

Prediction, prevention and management of postresection liver failure

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Background: Postresection liver failure (PLF) is the major cause of death following liver resection. However, there is no unified definition, the pathophysiology is understood poorly and there are few controlled trials to optimize its management. The aim of this review article is to present strategies to predict, prevent and manage PLF.

Methods: The Web of Science, MEDLINE, PubMed, Google Scholar and Cochrane Library databases were searched for studies using the terms 'liver resection', 'partial hepatectomy', 'liver dysfunction' and 'liver failure' for relevant studies from the 15 years preceding May 2011. Key papers published more than 15 years ago were included if more recent data were not available. Papers published in languages other than English were excluded.

Results: The incidence of PLF ranges from 0 to 13 per cent. The absence of a unified definition prevents direct comparison between studies. The major risk factors are the extent of resection and the presence of underlying parenchymal disease. Small-for-size syndrome, sepsis and ischaemia–reperfusion injury are key mechanisms in the pathophysiology of PLF. Jaundice is the most sensitive predictor of outcome. An evidence-based approach to the prevention and management of PLF is presented.

Conclusion: PLF is the major cause of morbidity and mortality after liver resection. There is a need for a unified definition and improved strategies to treat it.

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Introduction

Liver resection is performed as first-line treatment for certain types of benign and malignant liver tumours and for living donor liver transplantation. In the majority of patients this can be performed safely with low morbidity and mortality, but in a subgroup of patients with impaired regenerative capacity, or in those undergoing extended resection, the risk of postresection liver failure (PLF) is significant.

PLF is a devastating complication that is resource intensive¹ and carries with it considerable morbidity and mortality^{2–4}. The increasing prevalence of parenchymal liver diseases (cirrhosis⁵, non-alcoholic fatty liver disease⁶ (NAFLD) and chemotherapy-induced liver injury⁷), together with a push to extend the indications for liver resection⁸, means that more patients are at risk of PLF.

The pathophysiology of PLF remains poorly understood. Whilst there are parallels with the small-for-size

syndrome (SFSS) that occurs in a small graft after partial liver transplantation, the processes have fundamental differences, and other factors including sepsis and ischaemia–reperfusion injury (IRI) may precipitate or exacerbate PLF. Currently there are few treatments available for PLF and most strategies are derived from studies of acute liver failure (ALF) secondary to toxic rather than surgical liver injury. The aim of this review is to present strategies to identify those at risk of PLF, to enable optimization of patients before liver resection, to develop an algorithm for the management of PLF and to highlight areas for future research.

Methods

The Web of Science, MEDLINE, PubMed, Google Scholar and Cochrane Library databases were searched

using the terms ‘liver resection’, ‘partial hepatectomy’, ‘liver dysfunction’ and ‘liver failure’ in combination with the Boolean operators AND, OR and NOT for relevant studies from the 15 years preceding May 2011. The bibliography of extracted papers was also searched for relevant articles. Selection of papers for inclusion used the following criteria, in order of importance: randomized controlled trials, non-randomized case series, experimental data, case reports, and consensus statements of experts in the field. Three review articles on PLF were identified^{2–4}. Key older papers were included if more recent data were not available. Papers published in languages other than English were excluded.

Epidemiology

The mortality rate associated with liver resection used to be in excess of 10 per cent⁹. Improved understanding of the segmental anatomy of the liver¹⁰, developments in surgical¹¹ and anaesthetic¹² techniques, centralization of liver resection services^{13,14} and patient selection¹⁵ have led to a dramatic reduction in the mortality rate, which now ranges between 0 and 5 per cent^{15–18}.

The absence of a universally accepted definition for PLF and the heterogeneity of patient populations limit direct comparison between studies, and the incidence of PLF ranges from 0 to 13 per cent^{15–28}. Where resections were undertaken in patients with underlying parenchymal disease (cirrhosis²⁴, steatosis²⁹ and cholestasis²²), rates of PLF increased further. PLF is the major cause of death following liver resection (60–100 per cent of all deaths^{23,25–28}), and 25 per cent of patients who die from PLF do so more than 30 days after resection, highlighting the importance of assessing long-term mortality when comparing series²⁷.

Definition

PLF is characterized by jaundice, coagulopathy and hepatic encephalopathy^{26,28} (Table 1). A common definition is

based on a serum bilirubin concentration above 50 µmol/l (3 mg/dl) and a prothrombin time (PT) less than 50 per cent of baseline (international normalized ratio (INR) above 1.7) on postoperative day 5²⁸. Although this definition predicts death and other complications in up to 70 per cent of patients²⁷, it is limited because it cannot be applied before day 5 and does not stratify for severity. Another scoring system uses serum bilirubin, PT, serum lactate and encephalopathy to grade the severity of postresection liver dysfunction²⁶. Alternative systems might incorporate extent of resection³⁰, presence of parenchymal disease or biomarkers of liver function³.

Pathophysiology

For healthy regeneration of the liver remnant, hepatocytes and non-parenchymal cells must be present in adequate numbers, and retain their functional and regenerative capacity. The liver parenchyma must be able to accommodate the haemodynamic changes following liver resection without developing venous congestion^{31,32}. In addition, factors that promote ongoing parenchymal damage after liver resection, notably SFSS, sepsis and IRI must be absent (Fig. 1).

SFSS may occur after major resection or partial liver transplantation when the liver remnant or graft is too small. Of the many mechanisms that have been proposed³³, ‘hyperperfusion theory’ is the most widely accepted. This states that the surge in sinusoidal blood flow following reduction in parenchymal volume leads to a cycle of sinusoidal dilatation, shear stress, haemorrhagic infiltration, centrilobular necrosis, prolonged cholestasis, impaired synthetic function and inhibition of cell proliferation^{33,34}.

The key difference between SFSS after transplantation and that following major resection is the threshold amount of liver tissue below which SFSS develops. In liver resection a liver : bodyweight ratio of 0.6 per cent is usually adequate, whereas a ratio of at least 0.8 per cent is required after

Table 1 Scoring systems for postresection liver failure

Scoring system	Method		
Balzan criteria for PLF ²⁸	Bilirubin > 50 µmol/l (3 mg/dl) + PT < 50% baseline (INR > 1.7) on postoperative day 5		
Schindl score* for PLF ²⁶	0 points	1 point	2 points
Total serum bilirubin (µmol/l (mg/dl))	≤ 20 (≤ 1.2)	21–60 (1.3–3.6)	> 60 (> 3.6)
PT (seconds above normal)	< 4	4–6	> 6
Serum lactate (mmol/l)	≤ 1.5	1.6–3.5	> 3.5
Encephalopathy grade	None	1 or 2	3 or 4

*Severity of liver dysfunction: 0, none; 1–2, mild; 3–4, moderate; > 4, severe. PLF, postresection liver failure; PT, prothrombin time; INR, international normalized ratio.

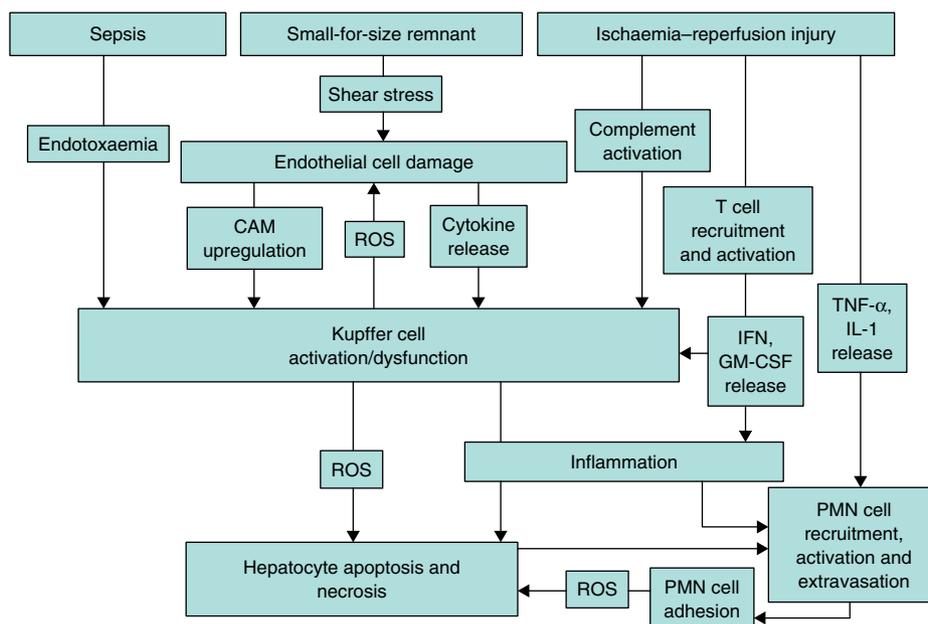


Fig. 1 Schematic illustrating the pathophysiology of sepsis, small-for-size syndrome and ischaemia–reperfusion injury, and their role in ongoing parenchymal loss following liver resection. CAM, cellular adhesion molecule; ROS, reactive oxygen species; IFN, interferon; GM-CSF, granulocyte–macrophage colony-stimulating factor; TNF, tumour necrosis factor; IL, interleukin; PMN, polymorphonuclear

partial liver transplantation. The reason for this is not known, but it may relate to portal hypertension, ischaemia, graft denervation and immunosuppression³³.

Rates of sepsis are as high as 50 per cent after major resection²⁶, and sepsis has the capacity to complicate or precipitate PLF. Following liver resection the population of Kupffer cells is reduced, resulting in an impaired innate immune response and increased susceptibility to infection. A relative increase in endotoxin delivery to the liver remnant is beneficial as it leads to activation of Kupffer cells and initiation of regeneration³⁵. However, prolonged endotoxaemia leads to Kupffer cell dysfunction, impaired liver regeneration and hepatic necrosis^{36,37}.

IRI is the best characterized cause of ongoing parenchymal damage after liver resection. It may occur following vascular occlusion, after *ex vivo* hepatic resection and reimplantation, or as a consequence of haemorrhagic shock³⁸. After a period of ischaemia the complement cascade is activated, leading to Kupffer cell activation, generation of reactive oxygen species (ROS) and endothelial cell damage. During reperfusion a cycle of cell adhesion molecule upregulation, cytokine release, T cell and polymorphonuclear cell recruitment and activation is initiated, resulting in microvascular injury, Kupffer cell-mediated inflammation and hepatocyte death^{38,39}.

Prediction

Table 2 lists the major risk factors for the development of PLF. The extent of resection correlates most closely with rates of PLF and death; 80 per cent of deaths from PLF occur after resection of more than 50 per cent^{15,16,18–21,23–28} and the incidence of PLF increases with the number of segments resected²⁶. The incidence of PLF is less than 1 per cent in patients with no underlying parenchymal disease when one or two segments are resected, around 10 per cent when four segments are resected, and 30 per cent when five or more segments are resected²⁶.

There is consensus that a future liver remnant volume (FLRV) of 25 per cent is the safe limit for liver resection³³. Thus, patients with normal hepatic parenchyma, no risk factors for PLF and a predicted FLRV of more than 30 per cent should proceed to resection. Patients with parenchymal disease but no hepatic insufficiency or portal hypertension, minor functional impairment and with a predicted FLRV greater than 50 per cent may also proceed to resection⁴⁰. In patients outwith these criteria, volume manipulating strategies can be considered.

Preoperative radiological assessment and volumetry using computed tomography (CT) or magnetic resonance imaging (MRI) enables prediction of FLRV and

Table 2 Risk factors for postresection liver failure

Operative factors	Patient factors
Extent of resection (> 4 segments)	Parenchymal disease: cirrhosis, non-alcoholic fatty liver disease, chemotherapy-induced liver injury (steatohepatitis and sinusoidal injury) and cholestasis
Use of vascular occlusive techniques	Age > 65 years
<i>Ex vivo</i> hepatic resection and reimplantation	Diabetes mellitus
Excessive blood loss and transfusion	Nutrition
Vascular or biliary reconstruction	Male sex

identification of underlying parenchymal disease^{41–43}. CT-guided three-dimensional reconstructions allow visualization of the hepatic venous outflow, improve tumour localization and facilitate operation planning⁴⁴. The sensitivity of volumetric assessment can be further enhanced by combining it with a body surface area or bodyweight calculation⁴⁵.

The use of vascular occlusive techniques and significant intraoperative blood loss can exacerbate the level of dysfunction. Vascular occlusive techniques induce ischaemia in the liver remnant⁴⁶. These effects are greatest following total vascular exclusion (inflow + outflow occlusion) but also occur after prolonged intermittent inflow occlusion^{47,48}.

Intraoperative blood loss (more than 1–1.2 litres) and the need for blood transfusion increase the risk of PLF and sepsis^{16,17,49}. This may relate to the immunosuppressive effects of blood transfusion⁵⁰ or the initiation of the inflammatory response that accompanies significant haemorrhage⁵¹.

Vascular reconstruction following *in situ en bloc* liver and inferior vena cava resection^{52,53} or *ex vivo* liver resection⁵⁴, is associated with increased rates of PLF. *Ex vivo* resection and reimplantation is associated with an unacceptably high mortality rate. Biliary reconstruction is associated with increased morbidity and mortality after liver resection but does not independently predict PLF^{16,22,55}.

Underlying parenchymal disease reduces the functional and regenerative capacity of the liver remnant. In patients with cirrhosis but no functional impairment or portal hypertension, resection of up to 50 per cent is safe^{40,56}. In patients with Child–Pugh grade B or C disease, even small resections can result in PLF. The Barcelona Clinic Liver Cancer staging system is an important aid when planning treatment in cirrhotic patients with HCC⁵⁷. NAFLD represents a spectrum of disease ranging from steatosis to steatohepatitis (non-alcoholic steatohepatitis, NASH), fibrosis and cirrhosis⁵⁸. The grade of steatosis

correlates with rates of PLF and death following major resection^{29,59}.

Chemotherapy-induced liver injury is increasingly prevalent as more patients receive chemotherapy for colorectal liver metastases before liver resection. The liver injury varies according to the chemotherapeutic agents, duration of treatment and presence of pre-existing parenchymal disease. The two major patterns of liver injury are sinusoidal injury and chemotherapy-associated steatosis and steatohepatitis (CASH)⁷.

Sinusoidal injury is associated with oxaliplatin-based chemotherapy⁶⁰. It may be mediated by ROS damaging sinusoidal endothelial cells⁷. Sinusoidal injury reduces functional liver reserve and increases morbidity following major resection. It is common with prolonged oxaliplatin treatment and is partially reversible upon cessation of treatment⁶⁰.

Chemotherapy-associated steatosis and steatohepatitis are associated with 5-fluorouracil and irinotecan treatment respectively. In the case of irinotecan therapy, steatohepatitis is more common in obese patients⁶¹. CASH, like NASH, reduces the regenerative capacity of the liver remnant and increases rates of postresection liver dysfunction^{8,60,62,63}.

Cholestasis reduces hepatic metabolic⁶⁴ and regenerative⁶⁵ capacity, and increases rates of liver dysfunction after major resection²². Although preoperative biliary drainage (PBD) improves the remnant function, its routine use in jaundiced patients with malignant hilar obstruction is contentious as it does not confer a survival benefit and increases morbidity, primarily from septic complications⁶⁶. The role of PBD may, therefore, be limited to those requiring major resection with a predicted FLRV of less than 40 per cent, who require volume manipulation or have cholangitis^{67,68}.

Other patient-based factors that predict PLF are age, malnutrition, diabetes mellitus and male sex. Age is important because the regenerative capacity of liver tissue decreases with age⁶⁹. Malnutrition is associated with an altered immune response^{70,71} and a reduction in hepatocyte regenerative capacity, possibly due to disordered mitochondrial function⁷². Diabetes mellitus is associated with increased morbidity and mortality after liver resection⁷³. This may be due to immune dysfunction or because insulin absence or resistance reduces regenerative capacity³¹. PLF is more common in males^{27,42} as testosterone may have immune-inhibitory effects, predisposing to septic complications⁷⁴.

Routine preoperative biochemical measurements (albumin, PT, bilirubin aminotransferases, γ -glutamyl transferase and alkaline phosphatase) can provide indicators of hepatic dysfunction and may reflect ongoing parenchymal

damage or cholestasis, but do not independently predict PLF⁷⁵.

A wide range of tests has been developed to measure liver function⁷⁶. The most commonly used is the indocyanine green retention rate at 15 min (ICGR15)⁷⁷. When hepatic function is impaired, ICGR15 increases. If ICGR15 is less than 14 per cent in patients with cirrhosis, major hepatectomy is well tolerated; when ICGR15 exceeds 20 per cent major hepatectomy should be avoided. Patients with a rate between 14 and 20 per cent benefit from volume manipulation^{40,56}.

The increasing prevalence of NASH, CASH and sinusoidal injury has renewed interest in the preoperative assessment of liver parenchyma. Screening of high-risk patients (increased body mass index and those receiving preoperative irinotecan- or oxaliplatin-based chemotherapy) with liver biopsy before resection has been proposed⁷⁸. Significant parenchymal disease could then prompt volume manipulation, or prolong the interval to surgery to allow resolution of parenchymal disease or non-surgical treatments. An alternative approach would be to develop non-invasive serum⁷⁹ or imaging⁸⁰ biomarkers for steatohepatitis and sinusoidal injury.

In cirrhotic patients with early hepatocellular carcinoma (HCC)⁵⁷ and subclinical portal hypertension, resection may lead to decompensation. Preoperative hepatic venous pressure gradient (HVPG) measurement could detect these patients⁸¹. Although HVPG measurement remains the standard for identifying portal hypertension, a range of non-invasive techniques is in development⁸².

Prevention

Diabetes mellitus should be screened for and treated before surgery. Nutrition should be evaluated and consideration given to preoperative oral carbohydrate loading in order to reduce postoperative insulin resistance⁸³. There is no evidence to support delaying liver resection for a period of nutritional preoptimization, unless the patient is severely malnourished^{71,84,85}. Microbiological screening and eradication therapy for methicillin-resistant *Staphylococcus aureus* should be performed⁸⁶.

The risk of PLF may be reduced by strategies to increase parenchymal volume and protect against parenchymal damage. Hepatoprotective techniques are attractive, but evidence for their use is lacking.

Strategies available for volume manipulation (*Table 3*) include portal vein occlusion (PVO) and two-stage resection⁴⁰. PVO is usually performed percutaneously by transhepatic portal vein embolization, but may also be achieved by surgical ligation. PVO induces apoptosis

Table 3 Strategies for volume manipulation/preservation and hepatoprotection

Volume manipulation and preservation	Hepatoprotection
Portal vein occlusion (embolization/ligation)	Ischaemic preconditioning
Combination neoadjuvant chemotherapy regimens	Intermittent portal clamping/avoidance of vascular occlusion
Two-stage resection	Hypothermic liver preservation
Tumorectomy/ablation	

in the ipsilateral lobe, and proliferation and growth of the contralateral lobe⁸⁷. This increases the functional capacity of the liver remnant, limits the effects of hepatic hyperperfusion that may occur in a small-for-size remnant, and predicts the regenerative response in the future remnant. PVO can boost contralateral lobe volume by up to 20 per cent, with the peak in growth occurring within 2–4 weeks of treatment^{87,88}. Failure to proliferate after PVO can be used to select patients with impaired regenerative capacity in whom major resection would not be tolerated⁸⁸. The primary concern over PVO is that it may increase tumour growth owing to an ipsilateral surge in hepatic arterial flow^{89,90}. Neoadjuvant systemic⁸ and locoregional⁹¹ chemotherapeutic strategies can be used in combination with PVO to control tumour load before resection. In patients with a resectable bilobar tumour distribution, two-stage resection in combination with PVO and/or chemotherapeutic modalities can be considered. Tumorectomy (metastasectomy)⁹² or radiofrequency ablation^{92,93} can also be used to maximize FLRV, but may be associated with higher rates of disease recurrence⁹³.

In order to limit parenchymal damage and optimize regenerative capacity, a series of hepatoprotective measures may be employed (intermittent portal clamping, ischaemic preconditioning and hypothermic liver preservation) (*Table 3*). Total vascular occlusion should be avoided unless resection cannot be undertaken without it (for example a tumour at the cavohepatic intersection). If resection without vascular occlusion is not possible, inflow occlusion is preferable to total vascular exclusion. Intermittent portal clamping with intervals allowed for reperfusion⁴⁶ is preferred to continuous clamping, usually applying a 15-min clamp–5-min release regimen^{39,47,48}.

Ischaemic preconditioning increases tolerance to prolonged hepatic ischaemia and adenosine 5'-triphosphate depletion by exposing the parenchyma to short intervals of ischaemia and reperfusion intraoperatively before the resection³⁸. This downregulates IRI and results in less hepatic injury³⁹. Ischaemic preconditioning reduces the

histological effects of IRI, however, without improving clinical outcome⁹⁴.

Hypothermic liver preservation in conjunction with total vascular exclusion attenuates IRI. The future remnant is infused with a preservative fluid and surrounded by crushed ice to maintain the liver at 4°C. This approach is a useful adjunct to complex resections when total vascular exclusion is anticipated⁹⁵.

A range of pharmacological interventions to protect against IRI has been investigated³⁹. These strategies have demonstrated promising results in experimental models, but none has yet entered the clinical setting. In trials of prophylactic *N*-acetylcysteine to protect against PLF, no reduction in PLF or other complications was demonstrated, although the studies were inadequately powered to detect such differences⁹⁶.

Intraoperative Doppler ultrasonography has been used in combination with hepatic portal inflow modulation to detect and offset hyperperfusion in a small-for-size graft. A number of methods of inflow modulation have been described, including splenic artery ligation⁹⁷ and mesocaval shunting with ligation of the superior mesenteric vein⁹⁸. In experimental major liver resection, SFSS was prevented by hepatic inflow modulation⁹⁹. The role for inflow modulation at the time of major liver resection or as a salvage therapy in humans remains undefined.

There is growing interest in modulation of portal hypertension in chronic liver disease using novel agents that target intrahepatic endothelial cell dysfunction¹⁰⁰. Although small studies have investigated octreotide and other agents to modulate portal inflow in small-for-size grafts¹⁰¹, pharmacological modulation of portal inflow in PLF has not been reported.

Management of postresection liver failure

The management of PLF is summarized in *Table 4* and described in detail below. Patients should undergo clinical and laboratory assessment after liver resection, with the frequency of monitoring and level of care stratified according to risk. It is normal for serum bilirubin levels and the INR to rise in the first 48–72 h postresection. However, bilirubin concentration above 50 µmol/l (3 mg/dl) or INR greater than 1.7 beyond 5 days is unusual and usually reflects liver dysfunction²⁸. Serum bilirubin remains the most sensitive predictor of outcome in PLF²⁷. PT and INR are also valuable, but interpretation may be compromised if the patient has received clotting factors. Serum albumin, although an indicator of hepatic synthetic function, will vary in response to inflammation and administration of intravenous fluids¹⁰². Increased levels of liver

enzymes are common after liver resection and do not predict outcome²⁸. C-reactive protein levels are dampened after major liver resection, and day 1 levels inversely correlate with PLF indices¹⁰³. Serum lactate has a prognostic value in severe sepsis¹⁰⁴ and ALF¹⁰⁵, with a serum lactate level above 3.0 mmol/l after fluid resuscitation predicting death in ALF.

Ascites and hepatic encephalopathy are important markers for liver failure, but may be difficult to assess in the immediate postoperative period²⁷. Ascites occurs as a result of surgery (portal hypertension, dissection, gross fluid overload), and altered mental state may occur in response to drugs such as opiates.

The systemic inflammatory response syndrome (SIRS)¹⁰⁶ is present in more than 50 per cent of patients with ALF and predicts a negative outcome¹⁰⁷. The incidence of SIRS in patients with PLF has not been evaluated formally, but as in ALF it is likely to be implicated in sepsis, encephalopathy and end-organ dysfunction¹⁰⁸.

Several studies have examined the role of postoperative functional assessment of the liver. The ICGR15 predicts PLF¹⁰⁹, but its value diminishes once liver failure is established because changes in hepatic blood flow also influence ICGR15.

Although PLF is a potentially reversible condition, mortality rates remain high and currently there is little scope for therapeutic intervention. Management of PLF must be undertaken in conjunction with critical care, hepatology, microbiology and radiology services³. In the absence of controlled trials for PLF, management relies on data from experience with ALF (predominantly ALF secondary to paracetamol toxicity)^{110–112}. The pattern of organ dysfunction that occurs as a result of PLF is similar to that in sepsis³. Cardiovascular failure is characterized by reduced systemic vascular resistance and capillary leak. Acute lung injury, pulmonary oedema and acute respiratory distress syndrome may ensue. Acute kidney injury can progress rapidly in PLF. Fluid balance should be managed judiciously with avoidance of salt and water overload¹¹³.

Identifying and treating underlying sepsis is key in managing patients with PLF. Sepsis may exacerbate PLF, and bacterial infection is present in 80 per cent of patients with PLF²⁶ and in 90 per cent of those with ALF¹¹⁴. Any acute deterioration should be attributed to sepsis until proven otherwise. Management of sepsis should be in accordance with the surviving sepsis guidelines¹⁰⁴. A trial of prophylactic antibiotics after liver resection failed to show a reduction in liver dysfunction or infective complications¹¹⁵. Trials in ALF have shown that prophylactic antibiotics reduce infections, but the impact on long-term outcome is inconclusive¹¹⁴. In critically ill

Table 4 Step-by-step management of postresection liver failure

Step	Management
Detection Monitoring	Bilirubin > 50 $\mu\text{mol/l}$ (3 mg/dl), INR > 1.7 \pm encephalopathy on postoperative day 5 Serial serum bilirubin, aminotransferases, albumin, INR, lactate and CRP Assess for SIRS criteria Grade encephalopathy
Treatment	
Hepatoprotection*	Commence <i>N</i> -acetylcysteine infusion 150 mg per kg per h loading for 1 h 12.5 mg per kg per h for 4 h 6.25 mg per kg per h for remaining 67 h
Stress ulceration prophylaxis	Commence proton pump inhibitor
Nutrition	Enteral preferred over total parenteral nutrition Maintain euglycaemia
Sepsis	Serial chest X-ray, sputum, urine and blood culture Ascitic fluid from drain site Consider CT abdomen Commence antibiotics if progression of encephalopathy, renal failure or worsening SIRS parameters
Multiorgan dysfunction	Cardiovascular: \downarrow SVR, \uparrow capillary leak \pm adrenal insufficiency Respiratory: pulmonary oedema, acute lung injury \rightarrow ARDS Renal: acute kidney injury \rightarrow volume overload, acidosis or electrolyte imbalance Patients should be managed in a critical care environment
Coagulopathy and thrombocytopenia	Coagulopathy: correct if bleeding, coagulopathy profound or interventional procedure planned (vitamin K and FFP if INR > 1.5) Thrombocytopenia: correct if bleeding, profound thrombocytopenia ($< 20 \times 10^6/\text{l}$) or interventional procedure planned ($< 70 \times 10^6/\text{l}$)
Vascular inflow/outflow	Doppler ultrasonography CT/MR angiography Formal angiography If evidence of inflow/outflow occlusion consider anticoagulation/revascularization
Large-volume ascites	Paracentesis if severe pain/respiratory impairment, ensuring adequate volume replacement to prevent circulatory dysfunction (8 g 20% albumin solution per litre ascites drained)
Encephalopathy	Commence lactulose If progression to grade 3–4 encephalopathy, CT head, ventilate and consider ICP monitoring

*Although *N*-acetylcysteine is used in many centres, there is no definitive evidence of its benefit in postresection liver failure. INR, international normalized ratio; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome; CT, computed tomography; SVR, systemic vascular resistance; ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; MR, magnetic resonance; ICP, intracranial pressure.

patients with PLF, chest radiography and cultures of blood, urine, sputum and drain site/ascitic fluid should be performed¹¹². Current guidelines for ALF propose that broad-spectrum antibiotics should be administered empirically to patients with progression to grade 3 or 4 hepatic encephalopathy, renal failure and/or worsening SIRS parameters¹¹².

Coagulopathy may occur transiently after major resection and is found in all patients with PLF. As in ALF, coagulation parameters can be used to chart the progress of PLF, provided blood products have not been given. In a multinational review of fresh frozen plasma given for transient coagulopathy after resection there was no consensus for its use¹¹⁶. In the absence of bleeding it is not necessary to correct clotting abnormalities, except for invasive procedures or when coagulopathy is profound. The level at which a coagulopathy should be corrected

before an interventional procedure in ALF has yet to be defined (the commonly used threshold for correction is an INR above 1.5)^{110,112,117}. Vitamin K may be given¹¹⁰, but this is not supported by clinical trials.

Thrombocytopenia may complicate liver failure¹¹⁸. Indications for platelet transfusion in ALF include bleeding, profound thrombocytopenia (less than $20 \times 10^6/\text{l}$), or when an invasive procedure is planned. A platelet count above $70 \times 10^6/\text{l}$ is deemed safe for interventional procedures¹¹⁹. Recombinant factor VIIa (rFVIIa) has been used to treat coagulopathy in patients with ALF¹²⁰. In a large controlled trial of rFVIIa following major liver resection, no reduction in bleeding events was observed¹²¹. Its role in PLF is yet to be defined.

Gastrointestinal haemorrhage is a recognized complication of liver failure. In ALF, H₂-receptor blockers and proton pump inhibitors (PPIs) reduce gastrointestinal

haemorrhage in mechanically ventilated patients^{122,123}. In the non-ventilated patient an oral or sublingual PPI or oral H₂-receptor blocker is likely to protect against gastrointestinal haemorrhage. High-risk patients or patients with established PLF should therefore receive prophylaxis.

Large-volume ascites may also complicate PLF. As in ALF, when this causes severe abdominal discomfort and/or respiratory compromise, consideration should be given to therapeutic paracentesis with simultaneous volume replacement with a plasma expander (ideally 20 per cent salt-poor albumin solution). The ratio for replacement is 8 g 20 per cent albumin per litre ascites drained¹²⁴.

Nutrition is important and supplementation should be established early in patients with liver failure. Enteral nutrition is the preferred route as it improves gut function and restores normal intestinal flora. Nasogastric and nasojejunal feeding in ALF or PLF have not been compared. Parenteral nutrition can be used when enteral feeding is not tolerated¹²⁵, but should be introduced with caution owing to the risk of infection. In critically ill patients ensuring euglycaemia improves survival and reduces morbidity¹²⁶.

The role of imaging in PLF is to assess hepatic blood flow, identify reversible causes of liver failure and locate sites of infection. Hepatic blood flow can be evaluated using non-invasive imaging. Doppler ultrasonography may identify portal vein, hepatic artery and hepatic vein thrombosis. Contrast CT or MRI can be used to establish hepatic blood flow, provide more details of vascular abnormalities and identify sites of infection. If patency of hepatic vessels is still in doubt on cross-sectional imaging, angiography is the 'gold standard'¹²⁷.

Vascular disorders may complicate liver resection and induce PLF, but are rare. Longitudinal exposure of hepatic veins and the use of ultrasonic dissection may lead to hepatic vein thrombosis¹²⁸. Portal vein thrombosis has also been implicated in the development of PLF. In these rare cases of inflow and outflow thrombosis with PLF, a decision must be made regarding the benefit of surgical or radiological thrombectomy or dissolution *versus* anticoagulation^{129–131}.

Cerebral oedema and intracranial hypertension may occur as a result of PLF. Cerebral oedema is unlikely in patients with grade 1 or 2 encephalopathy. With progression to grade 3 encephalopathy, a head CT should be performed to exclude intracranial haemorrhage or other causes of declining mental status. In patients with established ALF and encephalopathy, enteral lactulose might prevent or treat cerebral oedema, although the benefits remain unproven. Progression to grade 3/4

encephalopathy warrants ventilation and may require intracranial pressure monitoring¹¹².

The concept of hepatocyte transplantation has been investigated as a strategy to boost residual liver function. Intrahepatic hepatocyte transplantation¹³² has been used successfully to treat patients with metabolic disorders of the liver. However, results in liver failure (including patients with PLF) have been poor, principally because insufficient functional cells could be delivered. The potential for stem cell therapies has yet to be established¹³³.

The use of salvage hepatectomy and orthotopic liver transplantation for PLF has been reported in seven patients who underwent liver resection for cancer¹³⁴. Although the indications for transplantation in this study were questionable, overall 1-year (88 per cent) and 5-year (40 per cent) survival rates were promising. An editorial¹³⁵ accompanying this paper stated that salvage hepatectomy and liver transplantation should be limited to patients below the age of 70 years, with HCC and no macrovascular invasion, and, possibly, a small cholangiocarcinoma (less than 3 cm) without lymph node invasion. There is no indication for transplantation in patients with liver metastasis, except those with neuroendocrine tumours. It is not current practice to offer salvage hepatectomy and liver transplantation in the UK.

Extracorporeal liver support (ELS) devices fall into two categories: artificial and bioartificial systems. Artificial devices use combinations of haemodialysis and adsorption over charcoal or albumin to detoxify plasma. Bioartificial devices use human or xenogenic hepatocytes maintained within a bioreactor to detoxify and provide synthetic function. These systems have not been evaluated extensively in patients with PLF. A recent meta-analysis and systematic review showed that ELS may improve survival in patients with ALF (risk ratio (RR) 0.70, 95 per cent confidence interval 0.49 to 1.00), but not acute-on-chronic liver failure (RR 0.87, 0.64 to 1.18), in comparison with standard medical therapy¹³⁶.

Future directions

There are five key areas for research and development. There is a need for a unified definition and scoring system to enable comparison between studies and to guide prognosis. A better understanding of the pathophysiology of the disease will aid the development of biomarkers for those at risk. With the rising burden of cirrhosis, NAFLD and chemotherapy-induced liver injury, there needs to be a clearer understanding about how these patients should be assessed before resection, to determine the appropriateness and timing of neoadjuvant chemotherapy, and the safe

extent of resection. Also of interest are novel strategies: to improve the health of the underlying parenchyma before resection, for example vitamin E¹³⁷ or calorie restriction¹³⁸ in patients with steatosis; to boost functional liver mass and regenerative capacity postresection, such as intrahepatic delivery of growth factors via implantable scaffolds¹³⁹; and to reverse or attenuate parenchymal loss in cases of SFSS, IRI and sepsis. Finally, prospective multicentre trials are required to improve the management of PLF.

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