32 Bridging Therapies in Acute and Acute on Chronic Liver Failure

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32.1 Introduction

Liver is a multifunctional organ that plays crucial role in digestive, immune, metabolic, synthetic and excretory, and functions of the body [1]. Although the liver's functional reserve and regenerative capacity are great, these could be hindered in the face of severe acute liver injury. Rationale of bridging therapies is to support these multiple functions for a transient period as shown in Fig. 32.1.

Liver failure can develop as acute liver failure (ALF) in the absence of pre-existing liver disease, ACLF of known or unknown underlying chronic liver disease, or a chronic decompensation of an end-stage liver disease. ACLF should be clinically distinguished from ALF and decompensated liver disease. AASLD defines ALF as "acute hepatic injury characterized by evidence of coagulopathy, usually INR ≥1.5, and any degree of encephalopathy in a patient without pre-existing cirrhosis and with an illness of <26

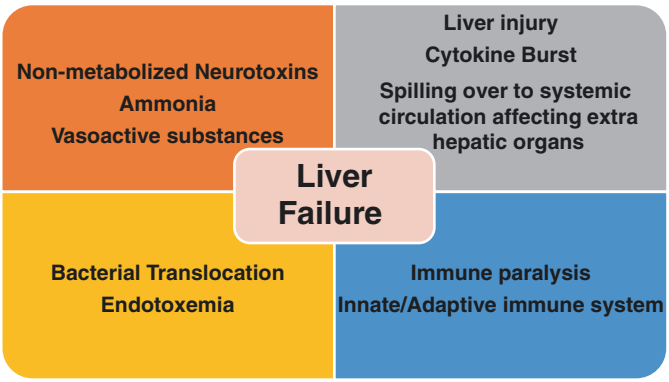

Fig. 32.1 Pleiotropic functions of liver and rationale of using bridging therapies in liver failure

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weeks' duration" [2]. Acute-on-chronic liver failure (ACLF) may occur either in decompensated or in compensated cirrhosis after an acute insult and is associated with organ failures and high short-term (28-day) mortality. ACLF has been defined differently by different consortia.

32.2 Bridging Therapies

The aim of bridging therapies is to provide adequate liver function and maintain the patient well enough until recovery of native liver function occurs (bridge-to-recovery) or until a graft is found (bridge-to-transplant). Bridging therapies can be broadly classified into two categories: (1) artificial liver support system (ALSS); (2) experimental therapies like regenerative and cell-based therapies. The artificial liver support system (ALSS) includes: (a) therapeutic plasma exchange, (b) artificial liver support, and (c) bioartificial liver support. The key concept is to remove harmful toxins, support the liver for spontaneous regeneration, and reduce the ongoing inflammatory injury.

32.3 Therapeutic Plasma Exchange (TPE)

The removal of patient's plasma and replacing it with plasma from a donor using an extracorporeal device refers to therapeutic plasma exchange (TPE). This has been found to be a very effective method of attaining blood purification in liver failure patients [3]. This increases hepatic blood flow and decreases blood ammonia levels. The TPE in addition also has the advantage of providing deficient clotting factors and albumin in these patients. TPE can cause hypocalcemia, metabolic acidosis, pulmonary and cerebral complications. Nevertheless, TPE continues to be one of the most frequently used methods of liver support for patients with acute hepatic failure.

Larsen et al. [4] in 2016 described the role of high-volume plasma exchange (HVP), defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma in a RCT of 182 patients with ALF. Patients received either standard medical therapy (SMT; 90 patients) or SMT plus HVP for 3 days (92 patients). It was shown that treatment with HVP improves outcome in patients with ALF by increasing liver transplant-free survival. This was attributable to attenuation of innate immune activation and amelioration of multi-organ dysfunction.

32.4 Liver Support System/Assist Devices

The liver assist devices can be classified into two major groups: artificial liver support devices and bioartificial liver support devices [5]. Artificial liver support devices are non-cell-based devices that mainly carry out the function of blood detoxification and blood purification. Human blood toxic substances can be classified into water soluble (ammonia, creatinine, interleukins (ILs), etc.) or protein bound (bilirubin, benzodiazepines, nitric oxide, etc.). Conventional techniques such as hemodialysis or hemofiltration remove only the water-soluble toxins. The protein-bound toxins can be removed only by addition of albumin to the dialysate or the use of large-pore filters [6].

Bioartificial liver support devices are cell-based liver support devices. They have a cellular component such as primary hepatocytes or hepatic cell lines. In majority of these devices, the hepatic cell lines are derived from porcine hepatocytes or from tumor cell line or harvested from organs that are deemed unsuitable for transplant. The former two cell lines raise safety concerns regarding infection and malignancy transmission. Human hepatocytes harvested from organs are in scarcity and stem cell research holds a promising future in this regard. The cellular components in these devices are intended to replace the important liver functions such as synthesis, detoxification, biotransformation, and excretion (Fig. 32.2).

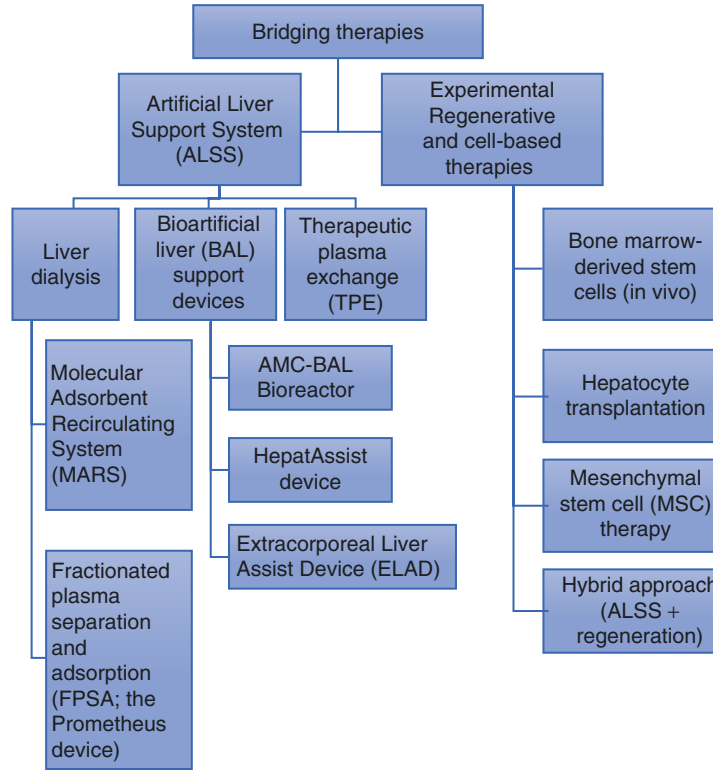

Fig. 32.2 Types of bridging therapies

32.5 Molecular Adsorbent Recirculating/Recycling System

Molecular adsorbent recirculating system (MARS) combines conventional dialysis against an albumin dialysate followed by a conventional dialysis procedure to remove the toxins from the dialysate. MARS system consists of two circuits: the blood circuit and the secondary circuit. The blood circuit passes the patient's blood over an albumin impermeable membrane through a high-flux dialyzer. The opposing side of the membrane contains 600 ml of 20% albumin in the secondary circuit. The toxins will diffuse across the membrane and bind to the albumin on the other side. The albumin in the secondary circuit is then cleared of toxins by anion exchange resin and activated charcoal columns [7].

MARS has been found to reduce bilirubin levels, encephalopathy, pruritus, and serum copper levels in Wilson's disease. Improvement in renal function, cerebral blood flow, and varied effects on intracranial pressure (ICP) have also been reported [8]. The overall effect of MARS on mortality seems inconclusive. MARS may be used to stabilize patients prior to transplantation and for allograft dysfunction after transplantation till the liver recovers. It may not improve survival without transplantation [9] (Fig. 32.3).

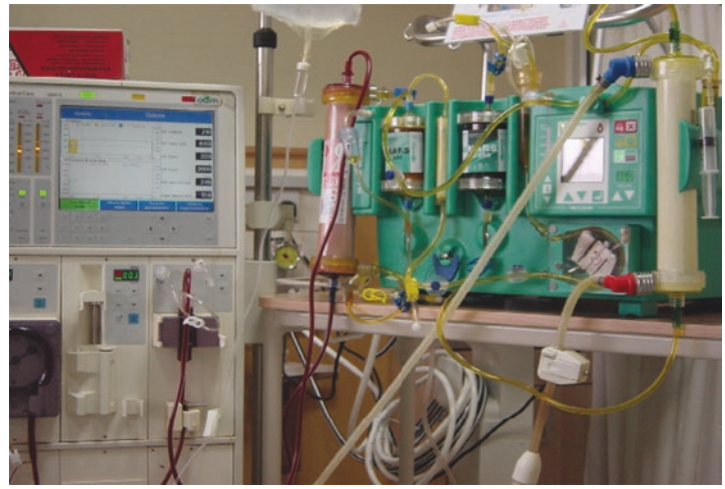

Fig. 32.3 Molecular adsorbent recirculating system

32.6 Fractionated Plasma Separation and Adsorption (Prometheus)

The Prometheus system uses purified blood without the use of exogenous albumin. In this system, the blood is passed over the AlbuFlow 250 kDa membrane which is permeable to albumin. The albumin-bound toxins pass through the albumin permeable membrane and the filtrate is passed through a column of neutral resin and anion exchange resin and returned to the patient. This removes the toxins from the albumin and is returned to the patient. The water-soluble, low molecular weight toxins are removed downstream with a high-flux hemodialysis [10]. It is postulated that patients treated with Prometheus would be detoxified much more effectively than those treated with MARS. However, the clinical experience with this system is limited and no definite conclusions can be made as of now [11].

In one study comparing MARS versus Prometheus in patients with alcoholic hepatitis or alcoholic cirrhosis, it was found that mean arterial pressure and systemic vascular resistance improved better with MARS in comparison to Prometheus. However, bleeding complications with Prometheus are rare and there might even be the need to use anticoagulation during the procedure [12] (Fig. 32.4).

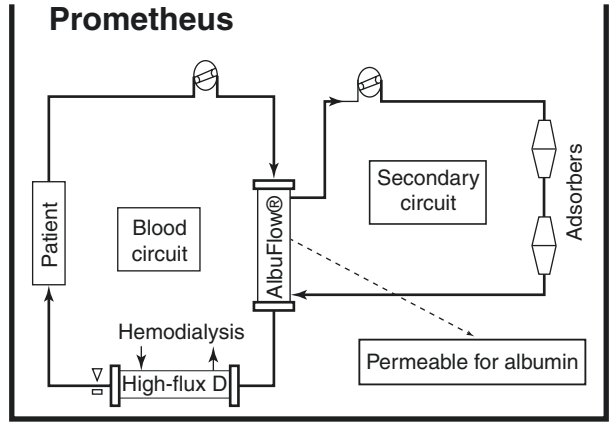

Fig. 32.4 Fractionated plasma separation and adsorption (Prometheus)

32.7 Single-Pass Albumin Dialysis

Single-pass albumin dialysis (SPAD) is a simple and inexpensive technique of blood purification where additional circuits are not needed. It is a simple veno-venous hemodialysis where the dialysate solution contains low concentration albumin (4.4%). The albumin toxin complexes are then discarded and not recycled. A single randomized controlled study has shown that MARS and SPAD were equally effective in reducing plasma bilirubin levels [13]. However, only MARS affected other paraclinical parameters such as serum bile acids, albumin-binding capacity, creatinine, and urea levels. Preliminary clinical experience shows that SPAD has a promising future with its simplicity and low cost [14].

32.8 Extracorporeal Liver Assist Device

Extracorporeal liver assist device (ELAD) is based on hepatoblastoma C3A cell line. This device was initially evaluated in King's College Hospital in London. The original device was assessed in 24 patients with acute liver failure. The device consisted of exposing the patient's whole blood for duration of about 3–168 h to the hepatocytes. The functioning cell mass was estimated to be about 80–90 g based on the rate of oxygen consumption of the device. The study, however, proved inconclusive in terms of survival rate [15].

Subsequently, modifications were done in the device to improve its efficiency and properties. These include increasing the functional cell mass to 300–400 g in adults, introducing oxygenation and nutritional components in the circuit to improve cell viability, whole blood exposure was replaced with ultra-filtrate exposure, and increasing pore size of the membrane to facilitate free movement of molecules in the device. This improved device was then evaluated in 25 patients who fulfilled criteria for liver transplant. The ELAD-treated and control patients had a similar 30-day survival rate. However, among the 19 patients who were listed for transplant, the ELAD-treated patients had a much higher 30-day survival rate of 81% in comparison to 56% in the control group [16].

32.9 Experimental Regenerative and Cell-based Therapies

Liver has the unique capability for regeneration; in fact, the liver failure is the failure of regeneration. This impressive regenerative power of liver is compromised in ACLF. The definitive therapy,

i.e., liver transplant is confounded by lack of donor, resource, expertise, and high medical costs. Cellular therapies such as hepatocyte, stem cell transplantation, and non-cellular therapies using growth factors for liver regeneration augmentation, and Bone Marrow Stem Cell (BMSC) mobilization are emerging alternatives.

32.10 Bone Marrow-derived Stem Cells (In Vivo)

It is a simple and novel method of mobilizing BMSCs using growth factor. Patients receiving Granulocyte-Colony Stimulating Factor (G-CSF) treatment showed significant improvement in survival as well as reduction in MELD and SOFA scores as well as the complications such as HRS, HE, and sepsis. It is supported by studies in HBV-ACLF cohort as well as severe alcoholic hepatitis with ACLF. The selection of patient for considering this therapy is crucial. Garg et al. [17] considered all patients of ACLF but mostly ethanol-related ACLF, and in similar way Singh et al. [18] considered patients, whereas Duan et al. [19] selectively considered HBV-reactivation cohort. The therapy is continued with a close monitoring for organ failure and worsening of clinical parameters, which needs early consideration for transplant.

Combination of growth factors, i.e., G-CSF and darbepoetin alfa has been shown to be effective in patients of decompensated cirrhosis and may be an attractive option to be extrapolated into ACLF cohort [20].

32.11 Hepatocyte Transplantation

Clinical use of adult hepatocyte and fetal hepatic progenitor cells have shown transient clinical benefit in metabolic liver diseases and ALF but with very limited benefits in CLD and ACLF [21]. Recently, Wang et al. [22] have shown significant improvement in the survival of ACLF patients with intrasplenic hepatocyte transplantation.

32.12 Mesenchymal Stem Cell (MSC) Therapy

Use of autologous BM-MSC in ACLF is not possible due to the time constraint in sicker patients to derive any benefit. A solitary study using umbilical cord-derived MSC in ACLF has demonstrated decrease in MELD scores, increased platelet counts and prothrombin activity with survival benefit [23].

Hybrid Approach (ALSS + Regeneration) Combination of ALSS to remove toxins and use of G-CSF to augment liver regeneration is an innovative concept and was published as a single case report. This could be a new approach in managing these patients. G-CSF therapy should be considered in a potential liver transplant candidate when transplantation is not feasible. It helps in prevention of sepsis and organ failure besides augmenting hepatic regeneration in a failing liver. It is not suitable for all patient groups and should be avoided in ACLF patients in the presence of AKI, ongoing sepsis, macrophage activation syndrome or hemolysis, hepato cellular carcinoma (HCC), portal vein thrombosis, multi-organ dysfunction, grade 3 or 4 HE (as per West Haven criteria) [24].

32.13 Role in ALF

The aim of bridging therapies in ALF is to provide adequate liver function and maintain the patient well enough until recovery of native liver function occurs or until a graft is found. Summary of important studies has been given in Table 32.1.

Table 32.1 Studies using ALSS in ALF

Study	No of patients	Device	Biochemical improvement	Cardio-vascular improvement	CNS improvement	Survival
Schmidt et al. [25]	13	MARS	Yes	Yes	N/A	No
El Banayosy et al. [26]	27	MARS	No	N/A	N/A	Yes (50% vs 32%)
Kantola et al. [27]	159	MARS	Yes	N/A	Yes	No
Saliba et al. [28]	102	MARS	Yes	N/A	N/A	No
Larsen et al. [4]	182	HVP	Yes	Yes	Yes	Yes
Gerth et al. [29]	73	MARS	Yes	N/A	N/A	No
Komardina et al. [30]	39	Prometheus	Yes	Yes	N/A	No

32.14 Role in ACLF

ACLF is a distinct clinical syndrome characterized by progressive liver failure due to an acute hepatic injury on an underlying chronic liver disease. As per EASL-CLIF Consortium [31], ACLF is defined as acute decompensation (AD) of cirrhosis associated with organ failure (OF) and high short-term mortality (28-day mortality ≥15%).

As per APASL [32], ACLF is defined as an acute hepatic insult manifesting as jaundice (serum bilirubin level of ≥5 mg/dL) and coagulopathy (INR of ≥1.5 or prothrombin activity of <40%), complicated within 4 weeks by ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease (including cirrhosis) and is associated with high 28-day mortality. Important studies of ALSS in patients with ACLF have been summarized in Table 32.2. When to consider bridging therapies in ACLF has been shown in Fig. 32.3.

Table 32.2 Studies using ALSS in ACLF

Study	No of patients	Device	Biochemical improvement	Cardio-vascular improvement	CNS improvement	Survival
Hessel et al. [33]	149	MARS	N/A	N/A	N/A	Yes
Kribben et al. [34]	145	Prometheus	Yes	N/A	N/A	Yes
Bañares et al. [35]	156	MARS	Yes	Yes	Yes	No
Xu et al. [36]	171	TPE	Yes	Yes	Yes	No
Gerth et al. [37]	101	MARS	Yes	N/A	Yes	Yes

32.15 Conclusion

Severe liver failure is associated with high mortality despite optimal medical treatment. Though, liver transplantation has emerged as a salvage therapy, many patients unfortunately die while waiting for transplant. Therefore, there is a clear need fora liver support system to provide a "bridge" to till recovery or transplant. Future large scale randomized trials are necessary before making recommendations regarding use of Bridge therapies in these high-risk group of patients with ALF and ACLF (Fig. 32.5).

Key Points

- ACLF has a burden of failing organ acutely as well as chronic liver failure
- Large number of ACLF have no identifiable trigger
- Bridging therapy can be bridge-to-recovery
- Bridging therapy could be bridging till a suitable donor liver is available leading to transplantation
- High-volume plasma exchange has limited role in ACLF
- Liver dialysis by MARS or Prometheus has a role in ACLF management
- Bioartificial liver support devices—AMC-BAL, Hepat Assist device, ELAD are being investigated
- Stem cells based therapies are in experimental stage at present.

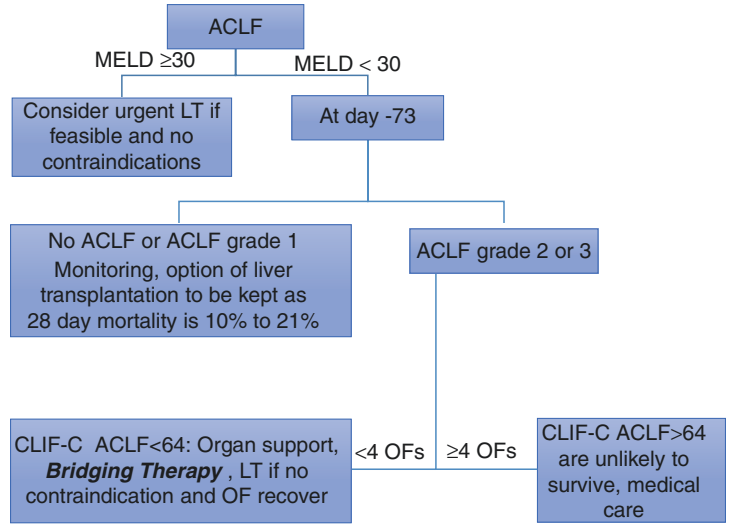

Fig. 32.5 Scope of bridging therapy in ACLF, modified from Choudhary et al. [38]

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