Acute Hepatic Failure

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Introduction

Acute liver failure (ALF) is an unpredictable and rapidly progressive, life-threatening multisystem condition that ensues when an insult causes diffuse necrosis of liver parenchyma disrupting hepatocyte function in patients who have no preexisting liver injury. The subsequent development of encephalopathy and coagulopathy within days or weeks represents the key features of ALF, but critically often culminates with multi-organ failure (MOF), which impacts significantly on mortality. Timely referral to specialist centers with expertise in the management of ALF and liver transplantation (LT) is crucial.

ALF is rare with around 2800 and 400 cases of ALF per year in the United Stated (US) and the United Kingdom (UK), respectively [1]. There are multiple etiologies of ALF that vary with worldwide geographical location, clinical presentation, time course, and prognosis. In the developing world the leading cause of ALF are the viral hepatitides, particularly Hepatitis B. In the US and the UK, drug induced liver injury, particularly paracetamol (acetaminophen) overdose and sero-negative hepatitis have emerged as the leading causes (Fig. 3.1) [1, 2].

The prognosis of ALF depends on age, etiology, and the time course over which the disease evolves. Survival rates vary significantly by etiology and have improved to around 60% overall without LT and over 85% with LT [3]. Improvement of survival rates over recent decades is related to improved critical care management, better prognostic assessment, and the timely prioritization of patients for LT. The management of ALF is focused on support of all organ systems and the prevention and treatment of complications, particularly sepsis. Liver necrosis acts as a focus of inflammation, driving vasoplegia and leading to cardiovascular collapse, which exacerbates dysfunction of other vital organs, particularly the kidney and brain. The identification and treatment of the cause of the

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underlying liver injury should be the primary goal, with a concurrent focus on the optimization of the circulation to promote hepatocellular regeneration and to prevent further insult due to ischemic injury. However, despite such endeavors timely recognition that hepatic regeneration will ultimately not be sufficient is crucial. Under these circumstances, Liver transplantation with removal of the necrotic liver mass offers the best chance of survival. The decision to prioritize for transplantation requires a multidisciplinary team approach incorporating specialist liver transplant surgeons, hepatologists, and intensivists who can utilize established prognostic criteria along with the daily assessment of the levels of organ support to best determine which patients are likely to benefit from being listed for transplant with high priority and indeed proceeding to OLT if levels of organ support permit (Fig. 3.2) [4].

The availability of donor organs is under continued pressure in the UK and worldwide. Patients with ALF must fulfill a strict set of selection criteria based on published risk factors for prioritization before being listed on the national super-urgent transplantation waiting list (Table 3.1). These patients are then stratified by blood group and time while on the super-urgent waiting list. In most cases a donor organ should be available within 48–72 h. Occasionally an ABO incompatible donor organ needs to be considered in light of the unavailability of an ABO compatible organ weighed against the projected deterioration of the clinical condition. The currently available selection criteria are imperfect and when coupled with improving transplant free survival rates, particularly for acetominophen overdose

[5], the decision of who and when to transplant is complex. There is emerging support for delaying transplant if the clinical situation is improving in patients with a favorable etiology [6]. The option of an auxiliary transplant graft is sometimes considered as it allows native regeneration and withdrawal of immunosuppression, but due to the increased risk of early postoperative complications it necessitates careful scrutiny of appropriate potential candidates.

Classification of ALF

The classifications for ALF have evolved since the initial definition by Trey and Davidson in 1970 in an attempt to reflect the impact that both etiology and the existence of chronic liver disease have on prognosis. The two most common definitions concentrate on the time period from jaundice to the onset of encephalopathy [1]. This classification is important, because the hyperacute forms of ALF including acetaminophen overdose and Hepatitis A are associated with mortality due to cerebral edema and kidney injury. However, survival without transplantation for this group is superior compared to more indolent subacute causes, including sero-negative and idiosyncratic drug reactions (Fig. 3.2) [4, 3]. These etiologies are not as frequently complicated by the cerebral and renal insults, but carry a higher mortality burden compared to hyperacute causes (Table 3.1) [2] (Fig. 1.3).

Table 3.1 Classifications of ALF (time from jaundice to onset of encephalopathy)

Definition	Time (days)	Most common etiologies	Definition	Time (weeks)
Hyperacute	<7 days	POD, hepatitis A and B	Fulminant	<2
Acute	8–28 days	Hepatitis A, B, E, idiosyncratic drug reactions		
Subacute	29 days to 8 weeks	Idiosyncratic drug reactions, sero-negative hepatitis	Subfulminant	>2

Fig. 3.1 Overall comparison of etiologies observed among 1033 patients with acute liver failure (ALF) in the ALF study Group registry, 1990–2004. A preponderance of acetaminophen cases is observed approaching 50%
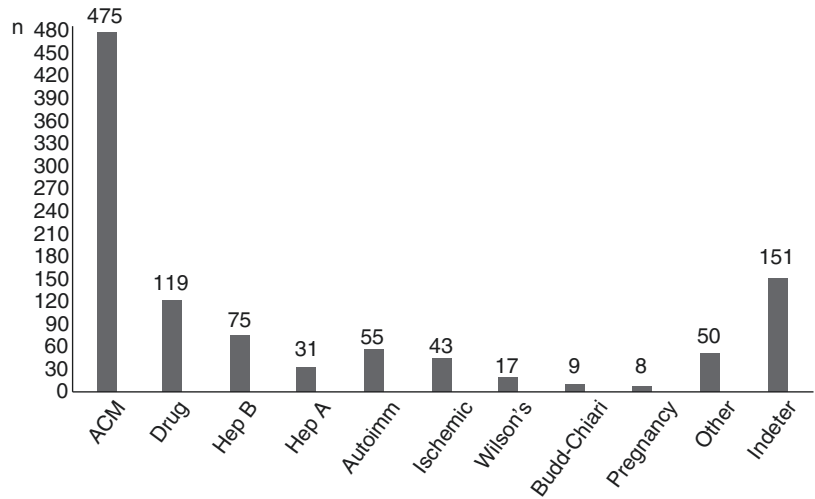
Fig. 3.2 Survival for different etiologies of ALF. Organ support to best determine which patients are likely to benefit from being listed for transplant with high priority and indeed proceeding to OLT if levels of organ support permit [4]
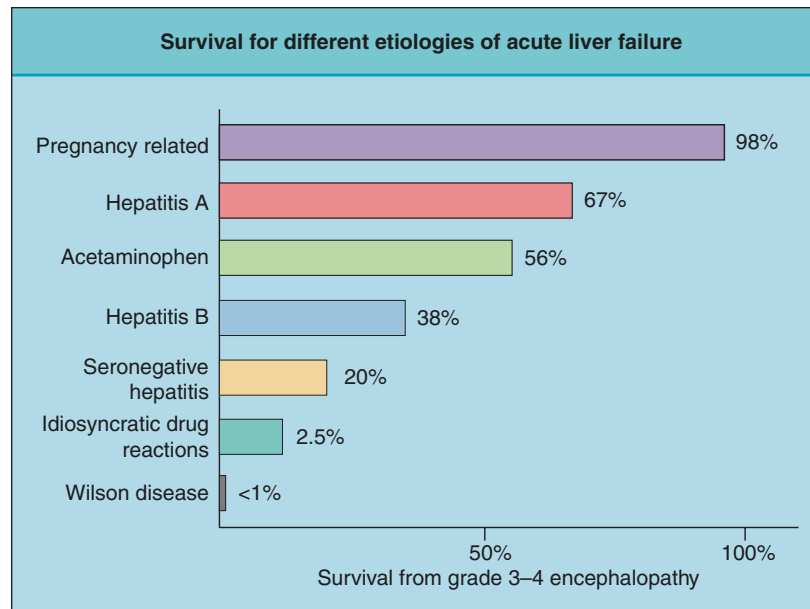
Etiologies of ALF

Paracetamol (Acetominophen) Overdose

Paracetamol overdose (POD) in the UK had been increasing steadily likely due to its easy availability [7]. In 1998 the Medicine Control Agency in the UK sought to limit the availability of paracetamol. Legislation was changed in line with World Health Organization recommendations and data from other countries with similar restrictive policies that had lower rates of paracetamol-induced hepatoxicity. Suicidal or para-suicidal actions are usually impulsive acts in reaction to crises; therefore, it was postulated that

limiting supply would result in reduced availability of paracetamol, thus reducing the quantity ingested and lowering rates of hepatoxicity. The general sale of paracetamol was restricted to sixteen 500 mg tablets, a total of 8 g per packet. Reports suggested that this was a successful policy that resulted in a reduction of intensive care admissions and of deaths from POD by 43% in the years following the legislation [8], despite some debate on the true mortality benefit of pack size reduction alone [9].

In the UK POD comprises up to 50% of all poisoning admissions, compared to only 10% in the US [10]. Due to a combination of the small doses absorbed and the efficacy of early antidote therapy, only 0.6% of these cases result in hepatoxicity in the UK. Studies assessing the rate of deliberate versus accidental POD display geographic variation. In Europe, studies have reported around 86% of POD cases were deliberate and 14% were accidental [11], while US poisons center data have reported rates of 35% and 65%, respectively [12]. Paracetamol medications combined with narcotics pose a potential for unintentional hepatoxicity when addiction to the narcotic within such combined analgesics leads to a gradual increase of the ingested dose [13]. This may be a significant reason for the discrepancy between the US and the UK with regard to deliberate and unintentional overdose. The assessment of the risk of developing ALF from POD, whether accidental or deliberate, is closely related to the total dose ingested, as well as the time from ingestion to presentation and treatment with *N*-acetylcysteine (NAC).

Higher doses and prolonged time to NAC result in increased length of time exposed to the active unstable paracetamol metabolite, *N*-acetyl *p*-benzoquinone imine (NAPQI). NAPQI depletes hepatic glutathione levels, with ensuing hepatocellular damage, unless the antidote, the glutathione precursor NAC or methionine is given in a timely fashion. NAC acts to augment the glutathione reserves in the body, which directly bind to toxic metabolites and protect hepatocytes in the liver from NAPQI toxicity. When administered within 12 h of an unstaggered ingestion of paracetamol, NAC can prevent hepatocellular damage.

A accurate and precise history regarding the timing and quantity of paracetamol ingested is important, as is establishing whether the ingestion was staggered. However, the circumstances that surround any parasuicidal event can make this information difficult to establish, especially if patients have ingested opiate-based medication in addition to paracetamol or are intoxicated with alcohol. Additionally, an assessment of potentiating factors that lower hepatic glutathione levels or increase cytochrome P450 enzyme activity and increase hepatoxicity should be undertaken. These factors include anorexia nervosa, malnutrition, chronic alcohol consumption, and enzyme inducing drugs such as phenytoin and carbamazepine.

In an unstaggered overdose presenting within 24 h a paracetamol level should be measured and applied to the revised paracetamol poisoning treatment graph. A paracetamol level of more than 150 mg/kg is generally considered to be hepatotoxic, though strong evidence ratifying this is lacking. In a staggered overdose the paracetamol level cannot be interpreted and one must assess the risk of hepatoxicity based on total dose alone. If there is any doubt about timing or if there was a delay in presentation, treatment should be commenced until it becomes clear that hepatotoxicity is unlikely. Patients presenting within 24 h of ingestion without signs of hepatotoxicity can be managed on the wards, while those with features of paracetamol-induced hepatoxicity should be managed in a critical care environment.

Viral Hepatitis

All hepatitides except for Hepatitis C have been implicated in cases of ALF [1]. Viral hepatitis A and B are the most common causes of ALF worldwide including France and Japan; Hepatitis E is predominant in India.

The risk of ALF is lowest with Hepatitis A at less than 0.35%, but this risk increases with age at the time of exposure. In the western world, it

appears that native immunity to Hepatitis A is decreasing. In the US the incidence of ALF due to Hepatitis A is around 3.1% with around 0.12% of all cases listed for liver transplantation. In the developed world the incidence of Hepatitis A has been decreasing since 1995 likely due to vaccination of high risk patients, improved sanitation, and improved food preparation techniques [14]. The treatment of Hepatitis A is largely supportive.

Hepatitis B infection is the cause of ALF in around 1% of all cases with over 50% associated with hepatitis D co-infection. The mortality of patients developing ALF ranges from 70 to 80% [15]. Hepatitis B has eight genotypes A–H and all have been associated with different clinical presentations. Antiviral therapy with nucleos(t)ide analogues can alter the outcome in ALF and is recommended in potential transplant candidates [16].

Hepatitis E is common in Asia and Africa with the risk of ALF greatest during pregnancy (greater than 20%), particularly during the third trimester. In the general population, Hepatitis E carries a low mortality of 0.5–4%, but it can exceed 75% in developing countries especially during the second and third trimester of pregnancy. It is transmitted by the fecal-oral route, often through contaminated water supply. Consequently, it has been the cause of epidemics in Asia, China, and Eastern Europe especially after heavy rainfall. The first such epidemics to be documented occurred in New Delhi, India in 1955 and affected 29,000 people [17].

Viruses including cytomegalovirus (CMV), Epstein Barr virus, herpes viruses type 1, 2 and 6, and varicella zoster have all been implicated in cases of ALF, frequently in profoundly immunocompromised patients. Falciparum malaria has also been reported as a cause of ALF, primarily in India. The mortality associated with atypical viral hepatitis is around 76% and for falciparum malaria 24% [1]. Antiviral therapies may be beneficial in some cases of ALF such as nucleos(t)ide analogues for hepatitis B, ribavirin for hepatitis E [18] and acyclovir and valganciclovir for herpes and CMV disease.

Idiosyncratic Drug Reaction

The administration of drugs directly affects the liver and may cause toxicity as the liver is the primary site of metabolism and elimination. In the US, hepatoxicity is the main cause for halting drug development and withdrawal from the market. Drug-induced liver injury (DILI) including cases of paracetamol toxicity, is the leading cause of ALF and indication for liver transplantation. The majority of non-paracetamol DILI cases are idiosyncratic reactions that occur in around 1 in 10,000 of exposed patients. More than 1000 drugs and herbal remedies have been implicated and idiosyncratic reactions comprise 10% of ALF cases [19]. Idiosyncratic DILI is a complex phenomenon that appears to be closely related to how cell mitochondria balance cellular injury and regeneration. The reactions are idiosyncratic as liver injury is unpredictable and not dose-dependant. There are non-allergic and allergic idiosyncratic DILI, the latter characterized by fever, skin reactions, eosinophilia with the formation of autoantibodies (for example drug-related eosinophilic syndrome—DRESS). Several risk factors for DILI have been identified and include age, female gender, concomitant diseases, and specific drugs. DILI algorithms and clinical scales may improve consistency and aid the clinicians to determine the causality of adverse drug reactions [20].

Genetic polymorphisms have been associated with increased risk of DILI, for example, cytokine polymorphism causing diclofenac hepatoxicity. Genetic variations are also involved in genetic deficiency of mitochondrial long-chain 3-hydroxyacyl-CoA dehydrogenase that is associated with acute fatty liver of pregnancy, presumably related to increased levels of female sex hormones. DILI is commonly diagnosed primarily by increased levels of alanine transferase (ALT) and gamma-glutamyl transferase (GGT). Metabolomic studies are currently conducted to identify biomarkers of DILI that will detect injury prior to elevations in ALT.

Seronegative (Indeterminate)

Seronegative ALF is the second most frequent etiology of ALF (after DILI) with 10–20% of all cases. With seronegative ALF no definite causes of ALF can be found, but a predictable clinical course is observed characterized in sub-acute liver failure due to hepatic necrosis with loss of liver volume and progressive coagulopathy. Patients with seronegative ALF often fulfill standard criteria late in the course of their illness, as overt hepatic encephalopathy is a late feature that may occur after many weeks of gradual clinical deterioration. In the future assessment using MELD score or liver volumes (as described below) may allow a better prediction of poor prognosis in this group and facilitate more timely access to LT.

Malignancy

There are numerous case reports of a wide range of solid and hematological tumors that can cause ALF. A literature review in 2005 cited 34 cases of primary and metastatic neoplastic infiltration of the liver resulting in ALF [21]. The pathophysiology of ALF in neoplastic infiltration is multifactorial. Parenchymal ischemia and infarction can be caused by diffuse tumor cell infiltration or vascular occlusion from tumor thrombi. It has also been postulated that diffuse tumor cell infiltration renders the remaining liver parenchyma highly susceptible to ischemic injury. A case series of three patients with metastatic disease demonstrated biopsy-proven hepatic ischemia in the absence of any discernible episodes of systemic hypotension [21, 22]. Additionally, cytokine-mediated liver injury has been implicated in lymphomatous infiltration [23]. Clinical suspicion and features suggestive of malignancy such as hepatomegaly, enlarged lymph nodes on physical examination along with computer tomography (CT) findings suggestive of an infiltrative process should prompt an attempt to obtain a biopsy for a definitive histological diagnosis. Radiological imaging including both ultrasonography and triple phase computer tomography should not solely be relied on due to their poor sensitivity for metastatic and lymphomatous infiltration of the liver. There are no specific biomarkers for tumour infiltration; elevations of ALT and AST with tumors are usually lower that than with ischemic hepatitis. Both appear to have greater sensitivity in the presence of hyperbilirubinemia. However, jaundice does not always manifest in the setting of tumor infiltration and cases with over 90% liver infiltration without jaundice have been reported. A transjugular liver, bone marrow aspiration, and trephine (bone marrow) or lymph node biopsy can be invaluable tools for establishing a diagnosis. Confirmed malignancy is a absolute contraindication for liver transplantation, establishing a diagnosis is therefore crucial.

Vascular Insults and Ischemic Hepatitis

ALF following vascular insults are uncommon. These include ischemic hepatitis often associated with low cardiac output due to left and right ventricular cardiac dysfunction. Veno-occlusive disorders, such as Budd-Chiari syndrome (BCS) are also a rare cause of ALF with an incidence of 1 in 2.5 million [24]. BCS is characterized by hepatic venous outflow obstruction and presents with ALF in around 20% of cases. In the western world occlusion of the hepatic veins is commonly due to thrombosis whereas in Asia a membranous web is the most frequent cause. Both inherited and acquired procoagulant conditions have been implicated in Budd-Chiari and often both conditions coexist. Veno-occlusive disorders have been associated with inherited conditions such as Factor V Leiden, Protein C, S and antithrombin deficiency; acquired conditions include paroxysmal nocturnal hemoglobinuria and antiphospholipid syndrome. The recently discovered Janus Kinase 2 (JAK-2) mutation has also been detected in around 40–59% of cases with BCS [25]. Myeloproliferative disorders also need to be ruled out as a cause with an examination of the bone marrow function using a trephine (bone marrow) biopsy and aspiration as these disorders are most commonly associated with both BCS and portal vein thrombosis [24].

Metabolic

ALF secondary to inherited and acquired metabolic disorders is uncommon, these include acute fatty liver of pregnancy, fructose intolerance, galactosemia, lecithin-cholesterol acyltransferase deficiency, Reye's syndrome, tyrosinemia, and Wilson's disease (WD).

WD is a rare autosomal recessive condition caused by a mutation to the WD gene ATP7B that encodes a copper transporting P-type ATPase leading to insufficient copper excretion into bile and subsequent copper accumulation in brain, liver, and corneas. The incidence of WD is approximately 1 in 30,000 and can present acutely, usually in pediatric or young female patients, or chronically in adults sometimes into their eighth decade of life. ALF in WD is unique as there is usually some preexisting liver disease at the time when ALF ensues. WD is diagnosed by measuring indices of copper metabolism, although in ALF these investigations can be misleadingly normal. Serum copper and caeruloplasmin, as an acute phase protein, can both be normal or elevated in other causes of ALF. Elevated levels of urinary copper are a good indicator of WD, but the high incidence of anuric acute kidney injury in ALF may eliminate this diagnostic tool. Ophthalmic exam of corneas can be useful to detect the presence of Kayser-Fleischer rings, which in combination with liver disease and copper metabolism abnormalities strongly supports the diagnosis. Additionally, Coombs negative hemolytic anemia and low serum cholinesterase levels can be a feature of WD [26]. The ALP/bilirubin and AST/bilirubin ratios are often significantly lower in fulminant Wilson's disease than in other categories of fulminant liver failure but this is not necessarily diagnostic [27].

Autoimmune Hepatitis

Twenty percent of patients with autoimmune hepatitis present with acute liver injury and a proportion of these will go on to develop sub-acute ALF. The decision on whether to initiate corticosteroid therapy can be challenging and MELD-Na score and the UK end stage liver disease score (UKELD) on day 7 after onset may the best predictors of failure of standard medical therapy [28]. Patients with hepatic encephalopathy or who do not respond rapidly to corticosteroid therapy should be assessed early for LT [28].

Miscellaneous

Other rare causes of ALF include HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome of pregnancy. Amphetamine derivatives such as 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") have caused a number of cases of ALF requiring OLT. Toxins of mushrooms such as *Amanita phalloides* or foodborne illnesses by *Bacillus cereus* are also potential causes of ALF.

Clinical Features and General Management

The identification of the underlying insult is crucial in determining potential therapies that could halt the injurious process and potentially reverse liver failure. Laboratory investigations should include hepatitis and atypical viral serology; autoantibodies (antinuclear, anti-smooth muscle, anti-liver kidney microsomal, anti-soluble liver antigen and anti-mitochondrial antibodies), paracetamol levels and urine and serum copper levels. A negative paracetamol level does not rule out paracetamol as a cause of ALF. Additionally ultrasonography of the liver and its vasculature should be performed as we as axial imaging with computer tomography if the history and laboratory investigations do not confirm viral or drug-induced insults. The outcome is largely determined by the severity of the underlying liver insult and the development of organ failure; any episodes of sepsis have a further strong impact on mortality. (Table 3.1) Early recognition and treatment of sepsis and the prevention and support of organ dysfunction is therefore key to gain time for hepatic regeneration. Finally, a timely

decision for super-urgent liver transplantation is required when it becomes sufficiently clear that hepatic regeneration will not occur in time. This decision carries particular importance given that the median time from listing to transplantation is around 48 h in the UK. 24% of patients who are listed will never receive a transplant; the majority (92%) of these patients will die while waiting for an organ and the remainder will become "too sick" for transplantation [29]. Several pre-transplant factors have been associated with poor outcomes after LT for ALF such as age >45–50 years, escalating vasopressor requirements, the use of high-risk organs and ABO-incompatibility [29, 30]. Other factors should also prompt a discussion about the suitability for transplantation include fixed dilated pupils for greater than 2 h, necrotizing pancreatitis, severe adult respiratory distress syndrome (ARDS), moderate to severe pulmonary hypertension, culture proven bacterial or fungal sepsis requiring more than 24 h of antimicrobial therapy before transplantation. All these conditions need to be evaluated in relation to age and the degree of associated organ failures. The complex nature of ALF requires the involvement of wide spectrum of expertise to form a cohesive multidisciplinary team. Critical care nurses, physiotherapists, pharmacists, transplant surgeons, hepatologists and liver intensivists should all be included in this team.

Cardiovascular

The circulatory symptoms of established ALF mirror the hemodynamic changes of sepsis with an elevated cardiac output and vasoplegia. The main vasoactive mediator, nitric oxide, causes regional vasodilatation primarily in the splanchnic bed. The management goals for the circulation in established ALF are similar to the recommendations for initial resuscitation in septic shock [31]. The early use of invasive hemodynamic monitoring is recommended as it may provide important additional clinical indices about central circulating volumes and cardiac output. Furthermore, a normal cardiac output (i.e. abnormally low for the vasodilatory state) or

substantially elevated central venous pressures should prompt further evaluation of myocardial function with echocardiography to evaluate left and right ventricular filling and function.

Early admission to critical care environment is recommended to detect and treat rapidly occurring deteriorations of clinical condition; patients with ALF and organ dysfunction should be cared for in a critical care unit. Some commonly used resuscitation parameters may be problematic in ALF; for example $ScvO_2$ is often significantly elevated reflecting the hyperdynamic circulation and microvascular shunting. Lactate concentrations in ALF may reflect sole circulatory disarray but also impaired hepatic clearance of lactate especially if adequate volume resuscitation has been implemented. Hyperlactatemia reflects liver, circulatory and cellular dysfunction; however the liver has a large reserve for lactate metabolism. Even after hepatectomy with resection of more than 50% of the liver lactate levels may remain normal [32]. High lactate levels are therefore frequently encountered in ALF where inadequate fluid resuscitation has lead to circulatory and cellular metabolism dysfunction. In general hyperlactatemia and the speed of its resolution acts as an important predictor of outcome in both critical illness and ALF [33]. Lactate is now recognized as an important prognostic variable. Persistently elevated lactate levels >3.0 mmol/L despite aggressive fluid resuscitation [34] have been incorporated into the Kings College Criteria (KCC) adding statistical strength to the original O'Grady criteria [35].

In ALF relative corticosteroid insufficiency, defined by an abnormal response to adrenocorticotrophic hormone, has a prevalence of 62% and steroid replacement therapy is associated with reductions in vasopressor requirements, albeit without any mortality benefit [36, 37]. The diagnosis and treatment of critical illness related corticosteroid insufficiency (CIRCI) was first encountered in sepsis with the demonstration that low dose hydrocortisone could accelerate the reversal of shock, but no significant effect on mortality [38]. The high prevalence of CIRCI in ALF can be explained by factors that affect cortisol production and metabolism. Firstly, both ALF

and sepsis often coexist and ALF represents an additional stress that can lead to RAI. Secondly, patients with ALF have low circulating cortisol levels for several reasons: the effects of low levels of HDL cholesterol that is central to cortisol production, increased conversion of cortisol to the inactive form cortisone and the negative effect of cytokines such as tumor necrosis factor alpha (TNF-α) on hypothalamic function all contribute to the low circulating TC levels [39].

The diagnosis of adrenal insufficiency is often established by performing the short synacthen test; however, during critical illness and ALF this is fraught with problems of interpretation as highlighted by the CORTICUS study and subsequent investigations [38, 40]. This is mostly related to the decrease of both albumin and cortisol-binding globulin (CBG), that leads to an increase of free cortisol (FC) levels, despite low measured total cortisol (TC) levels. Various alternative measures or calculations have been explored to better assess FC levels. Salivary cortisol levels correlate well with FC although in ventilated patients this may be difficult to obtain. Alternatively, the free cortisol index (see equation below) that be calculated by measuring both CBG and TC levels correlates well with FC levels [41]. These alternative measures of FC may prove to be better methods of assessing RAI rather than relying on TC levels alone. However, hydrocortisone therapy is frequently initiated empirically to impact on escalating vasopressor levels.

The free cortisol index: (Unbound cortisol (mmol/L) = (0.0167 + 0.182 (CBG−TC)) [2] + (0.01 22 × TC) 0.5 − (0.0167 + 0.182 (CBG − TC)) [42].

Respiratory

Hepatic encephalopathy in ALF is one of the primary indications for intubation and ventilation in order to protect the airway from aspiration. A significant number of patients will also develop respiratory complications. ARDS complicates up to 30% of paracetamol-induced ALF cases [43]. It affects primarily those with significant vasopressor requirements and evidence of intracranial hypertension (ICH). The mechanisms of lung injury in ALF include the directly toxic effects of acetominophen and the release of vasoactive mediators that affect not only the brain and circulation but also the lungs causing an increased vascular permeability and capillary leak. This is further exacerbated by fluid accumulation within the extravascular compartments as a result of large volumes of fluid administration to support a vasoplegic circulation. Additionally, there is a high incidence (around 51%) of gram-negative organisms isolated from tracheal aspirates in intubated ALF patients [44], that directly impact the development of ventilator-associated pneumonia (VAP). The management of ICH increases the risk of pulmonary and extrapulmonary sepsis and ARDS as adequate sedation and specific measures to avoid hyperthermia contribute to limited tracheobronchial toilet and retention of secretions. Endotracheal tubes with a large volume, low pressure cuffs and a subglottic suction port may help to mitigate some of the VAP risks. Other respiratory complications associated with both mechanical ventilation and critical illness have been described in patients with ALF. These include pleural effusions, atelectasis, and poor compliance due to raised intra-abdominal pressure (IAP) or reduced thoracic compliance due to chest wall edema.

Conventional lung-protective ventilation employed for ARDS may impact on cerebral perfusion and exacerbate ICH. A balanced approach is often required, though low tidal volumes (6–8 mL/kg) can achieve normal partial pressures of CO_2 (pCO_2) in most cases. Increased IAP and decreased lung compliance due to chest wall edema lead to increases in pleural pressure, rendering the plateau pressure a poor measure of transpulmonary pressure. Therefore, attempts to limit plateau pressure below 30 cm water can be difficult to attain and indeed are often unnecessary. The combination of ARDS with severely elevated intracranial pressure (ICP) with intact physiological autoregulation requires tight control of $PaCO_2$. When all conventional measures to optimize ventilation have been exhausted, extracorporeal devices can be considered but should be a strategy of last resort due the significant potential for bleeding complications associated

with cannulae insertion and limb ischemia. Such devices have been used successfully in traumatic brain injury and ARDS [45] and have also been employed on few occasions in ALF patients associated with ARDS, when management of ICH has remained problematic [46].

Patients with fulminant ALF should be positioned with the head elevated at 30° and attention to avoiding unnecessary turning and other interventions that will exacerbate ICH. Consequently, high positive end expiratory pressure (PEEP) is necessary to optimize recruitment and prevent atelectasis of basal lung segments. The adverse effect of high PEEP on ICH may be outweighed by the improvement of oxygenation and consequent improvement of cerebral blood flow. Recruitment maneuvers and prone positioning are usually contraindicated due to the impact on ICH. Refractory hypoxemia may be a reason to consider removing patients with ALF from the transplant waiting list. However, hypoxemia alone appears to be a nonspecific variable in the diagnosis of ARDS. Furthermore, a low partial pressure of oxygen (PaO_2) to FiO_2 ratio is common, often transient and not necessarily associated with poor outcomes [47]. Transpulmonary thermodilution cardiac output monitors can calculate an estimated measure of lung permeability, the extravascular lung water index, which can be a useful variable in guiding management [48].

Weaning patients from the ventilator occurs either once the acute phase of the liver injury has subsided or in the post-transplant period when ICH has settled. An assessment of the recovery of ICP auto regulatory mechanisms can be achieved by evaluating ICP responses to enforced elevations in $PaCO_2$, mean arterial pressure and reductions in sedation. The return of ICP autoregulation permits a more sustained withdrawal of sedation and weaning from mandatory modes of ventilation. However, once sedation is decreased or stopped neurological problems may arise such as slow emergence from sedation or critical care delirium. Critical illness acquired weakness is highly prevalent, due to the significant number of risk factors for this condition encountered in ALF, including sepsis, profound systemic inflammatory response syndrome (SIRS), exposure to

steroids, high protein catabolism and multi-organ failure [49]. A (percutaneous) tracheostomy is often necessary to facilitate weaning from the ventilator and sedating medication. Percutaneous tracheostomy can be performed safely in patients with ALF despite coagulopathy and thrombocytopenia [50].

Neurological

Traditionally intracranial hypertension was a major cause of mortality in ALF; fortunately more recent reports demonstrated that with modern critical care management the incidence is 20%, and mortality rates of affected patients have decreased [3]. Hepatic encephalopathy in ALF is multifactorial, however the principal mechanisms involve an accumulation of ammonia that can cross the blood brain barrier and results in a build-up of glutamine in astrocytes. Glutamine, ammonia and the systemic inflammatory process have direct toxic effects on astrocyte function, mitochondrial activity and contribute to astrocyte swelling resulting in cerebral oedema and intracranial hypertension [51].

Standard management should include early intubation and ventilation for airway protection in those with >grade 2 hepatic encephalopathy and standard "neuroprotective measures" including adequate sedation, nursing in the 30° head up position, avoidance of hyperglycaemia, normocapnoea, adequate oxygen delivery and adequate cerebral perfusion. Renal replacement therapy should be initiated once the arterial ammonia level is >150 μmol/L and should be continued with the aim of keeping ammonia levels <100 μmol/L [52]. Maintenance of adequate serum sodium levels (145–150 mmol/L, best achieved with an infusion of hypertonic (30%) saline) reduces the incidence of intracranial hypertension [53]. Rescue therapies for acute rises in ICP include bolus doses of Mannitol, an osmotic diuretic, and short-term hypoventilation to reduce the $PaCO_2$.

Invasive ICP monitoring has not demonstrated any short term mortality benefit and its routine use is not recommended. Surrogates of ICP, such as arterial flow on transcranial dopplers and jugular

venous oxygen saturations can be considered, but their accuracy has not been proven in ALF [54].

Therapeutic hypothermia (32–35 °C) has been used in the treatment of brain injury with the intention of reducing the cerebral metabolic oxygen demand, reducing cytokine activity and improving cerebral blood flow. Hypothermia to 33 °C in patients following cardiac arrest is no longer recommended after a large randomised trial (TTM) showed no benefit over avoidance of hyperthermia (with a target of 36 °C) [55]. A similar RCT assessing therapeutic hypothermia in AHF patients with high-grade hepatic encephalopathy showed similar results. Currently it is best to avoid hyperthermia and aim for a target temperature of 36 °C [56]. Active cooling devices are rarely required to achieve this.

Metabolic, Gastroenterology and Nutrition

Numerous metabolic abnormalities and their associated complications are encountered in ALF but only a few studies have been undertaken to assess and identify best practice.

Hypoglycemia is a frequent metabolic abnormality encountered in ALF due to the loss of hepatic glycogen stores, impaired gluconeogenesis and hyperinsulinemia. Hypoglycemia during the initial presentation is considered a poor prognostic predictor and hypoglycemia along with other parameters of hepatic necrosis may help determine which patients require referral to specialist centers (Table 3.2). ALF is also associated with impaired peripheral uptake of glucose and

Table 3.2 Criteria for referral/discussion with specialist center [3]

Organ system	Paracetamol overdose (time from ingestion, days)			Non-paracetamol overdose (ALF classification, time from jaundice to encephalopathy)		
	Day 2	Day 3	Day 4	Hyperacute	Acute	Subacute
Liver	INR > 3.0	INR > 4.5	INR > 6	INR > 2.0	INR > 2.0	INR > 1.5
	or	or	or	or	or	or
	PT > 50 s	PT > 75 s	PT > 100 s	PT > 30 s	PT > 30 s	PT > 20 s
						or
						Shrinking liver volume
Metabolic	pH < 7.3 or HCO₃ < 18	pH < 7.3 or HCO₃ < 18	pH < 7.3 or HCO₃ < 18	Hypoglycemia	Hypoglycemia	Hypoglycemia
	or	or	or	or	or	or
	Lactate > 3.0	Lactate > 3.0	Lactate > 3.0	Hyperpyrexia	Hyponatremia	Hyponatremia
	or	or	or	or	<130 μmol/L	<130 μmol/L
	Hypoglycemia	Hypoglycemia	Hypoglycemia	Hyponatremia < 130 μmol/L		
Kidney	Oliguria (<0.5 mL/kg/h for >12 h)	Oliguria (<0.5 mL/kg/h for >12 h)	Oliguria (<0.3 mL/kg/h for >24 h or anuria for 12 h)	AKI Stage 1–3	AKI Stage 1–3	AKI Stage 1–3
	or	or	or			
	SCr > 200 μmol/L	SCr > 200 μmol/L	SCr > 300 μmol/L			
Brain	HE	HE	HE	Any degree of HE	Any degree of HE	Any degree of HE
Hematology		Severe thrombocytopenia	Severe thrombocytopenia	Pancytopenia	Pancytopenia	Pancytopenia

HE hepatic encephalopathy, *AKI* acute kidney injury, *SCr* serum creatinine, *INR* international normalised ratio, *PT* prothrombin time

decreased peripheral insulin sensitivity; this is usually restored within 2 weeks in those patients that survive [57].

It is important to establish and maintain normoglycaemia early for example with infusions of 20–50% dextrose until enteral nutrition is commenced. Tight blood glucose control has been controversial since the landmark study by Van Den Berghe in 2001 and subsequent studies demonstrated more adverse effects and poorer outcome with hyperglycemia in critically ill patients. This was also demonstrated in patients with neurovascular brain injury and in ALF where hyperglycemia can contribute to poor ICH control [58]. However, meta-analyses assessing tight glycemic control studies since 2001 have not confirmed the mortality benefit demonstrated in the original study population but instead an increased rate of hypoglycemic episodes with intensive insulin regimens. Ultimately, a balanced approach is required with the goal of achieving blood glucose levels closer to the lower limit of 6–8 mmol/L (108–145 mg/dL) avoiding hypoglycemia and elevated levels greater than 12 mmol/L (216 mg/dL).

Early enteral nutrition within 24 h of admission aiming to achieve 25–30 kcal/kg/day is recommended. The use of opioid-based sedation, aggressive fluid regimens causing bowel wall edema, raised intra-abdominal pressure and constipation all contribute to abnormalities of gut motility resulting in decreased absorption. If gut failure and poor absorption persist despite attention to constipation therapy and the use of prokinetics early intervention with total parenteral nutrition (TPN) may be a last resort. Previous concerns about TPN-induced liver toxicity are not observed with newer hypocaloric regimens [59]. Normal protein intake of approximately 1 g/kg/day does not seem to worsen hyperammonemia and hepatic encephalopathy. This is important, because ALF patients are often catabolic with supra-normal energy expenditure despite significant hepatocyte loss. Furthermore, there is significant protein catabolism with muscle wasting, amino acid losses, and vitamin deficiency, that can affect immune function. Therefore supplementation of multiple vitamins and trace elements in patients with ALF is necessary, especially in patients requiring continuous renal replacement therapy (CRRT) regimen [60, 61]. Hypophosphatemia is frequently encountered with CRRT, especially high volume dialysis and requires prompt replacement. However, hypophosphatemia may also herald liver regeneration with increased hepatic ATP production and is considered as a good prognostic marker [62].

Immunity and Bacteremia

In ALF the incidence of clinical bacteremia is high (approximately 35%) [44] and there is evidence that the complex changes in the innate immunity are predominantly balanced toward an anti-inflammatory environment. The deactivation of monocytes is thought to be the leading cause of increased susceptibility to infection. Approximately 30% of cases of bacteremias manifest without pyrexia and elevation of white cell count reflecting a hypo-responsiveness to infection that may be associated with a mortality benefit over patients exhibiting classic SIRS criteria [63].

The use of empirical broad-spectrum antibiotics, attention to appropriate nutrition, consideration of gut decontamination, oral hygiene, ventilator care bundles, intense daily scrutiny of the indwelling intravenous catheters and vigilant infection control measures are important in limiting the occurrence of bacteremia. Such interventions have affected the epidemiology of bacteremia in ALF with longer median times to evolution of bacteremia and a shift toward greater incidence of gram-negative organisms [44]. Bacteremia and SIRS both appear to influence the degree of hepatic encephalopathy (HE) [64]. ALF is associated with a significant incidence of fungal sepsis (approximately 32%) predominantly due to *Candida* species; early empirical use of antifungal therapy, preferably with an echinocandin antifungal such as anidulafungin is recommended due to the relatively high rates of fluconazole resistant Candida and a lower rate of invasive aspergillosis [65, 66].

ALF generates marked changes of pharmaco-kinetics and pharmacodynamics that requires close drug monitoring. If drug level monitoring is not possible, antibiotic dosing should aim for higher drug levels because of the immuneparesis associated with ALF.

The innate immune system undergoes significant changes in response to acute liver injury and has a central role in the subsequent development of the clinical manifestations of ALF. Many of these changes closely resemble the features of systemic sepsis that results in vasoplegic circulation and MOF. The complex immune responses in ALF are closely related to some of the clinical complications of ALF, particularly, particularly bacteremia and encephalopathy.

The innate immune system is initially activated with the mobilization of immune cellular components, including neutrophils, monocytes, and macrophages. These cells are involved in the profound release of cytokines as part of the pro- and anti-inflammatory responses to sustained liver injury together with significant decrease of complement factors impairing opsonisation of bacteria [67]. Neutrophil function is impaired with reduced chemotaxis, bacteriocidal activity, and decreased production of superoxide and hydrogen peroxide. Both monocytes and macrophages are involved in initiation, propagation, and resolution of acute liver injury. Shortly after acute liver injury macrophages release chemokines and pro-inflammatory cytokines. This pro-inflammatory state is balanced by anti-inflammatory responses that accompany the recruitment of monocytes to the site of the liver injury to initiate repair processes. Activated macrophages release TNF-a, interleukin (IL)-1, IL-6, proteolytic enzymes, reactive oxygen intermediates, and lysosomal enzymes. These elevations of TNF correlate with the development of sepsis and increased IL-6 levels are associated with MOF and mortality (Fig. 3.3). High-volume plasma exchange (HVP) was recently studied in a randomized controlled trial. Patients with acute liver failure were randomized to either three cycles of HVP or standard medical therapy. HVP increased overall transplant-free survival with the largest effect on survival in patients who did not receive LT [68]. In this trial HVP was associated with significant reduction in circulating damage associated molecular pattern molecules and TNF-alpha, suggesting that HVP acts in part by controlling the innate immune response.

Acute Kidney Injury

The incidence of AKI in ALF is significantly higher than that of the general critically ill population ranging from 40 to 85% and approximately 75% for POD (AKI defined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines) [69]. Stage 3 (increase of serum creatinine greater than 300% from baseline) in patients with previously normal kidney function (SCr 80–120 μmol/L) is associated with poor prognosis in ALF and an important clinical criteria for referring to a specialist center and listing patients for LT (Fig. 3.4 and Tables 3.2 and 3.3).

The mechanisms involved in the development of AKI in ALF are similar to the pathophysiological models of hepatorenal syndrome and septic AKI. The release of vasoactive mediators, like nitric oxide and other free radicals, leads to a hyperdynamic circulation with circulatory splanchnic vasoplegia "cardiovascular failure" and relative hypovolemia. These vasoactive mediator-induced changes to the splanchnic circulation activate responses involving the sympathetic nervous system and renin angiotensin system (RAS) causing renal arterial vasoconstriction. Intraglomerular arteriolar vasoconstriction in addition to endothelial dysfunction, leukocyte activation and release of cytokines results in profound intracellular oxidative stress and ischemic acute tubular necrosis. Furthermore microcirculatory changes and renal venous congestion can impede cellular energy mechanisms independent of tissue oxygen availability [70].

Additional renal insults can be caused by drugs that are either directly nephrotoxic or cause tubulointerstitial nephritis. Specific glomerular pathologies, that result in rapidly progressive glomerulonephritides, should be excluded for example by urine dipstick and microscopy for red cell casts in conjunction with
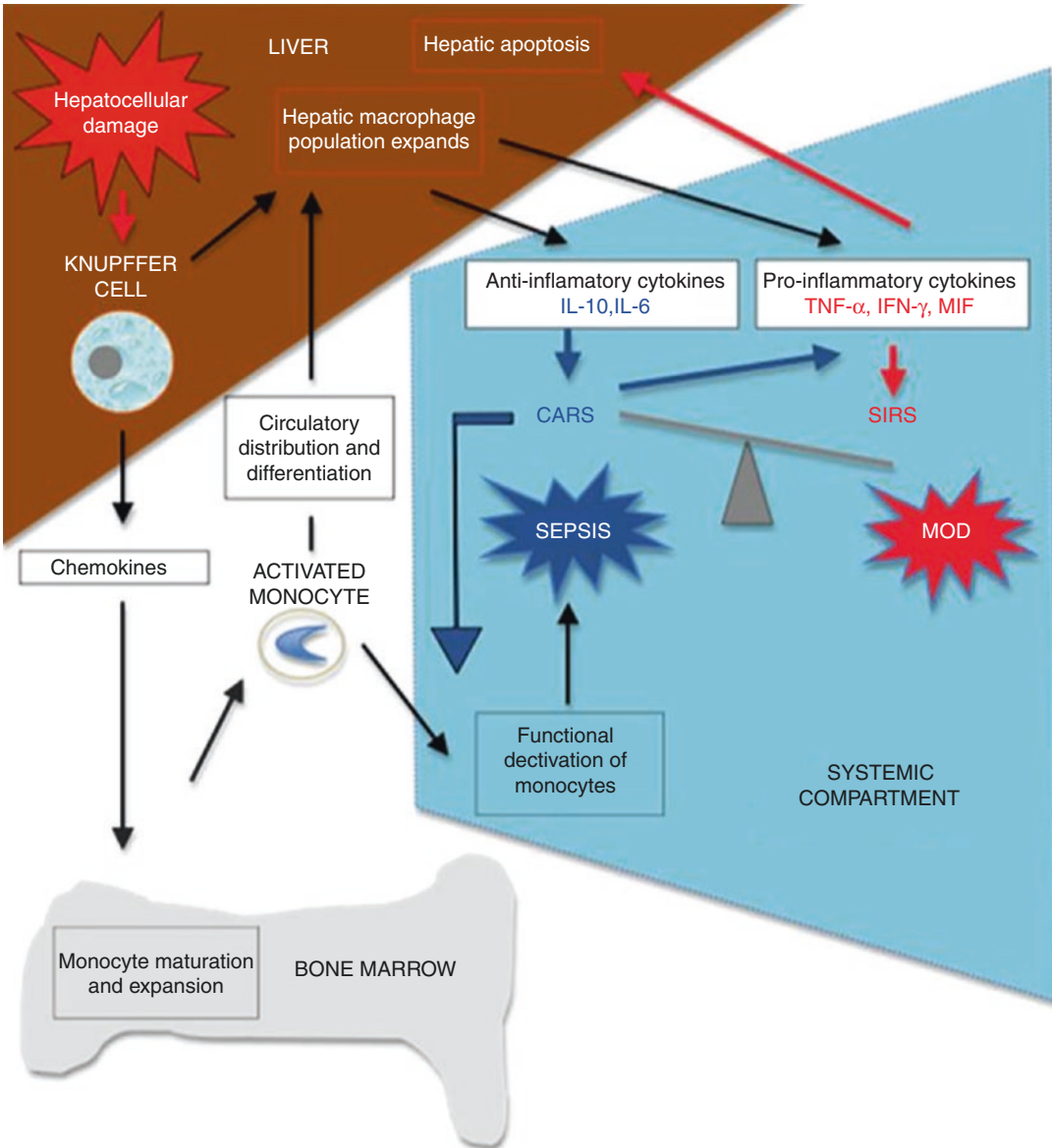
Fig. 3.3 A schematic of the inflammatory responses to hepatocellular damage. Adapted from [64]

testing for autoantibodies to exclude small vessel vasculitides and serological testing for leptospirosis (Weil's disease), if the history and examination suggest such diagnoses (See Fig. 3.4) [71].

The precise mechanism of renal cell death in paracetamol nephrotoxicity remains unknown and yet it is clear that it differs from the mechanisms involved in hepatotoxicity as in rat models NAC does not protect tubular cells [72]. Paracetamol is a phenacetin metabolite that has been implicated in proximal tubule cell apoptosis in AKI and chronic kidney disease (CKD). Consequently, cellular mechanisms and the induction of apoptosis in renal tubular cells has been the focus of studies of paracetamol-induced nephrotoxicity. It is likely that the mechanism for nephrotoxicity lies with endoplasmic reticulum

AKI in Acute Liver failure

Glomerular disease	Factors associated with greater AKI susceptibility
Rapidly progressive glomerulonephritis	
(A pathological classification based on immomofluorescence patterns [SS])	Reactive increases in afferent arteriolar tone
Typr I (3%) - anti glomerular basement membrane disease	'Vascular failure' – acute liver failure
Good pasture's	Sepsis including rarely leptosporosis
	Hepatorenal syndrome – Type 1
Type II (45%) - Immune complex mediated	Contrast
Postinfectious (staphylococci/streptococci)	Structural failure to decrease afferent arteriolar resistance
Collagen-vascular disease	
Lupus nephritis	Age
Henoch-Schonlein purpura (immunoglobulin A and systemic vasculitis)	Atherosclerosis – includes micro and macro vascular renovascular disease
Immunoglobulin A nephropathy (no vasculitis)	Cheonic kidney disease
Mixed cryoglobulinemia	Chronic hypertension
Primary renal disease	Malignant hypertension
Membranoproliferative glomerulonephrities	Severe pre-eclampsia
Idiopathic	
Type III (50%) Pauci immune - Antinuclear cytoplasmic antibody mediated	**Nephroroxix Drugs**
Wegener granulomatosis (WG)	**(Direct toxicity or tubulo-interstitial nephritis)**
Microscopic polyangiitis (MPA)	Paracetamol
Renal-limited necrotizing crescentic glomerulonephritis (NCGN)	Aminoglycosides
Churg-Strauss syndrome	Contrast
Other	Penicillin
Glomeruloendotheliosis - pre-eciampsis	Non-Steroidal anti-inflammatory drugs
Thrombotic microangiopathy – TTP, HUS	Herbal rememdies

Fig. 3.4 Acute kidney injury (AKI) in acute liver failure

Table 3.3 Criteria for super-urgent listing for liver transplantation [3]

Organ system	Paracetamol overdose	Sera-negative hepatitis (SNH), hepatitis A, hepatitis B, or an idiosyncratic drug reaction (IDR)
Liver	*INR > 6.5 or PT > 100 s* with both AKI Stage 3 and Grade 3/4 HE[a]	*INR > 6.5 or PT > 100 s or pH < 7.3* with any grade of HE or *three of the following*: (INR > 3.5 or PT > 50 s, bilirubin > 300 µmol/L, jaundice to HE > 7 days, unfavourable etiology SNH or IDR, age > 40)
Metabolic	*pH < 7.25 or lactate > 3.0 mmol/L*[a]	
Kidney	*AKI Stage 3* (SCr > 300 µmol/L or anuria) with both (INR > 6.5 or PT > 100 s and Grade 3/4 HE)[a]	
Brain	*Grade 3/4 HE* with both (INR > 6.5 or PT > 100 s and AKI Stage 3)[a]	*Any grade of HE* with INR > 6.5 or PT > 100 s
Cardiac	*In the UK increased inotrope or vasopressor requirement in the absence of sepsis* with 2 out of 3 (INR > 6.5 or PT > 100 s, AKI Stage 3, Grade 3/4 HE)[a]	

HE hepatic encephalopathy, *AKI* acute kidney injury, *SCr* serum creatinine, *INR* international normalised ratio, *PT* prothrombin time

[a]Assessment at > 24 h post-ingestion and should occur within a 24 h window, despite aggressive fluid resuscitation

stress and caspase-mediated apoptosis [73]. Other possible mechanisms include induction of oxidative enzymes such as cytochrome P-450 mixed function oxidase isoenzymes in the proximal tubule of the kidney [74]. Furthermore glutathione, an important element in the detoxification of acetaminophen and its metabolites has paradoxically also been implicated in the formation of glutathione conjugates that are considered nephrotoxic.

AKI in patients with ALF frequently requires the use of CRRT for renal-specific and non-renal-related reasons. ALF complicates the use of CRRT specifically when anticoagulation is required to extend filter life span. Despite the coagulopathy and thrombocytopenia associated

with ALF, CRRT circuits can clot as a result of losses of both pro- and anticoagulation factors [75]. Good vascular access, use of pre-dilution fluid replacement, high blood flows to reduce the ultrafiltration fraction, prompt attention to alarms and the use of prostacyclin anticoagulation may extend filter life. Prostacyclin has a half-life of seconds and therefore represents a safe anticoagulant in ALF in the absence of hemorrhage. Routine use of heparin for filter anticoagulation is not recommended and citrate anticoagulation is complicated by the risk of citrate toxicity, due to the integral role of the liver in citrate metabolism. However, the use of citrate-based intraoperative dialysis during a liver transplantation for a paracetamol-induced ALF patient and AKI with no signs of citrate toxicity has been reported [76]. The lack of toxicity was likely due to a low dose of citrate (0.8 mmol/L; only about one-fifth of the concentration necessary to achieve anticoagulation) and the predominant role of muscle metabolizing citrate. Citrate dialysate for RRT in ALF should if at all only used for short periods and is not a common practice.

Indications and timing of initiation, dose, anticoagulation and continuous versus intermittent CRRT remain controversial. The Randomized Evaluation of Normal versus Augmented Level (RENAL) study showed no mortality benefit of high ultrafiltration doses of 35–40 mL/kg/h compared to low rates of 20–25 mL/kg/h of CRRT in critically ill patients [77]. This has been confirmed by the IVOIRE (hIgh VOlume in Intensive Care) study in patients with septic shock (comparing 70 mL/kg/h with 35 mL/kg/h) and a subsequent meta-analyses [78–80]. RRT needs to be tailored to address the clinical fluctuations affecting fluid management and the profound metabolic disarray encountered in ALF.

Coagulation

As synthesis of procoagulant factors is impaired with acute hepatocyte necrosis coagulation tests may allow determination of prognosis but not necessarily bleeding risk in ALF. Prothrombin time (PT) is a measure of the extrinsic pathway of the classic Y-shaped model of coagulation and reflects activity of clotting factors V, VII, and X. Factor VII with the shortest half-life of approximately 2 h, is a good marker of synthetic liver function and the extent of hepatic necrosis. Factor V is a good prognostic indicator in Hepatitis B induced ALF [81]. However as the measurement of individual clotting factor levels is not routinely available, PT is commonly used for prognostic assessment. In POD a PT greater than 36 s 36 h after ingestion predicts that 50% of patients will proceed to develop ALF. A PT increasing on day 4 after ingestion with a peak PT of greater than 180 s is predictive of a 65% mortality [82]. Prolonged PT however does not predict bleeding risk in ALF and thrombin generation tests may be a better reflection of coagulation status [83]. ALF impairs synthesis of pro- and anticoagulant factors and therefore ALF patients can develop hypercoagulable states as well as bleeding diathesis [84]. The use of blood products containing clotting factors will affect the utility of PT as a predictive marker. Blood products to correct coagulopathy should only be used when there is active bleeding or an invasive procedure such as ICP bolt insertion is to be undertaken.

Prognosis of ALF

Recovery in ALF is largely determined by the underlying pathology; therefore, establishing a diagnosis is important not only to prognosticate but even more importantly to aid the decision if a patient should be listed for transplantation.

King's College Criteria

Clinical criteria predicting prognosis in patients with ALF were first described at King's College Hospital, London. A retrospective analysis of patients with ALF who were medically managed between 1973 and 1985 was performed with the aim of identifying significant clinical prognostic parameters. The King's College criteria (KCC: INR, hepatic encephalopathy,

acidosis, serum creatinine and lactate) have become the most widely used criteria for assessing prognosis in ALF. The KCC have a high specificity for mortality without transplantation but a low sensitivity and negative predictive value (NPV). Quality of life is significantly affected by transplantation and should be included as an aspect of the decision-making process especially for those patients with POD, who may also have chronic psychiatric conditions. The need to avoid unnecessary transplantations and the scarcity of donor organs have mandated an ongoing search for additional parameters that can predict prognosis earlier. Persistently elevated blood lactate has been closely associated with mortality and consequently incorporated into the KCC for paracetamol-related ALF [34]. The KCC have been developed for both paracetamol- and nonparacetamol-related ALF to assist decisions regarding referral to specialist centers that perform LT and to decide whom to priority list for transplantation as outlined in Tables 3.2 and 3.3.

Clichy Criteria

The Clichy criteria, developed from a group of 115 patients with ALF due to acute hepatitis includes two variables, hepatic encephalopathy and factor V levels. Factor V levels less than 20% for patients under 20 years and less than 30% for those older than 30 years were prognostically important. The Clichy criteria had a positive predictive value (PPV) of 75% and a NPV of 58% compared to a PPV 80% and NPV 77% for KCC in patients with ALF due to hepatitis B [85].

MELD and Liver Volumes

With changing etiologies of ALF sub-acute ALF is becoming more frequent in these patients the model for end-stage liver disease (MELD) may perform better than the KCC [86]. Assessment of liver volumes using CT is an additionally useful prognostic tool and is able to identify patients with a poor prognosis; in one study only 11% of patients with a liver volume of <1000 mL survived without LT [87].

Contraindications to Liver Transplantation

Prognostic criteria are inherently biased and often perform best in the study center where they were originally validated. All currently used criteria are associated with problems of accurate selection of patients for transplantation. The decision to proceed with transplantation greatly affects patient survival, graft use from a limited donor pool and physical and psychological consequences associated with long-term immunosuppression. An early initial assessment of prognosis must be individualized in the context of existing validated criteria and continuously reviewed during the hospitalization. The decision to list for transplantation needs to re-assessed in case of clinical deterioration that may nullify any mortality benefit from transplantation. The development of ongoing specific organ failure, despite maximal supportive therapies should prompt re-evaluation of any listing decision by the multidisciplinary team.

Age is an important prognostic factors and it has been incorporated into the non-paracetamol classification of ALF transplantation criteria and confirmed as a poor prognostic variable in a number of studies. The cut-off age associated with poor prognosis ranges from as low as 40 to as high as 60 years. Interestingly, while older age correlates with overall poor survival, however, there is no statistical difference between young and older patients in spontaneous recovery and survival (Fig. 3.5).

In our experience transplantation is unlikely to alter outcome if there is circulatory failure with any of the following: a low cardiac index, right heart failure, or pulmonary hypertension with a pulmonary artery pressure > 50 mmHg associated with escalating vasopressor requirements in association with ischemic extremities. In addition, severe lung injury requiring high PEEP (10–15 cmH$_2$O) and fractional inspired oxygen >0.8 with oxygen saturations <92% are
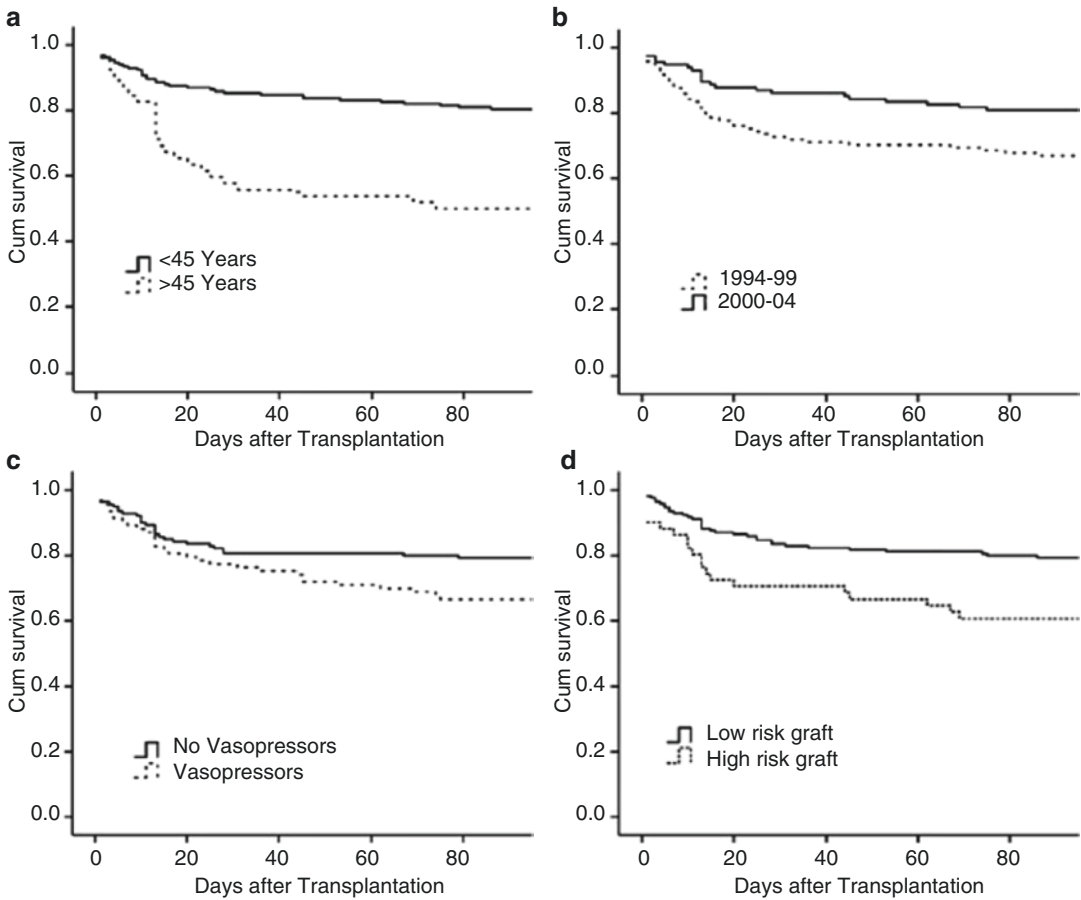
Fig. 3.5 Survival of patients transplanted (**a**) aged >45 and <45 years, (**b**) between 1994 and 1999 and 2000 and 2004, (**c**) requiring vasopressor or no vasopressor follow- ing transplantation and (**d**) with liver grafts with a calcu- lated donor risk score either high or low

associated with poor outcome in ALF and should possibly preclude transplantation. However toxic liver syndrome as a cause of lung injury, needs to be considered as transplantation may offer a ben- efit in this setting.

Bacteremia is also an important potential contraindication for transplantation that should delay the listing for transplantation until expo- sure to targeted antibiotics for a minimum of 24 h has elapsed. Both fungal sepsis and nec- rotizing pancreatitis are similarly associated with an extremely poor outcome in transplan- tation for ALF. Fixed dilated pupils for greater than 2 h and a prolonged cerebral perfusion pressure <45 mmHg in combination with other physiological variables such as a low cardiac index and hypoxemia are associated with a very poor prognosis.

Summary

ALF is a multisystem disorder requiring both predictive and reactive management strategies to support and protect organs from both the initial and subsequent insults. Early referral to a spe- cialist liver center with the option of liver trans- plantation and an experienced multidisciplinary team is recommended. (Table 3.1) Such teams include liver intensivists, transplant surgeons

and anesthesiologists, hepatologists, nurses and physiotherapists all working to ensure a high standard of care is delivered. Furthermore, a good understanding of the poor prognostic variables is necessary to determine those most at risk of developing ALF to facilitate timely and safe transfer.

The initial primary goal of management is to establish a diagnosis to facilitate the initiation of therapies that may prevent further liver injury. Additionally, optimization of the circulation with both appropriate early invasive monitoring directing aggressive fluid resuscitation, vasopressor support and assessment for high-volume plasma exchange is the key. The early use of empirical antibiotics and antifungal agents along with strict infection control measures are necessary. Due to the high frequency of sepsis without SIRS symptoms a low threshold for obtaining cultures and broadening antibiotic coverage is required when the clinical condition deteriorates. A keen awareness of the potential for raised ICH, particularly in the young, necessitates appropriate monitoring and management, which will be discussed in detail in a separate chapter. In parallel with supportive measures an assessment of the clinical history and prognostic variables must be undertaken to determine, which patient fulfills national transplantation criteria. The decision to list a patient for super-urgent liver transplantation is often difficult and can be affected by age, co-morbidities, the dynamics of the clinical condition and psychosocial factors. [6] The clinical course for those not transplanted is often precarious and associated with a high mortality [5]. Outcome is affected by the speed and degree of hepatic regeneration and the impact of the cumulative insults such as sepsis, AKI requiring prolonged RRT, and critical illness associated weakness that may result in extended periods of rehabilitation in those that survive. Patients who proceed to transplantation and receive a good functioning graft often experience swift resolution of the circulatory and neurovascular disarray and have significantly improved outcomes albeit offset by the long-term impact of lifelong immunosuppression.

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