# Acute Hepatic Failure

2

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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 pre-existing 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 centres with expertise in the management of ALF and liver transplantation is crucial.

ALF is rare with around 2,800 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 in worldwide geographical location, clinical presentation, time course, and prognosis. In the developing world the leading cause of ALF are the viral hepatitides, particularly jepatitis B. In the US and the UK, viral hepatitides are no longer the most common cause of ALF; in recent years, paracetamol (acetominophen) overdose, idiosyncratic drug reactions, and sero-negative hepatitis have emerged as the leading causes of ALF (Fig. 2.1) [1, 2].

The prognosis of ALF depends on age, etiology, and the time course over which the disease evolves. In the most severe cases the mortality of ALF without transplantation ranges from 10 to 90%; in recent years, survival has improved to around 40–90% [3]. This is related to improved critical care management, better prognostic assessment, and the timely prioritisation of patients for liver transplantation (LT). The management of ALF is focused on the 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 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 endeavours timely recognition that hepatic regeneration will ultimately not be sufficient is crucial. Liver transplantation with removal of the necrotic liver mass offers the best chance of survival. The decision to prioritise for transplantation requires a multidisciplinary team approach incorporating specialist liver transplant surgeons, hepatologist, and intensivists who can utilize established prognostic criteria along with the daily assessment of the levels of

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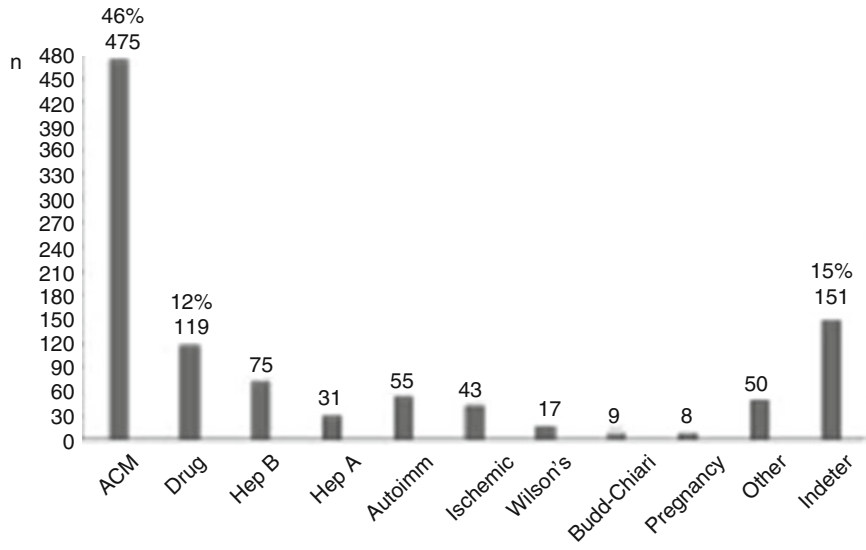


**Fig. 2.1** Overall comparison of etiologies observed among 1,033 patients with acute liver failure (ALD) in the ALD study Group registry, 1990–2004. A preponderance of acetaminophen cases is observed approaching 50%

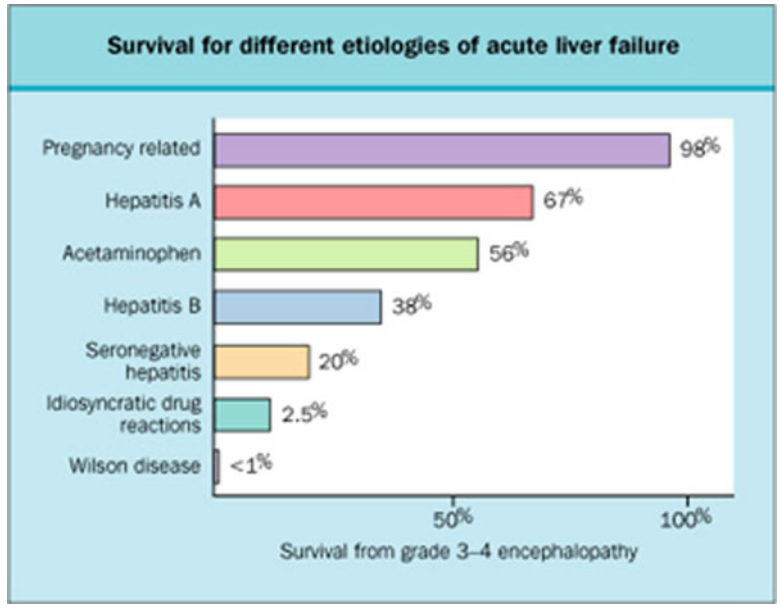


**Fig. 2.2** Survival for different etiologies of ALD

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. 2.2) [4].

The availability of donor organs is under continued pressure in the UK and worldwide. Patients with ALF must fulfil a strict set of selection criteria based on published risk factors for prioritisation before being established on the national super-urgent transplantation waiting list (Table 2.1). These patients are then stratified by blood group and time while on the super-urgent waiting list. In most cases a donor organ should

**Table 2.1** 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 |

be available within 48–72 h. Occasionally the option of an ABO incompatible donor organ has to be considered in light of the unavailability of an ABO compatible organ weighed against the projected deterioration of the clinical condition. It is widely accepted that the currently available selection criteria are imperfect with up to 10–20% of patients surviving without a transplant. 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 commonly used 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 acetominophen overdose and Hepatitis A are associated with mortality due to cerebral edema and kidney injury. However survival without transplantation for this group is superior to the more indolent subacute causes, including sero-negative and idiosyncratic drug reactions that are not as frequently complicated by the cerebral and renal insults, but carry a higher mortality burden compared with hyperacute causes (Table 2.1).

## Etiologies of ALF

### Paracetamol (Acetominophen) Overdose

Paracetamol overdose (POD) in the UK had been increasing steadily likely due to its easy availability [5]. In 1998 the Medicine Control Agency in the UK sought to limit the availability of paracetamol. Legislation was changed in line with World Health Organisation recommendations and data from other countries with similar restrictive policies that had lower rates of paracetamol-induced hepatoxicity. Suicidal or parasuicidal 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 16 500 mg tablets, a total of 8 g per packet. Studies have sought to demonstrate whether these restrictions have indeed been associated with a reduction in admissions to hospital and liver units, and in the need for liver transplantation. However, both short follow up periods and a diverse range of outcomes evaluated have hampered these studies in quantifying any change with certainty. Despite this, there is a trend towards an overall reduction of paracetamol-related hepatoxicity and hospital admissions following the change in legislation [6].

In the UK POD comprises up to 50% of all poisoning admissions and around 10% in the US [7]. 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 vs. accidental POD display geographic variation. In Europe, studies have reported around 86% of POD cases were deliberate and 14% were accidental [8], while US poisons centre data have reported rates of 35% and 65%, respectively [9]. Additionally, paracetamol medications combined with narcotics have been shown to pose a potential for unintentional hepatoxicity when addiction to the narcotic within such combined analgesics leads to a gradual increase of the ingested dose [2]. There has been the suggestion that this is 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).

The pathophysiological reasons behind this relate to the 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, 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 clear 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 para-suicidal event can make this information difficult to establish, especially if patients have ingested opiate-based medication combined with 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 anorexa nevosa, 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 one of the nomograms, based on the Prescott nomogram. 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 dose alone. If any doubt regarding timing exists or there has been 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 and this is thought to be related to high risk patients being vaccinated, improved sanitation, and improved food preparation techniques [10]. The treatment 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, mortality for those developing ALF ranges from 70 to 80% [11]. Hepatitis B has eight genotypes A–H and all have been associated with different clinical presentations. In Japan, Hepatitis B genotype B predominates and one study has shown increased efficacy

with lamivudine therapy and improved the survival of patients treated early in the course of the disease [11].

Hepatitis E is common is Asia and Africa with the risk of ALF greatest in pregnancy at greater than 20%, particularly during the third trimester. In the general population, Hepatitis E carries a low mortality of 0.5–4%, but this figure approaches >75% in developing countries like Bangladesh especially during the second and third trimester. It is transmitted by the fecal-oral route, often through contaminated water supplies. Consequently, it has been the cause of epidemics in Asia, China, and Eastern Europe especially after heavy rainfall. The first documented of these epidemics occurred in New Delhi, India in 1955 and affected 29,000 people [12].

Viruses including cytomegalovirus (CMV), Epstein barr virus, herpes viruses type 1, 2 and 6, and varicella zoster have all been implicated in case reports of ALF, frequently in patients with profound immunocompromised states. 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 that have been shown to be of benefit in some cases of ALF include, as mentioned, lamivudine for hepatitis B, valganciclovir and acyclovir for herpes 1, 2, and CMV disease.

## Idiosyncratic Drug Reactions

The administration of drugs directly affects the liver because it is the primary site of metabolism and elimination. This exposes the liver to the potential toxicity of many drugs. 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 acetominophen toxicity, is the leading cause of ALF and indication for liver transplantation. The remainder of DILI cases are idiosyncratic reaction, which occur in around 1 in 10,000 of exposed patients. However, more than 1,000 drugs and herbal remedies have been implicated in DILI and altogether comprise 10% of ALF cases [13]. Idiosyncratic DILI is a complex phenomenon, which appears to be integrally related to how cell mitochondria balance cellular injury and regeneration. Idiosyncrasy defines the unpredictable and non-dose dependant fashion with which liver injury can occur. There are non-allergic and allergic idiosyncratic DILI, the latter characterised by fever, skin reactions, eosinophilia with the formation of autoantibodies, one such example is drug-related eosinophilic syndrome (DRESS). Several risk factors for DILI have been identified and include age, female gender, concomitant diseases, and drugs. There are DILI algorithms and clinical scales that can be used to improve the consistency, accuracy of causality of adverse drug reactions [14].

Genetic polymorphisms have been associated with increased risk of DILI, for example, cytokine polymorphism and diclofenac hepatoxicity. The same applies to genetic variations involving mitochondrial function with a genetic deficiency of mitochondrial long-chain 3-hydroxyacyl-CoA dehydrogenase associated with acute fatty liver of pregnancy, presumably related to the increased levels of female sex hormones. DILI tends to be diagnosed primarily by increased levels of alanine transferase (ALT) and gamma-glutamyl transferase (GGT). Currently metabolomic studies are being conducted to identify biomarkers of DILI that will detect injury prior to elevations in ALT.

## Malignancy

There are numerous case reports in the literature that have documented a wide range of solid and hematological tumours as a rare cause of ALF. A literature review in 2005 cited 34 cases of primary and metastatic neoplastic infiltration of the liver resulting in ALF [15]. The pathophysiology of ALF in neoplastic infiltration is multifactorial. Parenchymal ischemia and infarction can be caused by diffuse tumour cell infiltration or vascular occlusion from tumour thrombi. It has also been postulated that diffuse tumour 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, which was in the absence of any discernable episode of systemic hypotension [15, 16]. Additionally, cytokine-mediated liver injury has been implicated in lymphomatous infiltration [17]. Clinical suspicion and features suggestive of malignancy such as 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. Furthermore, radiological imaging including both ultrasonography and triple phase computer tomography should not be relied on due to the poor sensitivity for metastatic and lymphomatous infiltration of the liver. The only serum markers of tumour infiltration are alkaline phosphatase (ALP) and aspartate and alanine aminotransferase (AST), though elevation of these is usually below levels seen in ischemic hepatitis. Both appear to have greater sensitivity in the presence of hyperbilirubinemia. However, jaundice does not always manifest in the setting of tumour infiltration with cases of over 90% liver infiltration without jaundice in the literature. A trans-jugular liver, bone marrow aspiration, and trephine or lymph node biopsy can all prove to be invaluable tools for establishing a diagnosis. The diagnosis of malignancy is a clear contraindication for liver transplantation and establishing the diagnosis therefore crucial.

## Vascular

ALF following vascular insults are uncommon; however, causes include ischemic hepatitis, which is often associated with low cardiac output states with variable degrees of left and right ventricular cardiac dysfunction. The veno-occlusive disorders, such as Budd-Chiari (BC) are also uncommon with the incidence of BC quoted at 1 in 2.5 million [18]. It is characterised 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 two conditions coexist. Veno-occlusive disorders have been associated with inherited conditions such as Factor V Leiden, Protein C, S and antithrombin deficiency and acquired conditions including paroxysmal noctural hemoglobinuria and anti-phospholipid syndrome. The recently discovered Janus Kinase 2 mutation (JAK2) has also been detected in around 40–59% of cases with BC [19]. Myeloproliferative disorders also need to be ruled out as a cause with an examination of the bone marrow function using a trephine biopsy and aspiration as these disorders are most commonly associated with both BC and portal vein thrombosis [18].

## Metabolic

ALF secondary to inherited and acquired metabolic disorders are uncommon, though remain important and 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, which encodes a copper transporting P-type ATPase leading to insufficient copper excretion into bile with subsequent copper accumulation in brain, liver, and cornea. The incidence of WD is around 1 in 30,000 and can present acutely, usually in pediatric or young female patients, or chronically in adult patients sometimes into their eighth decade of life. ALF in WD is unique in so far as there is usually some degree of 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 can extinguish the availability of this diagnostic tool. Ophthalmic

interrogation of corneas can be useful to detect the presence of Kayser-Fleischer rings, which together with evidence of liver disease and copper metabolism abnormalities strongly support the case for the diagnosis. Additionally, Coomb's negative hemolytic anemia and low serum cholinesterase levels can be a feature of WD [20]. The ALP/bilirubin and aspartate AST/bilirubin ratios are often significantly lower in fulminant Wilson's disease than in other categories of fulminant liver failure, but distinction between diagnostic categories on this basis is not possible [21].

### Miscellaneous

Other rare but also important causes of ALF include HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome of pregnancy. The amphetamine derivative, 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") has caused of a number of cases of ALF requiring OLT. Toxins of mushrooms such as *Amanita phalloides* or foodborne illnesses by *Bacillus cereus* are also causes of ALF.

## Clinical Features and Management

### General

The diagnosis of the underlying insult is crucial in determining potential therapies that could halt the injurious process and reverse liver failure. Investigations should include those for: hepatitis and atypical viral serology; autoantibodies, such as antinuclear, anti smooth muscle, anti-liver kidney microsomal, anti-soluble liver antigen, antimitochondrial antibodies; an illicit drugs screen, paracetamol levels; and urine and serum copper. A negative paracetamol level does not rule out paracetamol as a cause of ALF. Additionally, ultrasonography of the liver and its vasculature is important. Where possible, if the history and investigations do not suggest a viral or drug-induced insult, axial imaging with computer tomography is advisable. Patient outcomes are largely determined by the severity of the underlying liver insult and the development of organ failure and episodes of sepsis have a strong impact on mortality. Early recognition and treatment of sepsis and the prevention and support of organ dysfunction is therefore key to increasing the potential for hepatic regeneration. Finally, a timely decision regarding super-urgent liver transplantation is required when it becomes sufficiently clear that hepatic regeneration will not occur. This decision carries particular importance given that the median time from listing to transplantation is around 48 h. Consequently, 24% of patients listed will fail to proceed to transplantation with 92% of these patients dying [22]. Those that are not transplanted have a median time from listing to death of 2 days (2–4), with several pre-transplant factors associated with poor outcomes such as age <45 and escalating vasopressor requirement [22]. There are several other factors that should prompt discussion regarding the suitability to proceed to transplantation. These 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 and progression of ALF requires the involvement of wide array of expertise to form a cohesive multidisciplinary team. Such teams include critical care nurses, physiotherapists, pharmacists, transplant surgeons, and liver intensivists.

### Cardiovascular

The circulatory hallmarks 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, but it also acts globally resulting in a cumulative reduction in oxygen consumption, despite demonstrable increases in oxygen delivery,

as indicated by higher central and mixed venous saturations. The management goals for the circulation in established ALF should intuitively, follow the initial resuscitation recommendations outlined in the Surviving Sepsis Campaign (SSC), in view of the similarities and despite formal validation. The early use of hemodynamic monitoring is recommended as it often forms a vital aspect of management providing important additional clinical indices about central circulating volumes and cardiac output. Furthermore, a cardiac output in the normal range or particularly elevated central venous pressures should prompt further interrogation of myocardial function with echocardiography to evaluate left and right ventricular filling and function.

The SSC recommends commencing resuscitation in any patient who is hypotensive, MAP <70 mmHg, or with an elevated serum lactate >4 mmol/L with due consideration that management is conducted in a critical care environment. There are problems associated with some the SSC parameters as mentioned $ScvO_2$ are often significantly elevated reflecting the hyperdynamic circulation and microvascular shunting. The SSC threshold for lactate is 4 mmol/L; in ALF this is unlikely to reflect sole circulatory disarray, but it should be assumed to be so until adequate volume resuscitation has been implemented. Hyperlactemia broadly reflects liver, circulatory and cellular dysfunction, although the liver does have large reserves for lactate metabolism. The normal lactate levels encountered after hepatectomy with more than 50% of the liver resected supports this [23]. However, high circulating blood lactate levels are frequently encountered in ALF where inadequate fluid resuscitation has lead to circulatory and cellular metabolism dysfunction. Overall hyperlactemia and the speed of resolution acts as an important predictor of outcome in both critical illness and ALF [24]. It is now recognised as an important prognostic variable. Consequently, elevated serum lactate has been incorporated into the Kings College Criteria (KCC) adding statistical strength to the original O'Grady criteria [25], when persistently elevated >3.0 mmol/L despite aggressive fluid resuscitation [26].

In ALF relative adrenal insufficiency (RAI)—defined as a total cortisol (TC) level less than 248 nmol/L after corticotropin administration—has a reported prevalence of 62% and steroid replacement therapy is associated with reductions in vasopressor requirements, albeit without any mortality benefit [27, 28]. The diagnosis and treatment of RAI in critical illness was first encountered in sepsis with the demonstration that low dose hydrocortisone could accelerate the reversal of shock, despite a lack of significant mortality benefit [29]. The high prevalence of RAI in ALF can be explained by factors that affect cortisol 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 tumour necrosis factor alpha (TNF-α) on hypothalamic function all contribute to the low circulating TC levels [30].

The diagnosis of RAI 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 [29]. It is largely related to the fall in both albumin and cortisol-binding globulin (CBG), which leads to increases in free cortisol levels (FC), despite low measured TC level implying RAI. Therefore, to improve interpretation various alternative measures or calculations have been explored to better assess FC levels. The use of salivary cortisol has been shown to correlate well with FC, although in ventilated patients this may be difficult to obtain. Alternatively, the free cortisol index (see equation below) can be calculated by measuring both CBG and TC levels, which has also been shown to correlate well with FC levels [31]. 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 after a short synacthen test has been performed to impact on escalating vasopressor levels. The results of

the short synacthen test to limit the duration of hydrocortisone therapy and potential adverse effects of steroids.

The free cortisol index: (Unbound cortisol (μmol/L) = (0.0167 + 0.182 (CBG − TC))$^2$ + (0.0122 × TC)$^{0.5}$ − (0.0167 + 0.182 (CBG − TC)) [32].

## Respiratory

The development of hepatic encephalopathy in ALF is one of the primary indications for intubation and ventilation to establish a protected airway. A significant proportion of patients will also develop a spectrum of respiratory complications. Acute lung injury (ALI) and ARDS complicate up to 30% of paracetamol-induced ALF cases [33]. It affects primarily those with significant vasopressor requirements and evidence of intracranial hypertension (ICH). The mechanisms involved of ALI in ALF include the directly toxic effects of acetominophen and the pathophysiological overlap of changes involving vasoactive mediators that affect not only the brain and circulation, but also the lung with increased vascular permeability and capillary leak. This is further exacerbated by the additional fluid accumulation within extravascular compartments, due to large cumulative volumes of fluid administered to support the vasoplegic circulation. Additionally, there is a high incidence (around 51%) of cultured tracheal aspirates with gram-negative organisms in intubated ALF patients [34], which has a direct impact on the development of ventilator-associated pneumonia and ALI. Hepatic encephalopathy and ICH are also implicated in the development of ALI. The risk of pulmonary and extrapulmonary sepsis and indeed ARDS are specifically associated with aspects of ICH management. These include deep sedation, induction and maintenance of hypothermia and limited endotrachial suction, which all contribute to limited tracheobronchial toilet and retention of secretions. In ALF commonly encountered respiratory complication associated with both mechanical ventilation and critical illness have been described. 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 protective ventilation maneuvers frequently employed for ALI/ARDS can potentially impact on cerebral perfusion exacerbating 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 ALI/ARDS with severely elevated intracranial pressure (ICP) with intact physiological autoregulation necessitates tight control of $pCO_2$. When all conventional measures aimed at increasing $CO_2$ clearance have been exhausted extracorporeal $CO_2$ clearance devices to facilitate control in $pCO_2$ may be used. This 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 cases and ARDS [35] and have also been employed on few occasions in ALF patients with developed ARDS post-OLT, when ICH has remained problematic (unreported).

Patients with fulminant ALF are nursed 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 optimise 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 such as prone positioning are contraindicated due to the impact on ICH management. Hypoxemia and high fractions of inspired oxygen ($FiO_2$) can be reasons remove patients with ALF off the transplant waiting list. However, hypoxemia alone appears to be a nonspecific variable in the diagnosis of ALI. Furthermore, a

low partial pressure of oxygen ($PaO_2$) to $FiO_2$ ratio is common, but transient and not necessarily associated with poor outcomes [36]. Transpulmonary thermodilution cardiac output monitors can calculate an estimated measure of lung permeability, the extravascular lung water index, which has been shown to be a useful variable in guiding management [37].

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 $pCO_2$, 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 intensive care delirium. There is also a risk of both subclinical and clinical seizures likely related to ICH during ALF. Critical illness polymotorneuropathy (CIMPM) is also 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 MOF [38]. A (percutaneous) tracheostomy is often necessary to facilitate weaning from the ventilator and sedating medication. Despite the coagulopathy and thrombocytopenia in ALF it has been demonstrated that a percutaneous tracheostomy can be performed safely [39].

## Gastroenterology

### Nutrition

Numerous metabolic abnormalities and their associated complications are encountered in ALF but only few studies have been undertaken to assess and identify best practice. Hypoglycemia is a significant metabolic abnormality encountered in ALF. It is due to the loss of hepatic glycogen stores, impaired gluconeogenesis and hyperinsulinemia and a poor prognostic variable in the initial presentation of ALF. Along with other parameters of hepatic necrosis hypoglycemia may help determine which patients require referral to specialist centres (Table 2.2). ALF is also associated with impaired peripheral uptake of glucose and decreased peripheral insulin sensitivity, which is usually restored within 2 weeks in those patients that survive [40].

It is important to establish and then maintain normoglycemia early with infusions of 20–50% dextrose, which will continue until enteral nutrition is commenced. The control of blood glucose has attracted great attention since the landmark study by Van Den Berghe in 2001 that favoured tight glycemic control—glucose 4.4–6.1 mmol/L—being championed now included in the Surviving Sepsis Guidelines. Other studies have also demonstrated more adverse effects and worse outcome with hyperglycemia—glucose >12 mmol/L—in patients with neurovascular brain injury and indeed in ALF where it contributes particularly to poor ICH control [41]. However, meta-analyses assessing tight glycemic control studies since 2001 have not confirmed the impressive mortality benefit demonstrated in the original study population but an increased rate of hypoglycemic episodes intensive insulin regimens. Ultimately, a balanced approach is required with the goal of achieving blood glucose levels closer to the lower limit of 6 mmol/L (108 mg/dL) avoiding hypoglycemia and elevated levels greater than 12 mmol/L (216 mg/dL).

An early nutritional goal to start enteral feeding 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 IAP, 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 warranted. Previous concerns about TPN-induced liver toxicity are not encountered with newer hypocalorific regimens [42]. Furthermore, there is currently no evidence

**Table 2.2** Criteria for referral/discussion to specialist centre [3]

| Paracetamol overdose (time from ingestion, days) | | | | Non-paracetamol overdose (ALF classification, time from jaundice to encephalopathy) | | |
|---|---|---|---|---|---|---|
| Organ system | 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 $HCO_3$ < 18 | pH < 7.3 or $HCO_3$ < 18 | pH < 7.3 or $HCO_3$ < 18 | Hypoglycemia | Hypoglycemia | Hypoglycemia |
| | Or | Or | Or | Or | Or | Or |
| | Lactate > 3.0 | Lactate > 3.0 | Lactate > 3.0 | Hyperpyrexia | Hyponatremia < 130 μmol/L | Hyponatremia < 130 μmol/L |
| | Or | Or | Or | Or | | |
| | 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

suggesting that normal protein intake of approximately 1 g/kg/day worsens hyperammonemia and hepatic encephalopathy. This is important, because ALF patients are often catabolic with supranormal energy expenditure, despite significant hepatocyte loss. Furthermore there is significant protein catabolism with muscle wasting, amino acid losses, and vitamin deficiency, which all impact on immune function. This necessitates the supplementation of multiple vitamins and trace elements in patients with ALF, especially in those on continuous renal replacement therapy (CRRT) regimen where losses are exacerbated [43, 44]. Hypophosphatemia is frequently encountered with CRRT, especially high volume regimens and requires prompt replacement. However, hypophosphatemia may also herald liver regeneration with increased hepatic ATP production and serve as a good prognostic marker [45].

## Immunity and Bacteremia

The degree of SIRS is associated with an increase in mortality and macrophage-related cytokine release. In ALF the incidence of clinical bacteremia is high (approximately 35%) [34] evidence of the complex changes in the innate immunity that 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 bacteremias manifest without pyrexia and elevation of white cell count reflecting hypo-responsiveness to infection though this is associated with a mortality benefit [46]. Bacteremia and SIRS both appear to influence the degree of hepatic encephalopathy (HE) [47].

The use of empirical broad-spectrum antibiotics, attention to appropriate nutrition, 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 [34]. The grade of encephalopathy appears to be independently associated with bacteremia and Acute Physiology and Chronic Health Evaluation II scores (APACHE-II) independently predictive of mortality [34]. The significant incidence of fungal sepsis, around 32% with cases predominantly due to *Candida* species necessitates the early empirical use of antifungal therapy, usually fluconazole [48].

There are marked changes in the pharmacokinetics and pharmacodynamics of drugs during critical illness that requires close drug monitoring when possible. In the absence of drug monitoring, antibiotic prescriptions should aim to "overdose" treatments with a low toxicity. The immuneparesis associated with ALF makes avoidance of antibiotic under-dosing important. Furthermore, changes in renal replacement therapy (RRT) dose to higher volume exchanges often warrant the adjustment of antibiotic doses to compensate for potential increases in drug clearance.

The innate immunity 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 closely resemble the clinical features of systemic sepsis with a SIRS that often culminates with the development of a vasoplegic circulation and MOF. These complex immune responses have been integrally related to some of the clinical complications of ALF, particularly, the increased incidence of bacteremia and the degree of encephalopathy.

The innate immune system appears to be overwhelmingly activated initially with the mobilisation of immune cellular components, including neutrophils, monocytes, and macrophages. They are involved in the profound release of cytokines orchestrating the pro- and anti-inflammatory response to sustained liver injury and subsequent facilitation of cellular repair. There are also significant reductions in the production of complement factors impairing opsonisation of bacteria [49]. There is evidence of impaired neutrophil function with reduced chemotaxis, bacteriocidal activity, and impaired production of superoxide and hydrogen peroxide

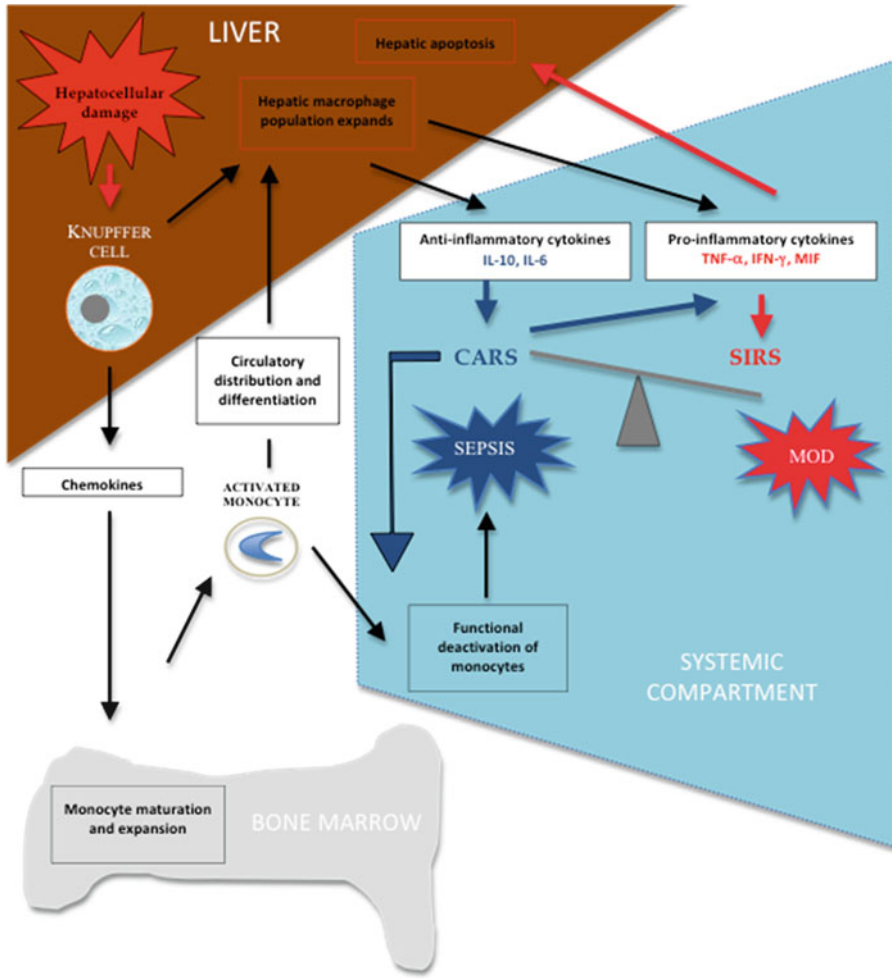


**Fig. 2.3** A schematic of the inflammatory responses to hepatocellular damage. Adapted from ref. [47]

with defective phagocytosis. Additionally, both monocytes and macrophage have been implicated in the initiation, propagation, and resolution of acute liver injury. It appears that shortly after acute liver injury macrophages enthusiastically release chemokines and pro-inflammatory cytokines. This response is balanced by the initiation of anti-inflammatory responses accompanying the recruitment of monocytes to the site of the liver injury to initiate repair processes. Activated macrophages release TNF-α, interleukin (IL)-1, IL-6, proteolytic enzymes, reactive oxygen intermediates, and lysosomal enzymes. Bacterial products can also induce TNF-α affecting microvascular permeability and further releases of IL-6. The elevation of TNF levels appears to correlate with the development of sepsis and IL-6 with MOF and mortality (Fig. 2.3).

## Acute Kidney Injury

The incidence of AKI, defined using either the acute kidney injury network (AKIN) or the RIFLE criteria developed by the acute dialysis quality initiative (ADQI) in one study of 16,784 critically ill patients in non-specialised intensive care units was shown to be 28.5 and 35.5%,

**Table 2.3** Criteria for super-urgent listing for orthotopic liver transplantation [3]

| Organ system | Paracetamol overdose | Sero-negative hepatitis (SNH), hepatitis A, hepatitis B, or an idiosyncratic drug reaction (IDR) |
|---|---|---|
| Liver | *INR >6.5 or PT >100 s*<br>WITH BOTH<br>AKI Stage 3 and Grade 3/4 HE[a] | *INR* >6.5 *or PT >100 s or pH < 7.3*<br>WITH any grade of HE<br>OR<br>*Three of the following*:<br>(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*<br>*OR*<br>*Lactate >3.0 mmol/L*[a] | |
| Kidney | *AKI Stage 3* (SCr >300 μmol/L or anuria)<br>WITH BOTH<br>(INR >6.5 or PT >100 s AND Grade 3/4 HE)[a] | |
| Brain | *Grade 3/4 HE*<br>WITH BOTH<br>(INR >6.5 or PT >100 s AND AKI stage 3)[a] | *Any grade of HE*<br>WITH<br>INR >6.5 or PT >100 s |
| Cardiac | *In the UK increased inotrope or vasopressor requirement in the absence of sepsis*<br>WITH<br>2 out of 3<br>(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

respectively. This is associated with an increase in hospital mortality of 36.4% [50]. In ALF the incidence of AKI is significantly higher than that of the general critically ill population ranging from 40 to 85% depending on etiology, with POD associated with a higher incidence of around 75% [51]. The AKI staging utilizing the serum creatinine (SCr) criteria classifies increases greater than 300% from baseline as stage 3; in patients with previously normal kidney function (SCr 80–120 μmol/L) this equates closely to the SCr of 300 μmol/L that is associated with poor prognosis in ALF. This is an important clinical criteria for referring to a specialist centre and listing patients for OLT (Tables 2.2 and 2.3).

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 vasoplegia "vascular failure" and functional hypovolemia. These vasoactive mediator-induced changes to the circulation cause heightened homeostatic responses involving the sympathetic nervous system and renin angiotensin system (RAS) culminating in arterial vasoconstriction in the kidney. The intraglomerular arteriolar vasoconstriction results in ischemic acute tubular necrosis that is now increasingly recognised as a complex interplay between endothelial dysfunction and leukocyte activation and release of cytokines causing profound intracellular oxidative stress. Furthermore, recent studies of hemodynamic changes in septic AKI suggest other microcirculatory changes, particularly renal venous congestion associated with disturbed cellular energy mechanisms independent of tissue oxygen availability [52].

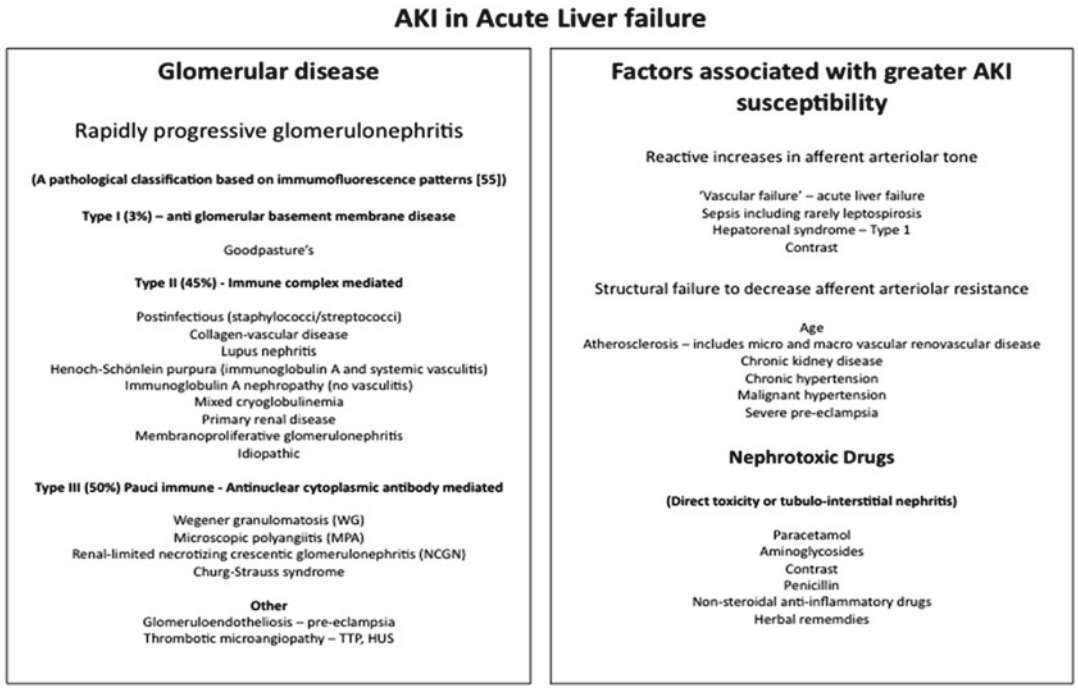


**Fig. 2.4** Acute kidney injury (AKI) in acute liver failure

Patients who are critically ill with ALF can display a wide spectrum of susceptibilities for AKI beyond those associated with the "vascular failure" and hemodynamic changes encountered. These are related to failure to increase or decrease afferent arteriolar vascular tone leading to reduced glomerular perfusion and ischemia in hypotensive states. Additional insult can be caused by the numerous drugs that patients are exposed to, which can be directly nephrotoxic or sometimes implicated in tubulointerstitial nephritis. Furthermore, specific glomerular pathologies, that result in rapidly progressive glomerulonephritides, should be considered and excluded by including urine dipstick and microscopy for red cell casts in conjunction with testing for autoantibodies to exclude small vessel vasculitides and serological testing for leptospirosis (Weil's disease), if the history and examination suggest such diagnoses (Fig. 2.4) [53].

The mode and mechanism of renal cell death in paracetamol nephrotoxicity remains obscure and yet it is clear that it differs from the mechanisms involved in hepatotoxicity. Evidence in support of this theory originates from rat models that demonstrate that NAC does not protect tubular cells [54]. 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 into paracetamol-induced nephrotoxicity. It seems likely that the mechanism for nephrotoxicity lies with endoplasmic reticulum stress and caspase-mediated mechanisms that cause apoptosis [55]. Other speculated mechanisms include induction of oxidative enzymes such as cytochrome P-450 mixed function oxidase isoenzymes in the proximal tubule of the kidney. Additionally, the role of prostaglandin synthetase and *N*-deacetylase enzymes have also been postulated to be involved [56]. Finally, it appears that 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 thought to be nephrotoxic.

The high incidence of AKI frequently requires the use of CRRT often for both renal-specific and

non-renal-related reasons. Numerous issues are associated with CRRT in patients with ALF, including the need for anticoagulation to extend filter life span. Despite the coagulopathy and thrombocytopenia seen in ALF it has been demonstrated that CRRT circuits continue to clot as a result of losses of both pro- and anticoagulation factors [57]. Good vascular access, as well as an expanded intravascular compartment, is essential to extend filter life. Specific, yet standard maneuvers to extended filter life include the use of predilution fluid replacement; high blood flows to reduce the ultrafiltration fraction, prompt attention to machine alarms, and use of prostacyclin anticoagulation. Prostacyclin has a half-life measured in seconds and represents a safe anticoagulant in ALF in the absence of hemorrhage. The use of heparin is not recommended during the initial presentation of ALF with evolving coagulopathy and citrate anticoagulation is complicated by the risk of citrate toxicity, due to the integral role of the liver in citrate metabolism. However, a case report of the safe use of a citrate-based dialysate, where heparin and regional citrate were contraindicated, demonstrating no signs of citrate toxicity intra-operatively during liver transplantation for a patient with paracetamol-induced ALF patient and AKI [58]. It is likely this was possible due to the low doses of citrate used (0.8 mmol/L; only about one-fifth of the concentration necessary to achieve anticoagulation) and the likely predominant role of muscle metabolising citrate. The role of citrate dialysate for RRT in ALF is, however, likely to be limited to short treatment periods and the intra-operative period and is not a common practice in the UK.

The use of RRT in the ICU continues to be the focus of much debate. The issues range from the mode, timing of initiation, indications for initiation; dose, anticoagulation use, and the perception that continuous replacement regimens are superior to intermittent regimens. There is, however, little compounding evidence available to clearly delineate any of these issues. Only the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study to date has endeavoured to answer and also establish some conclusions regarding the dose of ultrafiltration in AKI. No associated benefit was demonstrated with higher ultrafiltration doses of 40 mL/kg/h vs. lower rates of 25 mL/kg/h [59]. However, RRT often needs to be tailored to address the clinical fluctuations affecting fluid management and the profound metabolic disarray encountered. In ALF mortality is inextricably linked to the severity of the underlying liver insult. However, profound catabolism, hyperlactemia, SIRS, vasoplegia, and high vasopressor requirements often necessitate the use of pulse high volume hemofiltration (PHVH) at 60–90 mL/kg/h. PHVH has been shown in animal and clinical studies to effectively reduce vasopressor requirements, which in ALF patients can be valuable to prevent vasopressor-induced ischemic insults [60]. Although there is no proven mortality benefit, it does allow the effective management of episodes of deterioration often associated with sepsis limiting further hepatic damage.

## Coagulation

The integral relationship between clotting factor production and acute hepatocyte necrosis is key to understanding the significant role coagulation tests have in determining both bleeding risk and prognosis. The measurement of prothrombin time (PT) is a measure of the extrinsic pathway of the classically conceptualised Y-shaped clotting pathway and reflects activity of clotting factors V, VII, and X. The half-life of factor VII is around 2 h, which implicates it as a good marker of synthetic liver function and the extent of hepatic necrosis. Factor V has itself too has been shown to be good prognostic indicator in Hepatitis B induced ALF [61]. However the assay of individual clotting factors is not routinely available. Consequently, there is continued reliance on the PT for prognostic assessment. In POD a PT of 36 s at 36 h after ingestion predicts 50% of patients will go on to develop ALF. Furthermore, a PT increasing on day 4 after ingestion and a peak PT of greater than 180 s is predictive of a 65% mortality [62].

However, it should be highlighted that the role of PT in assessing bleeding risk needs to be cautioned in the context of ALF. Numerous disruptions have been observed to occur across the

range of the more accepted yet complex primary cell-based processes thought to be integral to normal hemostasis. Both thrombocytopenia and platelet function seem to correlate better with bleeding risk. Importantly, the use of blood products containing clotting factors can have a significant impact on the interpretation of the PT and the assessment of prognosis, impending ALF and mortality. Blood products to correct coagulopathy should only be used when there is active bleeding or an invasive procedure beyond central and arterial line insertion, such as ICP bolt insertion or if transplantation is to be undertaken. Furthermore, it is often advisable to establish central access early in the course of the clinical presentation of impending ALF.

## Prognosis of ALF

Spontaneous recovery in ALF is largely determined by the underlying pathology; therefore, establishing a diagnosis is important for determining prognosis and subsequent management, including the decision to undergo transplantation. Several prognostic variables have been identified and have been incorporated into different transplantation criteria for ALF.

### King's College Criteria (INR, Hepatic Encephalopathy, Acidosis, Serum Creatinine, Lactate)

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 prognostically significant clinical parameters. The value of these parameters was then assessed, with the subsequent development of the King's College criteria (KCC), which have become the most widely used criteria for assessing prognosis in ALF. However, despite demonstrating high specificity for mortality without transplantation it has been widely accepted that the sensitivity and negative predictive value (NPV) of the KCC are low. These criteria tend to fail to identify patients early enough in the clinical course of ALF or to predict those that will die without OLT. Furthermore, it has been reported that up to 25% of ALF cases survive without transplantation with a life expectancy of 13.4 years, which compares to 13.5 years with transplantation, though this falls to 8.1 years when adjusted for quality of life [63]. The impact of transplantation on quality of life is an important aspect of the decision-making process especially for those patients with POD, who may also have chronic psychiatric conditions predominate their lives. Ultimately, the combination of all these factors 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. The variability of blood lactate level in response to aggressive circulatory, fluid, resuscitation extends the importance of this aspect of care in determining the predictive strength of this parameter [26]. The KCC have been developed for both paracetamol- and non-paracetamol-related ALF to assist decisions regarding referral to specialist centres that perform OLT and to decide whom to priority list for transplantation as outlined in Tables 2.2 and 2.3.

### Clichy Criteria (Hepatic Encephalopathy and Factor V Levels)

The Clichy criteria were developed from a group of 115 patients with acute hepatitis B causing ALF utilising the two variables, hepatic encephalopathy and clotting factor V levels. Factor V levels were found to be prognostically important if these were less than 20% for patients under 30-year-old and less than 30% for those greater than 30 year. A comparison study assessing this group of adult patients with ALF due to hepatitis B yielded a positive predictive value (PPV) of 75% and a NPV of 58% for the Clichy criteria compared to the KCC, which had a PPV 80% and NPV 77% [64].

### BiLE Score (Lactate, Bilirubin, and Etiology)

This simple score has been evaluated in a number of studies as a tool for assessing prognosis in ALF. One study of ALF patients in Germany assessed the BiLE score and demonstrated a prognostic sensitivity of 79% and specificity of 83% [65]. A direct comparison of BiLE scoring against the KCC was assessed at King's College Hospital confirming a statistically significant difference between survivors and non-survivors using BiLE scores. However, patients that underwent liver transplantation with a BiLE score above a threshold set at 6.9 were compared to KCC criteria. In our institution, a BiLE score at this threshold performed with limited sensitivity and accuracy [66].

## Contraindications to Liver Transplantation

The assessment and comparison of prognostic criteria has always been open to bias with selected criteria performing best in the study centre where they were originally validated. Consequently, there will be an ongoing endeavour to develop improved criteria that identify patients with a high mortality earlier and with greater accuracy. All the current criteria are associated with problems of accurate selection of patients for transplantation, which can greatly affect patient survival, graft use from the limited donor pool and the physical and psychological consequences associated with long-term immunosuppression. Consequently, all patients with ALF require an early assessment of prognosis that must be individualized in the context of existing validated criteria. Thereafter, a process of continuous review of any such decision to list for transplantation is essential, due to the large potential for significant 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 one of the prognostic factors, that has been studied to some extent in terms of prognosis and extremes have been shown to affect mortality. Consequently, it has been incorporated into the non-paracetamol classification of ALF transplantation criteria and confirmed as poor prognostic variable in a number of studies. However the cut-off age associated with poor prognosis ranges from as low as 40 to as high as 60 years. Interestingly, older age does seem to be correlated with overall poor survival, however, there is no statistical difference between young and old in spontaneous survival. Ultimately, older patients require greater attention to co-morbidities and whole body biology than age per se (Fig. 2.5).

We have found anecdotally and without supportive evidence that 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 with high PEEPs (10–15 cm of water) and fractional inspired oxygen >0.8 with oxygen saturations <92% represent an extreme in the setting of ALF. However toxic liver syndrome as a cause of lung injury, needs to be considered and there is possibly a benefit associated with transplantation in this setting.

Bacteremia is also an important potential contraindication for transplantation that should delay the listing for transplantation until exposure to targeted antibiotics for a minimum of 24 h has elapsed. Both fungal sepsis and necrotising pancreatitis are similarly associated with an extremely poor outcome in transplanted ALF patients. Finally, fixed dilated pupils for greater than 2 h and a cerebral perfusion pressure <45 mmHg for prolonged lengths of time in the context of other related 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 specialist

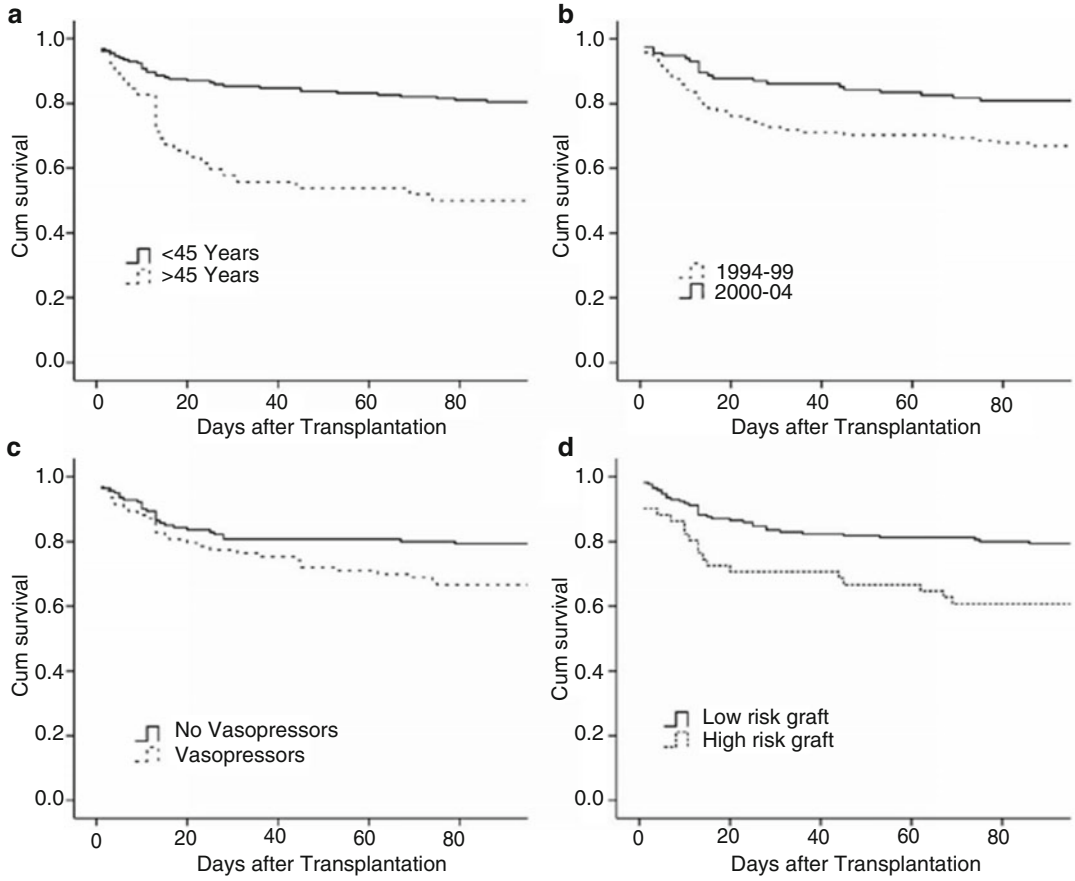


**Fig. 2.5** Survival of patients transplanted (**a**) aged >45 and <45 years. (**b**) between 1994-1999 and 2000-2004. (**c**) requiring vasopressor or no vasopressor following transplantation (**d**) with liver grafts with a calculated donor risk score either high or low

liver centre with the option of liver transplantation and an experienced multidisciplinary team is recommended. Such teams include liver intensivists, transplant surgeons, hepatologists, pharmacist, 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 can prevent further liver injury. Additionally, particular attention to the optimization of the circulation with both appropriate early invasive monitoring directing aggressive fluid resuscitation and vasopressor support is the key. The early use of empirical antibiotics and antifungal agents along with strict infection control measures are necessary. Furthermore, due to the high frequency of sepsis in the absence of SIRS symptoms a low threshold for obtaining cultures and broadening antibiotic cover deteriorates is required when the clinical condition. 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. Furthermore, in parallel with supportive measures an assessment of the clinical history and prognostic variables must be undertaken to determine, which patients fulfil 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. The clinical course for those that are not transplanted is often

precarious and associated with a high mortality. It is affected by the speed and degree of hepatic regeneration and the impact of the cumulative insults that include recurrent sepsis, persistent AKI requiring prolonged RRT, and critical illness neuropathy/myopathy resulting in extended periods of rehabilitation in those that survive. On the contrary, 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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