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15.22.5 Liver failure 3089 investigate novel sensitive and specific biomarkers, further validate existing investigative tools, and develop clear diagnostic algorithms. With the growing recognition of the importance of systemic in- flammation and immune dysfunction, novel therapeutic interventions are required to target this pathophysiological mechanism. Areas currently under investigation to target systemic inflammation in- clude plasmapheresis, albumin-based endotoxin removal systems, al- bumin infusion, and antioxidants. Interventions under investigation to target immune dysfunction include Toll-like receptor antagonists and the use of T-regulatory cells. Manipulation of the gut microbiome may have benefits for both systemic inflammation and immune dys function. Fecal Microbiota Transplant (FMT) therefore represents a promising area for development in the management of HE. A recent small randomized controlled trial of FMT versus standard of care found reduced hospitalization and improved cognitive testing in cir- rhotic patients with two previous documented episodes of overt HE. This trial however was designed with the primary outcome of proving safety of FMT. Further larger placebo controlled trials are required. FURTHER READING Als-Nielsen B, Gluud LL, Gluud C (2004). Non-absorbable disac- charides for hepatic encephalopathy: systematic review of ran- domised trials. BMJ, 328, 7447. Bajaj JA, et al. (2017). Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology, 66, 1727–38. Bajaj JS, et al. (2013). Cognitive dysfunction is associated with poor socio-economic status in patients with cirrhosis: an international Multicentre Study. Clin Gastroenterol Hepatol, 11, 1511–16. Bass NM, et al. (2010). Rifaximin treatment in hepatic encephalopathy. NEJM, 362, 1071–81. Bustamante J, et al. (1999). Prognostic significance of hepatic enceph- alopathy in patients with cirrhosis. J Hepatol, 30, 890–5. Coltart I, Tranah T, Shawcross D (2013). Inflammation and hepatic encephalopathy. Arch Biochem Biophys, 536, 189–96. Ferenci P, et al. (2002). Hepatic encephalopathy—definition, nomen- clature, diagnosis and quantification final report of the working party at the 11th World Congresses of Gastroenterology Vienna 1998. Hepatology, 35, 716–21. Lee WM, Larsen AM, Stravitz RT (2011). American Association for the Study of Liver Diseases, position paper: the management of acute liver failure: update 2011. https://www.aasld.org/sites/default/files/guide- line_documents/alfenhanced.pdf National Institute for Health and Care Excellence (NICE) (2015). Rifaximin for preventing episodes of over hepatic encephalopathy. Technology appraisal guidance. NICE, London. Shawcross D, Jalan R (2005). Dispelling myths in the treatment of hep- atic encephalopathy. Lancet, 365, 431–3. Shawcross DL, Wendon JA (2012). The neurological manifestations of acute liver failure. Neurochem Int, 60, 662–71. Sturgeon JP, Shawcross DL (2014). Recent insights into the patho- genesis of hepatic encephalopathy and treatments. Expert Rev Gastroenterol Hepatol, 8, 83–100. Vilstrup H, et al. (2014). Hepatic encephalopathy in chronic liver

dis- ease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 60, 715–35. Weissenborn K (2015). Challenges in diagnosing hepatic encephalop- athy. Neurochem Res, 40, 265–73. 15.22.5 Liver failure Jane Macnaughtan and Rajiv Jalan ESSENTIALS Liver failure occurs when loss of hepatic parenchymal function exceeds the capacity of hepatocytes to regenerate or repair liver injury. Acute liver failure is characterized by jaundice and pro- longation of the prothrombin time in the context of recent acute liver injury, with hepatic encephalopathy occurring within 8 weeks of the first onset of liver disease. Acute-on-chronic liver failure is characterized by hepatic and/or extrahepatic organ failure in pa- tients with cirrhosis associated with an identified or unidentified precipitating event. The commonest causes of acute liver failure are acute viral hepa- titis and drugs. Acute-on-chronic liver failure is most commonly precipitated by infection, alcohol abuse, and superimposed viral infection. The main clinical manifestations are hepatic encephalop- athy, coagulopathy, jaundice, renal dysfunction, and haemodynamic instability. Infection and systemic inflammation contribute to patho- genesis and critically contribute to prognosis. Management Specific therapy for the underlying liver disease is administered when available, but this is not possible for most causes of liver failure. Treatment is predominantly supportive, with particular em- phasis on (1) correction or removal of precipitating factors; (2) if en- cephalopathy is present, using phosphate enemata, nonhydrolysed disaccharide laxatives, and/or rifaximin; (3) early detection and prompt treatment of complications such as hypoglycaemia, hypo- kalaemia, cerebral oedema, infection, and bleeding. The onset of organ failure should prompt discussion with a liver transplantation centre. Course and prognosis The mortality of acute liver failure (without liver transplantation) is about 40%. Patients with acute liver failure who do not develop en- cephalopathy can be expected to recover completely. Those who recover from an episode of acute- on-chronic liver failure should be considered for liver transplantation because otherwise their subse- quent mortality remains high. Introduction Liver failure is a catastrophic event culminating in multiorgan failure, requirement for organ support in intensive care, and high mortality rates. Depending upon whether the liver failure occurs on the background of a previously healthy liver or in patients with underlying cirrhosis, the conditions are referred to as acute liver failure (ALF) or acute-on-chronic liver failure respectively. ALF is defined by the occurrence of hepatic encephalopathy in patients with severe acute liver injury within 6 months of the onset of symptoms. Acute-on-chronic liver failure is much more common than ALF. The condition is characterized by acute deterioration of a cirrhotic patient, with or without a recognized precipitating event,

section 15 Gastroenterological disorders 3090 associated with organ failures and high mortality rates. These condi- tions must be distinguished from decompensated cirrhosis, which is pathophysiologically different and typically represents patients that have end-stage cirrhosis with varying degrees of end-organ dysfunc- tion (Table 15.22.5.1). The following sections describe the two main types of liver failure: ALF and ACLF. The syndromes Acute-on-chronic liver failure Historically, major complications in patients with cirrhosis were thought to represent a stepwise progression, when a patient over years progressed from compensated to a decompensated state manifest clinically by the main complications of cirrhosis, namely, jaundice, variceal bleeding, ascites, hepatic encephalopathy, and infection. Over the last few years, large, prospective clinical studies have suggested that patients can progress from any stage of liver disease to ACLF (Fig. 15.22.5.1). The current working definition of ACLF is: ‘Acute-on-chronic liver failure is defined as acute de- terioration of pre-existing, chronic liver disease, usually related to a precipitating event

and associated with increased mortality at 3 months due to multisystem organ failure’. Diagnosis The diagnosis of ACLF is made in the context of a patient with cir- rhosis who is hospitalized with a liver-related complication such as variceal bleeding, ascites, hepatic encephalopathy, jaundice, or infection. The studies leading up to the establishment of criteria for the diagnosis of ACLF were predicated on finding a group with a 28-day mortality of 15% or higher. They identified that a scoring system based on a modification of the Sepsis Organ Failure Table 15.22.5.1 Types of liver failure Acute Subacute ACLF underlying cirrhosis Decompensated cirrhosis Time from symptoms to failure Weeks Months Weeks Years Common aetiology Toxic Viral Variable Variable Precipitating event Liver injury Liver injury Sepsis Alcohol Infection (others) Mortality 50% 50% 30–40% Variable Prognostic score King’s College criteria King’s College criteria CLIF-C ACLFs MELD score Liver histology Massive necrosis Submassive necrosis Apoptosis Necrosis Cholestasis Variable Benefit from liver transplantation Yes Yes Yes Yes Adapted from Jalan R, et al. (2014). Toward an improved definition of acute-on-chronic liver failure. Gastroenterology, 147, 4–10. Chronic liver disease Compensated cirrhosis Decompensated cirrhosis Type A ACLF TypeB ACLF Type C ACLF Hepatic and extrahepatic organ failures Precipitants • Virus • Drug • Surgery • Sepsis • Idiopathic • Jaundice • Hepatic encephalopathy • Variceal bleeding • Ascites • Ischemic • Alcohol Fig. 15.22.5.1 Clinical course of ACLF syndrome and effects on prognosis. Reprinted from Gastroenterology, Vol. 147, Jalan R, et al., Toward an improved definition of acute-on-chronic liver failure, Pages 4–10, Copyright © 2014 AGA Institute, with permission from Elsevier.

 Assessment (SOFA) score developed for patients with sepsis was appropriate for this purpose. This scoring system is referred to as the Chronic Liver Failure (CLIF) Consortium Organ Failure score (CLIF-OFs) and is illustrated in Table 15.22.5.2. Using this scoring system, patients can be classified into those with and those without ACLF and with a definition of severity. Patients with ACLF have high rates of short- and medium-term mortality compared with those without ACLF, and mortality rates are higher in those with more advanced grades (Fig. 15.22.5.2). ACLF is, however, a dy- namic syndrome with resolution to a non-ACLF state observed in approximately 50% of ACLF-1, 30% of ACLF-2, and 20% of ACLF-3 patients with supportive care within 2 to 5 days. Conversely, pa- tients with earlier stages of ACLF may deteriorate rapidly to the more advanced stages, emphasizing the key importance of expe- dient management at diagnosis. The common causes of cirrhosis and precipitating factors of ACLF are listed in Table 15.22.5.3. Prognosis Many scoring systems have been developed to define the prog- nosis of patients with cirrhosis. The most widely used of these are the Child–Pugh and Model for End-Stage Liver Disease (MELD) scores. The MELD score includes bilirubin, INR, and creatinine in the model, whereas the Child–Pugh score (Table 15.22.5.4) cap- tures the clinical features of encephalopathy and ascites in add- ition to the conventional hepatic synthetic markers of bilirubin, albumin, and INR. Neither incorporate markers of inflammation, a key prognostic determinant in ACLF, hence a scoring system spe- cific for patients with ACLF was developed, the CLIF Consortium ACLF score (CLIF-C ACLFs), composed of the CLIF-OFs, age, and white cell count (Table 15.22.5.5). The CLIF-C ACLFs has been shown to have superior prognostic accuracy compared to conven- tional measures such as the MELD and Child–Pugh scores. A fur- ther advantage is that the prognosis of the patient can be updated daily to determine prognosis as it relates to the effect of a given intervention. ACLF is an exceptionally dynamic disease with variable out- comes. Resolution occurs in approximately one-half of patients, with deterioration in approximately one-fifth. The clinical course of the ACLF syndrome during hospitalization is the chief determinant of short-term mortality. The 28-day survival in patients developing resolution of ACLF was similar to that in patients without ACLF. In

particular, it is the early course of ACLF over the time intervals of the first 1 to 2 days and subsequent 3 to 7 days which are of particular prognostic relevance. Table 15.22.5.2 Diagnostic criteria of acute-on-chronic liver failure Diagnosis Criteria No ACLF • Patients with no organ failure • Patients with single hepatic, coagulation, circulation, or respiratory failure, serum creatinine <1.5 mg/dl, and no hepatic encephalopathy • Patient with cerebral failure and serum creatinine <1.5 mg/dl ACLF-1 • Patients with renal failure • Patients with other single organ failure with serum creatinine ≥1.5 and <2 mg/dl and/or hepatic encephalopathy grade III ACLF-2 • Patients with 2 organ failures ACLF-3 • Patients with 3 or more organ failures Data reproduced from Jalan R, et al. (2014). Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol, 61, 1038–47. 1.0 0.8 0.6 0.4 42.9% 12.8% 5.1% 26.2% 58.4% 76% No d3-7 ACLF (n = 135) d3-7 ACLF-1 (n = 61) d3-7 ACLF-2 (n = 42) d3-7 ACLF-3 (n = 78) 3.8% 21.4% 53% 62% 78.7% 89.6% 0.2 0.0 1.0 0.8 0.6 0.4 0.2 0.0 0 28 60 90 Time (Days) Probability of transplant-free survival Probability of Survival 120 150 180 0 28 60 23.3% (95%CI: 15.8–30.8) 12.5% (95%CI:6.3–18.7) p<,0001 10% (95%CI:4.6–15.4) 80.9% (95%CI:64.2–97.7) 90.5% (95%CI: 77.9–100) 95.2% (95%CI: 86.1–100) Early transplanted d3-7 ACLF-2 or 3 patients (n = 21) Non-transplanted d3-7 ACLF-2 or 3 patients (n = 120) 90 Time (Days) 120 150 180 (a) (b) Fig. 15.22.5.2 Transplant-free survival curves with differing grades of ACLF determined at days 3 to 7. (a) Kaplan–Meier 180-day transplant-free survival curve. (b) Probability of survival in patients with ACLF-2/3 (at day 3–7) with and without early (28-day) liver transplantation. Reproduced with permission Gustot T, et al. (2015). Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology, 62, 243–52, Copyright © 2015, John Wiley and Sons.

section 15 Gastroenterological disorders 3092 Pathophysiology The pathogenesis of ACLF is unknown. There are two underlying factors in cirrhosis which render patients susceptible to the dele- terious effect of a superimposed insult. The first is the underlying cirrhosis and the structural disturbances, portacaval shunting, portal hypertension, and metabolic disturbance this entails. The second, perhaps equally important, is a ‘leaky gut’ with translocation of bac- terial and bacterial ligands to the liver and systemic circulation. This combination of factors ‘primes’ the patient’s organs to the effect of a superimposed secondary insult. The patient therefore responds ab- normally to the superimposed insult and this results in multiorgan failure. As is clear from this description, the pathogenesis of ACLF is complex as the condition occurs on the background of existing liver disease (Predisposition), is usually precipitated by some factor (Injury), is associated with an inflammatory response (Response), and characterized by organ failure (Organ), hence the pathophysio- logical basis of the syndrome can be considered under the ‘PIRO’ framework. Role of predisposing factors (P) A number of host factors appear to predispose to the development of ACLF, in particular the severity and aetiology of underlying liver disease. The severity of underlying cirrhosis as determined by MELD and Child–Pugh scores does not accurately predict the se- verity and prognosis of ACLF, highlighting the pathophysiological differences between ACLF and decompensated cirrhosis. Male sex and younger age have also been associated with higher risk of ACLF, although neither of these variables has been associated with an in- crease in mortality. In prospective, observational European studies of patients with ACLF and acute decompensation, alcohol was more frequently represented and hepatitis C less frequently represented as the underlying aetiology of cirrhosis in ACLF patients compared to those with acute decompensation. Conversely, hepatitis B is more frequently observed in Asian countries as a cause of cirrhosis. The outcome of ACLF even in this group of patients is dependent on the severity of organ dysfunction. Role of precipitating factors (I) Identifiable precipitating events have been described in approxi-

mately 60% of ACLF patients. These insults may either be directly hepatotoxic, such as alcoholic hepatitis, viral hepatitis, drug-induced liver injury, or vascular disorders, or an extrahepatic insult such as variceal haemorrhage or sepsis (Table 15.22.5.3), which is a common precipitating event in ACLF. Patients with cirrhosis frequently have a state of functional immune paresis with anti-inflammatory humoral and cellular immune phenotype. Patients with advanced cirrhosis are known to have reduced neutrophil phagocytosis, diminished HLA DR monocyte expression (diminishing capacity for antigen presentation to T cells), and high circulating interleukin-10 levels predisposing them to sepsis. Alcohol abuse in the prodromal period of ACLF is more frequently observed in Western countries and hepatitis B flares or superimposed viral hepatitis is more common in Asian populations. Cases of ACLF precipitated by extrahepatic insults, in contrast to direct hepatotoxic insults, were found to be associated with a higher 90-day and 1-year mortality in a cohort of 405 ACLF patients. Aetiology of the underlying cirrhosis has also been found to be asso- ciated with the development of ACLF. Demographic differences in prevalence of chronic disease are likely to result in a heterogeneity in the clinical picture but further elucidation of the mechanisms is required. Role of inflammatory response (R) Host response, in particular the nature and magnitude of the innate immune response, is a significant determinant of clinical course in ACLF. Higher leucocyte counts are associated with more severe grades of ACLF and are predictive of poor outcome. The presence of a dysregulated systemic inflammatory response syndrome (SIRS) is a cardinal feature of ACLF and appears to be a key driver pro- moting the transition from stable cirrhosis to ACLF associated with increased mortality (Fig. 15.22.5.3). Many lines of evidence implicate gut-derived endotoxin in pro- motion of a dysregulated immune response in ACLF. This may Table 15.22.5.3 Aetiologies of underlying cirrhosis and precipitating event in acute-on-chronic liver failure Causes of cirrhosis (chronic insult) Alcohol Viral hepatitis (hepatitis B, C, delta) Autoimmune liver disease (primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis) Metabolic liver disease (nonalcoholic steatohepatitis, Wilson’s disease, haemochromatosis, α1-antitrypsin deficiency) Precipitating factors (acute insult) Sepsis: bacterial/viral/fungal—de novo or reactivation Alcoholic hepatitis Variceal haemorrhage Viral hepatitis Drug/toxin-induced liver injury Vascular (Budd–Chiari syndrome, ischaemic hepatitis, portal vein thrombosis) Surgery None identified Table 15.22.5.4 Child–Pugh score Parameter Points assigned 1 2 3 Ascites Absent Slight Moderate Bilirubin, mg/dL ≤2 2–3

> 3 Albumin, g/dL 3.5 2.8–3.5 <2.8 Prothrombin time
> (s over control) 1–3 4–6 6 INR <1.8 1.8–2.3 2.3 Encephalopathy None Grade 1–2
> Grade 3–4 Grade Points 1-year patient survival (%) 2-year patient survival (%)
> A: well-compensated disease 5–6 100 85 B: significant functional compromise
> 7–9 80 60 C: decompensated disease 10–15 45 35

 account for the generation of a SIRS response in the 40% of patients without an identifiable precipitating factor. The presence of SIRS is associated with more severe encephalopathy, renal failure, and an increased incidence of bacterial infection. SIRS is associated with a hyperdynamic circulation with low systemic vascular resistance and a low mean arterial pressure resulting in low organ perfusion com- pounding organ injury. Features of a compensated anti-inflammatory response syndrome may predominate over SIRS in subgroups of patients with ACLF in particular during later stages of the syndrome. Such patients are immune deficient and

prone to nosocomial infection. This state of immunological dissonance in ACLF is evident at the level of both cell-mediated and humoral innate immunity. Organ dysfunction (O) Development and degree of organ failure is the most important de- terminant of outcome in ACLF patients and is the defining feature. In contrast to end-stage decompensated disease, recoverability of organ function is potentially achievable and should be managed accordingly. Hepatic failure Hyperbilirubinaemia is almost invariably present, manifest as jaundice, and in the context of coagulopathy is considered a key criterion of ACLF. Ongoing liver injury promotes an inflammatory response, which further exacerbates liver failure. Current data suggest that apoptosis is the predominant mechanism of cell death in ACLF in patients with alcoholic cirrhosis in contrast to patients with hepatitis B in which necrosis appears to be the pre- dominant mechanism. The exact molecular mechanisms involved remain unclear, but it is likely that hepatic inflammation causes cell death and release of damage-associated molecular patterns (DAMPs) which further exacerbate inflammation and cell death. The net result is a vicious cycle that is associated in a self-amplifying cycle with worsening hepatic perfusion and more severe portal hypertension consequent on increased intrahepatic resistance. Kidney dysfunction Acute kidney injury is common in patients with ACLF. From the pathophysiological standpoint, this may be due to hypovolaemia, acute tubular injury, or hepatorenal syndrome. Distinction between these entities is important. Hypovolaemic renal failure resolves quickly with volume resuscitation. Hepatorenal syn- drome has classically been considered as a functional disorder in which there is splanchnic vasodilatation and reduction in mean arterial pressure occurs with consequent activation of the sympa- thetic and renin–angiotensin systems, resulting in intense renal Table 15.22.5.5 The CLIF Organ Failure scoring system Organ system Score = 1 Score = 2 Score = 3 Liver Bilirubin <6 mg/dl (<100 µmol/litre) 6 ≤ Bilirubin ≤ 12 mg/dl (100–200 µmol/litre) Bilirubin >12 (>200 µmol/litre) Kidney (mg/dl) Creatinine <2 mg/dl (<175 µmol/litre) 2 <Creatinine <3.5 mg/dl (175–310 µmol/litre) Creatinine ≥3.5 mg/dl (>310 µmol/litre) or renal replacement Brain (West Haven) Grade 0 Grade 1–2 Grade 3–4 Coagulation INR <2.0 2.0 ≤INR <2.5 INR ≥2.5 Circulation MAP ≥70 mm/Hg MAP <70 mm/Hg Vasopressors Respiratory: Pao2/Fio2 or Spo2/Fio2

> 300 357 ≤300–>200 214– ≤357 ≤200 ≤214 The bold entries represent organ failure. Fio2, Fractional inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; Pao2, Partial pressure of oxygen; Spo2, oxygen saturation. Reprinted from J Hepatol, Vol. 62, Jalan R, et al., The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure, Pages 831–40, Copyright © 2015 European Association for the Study of the Liver, with permission from Elsevier. Liver failure/bacterial translocation Immune paralysis • Endotoxaemia • Reduced protein/complement synthesis • Reduced immune surveillance • Reduced albumin function Innate immunity • Neutrophils: phagocytic defect • Monocytes: DR loss • NK cells • T-cell exhaustion • Inability to profilerate • Increased apoptosis CARS: compensatory anti-inflammatory response SIRS: systemic inflammatory response Normal ACLF: survivor ACLF: nonsurvivor Immune response Adaptive immunity Fig. 15.22.5.3 Immunopathology of ACLF.

section 15 Gastroenterological disorders 3094 vasoconstriction (Box 15.22.5.1). A significantly higher proportion of patients have evidence of acute tubular injury. Although distinct, all three entities overlap to some extent in individual patients, and all are reversible with improvement in liver function, although a few patients require prolonged renal replacement therapy despite re- covery of liver function. Brain dysfunction The demographics and prognosis of hepatic encephalopathy (HE) in ACLF and acute decompensation appear to be different. Hepatic encephalopathy associated with ACLF is associated with a higher mortality, occurring more frequently in young alcoholic cirrhotic patients with severe liver failure and a pronounced SIRS response. In contrast, hepatic enceph- alopathy not associated with ACLF occurred in older abstinent cirrhotic patients with features of SIRS or severe liver failure. A proinflammatory response and hyperammonaemia operate syn- ergistically to result in astrocyte swelling, clinically manifest as hepatic encephalopathy in the ACLF patient. Unlike in ALF, hep- atic encephalopathy is rarely complicated by raised intracranial pressure. Cardiac and circulatory dysfunction Circulatory support re- quirements with inotropes and/or vasopressor agents are often significant. High circulating nitric oxide levels coupled with endo- thelial dysfunction result in a low peripheral vascular resistance. Unlike in decompensated cirrhosis in which a high cardiac output is typically observed, cardiac output is frequently reduced in ACLF. This cardiovascular abnormality is associated with an increased risk of death, particularly in those patients who present with renal dysfunction. Adrenal insufficiency Adrenal insufficiency is reported in 51 to 68% of patients with cirrhosis and severe sepsis, and the incidence may be higher in ACLF patients. The mechanisms underlying this are not clear, but its presence is associated with increased mortality compared to patients without adrenal insufficiency. Acute liver failure ALF is a rare but rapidly progressive clinical entity associated with a high mortality without treatment. It is defined as ‘a rapid decline in hepatic function characterized by jaundice, coagulopathy (INR

> 1.5), and hepatic encephalopathy in patients with no evidence of prior liver disease’. Patients with ALF are classified according to the interval between the onset of jaundice to the development of encephalopathy as this carries prognostic significance: hyperacute liver failure (<7 days); ALF (7–28 days); or subacute liver failure (28 days–24 weeks). Drug-induced liver injury, in particular paracetamol, is a fre- quent cause of ALF in Europe and the United States of America, accounting for more than 50% of cases. In contrast, viral hepatitis as a cause of ALF is commoner in the East, with high rates of hepa- titis B and E responsible. Causes of ALF are listed in Box 15.22.5.2. Pathophysiologically, ALF is characterized by massive hepatocyte necrosis and a pronounced SIRS. Clinical features of SIRS are com- monly observed together with a heightened susceptibility to sepsis. Significant progress has been made over the last 30 years with re- gard to management of this disorder. An improvement in critical care management (in particular with regard to raised intracranial pressure) and a well-defined emergency liver transplantation pro- gramme are chiefly responsible for the observed significant im- provement in mortality. Clinical features Many of the clinical features of ALF may be attributed to an acute SIRS with multiorgan failure and a hyperdynamic circulation. Hepatic encephalopathy is a much feared complication of ALF and occurs as a

consequence of cerebral oedema with raised intracra- nial pressure. Clinically this may be graded using the West Haven criteria. Progression of encephalopathy may be rapid and so early identification is key. ALF follows a very dynamic clinical course, the nature of which has prognostic significance. Patients with hyperacute ALF have rapid onset of hepatocellular injury evidenced biochemically by very high transaminase but often low bilirubin levels. Typical causes include paracetamol and ischaemic hepatitis. Recovery may be as rapid as onset. In contrast, subacute liver failure develops over sev- eral weeks and a biochemical picture of hyperbilirubinaemia with lower transaminases is commonly observed. Patients with subacute liver failure may manifest with clinical features of portal hyperten- sion. Such patients may be mistakenly diagnosed as ACLF or acute decompensation, hence care must be taken to clearly determine chronicity of disease. Typical causes include indeterminate hepa- titis, drug-induced liver injury, hepatitis B, and autoimmune hepa- titis. Prognosis is poor. Establishing the underlying aetiology is an important goal of clinical assessment and may frequently be achieved from a detailed Box 15.22.5.1 Criteria for diagnosis of hepatorenal syndrome in cirrhosis • Cirrhosis with ascites • Serum creatinine greater than 1.5 mg/dl (133 µmol/litre) • Absence of shock • Absence of hypovolaemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 µmol/litre) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day • No current or recent treatment with nephrotoxic drugs • Absence of parenchymal renal disease as defined by proteinuria less than 0.5 g/day, no microhaematuria (<50 red cells/high powered field), and normal renal ultrasonography Box 15.22.5.2 Causes of acute liver failure • Dose-dependent drug-induced liver injury: paracetamol (acetamino- phen), ecstasy, herbal toxicity, Amanita phalloides mushroom ingestion • Idiosyncratic drug-induced liver injury: rifampicin, isoniazid, non steroidal anti-inflammatory drugs, sodium valproate, halothane • Recreational drug use (MDMA, cocaine, khat) • Viral hepatitis: (hepatitis A, B, C, D, and E, herpes simplex virus, cyto- megalovirus, Epstein–Barr virus, varicella zoster virus, parvovirus, adenovirus) • Vascular: right heart failure, Budd–Chiari syndrome, veno-occlusive disease, ischaemic hepatitis, heat stroke • Metabolic: acute fatty liver of pregnancy, Wilson’s disease, Reye’s syn- drome, galactosaemia, hereditary fructose intolerance, tyrosinaemia • Autoimmune hepatitis • Other: sepsis, malignant infiltration, primary nonfunction of a trans- planted liver

15.22.5 Liver failure 3095 history and serological investigations. Prognostic scoring systems based on aetiology and clinical measures of organ injury iden- tify high-risk groups in which spontaneous recovery and survival without transplantation is poor. Prognosis ALF has a poor prognosis with an overall mortality of 40 to 62%, transplant-free survival of 25 to 43%, and overall survival of 67%. The principal causes of death are cerebral oedema, sepsis, and multiorgan failure. Prognosis is heavily influenced by aetiology. Spontaneous survival is higher in paracetamol-induced liver injury,

hepatitis A virus infection, ischaemic hepatitis, and pregnancy-related ALF. In contrast, short-term transplant-free survival is lower in patients with indeterminate causes, nonparacetamol drug-induced liver injury, hepatitis B, autoimmune hepatitis, Wilson's disease, and Budd–Chiari syndrome. Criteria for transplantation are based on adverse prognostic de- terminants. As a consequence of better supportive care of patients with ALF, improvements in survival over the last 40 years have been observed (Fig. 15.22.5.4). Pathophysiology Liver failure occurs when hepatocellular death (either via necrosis and/or apoptosis) exceeds regeneration. While apoptosis results in minimal inflammation, cell lysis from necrosis results in secondary inflammation. Apoptosis appears to be the principal mechanism of cell death in toxicity and viral-induced ALF. Clinically, however, neither apoptotic nor necrotic cell death markers accurately predict survival following paracetamol-induced ALF. The M30 antigen, a marker of apoptotic hepatocyte cell death was found to be 10-fold elevated in ALF patients compared with normal or hepatitis C- infected controls. Inhibition of apoptosis with caspase inhibitors has shown early promise in preclinical studies. The development of a SIRS is a cardinal clinical feature of patho- genesis in ALF (Fig. 15.22.5.5). An expansion of tissue-resident macrophages and infiltration of monocytes occurs in response to hepatocellular apoptosis and necrosis. While monocyte/macro- phage populations play a key role in resolution of disease, heightened M1 proinflammatory activity further contributes to oxidative injury and exacerbation of hepatic and extrahepatic organ failure and de- velopment of a hyperdynamic circulation. Heightened neutrophil oxidative stress in concert with hyperammonaemia due to impaired urea cycle metabolism have been shown to play an important role in the development of hepatic encephalopathy with the development of cerebral oedema. The nature of the signalling pathways utilized in the innate in- flammatory response in ALF is aetiology specific. Hepatotropic viruses signal directly via pathogen-associated molecular pat- terns (PAMPs), whereas DAMP signalling pathways have a more central role in drug toxicity. The situation is in fact more compli- cated, and convergence of PAMP and DAMP signalling potentiates organ injury. While in ALF the predominant drivers of this pathway are en- dogenous ligands such as apoptotic markers, there is increasing interest in the role of endotoxin signalling in augmenting this process. ALF has been shown to be associated with the development of sys- temic endotoxaemia and a proinflammatory response responsible for many of the deadly clinical features in ALF as previously discussed. Removal of endotoxin in a porcine model of paracetamol-induced ALF has been shown to be associated with a significant improvement in mortality. Several lines of evidence from murine studies also con- firm the importance of the endotoxin receptor (TLR4) pathways in the pathogenesis of paracetamol-induced ALF. The TLR4 antagonist STM28 significantly reduced liver injury, renal function, and time to encephalopathy in a murine model of paracetamol toxicity. A compensatory anti-inflammatory response subsequently de- velops, conferring a propensity to sepsis commonly observed in ALF patients. Indeed, elements of both SIRS and compensated anti-inflammatory response syndrome responses frequently coexist. Previous studies have demonstrated monocyte hyporesponsiveness in ALF but coincident with elevated anti-inflammatory cytokines. Investigation of liver failure Broad assessment of all organ systems is required in patients with ALF or ACLF to determine precipitants, identify reversible precipitating factors, and determine prognosis. Blood tests Conventional laboratory blood assays are required to provide measures of organ injury and failure (Table 15.22.5.6). These in- clude determination of coagulation status, liver and renal bio- chemistry, arterial blood gas measurements, lactate, and full blood count. Dynamic assessment of organ injury and inflammatory in- dices provides a more accurate assessment of clinical status and is used with recognized scoring systems such as the CLIF-OFs and Kings College criteria. Comprehensive screening for sepsis is an essential element of

in- vestigation of patients with ACLF and ALF given the state of func- tional immune compromise. Cultures from blood, ascites, urine, and sputum should be collected on admission, and prompt ascitic fluid microscopy performed. Urinary dipstick analysis and (if posi- tive for protein) urinary albumin-to-creatinine ratio should be de- termined to identify coincident intrinsic renal disease. Initial investigations should also include a screen for aetiology of liver disease and to risk stratify patients (Table 15.22.5.6). If Wilson's disease is suspected, slit lamp examination for Kayser–Fleischer rings should be performed. 90 80 70 60 50 40 30 20 10 Years Hospital survival (%) 0 1973–78 1979–83 1984–88 1989–93 1994–98 1999–2003 2004–08 Fig. 15.22.5.4 Hospital survival in admissions with ALF. Reproduced from Bernal W, et al. (2013). Clinical management of acute liver failure: results of an international multi-center survey. J Hepatol, 59, 74–80.

section 15 Gastroenterological disorders 3096 Radiological Abdominal ultrasonography with hepatic and portal vein Dopplers is often the first-line radiological investigation performed in ALF and ACLF. Establishing features of chronicity such as parenchymal changes in the liver and kidneys and features of portal hypertension is important in achieving the correct diagnosis. It must be noted, however, that ultrasonography is a relatively insensitive tool for the identification of cirrhosis. It is also worth noting that portal hyper- tension may be a feature of subacute liver failure and should be in- terpreted in context. A CT head scan is indicated in patients with severe encephalopathy to exclude other intracranial pathology such as haemorrhage. In ALF, quantification of liver volumes with cross-sectional imaging modalities using CT or MRI has been used as an adjunct to provide information regarding hepatocellular mass. While this does not provide a measure of functionality, some clinical studies have suggested that low liver volumes (<1000 ml) in ALF constitute an adverse prognostic determinant, with a predicted mortality of 97%. This must be interpreted in the context of the entire clinical picture. Interval imaging (on admission and day 5) may provide further in- formation regarding the time course of disease. circulation SIRS monocyte activation TNF IL-6 monocytes "pro-inflammatory" monocytes "pro-inflammatory" macrophage macrophage activation AIAT hepatocyte death DAMPs (HMGB I, DNA, histones) TNF phagocytosis efferocytosis recruitment of monocyte-derived macro phages Kupffer cell portal vein steroids IL-10 SLPI IL-10 SLPI DR CD163 phagocytosis hepatocyte regeneration IL-6 "'anti-inflammatory" -immune-paresed- monocytes "'anti-inflammatory" macrophage hepatic vein DR CD163 phagocytosis TNF IL-6 risk of sepsis "spill-over" of inflammatory mediators CARS liver initiation propagation resolution Fig. 15.22.5.5 Pathological role of the immune response in ALF. CARS, compensatory anti-inflammatory response syndrome. Reprinted by permission from Springer Nature: Bernsmeier C, Antoniades CG, Wendon J (2014). What's new in acute liver failure? Intensive Care Medicine, 40, 1545–8, copyright © 2014. Table 15.22.5.6 Investigations for acute liver failure Haematology Full blood count, coagulation screen including INR ABO blood group Biochemistry Liver function tests (bilirubin, ALT, AST, γGT, ALP, albumin) Urea, creatinine, electrolytes (sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate) Glucose Arterial blood analysis pH, lactate, ammonia, Po2, Pco2 Toxicology screen Paracetamol level, toxicology screen Viral screen HAV/HEV IgM/G, HBc IgM/G, HBsAg, HCVIg EBV/CMV/HSV/parvovirus IgM/G HIV1/2 Metabolic screen Serum and urinary copper, caeruloplasmin Autoantibodies ANA, SMA, LKM, immunoglobulins ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein–Barr virus; γGT, γ-glutamyl transferase; HAV, hepatitis A virus; HBc, hepatitis B virus core antigen; HBsAg, hepatitis B virus surface antigen; HCVIg, hepatitis C immunoglobulin; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LKM, liver–kidney microsomal antibody; SMA,

anti-smooth muscle

15.22.5 Liver failure 3097 Endoscopic Prompt endoscopic assessment of the upper gastrointestinal tract should be performed in all patients in whom variceal haemorrhage is suspected. Anaesthetic support with airway management should be provided in the presence of large volume gastrointestinal bleeding or an encephalopathic state. Histological Transjugular liver biopsy may contribute to the assessment of ACLF patients in terms of both establishing the aetiology of pre- cipitant (such as alcoholic hepatitis) or underlying disease, and establishing the hepatocellular regenerative potential. Other fea- tures such as ductular bilirubinostasis have been associated with high risk of sepsis and an adverse prognosis. Transjugular liver biopsy is recommended in ALF if the aetiology is unclear after ex- tensive initial investigation, or if there is suspicion of underlying chronic disease. Management General Prompt institution of high-level supportive and aetiology-specific therapy is required to optimize the opportunity for reversibility of organ failure, a key determinant of outcome in ACLF and ALF. Early identification of adverse prognostic features to inform decisions to list for transplantation is important as the subsequent clinical de- terioration may be rapid. Management may be considered broadly under two categories: organ system support and aetiology-specific therapy. Organ system support ACLF and ALF should be managed in a high-level clinical care envir- onment. An algorithm for supportive care is shown in Fig. 15.22.5.6. Individual organ systems will be considered. Fig. 15.22.5.6 Management approaches for patients with cirrhosis who are admitted to the intensive care unit. ABG, arterial blood gases; BP, blood pressure; CPAP, continuous positive airway pressure; CT, computed tomography; CXR, chest X-ray; ECG, echocardiogram; FiO2, fraction of inspired oxygen; GCS, Glasgow Coma scale; Hb, haemoglobin; HPS, hepatopulmonary syndrome; IAP, intra-abdominal pressure; IJ, internal jugular; PA, pulmonary artery; PaO2, arterial partial pressure of oxygen; PCWP, pulmonary capillary wedge pressure; PPH, portopulmonary hypertension; RAP, right atrial pressure; RRT, renal replacement therapy; ScvO2, central venous oxygen saturation; SVV, stroke volume variation. Reproduced with permission from Olson JC, Wendon JA, Kramer DJ, Arroyo V, Jalan R, Carcia-Tsao G, Kamath PS (2011). Intensive care of the patient with cirrhosis. Hepatology, 54, 1864–72, Copyright © 2011, John Wiley and Sons.

section 15 Gastroenterological disorders 3098 Brain Hepatic encephalopathy is an important prognostic determinant in both ACLF and ALF. Identification and management of patients with or at high risk of developing hepatic encephalopathy is of cen- tral importance in the management of patients. Intubation is re- quired in patients with severe hepatic encephalopathy (grade III or IV) for airway protection. Appropriate nutritional support to ensure normoglycaemia, repletion of micronutrients and electrolytes and appropriate nitrogen balance will minimize superimposed meta- bolic encephalopathy. In ACLF, the mainstay of therapy of a hospitalized patient with cirrhosis is lactulose with administration of enemas to clear the bowel as a useful adjunct. The nonabsorbable antibiotic rifaximin has been shown to improve recurrence of hepatic encephalopathy in decompensated cirrhotic patients but is frequently used in an acute context. Cerebral oedema complicated by intracranial hypertension is a potentially life-threatening feature of severe hepatic encephalop- athy secondary to ALF but does not appear to be a predominant feature of ACLF. Reduction in ammonia and cerebral oedema is the therapeutic goal of management in this context. Reduction in cerebral ammonia uptake and metabolism may be achieved by use of sedation with intubation and moderate hypothermia. Renal re- placement therapy may also be instituted to remove high systemic ammonia. Reduction in cerebral oedema

may be achieved by use of osmotherapy with boluses of hypertonic saline and/or man- nitol and limited periods of hyperventilation-induced hypocapnia. Invasive intracranial monitoring with direct intracranial pressure monitoring, reverse jugular oxygen saturations, and transcranial ultrasonography is indicated in patients in whom intracranial hypertension is suspected clinically. This should be performed only in tertiary units with appropriate expertise. Circulation Circulatory dysfunction is frequently observed in ACLF and ALF and is typically a composite function of hypovolaemia and circula- tory dysfunction in the presence of a pronounced systemic inflam- matory response potentially compounded by sepsis. Hypotension refractory to volume repletion warrants circulatory support to ensure adequate mean arterial and cerebral perfusion pressures, in which instance noradrenaline would be the first vasopressor of choice. The nature of circulatory support must take into account potential coexistence of cirrhotic cardiomyopathy or pulmonary hypertension. Terlipressin by means of splanchnic vasoconstriction coupled with weak peripheral vasoconstrictor properties may be used to improve renal perfusion in the hepatorenal syndrome of ACLF. Terlipressin, however, is contraindicated in the hepatorenal syn- drome of ALF as it has been shown to cause cerebral hyperaemia in severe hepatic encephalopathy, exacerbating cerebral oedema and intracranial hypertension. Kidneys The development of renal impairment in either ALF or ACLF confers a poor prognosis and hence treatment should be insti- tuted promptly to optimize organ reversibility. The mechanisms which underlie renal impairment in ALF and ACLF are frequently multiple. Circulatory dysfunction and intrinsic renal pathology fre- quently coexist and so care must be taken to thoroughly investigate to ascertain the underlying aetiologies. Renal failure is commonly observed in ALF, particularly in paracetamol-induced ALF and the elderly, and is an adverse prognostic determinant. Management of intrinsic renal pathology should be supervised by a nephrologist. Intravenous terlipressin in combination with albumin support is first-line therapy for management of the hepatorenal syndrome in ACLF. Caution must be used in patients at risk of ischaemic heart disease and peripheral vascular disease due to known possible extrasplanchnic vasoconstrictor effects. The role of renal replacement therapy with haemofiltration must be determined on a case-by-case basis, informed by the likely contribution of recoverable intrinsic renal disease versus nonrecoverable circulatory failure. Continuous rather than inter- mittent renal replacement therapy is recommended in this setting. Specific Common identifiable precipitants of ACLF include bacterial in- fection, alcoholic hepatitis, and variceal haemorrhage. As previ- ously discussed, many patients presenting with ACLF do not have a clear precipitant, and some have more than one precipitant. Drug- induced liver injury and viral hepatitis are common causes of ALF. Antibiotics Sepsis is a common precipitant in ACLF and complicating factor of ACLF and ALF due to the anti-inflammatory phenotype of the innate immune response, which develops as an attempt to resolve disease. Prompt administration of empirical antibiotics is clearly im- portant in the management of sepsis. Spontaneous bacterial peritonitis is a common cause of sepsis in patients with advanced cirrhosis and occurs in approxi- mately 30% of patients managed with antibiotics alone. Prompt coadministration of albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) has been associated with an improvement in hepatorenal syndrome and survival and is therefore recommended in national and international guidelines. Bacterial infections other than SBP are less frequently associated with renal failure. The role of empir- ical coadministration of albumin in non-SBP sepsis without renal failure remains the subject of ongoing studies. Prophylactic antibiotic and antifungal agents are often prescribed in ALF although there is not a strong evidence base to support this strategy. Other treatments Prognostic tools such as the Maddrey and Lille scoring systems identify patients with a high risk of mortality and for whom therapy for alcoholic hepatitis should be considered. Steroids are first-line therapy but have no long-term mortality benefit and

the risk of sepsis must be taken into consideration. Appropriate nutritional support should be instigated. The management of variceal haemorrhage is outside the scope of this chapter but is outlined in national and international guide- lines. Specific therapies include prophylactic antibiotic and vaso- active drug administration in conjunction with endoscopic therapy. Transjugular portosystemic shunt insertion may be relatively contraindicated by the degree of organ failure.

15.22.5 Liver failure 3099 Intravenous N-acetylcysteine should be commenced promptly in suspected paracetamol-induced ALF and may be beneficial in nonparacetamol drug-induced liver injury. Institution of antiviral therapy has been shown to significantly reduce mortality in ACLF secondary to hepatitis B reactivation. In contrast, no specific antiviral therapy has been proven efficacious in ALF, but nucleos(t)ide analogues should be considered for hepa- titis B-associated ALF to minimize the risk of post-transplantation recurrence. ALF patients with known or suspected varicella zoster or herpes simplex hepatitis should be treated with intravenous aciclovir. Oral prednisolone may be considered for ALF with mild hepatic encephalopathy due to autoimmune hepatitis but should not delay listing for transplantation. Obstetric delivery is the first line of management of ALF secondary to acute fatty liver of pregnancy/HELLP syndrome (haemolysis, ele- vated liver enzyme levels, and low platelet levels). Synthetic function may indeed further decline within the first week postpartum and consideration of liver transplantation may be required. Extracorporeal liver assist Given the potential for recoverability of liver failure in ALF and ACLF in contrast to end-stage decompensated cirrhosis, liver sup- port devices to bridge to recovery or transplantation are an im- portant therapeutic goal. Currently available liver support systems are not recommended outside of clinical trials, although several sys- tems (biological and nonbiological) have been evaluated. Nonbiological devices such as fractionated plasma separation and adsorption (Prometheus) and molecular adsorbent recircu- lating system (MARS) have been shown to be effective in improving cholestasis and severe hepatic encephalopathy in ACLF. This is attrib- utable to removal of protein-bound toxins via albumin. The devices have acceptable safety and tolerability profiles in ACLF and ALF, but randomized controlled trial data have failed to show an improve- ment in survival. Interestingly, one study found that downgrading the MELD score (to <30) in ACLF using an artificial liver support system as bridging therapy improved outcomes in the responders to levels similar to those who underwent primary liver transplantation. Biological devices that incorporate hepatic cells in bioreactors are also under development. Recent data from pilot studies suggested improvement in survival rates in some groups of patients with ACLF, but their effects on patient survival in randomized controlled trials are still unknown. The HepatAssist device which utilizes porcine hepatocytes has been studied in ALF but is yet to show a survival advantage in clinical trials. Liver transplantation Liver transplantation remains the only curative treatment for ACLF in patients with failed medical treatment. Good 5-year transplant survival data have been observed in patients with prior ACLF (74–90%), even with a high MELD score. Outcomes with deceased circulatory death organs and live-donor organs were found to be equivalent in this context. The Asian Pacific Association for the Study of the Liver guidelines state that ACLF patients with a MELD score higher than 30 should be considered for urgent transplant- ation. Noncardiorespiratory organ failure is not a contraindication to transplantation. While much progress has been made defining patient outcome with ACLF using the CLIF-C ACLFs, this system has not been specif- ically applied or validated in a post-transplantation cohort to inform listing criteria for ACLF. There is no validated criteria and scoring system for early and correct identification of patients with ACLF who would benefit from early liver transplantation. While there are many predictors of mortality, there are no reliable predictors of re- versibility of ACLF, hence there is an urgent need to identify such variables to facilitate early liver transplantation in patients

likely to benefit from it. The King’s College criteria for transplant listing of ALF were first described in 1989, incorporating adverse prognostic determinants identified from a retrospective analysis of a single-centre cohort of 588 patients over 22 years (Table 15.22.5.7). Separate criteria were described for paracetamol and nonparacetamol-induced ALF due to the different performance characteristics of parameters correlating with prognosis in the two aetiologies. Current criteria include factors influencing hepatic regeneration (age, poor prognostic aetiologies such as drug-induced or seronega- tive ALF) together with conventional markers of hepatocellular function such as INR and bilirubin. The criteria are weighted to- wards encephalopathy, reflective of their key influence on prog- nosis. The inclusion of pH reflects not only hepatocellular but also multiorgan failure and, more recently, lactate has been incorporated into the criteria and is of particular prognostic use in paracetamol- induced ALF. A particular emphasis is laid on the course of enceph- alopathy and multiorgan failure. In nonparacetamol-induced ALF, prognostic criteria reflect a greater contribution of hepatic regener- ation on outcome. Subsequent studies have identified that while King’s College criteria have good positive predictive values, negative predictive values are poorer (particularly in the nonparacetamol group), sug- gesting that patients who do not meet them may still have a signifi- cant chance of dying. While they continue to be widely used, other scoring systems have been evaluated (including MELD, SOFA, and APACHE II scores) and in some studies have been shown to be su- perior to the King’s College criteria. In practice, the best method of assessment is a dynamic one, with daily monitoring of prognostic- ally important parameters.
Table 15.22.5.7 King’s College criteria Paracetamol- induced ALF Arterial pH <7.3 (regardless of presence of hepatic encephalopathy) Or all 3 of the following: INR >6.5 Creatinine >300µmol/L Hepatic encephalopathy grade III–IV Lactate >3.5 (4 h after resuscitation) or >3
(12 h after resuscitation) Nonparacetamol- induced ALF INR >6.5 (regardless of presence of hepatic encephalopathy) Or 3 of 5 the following (regardless of presence of hepatic encephalopathy): Age <10 or >40 years Bilirubin >300µmol/L Coagulation: INR >3.5 Duration of jaundice to encephalopathy >7 days Aetiology: indeterminate, drug-induced

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