocytes was found to be anti-apoptotic [10]. Systemic application of caspase 8 small interfering RNA inhibited hepatic caspase 8 gene expression and significantly attenuated acute liver damage [11]. It is particularly interesting that application of caspase 8 small interfering RNA was also successful in a model resem-

Table 2. Etiologies of acute liver failure

Viral	Hepatitis A virus (HAV) Hepatitis B (D) virus (HBV, HDV) Hepatitis E virus "Non-A-E hepatitis" Herpes simplex virus-1, human herpesvirus-6 Epstein Barr virus Cytomegaly virus
Toxic	Paracetamol / Paracetamol-alcohol syndrome Idiosyncratic reaction to drugs (isoniazide, halothane, antibiotics; antiepileptics, amiodarone, NSAIDs) "Ecstasy" (3–4 methylendioxymethamphetamine, MDMA) Amanita phalloides Reye syndrome Bacterial toxins (bacillus cereus)
Metabolic	Wilson's disease
Various	Ischemic hepatitis Budd-Chiari Syndrome Lymphoma Acute fatty liver of pregnancy Autoimmune hepatitis Leptospirosis

bling the multiple pathogenetic mechanisms of fulminant viral hepatitis, raising the hope for successful clinical application in human ALF. The inflammatory cytokine interleukin-6 is a further key factor in liver regeneration and reversed hepatic injury in IL-6 knockout mice [12]. Certainly it will require further progress to unravel the complex interplay of pro-and anti-inflammatory cytokines with cellular signaling and growth factors in order to develop successful therapeutic interventions in ALF.

Hepatitis viruses

Depending on their variable prevalence in different geographic regions, the classic hepatitis viruses account for about 20–40% of infections leading to ALF. Due to the rapidly changing epidemiology, immunity against *hepatitis A* is steadily declining, leading to increased rates of severe adult infections, particularly in some northern European countries. The risk of severe hepatitis increases after the age of 40 years but most HAV infections still do not progress to ALF. Mortality was only 0.1% in a large outbreak involving >300.000 Chinese patients [13]. In a recent U.S. epidemic involving 580 patients infected by contaminated spring onions, 3 fatalities were related to hepatic failure (0.5%). Fatal hepatitis develops more frequently with concurrent use of paracetamol, excessive host response, low viral load, high bilirubin values, underlying chronic liver disease, intravenous drug use, excessive alcohol intake and female sex [14]. Late onset of encephalopathy predicted poor outcome [15] whereas co-infection with HBV or HCV plays a comparatively minor role.

Most cases of fulminant *hepatitis B* in the western world occur as primary infection in intravenous drug users or are transmitted sexually, but fulminant reactivation of latent infection is a well-documented complication of cytotoxic chemotherapy and immunodepression. Acute HBV infection is diagnosed in the presence of IgM antibody to hepatitis core antigen (Anti-HBc). Early absence of HBs antigen has a favorable prognostic value. The role of core- and precore mutation of the HBV-DNA seems to be etiologically less important for development of fulminant hepatitis than previously considered. In contrast, fulminant hepatitis is frequently related to co-infection with delta agent or other hepatotropic viruses. A nationwide Hepatitis B vaccination campaign in Taiwan protected children from HBV-related ALF [16].

Hepatitis C is virtually absent as a cause of ALF in western countries, but has been occasionally reported in Asia. In India, the most common cause of ALF are hepatitis B and *E*, the latter being particularly severe in pregnant women. While several putative hepatitis viruses have been proposed as cause of fulminant non A–E hepatitis, none has convincingly been demonstrated to cause ALF. The recently described SEN-virus has no etiological role in acute liver failure [17]. *Herpes simplex virus type 1 and 2, human herpes virus-6, cytomegaly, yellow fever and parvovirus* are the most frequent non-hepatotropic viruses that are capable of causing ALF. In patients with concomitant leucopenia, HSV-1/2 and CMV should be considered in differential diagnosis as early antiviral treatment may prevent liver transplantation [18]. The risk of fulminant herpes simplex hepatitis is increased in pregnancy, neonatal period, and in immunosuppressed individuals. A high rate of human herpes virus-6 infection was detected in the liver and serum of patients with ALF of unknown etiology (Fig. 2) [19].

Toxins/Drugs

While virtually any chemical compound has the potential to cause severe hepatotoxicity, only a small fraction is intrinsically hepatotoxic. Nonetheless, hepatotoxicity has to be considered in any patient presenting with ALF after chronic or acute exposure to chemical agents, drug or herbal preparations. The use of potentially toxic herbal supplements has been reported in a significant proportion of patients with ALF [20]. Whether co-medication with paracetamol is a relevant risk factor is a matter of discussion. Three epidemiologic studies on drug-related ALF performed in different populations report an incidence of 5–10 cases per 100.000 patient years, explaining that hepatotoxicity by agents such as troglitazone, trovafloxacin and several antiretroviral agents [21] was recognized only by postmarketing surveillance. Increased awareness of the hepatotoxicity of popular herbal mixtures and alcoholic or acetonic Kava extracts has recently prompted retraction of Kava-containing drugs in Germany [22].

Only a small proportion of hepatotoxic compounds shows dose-related (obligatory) hepatotoxicity (paracetamol, carbon tetrachloride, phosphorus, mercaptopurine, methotrexate, tetracyclines, valproic acid). The majority of compounds has the potential to cause idiosyncratic or toxic drug reactions, whose incidence differs widely between individuals and populations. *Idiosyncratic* drug reactions are dose-independent, occur after re-exposure to a drug and are frequently caused by the formation of reac-

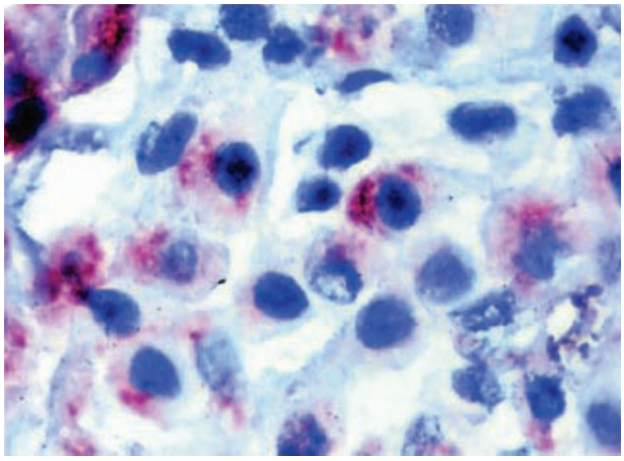

Fig. 2. HHV-6 positive mononuclear cells lymphocytes in hepatocytes of an explanted liver with ALF demonstrated by immunoperoxidase staining by a monoclonal antibody against the HHV-6 B subtype (purple red). Reprinted with permission from Härmä et al. [19]

tive intermediates, which bind to intracellular epitopes and induce an immunological attack after re-exposure; involving humoral and cellular immunity and apoptosis [23]. *Toxic* drugs reactions are caused by altered drug metabolism, leading to increased intracellular drug concentrations or formation of toxic metabolites. Variations in the cytochrome P450 enzyme genotype appear to define individual susceptibility. Moreover, increased age and female sex increase the risk for hepatotoxicity. The most frequent triggers of idiosyncratic drug reactions are antibiotics (isoniazide, rifampicin, amoxicillin-clavulanic acid, sulfonamides, tetracyclines, dapsone), antiepileptics (valproic acid, phenytoin) and halothane, amiodarone, non-steroidal antiphlogistics, troglitazone, MAO-inhibitors, and MDMA (Ecstasy).

Paracetamol intoxication: In the UK, most cases of the cycloxygenase III inhibitor paracetamol (acetaminophen) toxicity are related to the deliberate suicidal ingestion of toxic doses (> 140 mg/kg BW). In contrast, a recent U.S. multicenter study reports comparatively more cases of severe hepatotoxicity with therapeutic doses [24]. Coagulopathy peaks at 72–96 hours after ingestion, and the maximum of encephalopathy is observed after further 1–2 days, requiring early decision for transplantation. A continued increase in prothrombin time on day 4 after overdose and a peak prothrombin time of greater than or equal to 180 seconds identified patients with a less than 8% chance of survival without transplantation [25]. Severity of deliberate intoxication can be assessed by the Rumack diagram based on time from ingestion and serum paracetamol levels [26]. Paracetamol levels > 300 µg/ml at four hours of ingestion and a serum half life of > 5.5 hours indicate poor prognosis, levels < 150 µg/ml are favorable [27]. Individual toxicity is also determined by a) cytochrome P-450 enzyme activity, which oxidizes paracetamol to the toxic metabolite NABQI and b) hepatic glutathion content, representing the main scavenger of NABQI. Consequently, both increased P-450 activity (chronic alcoholism, use of antiepileptic drugs, cigarette smoking [28]) and reduced hepatic glutathion stores (alcoholism, malnutrition) are risk factors for development of hepatic necrosis, which may occur with doses of paracetamol as small as 2–5 g. Activated charcoal seems the best choice to reduce paracetamol absorption. The "paracetamol-alcohol syndrome" is clinically characterized by massive elevation of aspartate-aminotransferase activity and poor prognosis.

Amanita phalloides (death cap), a member of the Amanita mushroom family, is responsible for > 90% of all fatal mushroom poisonings. Hepatotoxicity is due to a family of heat-stable bicyclic octapeptids (α- and β-amanitin). Toxins are rapidly absorbed from intestinal lumen and transported across hepatocytes by the sinusoidal bile-salt transport system. Following a latency period of 6–12 hours, severe gastroenteritis emerges. Subsequently, inhibition of RNA-polymerase II causes collapse of cellular protein synthesis, hepatic and renal failure, pancreatitis and toxic hemolysis. No specific antidote exists to date and therapy is mainly supportive. Nasogastric suction and gavage of powdered charcoal have been recommended for reducing resorption of biliary excreted amanitin. Clinical efficacy of these interventions is undocumented. Extracorporeal detoxification using hemoperfusion, hemofiltration or hemodialysis should be restricted to patients presenting very early (< 24 hours after ingestion) with potentially lethal doses (> 50 g), since most of the amanitin ingested is excreted renally within 48 hours of intoxication. A recent review of 2108 cases suggests that the intravenous application of silibinin (20–50 mg/kg/day) and N-acetylcysteine appears to be more effective compared to other medical interventions including high-dose penicillin G [29]. Current mortality rate is 20–30% but increases up to 50% in children below 10 years of age, which advocates early listing for transplantation in this particular group. Considering the usually favorable prognosis in the absence of renal and multiorgan dysfunction, decision for transplantation should be probably based on King's College criteria for paracetamol intoxication (see below).

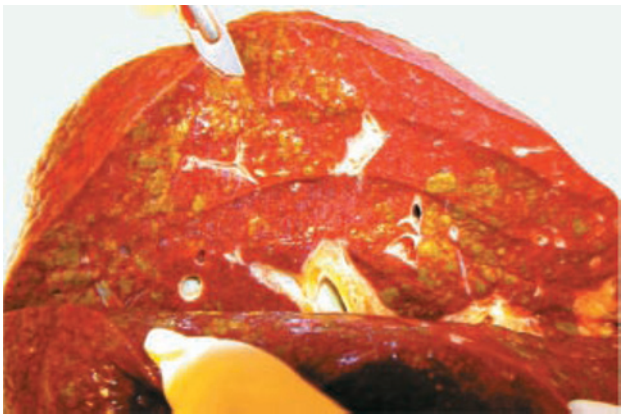

Fig. 3. Scattered distribution of necrosis in subacute liver failure. Histologic evaluation revealed 70% necrotic hepatocytes and widespread presence of apoptosis. © Prof. Dr. R. Steininger, Vienna

Fulminant hypoxic (ischemic) hepatitis

Fulminant hypoxic (ischemic) hepatitis occurs secondary to massive myocardial infarction, pericardial tamponade, pulmonary embolism or Budd-Chiari syndrome (hepatic vein thrombosis) and is defined as acute reversible elevation in either the serum alanine or aspartate aminotransferase level of at least 20 times the upper limit of normal. Pathophysiology is poorly understood. Histologic evaluation typically reveals centrilobular necrosis. Development of hypoxic hepatitis appears to be linked to pre-existing cardiac disease but has also been reported in severe hypoxemia or anemia without cardiovascular complications or shock. A recent case control study has suggested evidence of underlying organic heart disease in 100% of patients, 94% of whom had right-sided heart failure [30]. Nonetheless, a large hemodynamic investigation concluded that hepatic injury was primarily associated with hypoxia [31].

Wilson disease

Most cases of fulminant Wilsonian hepatitis are observed in the second decade of life, with females being predominantly affected. Characteristic findings include a Coombs-negative hemolytic anemia, marked hyperbilirubinemia and comparatively low serum activity of liver enzymes, in particular alkaline phosphatase. Kayser-Fleischer corneal rings are infrequently present. The copper transporter ceruloplasmin is reduced in serum of most patients (< 20 mg/dl), while non-ceruloplasmin- bound and urinary copper levels are elevated. Both of these findings are not specific for fulminant Wilson disease. Chelation therapy is usually insufficient to rescue the patient; and even prolonged extracorporeal removal of copper by exchange transfusion, conventional hemodialysis or albumin dialysis was ineffective in preventing the need for transplantation but seems to delay progression to multiorgan failure. Since patients with fulminant Wilson disease have underlying hepatic fibrosis or cirrhosis, indication for transplantation should be made before multiorgan failure and irreversible neurological damage ensue. As transplantation corrects the underlying metabolic disorder, long-term prognosis is particularly favorable.

Various causes

Acute fatty liver of pregnancy is characterized by microvesicular steatosis, lactic acidosis, and hyperammonemia with encephalopathy developing in the last trimenon of pregnancy. Pre-ecclampsia is present in up to 70% of patients. A retrospective study yielded comparatively favorable maternal and perinatal outcomes [32]. The HELLP Syndrome (hemolysis, elevated liver enzymes, low platelets) presents as gestosis with microangiopathy, hemolysis and thrombocytopenia in the last trimenon and usually takes a favorable course after termination of pregnancy. Further causes of ALF comprise lymphoma, graft-versus-host-disease after bone marrow transplantation, physical causes including heat stroke, bacterial toxins (bacillus cereus, leptospirosis) or Reye syndrome. Acute liver failure induced by autoimmune hepatitis is characterized by predominance of female sex, increased serum concentration of IgG globulins and presence of serum antinuclear antibodies (ANA). Early corticosteroid therapy (prednisolone, 1 mg/kg/d) may halt progression in patients with marked inflammatory activity but is less successful if fibrosis or ascites are already present.

Risk factors

The risk of ALF is increased by 40% in diabetic patients even after exclusion of those with chronic hepatic disease or virus infections. In a large UK study, however, risk for ALF was restricted to patients taking antidiabetic drugs. Given beneficial effects of intensive insulin treatment in critically ill patients [33] and a possible association of high glucose (> 12 mmol/L) with high ICP values [34], normoglycemia should be meticulously maintained in patients with ALF. Hyperthyroidism greatly increases the risk and severity of halothane hepatitis. As indicated above, constitutional or induced activity of P450 is a risk factor for development of hepatotoxicity. A number of polymorphisms in the human DNA are known to modulate individual metabolism and may be evaluated for their prognostic role if c-DNA microarray technology becomes routinely available [35].

Clinical diagnosis of acute liver failure

Patient history

Clinical diagnosis is based on history, clinical symptoms (jaundice, small liver size, encephalopathy) and typical laboratory characteristics. Initial symptoms of disease are usually unspecific and include diarrhea, anorexia, fever or exanthema, which may indicate a viral etiology. A systematic history should assess prognostic details (first occurrence of jaundice, encephalopathy) but also include a full medical history including past and current medication, history of injection drug consumption, transfusions, operations, recent travels, ingestion of self-collected mushrooms or recent change of sexual partners. A family history of fatal liver diseases in young adults is suggestive of Wilson's disease.

Physical examination

Jaundice is usually the first specific symptom and is clinically recognized at serum bilirubin values of 2.5–4 mg/dl. Its magnitude correlates mainly with duration of disease. A long interval between occurrence of jaundice and first episode of hepatic encephalopathy is only infrequently associated with cerebral edema but indicates poor prognosis due to lack of spontaneous regeneration. The liver can be enlarged in initial stages, giving rise to upper abdominal discomfort. Liver volume is also increased in lymphoma, diffuse metastatic disease, Budd-Chiari-syndrome or veinocclusive disease. Reduction of liver size can be quantified using CT volumetry and indicates poor regenerative capacity and limited prognosis without transplantation [36]. Increasing disturbance of hepatic architecture in patients with acute or subacute liver failure may promote development of ascites and hepatorenal syndrome.

Laboratory characteristics

Severity of hepatic damage can be assessed by activity of serum *transaminases,* which correlate to necroinflammatory activity but are not suitable as prognostic

factor. Viral etiologies are characterized by higher activity of the cytosolic, liver-specific alanine-aminotransferase (ALT); toxic and ischemic etiologies are associated with higher initial activity of mitochondrial aspartate-aminotransferase (AST); with values > 2000 U/L strongly suggestive for paracetamol intoxication or hypoxic hepatitis. High serum transaminase activity suggests recent onset of disease and intact regenerative potential. Increased systemic *ammonia* concentrations reflects a mismatch of increased splanchnic ammonia release and reduced hepatic capability to incorporate ammonia to urea and glutamine. As glutamine synthesis takes also place in skeletal muscle and astrocytes, ammonia concentrations are usually lower in venous compared to arterial blood. The failure to metabolize lactate is common in hepatic failure. Lactate levels were useful as early prognostic marker in paracetamol intoxication [37]. Lactic acidosis indicates microcirculatory failure and/or mitochondrial dysfunction with poor prognosis. Reduced indocyanine green clearance has been used to characterize early graft dysfunction but is not established to quantify hepatic dysfunction in ALF. Synthetic capacity is the most important prognostic factor and best assessed using coagulation tests (prothrombin time INR, factor V levels).

Transjugular biopsy

Quantitative assessment of hepatic necrosis by transjugular biopsy has been used to decide transplantation (with >70% necrotic cells indicating poor prognosis) [38]. The method is prone to sampling error and requires sedation and intubation in encephalopathic or agitated patients. Figure 3 demonstrates the scattered distribution of necrotic and apparently normal liver tissue in an explanted organ.

Hepatic imaging

Due to rapid availability at the bed-side, sonography is suitable for providing initial information on liver size and structure, and detection of small amounts of ascites. Doppler sonography of the hepatic artery provides additional information (increased resistive index in severe disease, perpendicular flow in hepatic vein thrombosis). Computed tomography has been used for volumetric examination (< 1000 ml indicating poor prognosis), but may be also helpful in the diagnosis of Budd-Chiari-syndrome, steatosis, diffuse metastatic disease or cerebral edema.

Acute hepatic encephalopathy and cerebral edema

Acute hepatic encephalopathy is the most characteristic complication of ALF. Development of severe encephalopathy (grades III/IV) and cerebral edema is associated with a dramatic impairment of prognosis. Cerebral herniation is responsible for most deaths in patients with hyperacute liver failure and requires early initiation of specific therapy and listing for transplantation. The clinical stages of acute hepatic encephalopathy are represented in Table 3. Severity of HE may be impossible to determine in sedated and mechanically ventilated patients, whose therapy should be guided by intracranial pressure measurements.

Table 3. Stages of hepatic encephalopathy (HE) in acute liver failure

Grade of HE	Clinical characteristics
I	Mod disturbance, mild confusion, slurred speech, disturbance of biorhythm, flapping tremor (Asterixis), mood disturbance, mild confusion, slurred speech, disturbance of biorhythm, flapping tremor (Asterixis)
II	Lethargy or agitation, aggressive mood, moderate confusion, marked flapping tremor
III	Severe confusion or somnolence, arousable on verbal stimuli
IV	Coma, initially arousable on painful stimuli (IVa), not arousable in later stages (IVb), sluggish reaction to light, myoclonus, epileptic fits or other signs of intracranial hypertension (IVc)

Transcranial duplex sonography of the middle cerebral artery may detect episodes of cerebral hyperperfusion prior to development of intracranial hypertension but requires a skillful investigator and is not routinely available.

Ammonia-glutamine hypothesis

Arterial ammonia levels > 200 µmol/L predicted cerebral herniation within 24 hours after development of grade III/IV HE (Fig. 4) and should be used for early individual risk stratification [39].

There is a direct correlation between arterial ammonia concentrations and cerebral ammonia uptake (Fig. 5) [40]. Due to ammonia uptake in brain and muscle tissue, venous ammonia levels are usually lower and less suitable for assessing cerebral risk. Glutamine is released from skeletal muscle, which occurs not only as a result of ammonia removal but also due to a net catabolic state in ALF [41]. Stimulation of skeletal muscle ammonia metabolism ap-

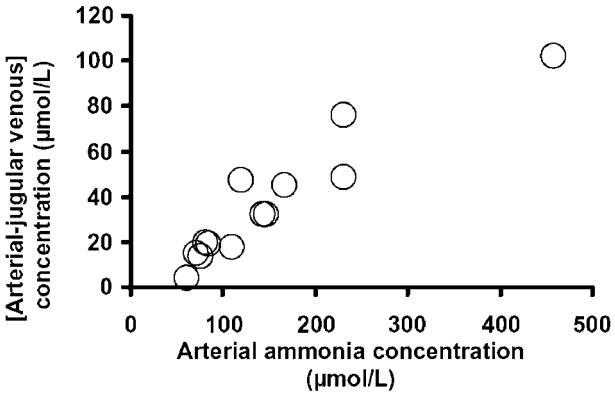

Fig. 4. High arterial ammonia values are associated with increased cerebral ammonia uptake (arterial-internal jugular venous NH_3 concentration difference, n = 13). Reproduced with permission from Ott and Larsen [103]

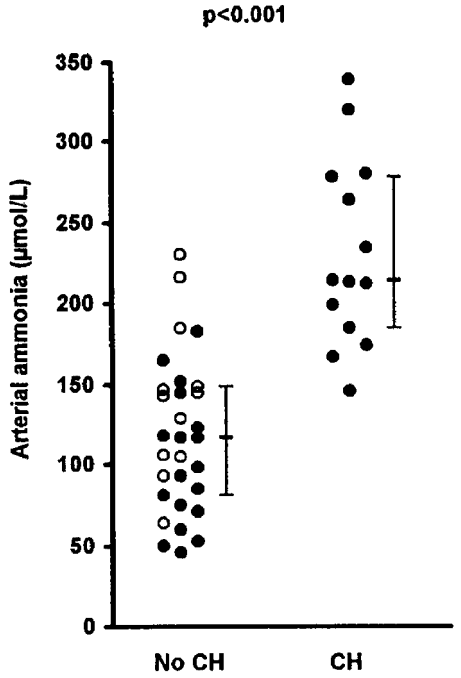

Fig. 5. Arterial plasma ammonia concentration in 30 patients with ALF who did not develop cerebral herniation (*No CH*) and 14 patients who died from cerebral herniation (*CH*). Left side: open circles indicate patients who underwent liver transplantation; full circles indicate patients who died from other reasons. Reproduced with permission from Clemmessen et al. [39]

pears to be a promising target for the treatment of patients with acute liver failure.

Ammonia exerts neurotoxicity mainly via accumulation of glutamine in astrocytes (Fig. 6). Moreover, the rapid astrocytic increase of osmolarity triggers cerebral vasodilatation and potentially deleterious cerebral hyperemia by unknown mechanisms [42]. In contrast, a gradual increase of astrocytic glutamine concentration can be compensated by a reduced levels of *myo*-inositol and other intracellular osmolytes. The higher incidence of cerebral herniation in hyperacute liver failure reflects the imbalance between rapid glutamine accumulation and osmoregulatory compensation. There are preliminary data to suggest that a deficit in brain glucose metabolism could be an additional cause of cerebral complications [43].

Modifying factors and implications for treatment

A sudden decrease in plasma osmolarity caused by infusion of hypotonic fluids or hemodialysis using low dialysate osmolarity may exacerbate glutamine-induced glial swelling [44]. The role of cerebral glutamine transporters in the pathogenesis of cerebral edema is currently unclear [45]. Metabolic alkalosis raises partial pressure of ammonia (pNH_3), increasing the driving force for ammonia diffusion into the brain [46]. The cyclooxygenase inhibitor indomethacin prevented cerebral vasodilatation, decreased refractory cerebral hypertension in rats [47], and reversed intractable intracranial pressure (ICP) surges in a patient with ALF, suggesting involvement of prostaglandins in vasodilatation [48]. Increased extracellular glutamate concentrations may promote neuronal hyperexcitation, leading to overt or subclinical seizure activity [49]. Up-regulation of aquaporin-4 may also contribute to development of cerebral edema by increasing water permeability [50]. Vasopressin infusion accelerated edema formation in experimental ALF due to development of cerebral hyperperfusion [51]. The contribution of neurotoxins related to encephalopathy in chronic liver failure, such as aromatic amino acids, benzodiazepines, free fatty acids, octopamine, mercaptane, or oxindole to the development of cerebral edema in FHF is currently unclear.

Serum concentrations of proinflammatory cytokines and endotoxin are increased in the circulation of patients with ALF and may contribute to the systemic inflammatory response syndrome (SIRS), a predictor of poor prognosis [52]. Inflammatory cytokines apparently also contribute to development of cerebral edema, increased vascular permeability and impaired hepatic regeneration. Nearly half of the patients in the recent U.S. Acute Liver Failure Study Group acquired a culture-positive infection and there was a clear relationship between early infection and progression to more severe encephalopathy [24]. Combined infusion of endotoxin and amanita toxin exacerbated liver damage, cerebral edema and significantly increased mortality compared to either compound alone [53]. It is also conceivable that inflammatory and antiregenerative stimuli derive from the necrotic liver [54]. While total hepatectomy has been anecdotally used to treat intracranial hypertension in FHF [55], the reported effects on ICP seem to be better explained by the concomitant application of hypothermia, which decreased ICP in patients with uncontrolled intracranial hypertension [56, 57]. Of note, normothermic hepatectomy worsened brain edema in an animal model [58] and total hepatectomy is currently not recommended to treat patients with FHF.

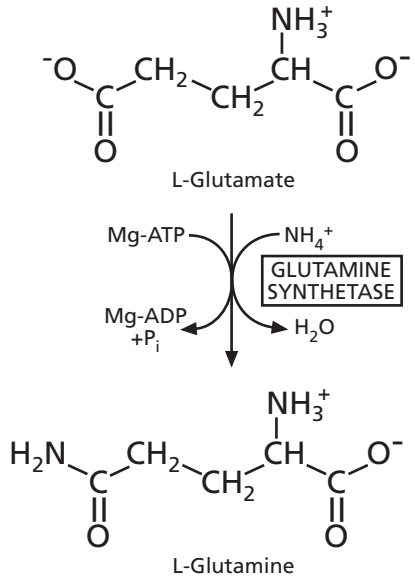

Fig. 6. Astrocytic incorporation of ammonium into L-glutamine as first step for development of cell swelling, cerebral edema and hyperemia

Extrahepatic complications of ALF

Circulatory failure

Hemodynamic abnormalities in ALF resemble those observed in septic shock and decompensated cirrhosis (hyperdynamic circulation, peripheral vasodilatation). Patients admitted with encephalopathy or coma usually have some degree of hypovolemia. Volume expansion by isotonic saline increased renal ammonia excretion in cirrhotic patients [59] and may be beneficial in ALF. Noradrenaline is the standard vasopressor in patients with ALF. No study has investigated the use of vasopressin analogues such as terlipressin, which are increasingly used in cirrhotic patients with the hepatorenal syndrome. Vasopressin worsened cerebral hyperemia in experimental ammonia-induced brain edema and should be probably avoided [51]. While evidence has accumulated for a major role of increased vascular production of nitric oxide as the primary cause of arterial vasodilation, pharmacologic inhibition of nitric oxide synthesis produced detrimental clinical effects. Adrenal insufficiency (defined as pathologic synacthen test) contributed to circulatory failure in a significant proportion of patients and was associated with worse prognosis [60]. In a small retrospective study, supraphysiologic doses of corticosteroids reduced noradrenaline requirement but did not appear to change the course of disease [61].

Acute renal failure

Acute renal failure is present in 30% of all patients with ALF and occurs most frequently in patients with paracetamol and amanita intoxication due to toxic tubular necrosis. Early high-volume veno-venous hemofiltration may prevent deterioration of cerebral edema by removing ammonia, minimizing osmolarity shifts and improving hemodynamics. Initial metabolic acidosis in paracetamol intoxication indicates hypovolemia and should be treated by volume expansion, as correction of acidosis using bicarbonate may increase ammonia toxicity by raising its partial pressure (pNH_3) [46]. In paracetamol intoxication, severe metabolic acidosis carries a grave prognosis despite transplantation [62].

Hepatorenal failure

According to the current definition, diagnosis of hepatorenal failure should be confined to patients with evidence or strong suspicion of portal hypertension, which may develop in patients with subacute hepatic failure. Comparing patients with acute liver failure and cirrhosis, Ring-Larsen et al. reported similar incidence, relative frequency, and prognosis of hepatorenal failure and acute tubular necrosis [63]. No study has investigated the effects of vasoconstrictor therapy for the hepatorenal syndrome in patients with ALF.

Infection

Dysfunction of Kupffer cells, neutrophils and complement system predisposes patients with ALF to bacterial and fungal infections. A large retrospective study has identified microbiologically confirmed infections in 38% of patients with ALF before and during initiation of antibiotic prophylaxis [64]. Gram-positive bacteria predominated, with streptococcal, staphylococcal, coagulase-negative staphylococcal and enterococcal infections emerging within eight days. Escherichia coli infections occurred earlier than those due to klebsiella and enterobacter. Increased levels of inflammatory cytokines are associated with higher incidence of encephalopathy, multiorgan failure and poor prognosis [52]. The most frequent infections at King's College Hospital were pneumonia, urinary tract infections, septicemia and catheter-related infections. Fever may advance progression to hyperammonemia and cerebral edema as temperatures $>38.5\,°C$ were identified as independent risk factor for cerebral herniation and death [65].

Hemorrhage

Hepatic coagulopathy has a comparatively low risk of hemorrhage. Since any improvement in hepatic function is quickly reflected by coagulopathy, prophylactic correction is not recommended unless required for bleeding episodes or placement of an intracranial pressure measurement device. Clinical bleeding is frequently related to development of disseminated intravascular coagulation, thrombocytopenia and disturbance of platelet aggregation. Infusion of coagulation factor concentrates may also promote intravascular coagulation, which may be less pronounced with the use of fresh frozen plasma. The risk of stress ulcer bleeding advocates prophylaxis using proton pump inhibitors.

Prognosis and criteria for transplantation

The advent of liver transplantation has dramatically improved the outcome of ALF. Based on early assessment of individual prognosis, transplantation should be performed before irreversible complications emerge, while unnecessary transplantation should be avoided. Wide geographic variations in etiology would theoretically advocate the use of regional prognostic criteria, which is impossible due to the low incidence of ALF. A set of static and dynamic variables identified at King's College Hospital, London, (Table 4) has been proposed for deciding transplantation and has been validated by several groups in Europe and U.S. [66, 67] In paracetamol intoxication, arterial lactate concentrations >3.5 mmol/l at 4 hours of admission and >3.0 mmol/l after 12 hours of fluid therapy were equally accurate but fulfilled earlier compared to original criteria [68]. Similarly, hyperphosphatemia (serum levels ≥ 1.2 mmol/L at 48 to 96 hours after ingestion) had a higher sensitivity and prognostic accuracy compared to the King's College criteria in severe paracetamol intoxication and allowed earlier identification of patients with poor prognosis [69]. Combination of hyperphosphatemia and King's College criteria improved sensitivity to 94%.

The French or "Clichy" criteria were proposed for patients with fulminant viral hepatitis and predict poor prognosis in patients with coma or confusion and factor V levels of $<20\%$ in patients below 30 years of age and $<30\%$ in older patients [70]. Further criteria for predicting mortality were higher Acute Physiology and Chronic Health Evaluation (APACHE) scores [71], absence of cortical sensory evoked potentials [72], serum Gc protein

[73] and development of a systemic inflammatory response syndrome [52]. Indicators of poor prognosis in viral hepatitis of a tropical population were encephalopathy grade III/IV, cerebral edema, high levels of bilirubin, higher age and a long interval between first occurrence of jaundice and encephalopathy [74]. A recent study has demonstrated a tendency toward greater circulating neuron-specific enolase levels in patients with FHF who subsequently developed cerebral herniation [75].

Treatment guidelines

Intensive care unit (ICU) and transplantation center referral

Patients with severe reduction of synthetic liver function (INR > 2, spontaneous hypoglycemia), extrahepatic organ failure, impairment of consciousness or massive hyperammonemia should be immediately referred to an ICU. Main therapeutic goals of ICU management are monitoring and stabilizing vital functions to support hepatic regeneration and to prevent or delay life-threatening complications. Patients progressing to advanced hepatic or renal failure and hepatic encephalopathy grade > I should be referred to a transplant center for interdisciplinary evaluation. Early referral is essential as transportation of encephalopathic patients usually requires intubation and sedation, which hampers assessment of encephalopathy. Non-invasive ventilation is insufficient in agitated or obtunded encephalopathic patients and carries the risk of aspiration pneumonia.

Table 4. Criteria used for consideration of liver transplantation in acute liver failure ("King's College Criteria", including proposed modifications by Bernal et al. [68], Schmidt et al. [69]

Paracetamol intoxication	pH < 7.3 irrespective of encephalopathy severity[1] *or* Arterial lactate concentrations > 3.5 mmol/l following early fluid substitution[2] *or* Serum phosphate levels ≥ 1.2 mmol/l at 48 to 96 hours after ingestion *or* Encephalopathy III/IV *and* Prothrombin time > 100s (INR > 6.5) *and* Creatinine > 300 µmol/l (3.4 mg/dl) *within a 24 hour period*
Other etiologies	Prothrombin time > 100 seconds (INR > 6.5) *or at least 3 of the following criteria* Age < 10 or > 40 years Etiology hepatitis non A-E, halothane hepatitis, idiosyncratic drug reaction Jaundice to encephalopathy time > 7 days Prothrombin time >50 s (INR > 3.5) Serum bilirubin > 300 µmol/l (> 17.4 mg/dl)

[1] > 24 hours after admission to hospital and fluid resuscitation; [2] alternatively > 3 mmol/l after at least 12 hours of fluid resuscitation.

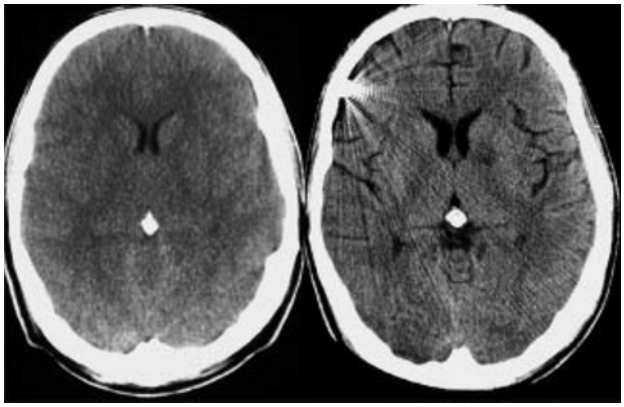

Fig. 7. Effects of early extracorporeal detoxification (FPSA-Prometheus®) in a patient with ecstasy/cocaine induced ALF and refractory cerebral edema. Transplantation was declined due to active injection drug abuse. Comparison of cranial computed tomography scans obtained before (arterial ammonia, 318 µmol/L, left) and after 4 days of continuous treatment (arterial ammonia, < 50 µmol/L) demonstrates restoration of gray-white differentiation and normalization of sulci and ventricles width. Note ischemic infarcts of left internal capsule and occipital cortex and metallic artifact of epidural transducer. Reproduced with permission from Kramer et al. [77]

Monitoring and therapy of increased intracranial pressure

Symptoms of raised ICP (increased muscular tonus, myocloni, sluggish pupillary reaction to light, bradycardia, arterial hypertension) frequently develop only at ICP values > 30 mm Hg. Early intervention guided by extradural ICP monitoring can prolong survival and gain time for transplantation [76]. Consequently, ICP monitoring devices should be inserted in patients with grade III or IV encephalopathy who are candidates for transplantation. They may be inserted in patients with hyperacute liver failure and grade IV encephalopathy who are not eligible for transplantation but might benefit from extracorporeal detoxification [77]. Due to their lower complication rate, epidural transducers are preferred [78]. Cerebral perfusion pressure (mean arterial blood pressure – mean ICP) should be kept at least > 50 mm Hg to safely prevent cerebral ischemia, although a full neurologic recovery has been reported in patients with lower values. Therapeutic hyperventilation is important for the treatment of ICP surges refractory to osmotherapy but may worsen cerebral hypoperfusion, which is a frequent finding in early hepatic encephalopathy [79]. Semirecumbent body position facilitates venous return, lowers brain volume and prevents aspiration pneumonia in ventilated patients.

Therapy of hepatic encephalopathy and cerebral edema should address the underlying pathophysiology. It is essential to recognize a delay of 12–24 hours between emergence of massive hyperammonemia and cerebral herniation, which opens the opportunity for early therapeutic interventions (Fig. 7). Unfortunately, no specific therapy of cerebral ammonia/glutamine toxicity is available. Mannitol is the mainstay of medical therapy (Table 5). The use

Table 5. Current treatment of intracranial hypertension in acute liver failure

Treatment	Commentary
Mannitol (0.5 g/kg BW)	Mainstay of pharmacotherapy. IV infusion of 10–20% mannitol over 15–20 minutes, serum osmolarity check after 3 applications, discontinue if > 320 mOsm/l
Moderate hyperventilation ($paCO_2$ 30–35 mmHg)	Restores cerebral autoregulation, recommended as temporal measure for refractory ICP surges
Propofol (30–90 µg/kg/min)	More favorable mode of action and faster return to wakefulness compared to barbiturates [101]
Indomethacin (25 mg bolus)	Reversal of cerebral vasodilatation, anecdotally effective in refractory intracranial hypertension
Moderate hypothermia (core temperature, 31–34 °C)	Promotes cerebral vasoconstriction, reduces cerebral ammonia uptake, energy metabolism and splanchnic ammoniagenesis [56]. More effective than hemofiltration in neonatal hyperammonemic coma [102]
N-Acetylcysteine	Anti-oxidant, beneficial action in cerebral edema due to paracetamol overdose and ischemic brain injury
High-volume hemofiltration / hemodialysis	Provides renal support, fluid and osmolarity management. Ammonia clearance equates that of urea and depends on dialyzer size, blood and dialysate flow. May reverse hyperammonemia and prevent astrocytic swelling. Increased dialysate sodium may prevent osmotic brain swelling in high-flux hemodialysis
High-volume plasmapheresis	Improvement of cranial perfusion pressure by increasing systemic vascular resistance. Increases cerebral blood flow and cerebral metabolic rate, lowers ammonia levels but not ICP. Fresh frozen plasma may activate complement system causing lung injury
(Bio-)artificial liver support	Detoxification increasingly recognized as most important mode of action. Clinical application should be restricted to scientific trials

of L-ornithine-L-aspartate aims to enhance extrahepatic ammonia metabolism but has not been evaluated prospectively in ALF. Based on beneficial effects on cerebral edema in paracetamol intoxication [80] and ischemic brain damage [81], N-acetylcysteine might improve cerebral edema also in non-paracetamol ALF. The effects of lactulose or non-absorbable antibiotics on cerebral edema are essentially unknown. The benzodiazepine antagonists flumazenil is ineffective treatment for cerebral edema but may reverse prolonged effects of exogenous benzodiazepines.

Specific medical treatment

Antibiotic prophylaxis

Given the considerably poorer outcome of infected patients, antibiotic prophylaxis should be administered to all patients with hepatic encephalopathy or evidence of additional extrahepatic organ injury. A recent multicenter US study reported infections and/or the resulting systemic inflammatory response contributing to worsening of encephalopathy, at least in patients with paracetamol intoxication, who displayed a clear temporal association between acquisition of infection and subsequent worsening of encephalopathy [82]. As a general rule, gram-positive organisms are the major cause of infections, particularly during the first week of hospital admission; while gram-negative and multi-resistant organisms predominate in patients with prolonged or worsening organ failure. Antibiotic prophylaxis and therapy should be selected according to locally established hospital guidelines. While parenteral antibiotics were effective in reducing the risk of infection in patients with ALF, enteral decontamination provided no additional benefit [83].

Nutritional therapy

Resting energy expenditure is increased by 20–30% in ALF, suggesting nutritional supply of at least 30 kcal/kg/day. Since malnutrition favors bacterial translocation, early enteral nutrition, aiming to preserve both integrity of the intestinal barrier and bowel motility, seems to be a key factor in the prevention of SIRS and multiorgan dysfunction. There is no evidence for beneficial effects of immunonutrition or branched chain amino acid supplementation in ALF; and standard enteral nutrition is currently preferred by many intensivists. Impairment of gluconeogenesis increases the risk for hypoglycemia-induced dysfunction of brain, hematopoietic system or renal medulla, requiring close metabolic monitoring and immediate exclusion of hypoglycemia in any neurological deterioration. Giving normal or increased protein requirements and a questionable effect on hyperammonemia, protein restriction is no longer recommended in ALF. Nutritional substitution of ammoniagenic amino acids such as glutamine should probably be avoided as hyperammonemia may be precipitated. Orogastric feeding tubes may be used in ventilated patients with severe coagulopathy, thrombocytopenia and a high risk for nasopharyngeal bleeding.

N-Acetylcysteine (NAC)

N-Acetylcysteine (NAC) acts as radical scavenger and glutathione donor in paracetamol intoxication and additional causes of toxic and hypoxic liver failure. NAC is

administered as initial bolus of 150 mg/kg to be continued by 50 mg/kg over 4 hours and 100 mg/kg over 16 hours. Indication for NAC in patients with non-paracetamol ALF has been questioned. Administration of NAC resulted in decreased nuclear factor-kappa B activation in patients with sepsis, representing an additional mechanism for hepatoprotection [84]. Preliminary data also support a role of prolonged NAC infusion (50–150 mg/kg/day) for improvement of microcirculation including renal medullar vasodilatation in hepatorenal syndrome.

Antiviral therapy

Lamivudine (100–150 mg/day) appears to be safe and effective in patients with fulminant HBV infection but has not yet been studied in a randomized trial [85].

Sedatives

Patients with encephalopathy grades II and III frequently develop severe agitation and may benefit from low doses of sedatives and noise reduction, which may be difficult to provide in busy ICUs. It is essential to rule out hypoxia in all agitated patients. Agitation usually indicates progression of encephalopathy, requiring intubation and ventilatory support. If intubated, patients may be managed with bolus doses of sedatives instead of continuous infusions. Opioids such as fentanyl have a favorable risk/benefit profile and may be entirely sufficient for encephalopathic or comatose patients on the ventilator. Midazolam should be probably avoided as its metabolism depends on hepatic P-450 systems, causing prolonged sedation. Patients with increased intracranial pressure should be managed using either barbiturates (thiopentone, methohexital) or propofol (Table 5). The hypothesis of subclinical fitting and its possible amelioration with phenytoin would require anti-epileptic prophylaxis and electroencephalographic monitoring [49]; but this has not been confirmed by other investigators. Since fitting events in ALF usually indicate presence of intracranial hypertension, osmotherapy (and possibly intracranial pressure monitoring) should be commenced at first hand.

Liver transplantation

Introduction of emergency liver transplantation was the most effective therapeutic step in ALF and reduced mortality from 60–85% to 40–50%. The Eurotransplant registry lists 3702 patients who have been transplanted between 1988 and 2002 due to ALF, with 90% classified as fulminant hepatic failure. Due to infectious and neurologic complications in the perioperative phase, the one-year survival rate of approximately 60% is substantially lower compared to elective liver transplantation [86]. As early listing of appropriate candidates is mandatory, the increasing shortage of donor organs poses an additional threat to patients with ALF, in whom a delay of few hours can be associated with emergence of irreversible neurologic damage or death. Auxiliary transplantation and living-related donor transplantation have been proposed as potential alternatives to orthotopic transplantation: Auxiliary transplantation allows cessation of immunosuppression after regeneration of the native liver in 65% of patients at the cost of a slightly higher perioperative complication rate [87]. Organization of a living-related donor transplantation is usually too time-consuming for patients with hyperacute liver failure but can be an option for patients with acute and subacute liver failure [88]. Sensory evoked potentials may help to identify a subgroup of patients with severe brain dysfunction who should undergo early liver transplantation even though not fulfilling King's College criteria, whereas loss of cortical sensory evoked potentials in the presence of preserved spinal potentials indicates irreversible cortical damage and should obviate transplantation [72]. Further contraindications to transplantation are septic multiorgan failure and uncontrolled infection, lack of cerebral perfusion as demonstrated by angiography or transcranial Doppler sonography, AIDS, and ALF due to lymphoma and metastatic disease, where improvement by cytotoxic chemotherapy has been occasionally reported.

A role for artificial and bioartificial liver support in ALF?

Advances in the pathophysiology of cerebral edema have challenged some of the traditional assumptions on which most blood detoxification systems were based [89]. These advances should be integrated in the overall treatment of FHF, which inevitably affects extracorporeal treatment. Potential consequences of mild therapeutic hypothermia appear to have the greatest impact on therapy of HE, at least during the bridging period to transplantation. Effects of mild hypothermia should be considered as alternative explanation of the ICP reductions reported to occur following artificial [90] and bioartificial liver treatment [91]. Future liver support systems should ideally combine mild hypothermia with detoxification. Among the potential side effects of hypothermia, inhibition of hepatic regeneration and increased risk of infection appear to be most relevant [92].

Given the importance of arterial ammonia levels in FHF and cerebral edema, they need to be reported in all studies of extracorporeal treatment. Ammonia and glutamine can be removed by hemodialysis or hemofiltration at a rate dependent of dialyzer surface, blood flow and dialysate flow, which all do not match a healthy liver [93]. Mass transfer rates are even more reduced in plasma separation systems. High extracorporeal blood flow rates require extreme caution since they increase the risk for rapid osmolarity shifts, which potentially aggravate cerebral edema and may cause hypotensive episodes. Anticoagulation and shear-stress induced platelet dysfunction may further increase the risk of intracranial hemorrhage with ICP monitors. Alternative ways of ammonia removal such as acidifying enemas [94], or L-ornithine-L-aspartate, which improves ammonia utilization in muscle [95] may be an option. Removal of yet unidentified vasodilating factors by albumin dialysis (MARS system) may represent an additional mode of action [96].

The role of biologic liver support in the treatment of FHF should be investigated in the light of current pathophysiologic knowledge. Potential beneficial factors produced by hepatocytes that cannot be replaced by infusion of blood products need to be identified. This seems particularly important as the role of heterologous proteins in the human body is unclear. Moreover, induction of xenoreac-

tive antibodies has been demonstrated following bioartificial liver support using porcine cells [97]. Given considerable limitations in flow rates and cell mass, current strategies of biologic liver support appear to be severely limited in performing the complex metabolic tasks of healthy liver. While hepatocyte suspensions and monolayers are characterized by short function periods and minimal biologic activity, carrier-bound hepatocytes may survive for longer periods but are subjected to considerable limitations in mass transfer rate. Immortalized hepatoma cell lines perform metabolically poorly compared to normal hepatocytes [98] and may expose patients to potential biologic risks [99]. Thus, sufficient rates of detoxification cannot be expected by extracorporeal cell perfusion and might be rather provided by measures such as hemodialysis, hemofiltration, plasma exchange or possibly extracorporeal whole-liver perfusion [100].

Future aspects

Available strategies of artificial and bioartificial liver support in FHF are still insufficient to replace the multiple hepatic functions required for prevention or reversal of hepatic encephalopathy, cerebral edema, infection and progressive hepatic failure. In particular, specific effects of biologic liver support systems on hepatic regeneration still remain to be demonstrated. Current pathophysiologic knowledge would therefore suggest to employ efficient extracorporeal detoxification preferably in patients with hyperacute ALF and severe hyperammonemia before they progress to coma and cerebral edema; possibly in combination with mild hypothermia. Future pharmacological developments may prevent cerebral hyperperfusion and increase of brain water at a cellular level by specific interaction with vasopressin receptors [58], aquaporins [50], glutamine synthetase or other pathways. Positron emission tomography, high-field magnetic resonance spectroscopy and c-DNA microarray technology provide powerful tools to identify the metabolic and gene expression abnormalities contributing to development of cerebral edema in ALF, which may have therapeutic implications.

Expanding knowledge on the regulation of hepatic regeneration, and particularly on the prominent role of apoptosis in evolution of FHF may lead to therapeutic interventions that modulate inflammatory and apoptotic pathways and stimulate regeneration. Experimental evidence of significantly attenuated acute liver damage by caspase-8 small interfering RNA, infliximab or other antiapoptotic agents may pave the way for clinical studies in human ALF. The preventive effects of widespread hepatitis B vaccination are already well-documented and appear to be cost-effective. Antiviral therapeutics including lamivudine or acyclovir seem to reduce the extent of hepatic damage and could possibly reduce the need for transplantation in certain viral causes of ALF. In addition to antibiotic prophylaxis, the critical role of gut-derived endotoxin in activation of inflammatory cytokines and apoptosis would suggest to study the effects of probiotic agents, in addition to early enteral nutrition. For those patients still requiring transplantation, improved availability and technical success of living-related OLT may partially ameliorate the increasing dilemma of donor organ shortage.

References

1. O'Grady JG, Schalm SW, Williams R (1993) Acute liver failure: redefining the syndromes. Lancet 342: 273–275
2. Acharya SK, Panda SK, Saxena A, Gupta SD (2000) Acute hepatic failure in India: a perspective from the East. J Gastroenterol Hepatol 15: 473–479
3. Trey C, Davidson LS (1970) The management of fulminant hepatic failure. In: Popper H, Schaffner F (eds) Progress in liver diseases. Grune and Stratton, New York, pp 282–298
4. Bernuau J, Rueff B, Benhamou JP (1986) Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 6: 97–106
5. O'Grady JG, Schalm SW, Williams R (1993) Acute liver failure: redefining the syndromes. Lancet 342: 273–275
6. Bernuau J, Benhamou JP (1993) Classifying acute liver failure. Lancet 342: 252–253
7. Tandon BN, Bernuau J, O'Grady J, et al (1999) Recommendations of the IASL subcommittee on nomenclature of acute and subacute liver failure. J Gastroenterol Hepatol 14: 403–404
8. Galun E, Axelrod JH (2002) The role of cytokines in liver failure and regeneration: potential new molecular therapies. Biochim Biophys Acta 1592: 345–358
9. Streetz K, Leifeld L, Grundmann D, et al (2000) Tumor necrosis factor alpha in the pathogenesis of human and murine fulminant hepatic failure. Gastroenterology 119: 446–460
10. Heyninck K, Wullaert A, Beyaert R (2003) Nuclear factor-kappa B plays a central role in tumour necrosis factor-mediated liver disease. Biochem Pharmacol 66: 1409–1415
11. Zender L, Hutker S, Liedtke C, et al (2003) Caspase 8 small interfiring prevents acute liver failure in mice. Proc Natl Acad Sci USA 100: 7797–7802
12. Galun E, Axelrod JH (2002) The role of cytokines in liver failure and regeneration: potential new molecular therapies. Biochim Biophys Acta 1592: 345–358
13. O'Grady J (2000) Fulminant hepatitis in patients with chronic liver disease. J Viral Hepatitis 7 [Suppl 1]: 9–10
14. Rezende G, Roque-Alfonso AM, Samuel D, et al (2003) Viral and clinical factors associated with the fulminant course of hepatitis A infection. Hepatology 38: 613–618
15. Kyrlagkitsis I, Cramp ME, Smith H, Portmann B, O'Grady J (2002) Acute hepatitis A virus infection: a review of prognostic factors from 25 years experience in a tertiary referral center. Hepatogastroenterology 49: 524–528
16. Kao JH, Chen DS (2002) Global control of hepatitis B virus infection. Lancet Infect Dis 2: 395–403
17. Umemura T, Tanaka E, Ostapowicz G, et al (2003) Investigation of SEN virus infection in patients with cryptogenic acute liver failure, hepatitis-associated aplastic anemia, or acute and chronic non-A-non-E hepatitis. J Infect Dis 188: 1545–1552
18. Pinna AD, Rakela J, Demetris AJ, Fung JJ (2002) Five cases of fulminant hepatitis due to herpes simplex virus in adults. Dig Dis Sci 47: 750–754
19. Härmä M, Höckerstedt K, Lautenschlager I (2003) Human herpesvirus-6 and acute liver failure. Transplantation 76: 536–539
20. Estes LD, Stolpman D, Olyaei A, et al (2003) High prevalence of potentially hepatottoxic herbal supplement use in patients with fulminant hepatic failure. Arch Surg 138: 852–858

21. Koch RO, Graziadei IW, Zangerle R, Romani N, Maier H, Vogel W (2003) Acute hepatic failure and lactate acidosis associated with antiretroviral treatment for HIV. Wien Klin Wochenschr 115: 135–140
22. Stickel F, Baumüller HM, Seitz K, et al (2003) Hepatitis induced by Kava (Piper methysticum rhizoma). J Hepatol 39: 62–67
23. Beaune PH, Lecoer S (1997) Immunotoxicology of the liver: adverse reactions to drugs. J Hepatology 26: 37–42
24. Ostapowicz G, Rontana RJ, Schiødt FV (2002) Results of a prospective study of acute liver failure at 17 tertiary care centers in the unites states. Ann Intern Med 137: 947–954
25. Harrison PM, O'Grady JG, Keays RT, Alexander GJ, Williams R (1990) Serial prothrombin time as a prognostic indicator in paracetamol induced fulminant hepatic failure. BMJ 301: 964–966
26. Rumack BH, Metthew H (1975) Acetaminophen poisoning and toxicity. Pediatrics 55: 871–876
27. Schiodt FV, Ott P, Christensen E, Bondesen S (2002) The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdosage. Clin Pharmacol Ther 71: 221–225
28. Schmidt LE, Dalhoff K (2003) The impact of current tobacco use on the outcome of paracetamol poisoning. Aliment Pharmacol Ther 18: 979–985
29. Enjalbert F, Rapior S, Nouguier-Soule J, Guillon S, Amouroux N, Cabot C (2002) Treatment of amatoxin poisoning: 20-year retrospective analysis. J Toxicol Clin Toxicol 40: 715–757
30. Seeto RK, Fenn B, Rockey DC (2000) Ischemic hepatitis: clinical presentation and pathogenesis. Am J Med 109: 109–113
31. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR (2003) Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore) 82: 392–406
32. Pereira SP, O'Donohue J, Wendon J, Williams R (1997) Maternal and perinatal outcome in severe pregnancy-related liver disease. Hepatology 26: 1258–1262
33. Van den Berghe G, Wouters PJ, Bouillon R, et al (2003) Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 31: 359–366
34. Kodakat SK, Gopal PB, Wendon JA (2001) Hyperglycemia is associated with intracranial hypertension in patients with acute liver failure. Liver Transpl 7: C21
35. Bernal W, Donaldson P, Underhill J, Wendon J, Williams R (1998) Tumor necrosis factor genomic polymorphism and outcome of acetaminophen (paracetamol)-induced acute liver failure. J Hepatol 29: 53–59
36. Shakil AO, Jones BC, Lee RG, Federle MP, Fung JJ, Rakela J (2000) Prognostic value of abdominal CT scanning and hepatic histopathology in patients with acute liver failure. Dig Dis Sci 45: 334–339
37. Bernal W, Donaldson N, Wyncoll D, Wendon J (2002) Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 359: 558–563
38. Donaldson BW, Gopinath R, Wanless IR, et al (1993) The role of transjugular liver biopsy in fulminant liver failure: relation to other prognostic indicators. Hepatology 18: 1370–1376
39. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P (1999) Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 29: 648–646
40. Ott P, Larsen FS, Kondrup J, Hansen BA, Clemmesen JO (1999) Reversed inter-organ ammonia fluxes in patients with acute liver failure and coma. In: Yurdaydin C, Bozkaya H (eds) Advances in hepatic encefalopathy and metabolism in liver disease, ISHE. Ankara University Press, Ankara, pp 357–365
41. Clemmesen JO, Kondrup J, Ott P (2000) Splanchnic and leg exchange of amino acids and ammonia in acute liver failure. Gastroenterology 118: 1131–1139
42. Larsen FS, Gottstein J, Blei AT (2001) Cerebral hyperemia and nitric oxide synthase in rats with ammonia-induced brain edema. J Hepatol 34: 548–554
43. Chatauret N, Zwingmann C, Rose C, Leibfritz D, Butterworth RF (2003) Effects of hypothermia on glucose metabolism in acute liver failure: a H/C-nuclear resonance study. Gastroenterology 125: 815–824
44. Cordoba J, Gottstein J, Blei AT (1998) Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 29: 589–594
45. Lee WJ, Hawkins RA, Vina JR, Peterson DR (1998) Glutamine transport by the blood-brain barrier: a possible mechanism for nitrogen removal. Am J Physiol 274: C1101–1107
46. Kramer L, Tribl B, Gendo A, Zauner C, Schneider B, Ferenci P, Madl C (2000) Partial pressure of ammonia versus ammonia in hepatic encephalopathy. Hepatology 31: 30–34
47. Clemmesen JO, Hansen BA, Larsen FS (1997) Indomethacin normalizes intracranial pressure in acute liver failure: A 23-year old woman treated with indomethacin. Hepatology 25: 1423–1426
48. Chung C, Gottstein J, Blei AT (2001) Indomethacin prevents ammonia – induced brain edema in rats after portocaval anastomosis. Hepatology 34: 249–254
49. Ellis AJ, Wendon J, William R (2000) Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. Hepatology 32: 536–541
50. Margulies JE, Thompson RC, Demetriou AA (1999) Aquaporin-4 water channel is up-regulated in the brain in fulminant hepatic failure. Hepatology 30; S2: 938
51. Chung C, Vaquero J, Gottstein J, Blei AT (2003) Vasopressin accelerates experimental ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 39: 193–199
52. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R (2000) The systemic inflammatory response syndrome in acute liver failure. Hepatology 32: 734–739
53. Takada Y, Ishiguro S, Fukunaga K, Gu M, Taniguchi H, Seino KI, Yuzawa K, Otsuka M, Todoroki T, Fukao K (2001) Increased intracranial pressure in a porcine model of fulminant hepatic failure using amatoxin and endotoxin. J Hepatol 34: 825–831
54. Shi Q, Gaylor JD, Cousins R, Plevris J, Hayes PC, Grant MH (1998) The effects of serum from patients with acute liver failure on the growth and metabolism of Hep G2 cells. Artif Organs 12: 1023–1030
55. Rozga J, Podesta L, LePage E, Hoffman A, Morsiani E, Sher L, Woolf GM, Makowka L, Demetriou AA (1993) Control of cerebral oedema by total hepatectomy and extracorporeal liver support in fulminant hepatic failure. Lancet 342: 898–899

56. Jalan R, Olde Damink SWM, Deutz NEP, Jee A, Hayes PC (1999) Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. Lancet 354: 1164–1168
57. Blei AT (2000) Brain edema and portal-systemic encephalopathy. Liver Transplantation 6: S14–S20
58. Olafsson S, Gottstein J, Blei AT (1995) Brain edema and intracranial hypertension in rats after total hepatectomy. Gastroenterology 108: 1097–1103
59. Jalan R, Kapoor D (2003) Enhanced renal ammonia excretion following volume expansion in patients with well compensated cirrhosis of the liver. Gut 52: 1041–1045
60. Harry R, Auzinger G, Wendon J (2002) The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 36: 395–402
61. Harry R, Auzinger G, Wendon J (2003) The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. Liver Int 23: 71–77
62. Devlin J, Wendon J, Heaton N, Tan KC, Williams R (1995) Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. Hepatology 21: 1018–1024
63. Ring-Larsen H, Palazzo U (1981) Renal failure in fulminant hepatic failure and terminal cirrhosis: a comparison between incidence, types, and prognosis. Gut 22: 585–591
64. Wade J, Rolando N, Philpott-Howard J, Wendon J (2003) Timing and aetiology of bacterial infections in a liver intensive care unit. J Hosp Infect 53: 144–146
65. Kodakat SK, Gopal PB, Wendon JA (2001) Intracranial pressure is related to body temperature in acute liver failure. Liver Transpl 7: C87
66. O'Grady JG, Alexander GJM, Hayllar KM, Williams R (1989) Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 97: 439–445
67. Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J (2000) Acute liver failure: clinical features, outcome analysis and comparison of prognostic criteria. Liver Transplantation 6: 163–169
68. Bernal W, Donaldson N, Wyncoll D, Wendon J (2002) Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. Lancet 359: 558–563
69. Schmidt LE, Dalhoff K (2002) Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. Hepatology 36: 659–665
70. Bernuau J, Samuel D, Durand F, et al (1991) Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V below 50% of normal: a prospective study. Hepatology 14: 49A (abstract)
71. Mitchell I, Bihari D, Chang R, et al (1998) Earlier identification of patients at risk from acetaminophen-induced acute liver failure. Crit Care Med 26: 279–284
72. Madl C, Grimm G, Ferenci P, et al (1994) Serial recording of sensory evoked potentials: a noninvasive prognostic indicator in fulminant liver failure. Hepatology 20: 1487–1494
73. Schiodt FV, Ott P, Bondesen S, Tygstrup N (1997) Reduced serum Gc-globulin concentrations in patients with fulminant hepatic failure: association with multiple organ failure. Crit Care Med 25: 1366–1370
74. Acharya SK, Dasarathy S, Kumer TI, et al (1996) Fulminant hepatitis in a tropical population: clinical course, cause and early predictors of outcome. Hepatology 23: 1448–1455
75. Strauss GI, Christiansen M, Moller K, Clemmesen JO, Larsen FS, Knudsen GM (2001) S-100b and neuron-specific enolase in patients with fulminant hepatic failure. Liver Transpl 7: 964–970
76. Keays RT, Alexander GJ, Williams R (1993) The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. J Hepatol 18: 205–209
77. Kramer L, Bauer E, Schenk P, Steininger R, Vigl M, Mallek R (2003) Successful treatment of refractory cerebral oedema in ecstasy/cocaine-induced fulminant hepatic failure using a new high-efficacy liver detoxification device (FPSA-Prometheus). Wien Klin Wochenschr 115: 599–603
78. Blei AT, Olafsson S, Webster S, Levy R (1993) Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet 341: 157–158
79. Ede RJ, Gimson AE, Bihari D, Williams R (1986) Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. J Hepatol 2: 43–51
80. Keays R, Harrison PM, Wendon JA, et al (1991) Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 303: 1026–1029
81. Cuzzocrea S, Mazzon E, Costantino G, et al (2000) Beneficial effects of n-acetylcysteine on ischaemic brain injury. Br J Pharmacol 130: 1219–1226
82. Vaquero J, Polson J, Chung C, et al (2003) Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 125: 755–764
83. Rolando N, Wade JJ, Stangou A, et al (1996) Prospective study comparing the efficacy of prophylactic parenteral antimicrobials, with or without enteral decontamination, in patients with acute liver failure. Liver Transpl Surg 2: 8–13
84. Paterson RL, Galley HF, Webster NR (2003) The effect of N-acetylcysteine on nuclear factor-kappa B activation, interleukin-6, interleukin-8, and intercellular adhesion molecule-1 expression in patients with sepsis. Crit Care Med 31: 2574–2578
85. Lee WC, Wu MJ, Cheng CH, Chen CH, Shu KH, Lian JD (2001) Lamivudine is effective for the treatment of reactivation of hepatitis B virus and fulminant hepatic failure in renal transplant recipients. Am J Kidney Dis 38: 1074–1081
86. Adam R, Cailliez V, Majno P, Karam V, McMaster P, Calne R, et al (2000) Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 356: 612–627
87. van Hoek B, de Boer J, Boudjema K, Williams R, Corsmit O, Terpstra OT (1999) Auxiliary versus orthotopic liver transplantation for acute liver failure. EURALT Study Group. J Hepatol 30: 699–705
88. Miwa S, Hashikura Y, Mita A, et al (1999) Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure. Hepatology 30: 1521–1526
89. Hughes RD (2003) Liver Support in acute liver failure. Wien Klin Wochenschr 115: 547–548
90. Abraham RB, Szold O, Merhav H, et al (2001) Rapid resolution of brain edema and improved cerebral perfusion pressure following the molecular adsorbent recycling system in acute liver failure patients. Transplant Proc 33: 2897–2899
91. Chen SC, Mullon C, Kahaku E, Watanabe F, Hewitt W, Eguchi S, et al (1997) Treatment of severe liver failure with a bioartificial liver. An NY Acad Sci 831: 350–360

92. Kurz A, Sessler DI, Lenhardt R (1996) Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med 334: 1209–1215
93. Cordoba J, Blei AT, Mujais S (1996) Determinants of ammonia clearance by hemodialysis. Artif Organs 20: 800–803
94. Uribe M, Campollo O, Vargas-F, Ravelli GP, Mundo F, Zapata L, Gil S, et al (1987) Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology 7: 639–643
95. Rose C, Michalak A, Rao KV, Quack G, Kircheis G, Butterworth RF (1999) L-ornithine-L-Aspartate lowers plasma and CSF ammonia and prevents cerebral edema in rats with acute liver failure. Hepatology 30: 636–640
96. Schmidt LE, Wang LP, Hansen BA, Larsen FS (2003) Systemic hemodynamic effects of treatment with the molecular adsorbents recirculating system in patients with hyperacute liver failure: a prospective controlled trial. Liver Transpl 9: 290–297
97. Baquerizo A, Mhoyan A, Kearns-Jonker M, et al (1999) Characterization of human xenoreactive antibodies in liver failure patients exposed to pig hepatocytes after bioartificial liver treatment: an ex vivo model of pig to human xenotransplantation. Transplantation 67: 5–18
98. Nyberg SL, Misra SP (1998) Hepatocyte liver-assist systems – a clinical update. Mayo Clin Proc 73: 765–771
99. Martin U, Kiessig V, Blusch JH, et al (1998) Expression of pig endogenous retrovirus by primary porcine endothelial cells and infection of human cells. Lancet. 352: 692–694
100. Abouna GM, Ganguly PK, Hamdy HM, Jabur SS, Tweed WA, Costa G (1999) Extracorporeal liver perfusion system for successful hepatic support pending liver regeneration or liver transplantation: a pre-clinical controlled trial. Transplantation 67: 1576–1583
101. Wijdicks EF, Nyberg SL (2002) Propofol to control intracranial pressure in fulminant hepatic failure. Transplant Proc 34: 1220–1222
102. Whitelaw A, Bridges S, Leaf A, Evans D (2001) Emergency treatment of neonatal hyperamonaemic coma with mild systemic hypothermia. Lancet 358: 36–38
103. Ott P, Larsen FS (2004) Blood-brain barrier permeability to ammonia in liver failure: a critical reappraisal. Neurochem Int 44: 185–198

Correspondence: Ludwig Kramer, M.D., Associate Professor of Medicine, Department of Medicine IV, University of Vienna, Währinger Gürtel 18–20, A-1090 Wien, Austria,
E-mail: L.Kramer@akh-wien.ac.at

(Received December 15, 2003, accepted after revision January 21, 2004)