overall survival was 94% in the treated group vs 69% in those who did not receive HVPE. After HVPE, coagulopathy, bilirubin, and ammonia levels were improved (96). However, there remains concern regarding its applicability across the varying etiologies of ALF (95).

Artificial liver support systems deserve special mention in the discussion of management of ALF. There is great interest in support devices that can be a bridge to transplant or liver recovery. There are 2 types of extracorporeal liver support devices: artificial liver support and bioartificial liver support. Currently, none have received US marketing approval from the US Food and Drug Administration (FDA) but are available for investigational or compassionate use. The best-known artificial systems are plasma exchange and those based on albumin dialysis, the Molecular Adsorbent Recirculating System, the Single-Pass Albumin Dialysis system, and Fractionated Plasma Separation and Adsorption system FPSA (FPSA; Prometheus). Martinez et al (97) presented efficacy data that found a lack of evidence to support any particular system. In the only randomized clinical trial of 102 patients, there was improved 6-month survival only in the APAP-induced ALF group (98).

Key concept

- There is insufficient evidence to recommend for or against the routine use of HVPE or artificial/bioartificial liver support devices in patients with ALF.

ETIOLOGY-SPECIFIC MANAGEMENT

In addition to the general management of the patient described earlier, the clinician needs to be aware of time-sensitive, etiology-specific interventions that should be instituted (Table 10).

Table 10. Etiology-specific management

Recommended treatment based on etiology of Acute Liver Failure	
Etiology	**Treatment**
Acetaminophen	IV protocol 300 mg/kg total dose • 1st bag = 150 mg/kg/loading dose over 1 hr • 2nd bag = 50 mg/kg over 4 hr = 12.5 mg/kg/h • 3rd bag = 100 mg/kg over 16 hr = 6.25 mg/kg/h Extended IV protocol (Fontana 2008) • 1st bag = 50 mg/kg over 4 hr • 2nd bag = 125 mg/kg over 19 hr • Remaining bag = 100 mg/kg over 24 hr × 2 d or until INR <1.5 Oral protocol 72 hr 1,330 mg/kg total dose • Loading dose 140 mg/kg = 35/mg/kg/hr (for 4 hr) • Maintenance doses 70 mg/kg every 4 hr × 17 doses (for 68 hr) = 17.5 mg/kg/h
Drug-induced liver injury	• Discontinue offending agent • Consider NAC for early coma grade • Corticosteroids for those with hypersensitivity or autoimmune features
Hepatitis B	Nucleoside analog (e.g., Entecavir, tenofovir)
HSV or VZV hepatitis	IV Acyclovir
CMV hepatitis	IV ganciclovir
Mushroom poisoning	• IV silibinin • IV penicillin
Wilson disease	• Continuous hemofiltration • Plasma exchange
Autoimmune hepatitis	IV corticosteroids
HELLP syndrome/ AFLP	• Prompt delivery of fetus • Supportive care
Budd-Chiari syndrome	• Anticoagulation with low-molecular weight heparin • Portal decompression with TIPS • Revascularization with angioplasty or stent

AFLP, acute fatty liver of pregnancy; ALF, acute liver failure; CMV, cytomegalovirus; HELLP, hemolysis, elevated liver enzymes, low platelets; HSV, herpes simplex virus; INR, international normalized ratio; IV, intravenous; NAC, *N*-acetylcysteine; VZV, varicella zoster virus.

Drug-induced liver injury

Acetaminophen hepatotoxicity. The analgesic-antipyretic agent acetaminophen (paracetamol; APAP) has become ubiquitous to nearly every household across the world. Although safe at the usual therapeutic dosage of up to 4,000 mg every 24 hours, the drug has emerged as the leading cause of DILI and ALF in the United States and many western countries (99,100). APAP-induced ALF may occur after a single intentional overdose of greater than 10–15 g, usually as part of a suicide attempt. Unintentional overdoses also occur with ingestion of large quantities (>10 g) over several days, generally for the treatment of acute or chronic illness and often involve multiple APAP-containing products. Fasting or ingestion of alcohol may further contribute to toxicity, even at the use of recommended dosages (99,100).

Acetaminophen hepatotoxicity occurs in a dose-dependent fashion. High doses overwhelm favorable sulfation and glucuronidation metabolism pathways. APAP is then shunted toward cytochrome P450-mediated oxidase pathways resulting in the formation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI reacts with cellular proteins to NAPQI-protein adducts that induce oxidative hepatocyte injury and inflammatory processes leading to hepatic necrosis (99,100). APAP levels may be undetectable at presentation, and the detection of NAPQI-protein adducts may aid in the identification of APAP-induced liver injury when they become clinically available (101,102).

Patients with APAP-induced ALF may be asymptomatic or have nonspecific, constitutional symptoms on initial presentation, with relatively rapid progression to liver failure within 72–96 hours after toxic ingestion. Laboratory studies characteristically show a predominantly hepatocellular pattern of liver injury with marked transaminase elevations often exceeding 3,000 U/L with coagulopathy and relatively mild hyperbilirubinemia.

Most patients with APAP-induced ALF will recover with aggressive medical management, particularly when an overdose has been identified early and treatment initiated promptly. However, APAP-induced ALF is associated with an approximately 28% mortality rate, and up to a third of patients will require LT (103).

Management of acetaminophen hepatotoxicity. Patients with suspected APAP hepatotoxicity should receive immediate intervention. Early gastric decontamination with 1–2 g/kg of single-dose activated charcoal is effective if administered within the first 4 hours after ingestion (104). There are data to support administration after 4 hours with improved outcomes especially when coadministered with *N*-acetylcysteine (NAC) (105,106). Use of activated charcoal must take into consideration the