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Acute liver failure: Bridging to transplant or recovery – are we there yet?

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1. Introduction

The main goal in the management of patients with acute liver failure (ALF) is to provide support until the liver regenerates sufficiently to restore normal function or, if this is not achievable, until a graft becomes available. Despite advances, overall mortality remains high. To date, only liver transplantation has been convincingly

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Abbreviations: ALF, acute liver failure; ACLF, acute on chronic liver failure; OLT, orthotopic liver transplant; ALT, suxiliary liver transplant; APOLT, auxiliary partial orthotopic liver transplant; HALT, heterotopic auxiliary liver transplant; BAL, bioartificial liver; MARS, Molecular Adsorbents Recirculating System; HT, hepatocyte transplantation; PNF, primary graft non-function.

shown to improve outcome in ALF [1]. However, orthotopic liver transplant (OLT) in setting of ALF is not without its problems: a significant number of patients may die while waiting for graft [2]. Furthermore, life after transplantation is reduced both in length [3] and quality, due, largely to the consequences of immunosuppression. After transplantation, the patient's quality of life, while usually excellent, rarely reaches the level seen prior to the onset of liver failure and this, together with the inevitable lack of patient education, may lead to problems of adjustment. In contrast, where recovery does occur, the liver usually returns to normal structure and function and the patient returns to the quality and length of life that was present before the onset of liver failure. Balancing the risks and benefits of transplantation is difficult: prognostic models have only limited sensitivity and specificity [2,4].

There has, therefore, been considerable interest in developing techniques that provide liver support during the acute phase of liver failure, that will act either as a bridge to transplant (supporting the patient through the acute illness and allow time to find suitable donor organ before the onset of complications that make the procedure futile) or as a bridge to recovery (allowing the native liver to recover so liver replacement is unnecessary). Demonstrating the benefit of such techniques is difficult and best assessed in the setting of controlled clinical trials but undertaking such trials in the context of ALF is a formidable challenge: trials need to be adequately powered with clearly defined inclusion criteria; survival (with or without liver replacement) should be the primary end point [5]. Generating adequate numbers of defined cohorts of patients, the variable impact of liver transplantation and the level of funding required make large multi-centre studies very difficult to establish. Surrogate markers of survival are often used in assessing the impact of liver support mechanisms but these have not been validated and must be interpreted with caution.

2. 'Bridging Options'

The aim of bridging devices 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. The many and diverse functions of the liver (metabolic, immunologic, physiologic) make the task of developing simple devices a major challenge: the effects of the 'toxic liver' itself also require consideration.

Bridging devices can be classed into four categories: (1) auxiliary transplant; (2) liver support devices (biological and non-biological); (3) hepatocyte transplantation; (4) innovative/experimental techniques.

The role of auxiliary transplantation is covered in the article by Dr. Jaeck in this forum and will not be discussed any further here.

3. Liver support devices

Extracorporeal liver support devices have been attempted for more than 40 years. These devices can broadly be grouped as bioartificial and artificial or non-biological devices. While biological devices aim to replace all the essential functions of the liver, the artificial devices provide mainly detoxification [6,7].

3.1. Bioartificial devices

Bioartificial liver (BAL) devices typically incorporate isolated cultured hepatocytes in the bioreactors. The important issues are choice of cellular component, stabilization of hepatocyte phenotype, the amount and efficacy of the biomass, the design of bioreactor and its safety [7]. Various bioartificial devices used in clinical trials and their characteristics are summarised in Table 1.

In the normal liver, the hepatocytes account for about 70% of the cell mass: other cell types are, however, important not only to support and maintain hepatocellular function but also have their own functional roles. Thus, devices that consist of just hepatocytes may not be adequate to replace hepatic function. Furthermore, the mass of hepatocytes required to sustain life is unknown: in the allograft, a 0.8–1% weight/body weight ratio is considered a minimum to prevent small-for-size syndrome [8]; but the minimum mass of hepatocytes required for bioartificial devices is not established. Most studies suggest that 150–450 g (10^{10} hepatocytes) is required to support the failing liver [7].

The ideal hepatocellular component is human hepatocyte which are of limited availability and cannot be stored for long term use as the cells become phenotypically

Table 1
Summary of characteristics of bioartificial liver support systems

Bioartificial device	Cell type	Cell amount	Detoxification module
Demetriou's Hepatassist Bioartificial Liver (BAL) [9]	Porcine (cryopreserved)	$5–7 \times 10^9$	Charcoal column pre-bioreactor
Amsterdam Medical Centre Bioartificial Liver (AMC-BAL) [10]	Porcine (fresh isolated)	10×10^9	No
Extracorporeal liver assist device (ELAD) [12]	Human, tumour derived (cultured C3A)	200–400 g	No
Modular Extracorporeal Liver Support (MELS) [13]	Human (fresh isolated)	Upto 600 g	Single pass albumen dialysis
Bioartificial liver support system (BLSS) [47]	Porcine (fresh isolated)	70–120 g	No