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REVIEW ARTICLE

Post Hepatectomy Liver Failure: Concept of Management

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Abstract
Background In literature, the reported mortality of posthepatectomy liver failure is <5 % and morbidity is 15–30 %. Around 3–8 % of patients develop liver failure after major hepatic resection.
Objective The objective of the study was to provide current definitions and managing posthepatectomy liver failure (PHLF) as per severity and ISGLS grading.
Method A systemic search of pubmed indexed articles was done and relevant articles were selected to formulate latest guidelines for PHLF.
Conclusion We were able to make an algorithm for standardizing management so as to identify and treat PHLF as early as possible.

Keywords Posthepatectomy liver failure (PHLF) · Future liver remnant (FLR) · Hepatocellular carcinoma

Background

A breakthrough in technology and continuous dedication for refinement of surgical skills make it possible today to perform major hepatic resection with acceptable morbidity and mortality; however, struggle for refinement always keeps going on [1–4]. Resection of four or more segments results in higher incidence of postoperative mortality (7.4 vs. 2.7 %) and morbidities (25.6 vs. 6.4 %) compared to three or less segments resection, so major hepatic resection is defined as the resection of four or more liver segments [5]. In literature, the reported mortality of posthepatectomy liver failure is <5 % and morbidity is 15–30 % [1–4]. Approximately 3–8 % of patients develop liver failure after major hepatic resection [6, 7]. Posthepatectomy liver failure (PHLF) is the major cause of mortality.

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Methodology

A systemic search of Pubmed-indexed articles was done. Studies which focused on PHLF with keywords PHLF, liver failure after hepatic resection, and liver insufficiency following liver resection were selected. Review of available evidence from these studies helped us to formulate an algorithm for PHLF management.

History and Current Definition of PHLF

Over time, PHLF has been defined in numerous ways by the literature. Eguschi et al. in 2000, defined posthepatic failure when three findings were present in the patient: (1) hepatic encephalopathy, (2) progressive hyperbilirubinemia, and (3) reduced hepaplastin test [8]. First attempt for reasonable and quantitative definition of postoperative liver failure was provided by Balzan and Belghiti using the "50-50" criteria [9]. This criteria has also been validated in a recent large study by Paugam-Burtz C et al. [10] This retrospective study showed a sensitivity of 50 % and a specificity of 96.6 % for the prediction of postoperative liver failure-related death in a cohort of patients without underlying liver disease undergoing major hepatic resection. Bilirubin level of 7.0 mg/dL (120 μmol/L) was identified as a sensitive and specific cutoff value for prediction of postoperative liver failure-related death. Mullen et al. concluded that postoperative hepatic insufficiency (PHI) defined as peak bilirubin of >7.0 mg/dl accurately predict liver-related morbidity and mortality after major hepatectomy [11]. In 2010, Rahbari and other members of the International

Study Group of Liver Surgery (ISGLS) introduced posthepatic liver failure (PHLF) definition and grades for standardization of international reporting [12]. As ISGLS definition is easily applicable and comparable, it should be used for reporting and management decision. But the 50–50 criteria is also commonly used.

In general, PLF is characterized as failure of one or more of the hepatic synthetic, metabolic, and excretory function, leading to hyperbilirubinemia, hypoalbuminemia, prolonged prothrombin time, elevated serum lactate, and/or different grades of hepatic encephalopathy (HE).

50-50 Criteria

Prothrombin index <50 % (equal to an international normalized ratio (INR >1.7) and serum bilirubin >50 mmol/L (2.9 mg/dl) on post-operative day 5 [9]. When fulfilled, the patient had a 59 % risk of mortality compared with 1.2 % when criteria not met (sensitivity 69.6 % and specificity 98.5 %) [9, 10].

ISGLSA

Postoperatively-acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying function was characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cutoff levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day) [12]. Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out.

Grades-

A: PHLF resulting in abnormal laboratory parameters, but requiring no change in the clinical management of the patient.
B: PHLF resulting in a deviation from the regular clinical management, but managed without invasive treatment.
C: PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

Pathogenesis of PHLF

PHLF occurs as a result of insufficient remnant functional hepatocyte mass after partial liver resection. After liver resection, both death and regeneration of the remaining hepatocytes occur. Physiologically, regeneration outcomes death and liver restored both functionally and by volume [13, 14]. For example, during the first 10 days after right hepatectomy for living donor liver transplantation, restoration of liver mass up to 74 % of the initial volume has been reported [13]. This regeneration is initiated as a result of increased metabolism to be met by the remaining hepatocytes. Interrelation of various intraoperative and postoperative hits may affect regenerating capacity of hepatocytes leading to liver function insufficiency, the most dreadful complication of major hepatectomy (Fig. 1).

Risk Factors for PHLF

Discussed as they come to play a role i.e., preoperative, intraoperative, and postoperative

(A) Preoperative: mainly related to patient comorbidities and preoperative preparation. Established independent predictors are: pre-existing liver diseases e.g., steatosis, cirrhosis, cholangitis, and chemotherapy-associated hepatotoxicity; small future liver remnant (FLR), hypoalbuminaemia, male gender, and advanced age [15–17].

1. Liver steatosis: presence of moderate to marked steatosis (≥30 %) have considerable impact on operative morbidity and mortality, and steatohepatitis carry an even higher risk (Table 1) [18]. Preoperative CT and MRI has good correlation with hepatic steatosis [19].
2. Cholestasis: may be caused by either obstruction to biliary drainage or by parenchymal liver disease. External biliary drainage for obstructive jaundice suppresses liver regeneration after hepatectomy where internal biliary drainage preserves this capacity by maintaining enterohepatic circulation [20]. Cherqui et al. observed that although morbidity is higher in patients with obstructive jaundice compared to patients with normal serum bilirubin (50 vs. 15 %), incidence of posthepatectomy liver failure was not different [21].
3. Cirrhosis: impairs liver regeneration capacity [22]. Patients with cirrhosis have a higher risk of PHLF depending on the functional reserve of the liver. Liver functions in cirrhotic patients are assessed preoperatively by Child-Pugh score (Table 2). According to AASLD and EALD, only Child A patients with resectable hepato cellular carcinoma (HCC) are candidates for hepatic resection and Child B and C patients with early stage HCC are better served with

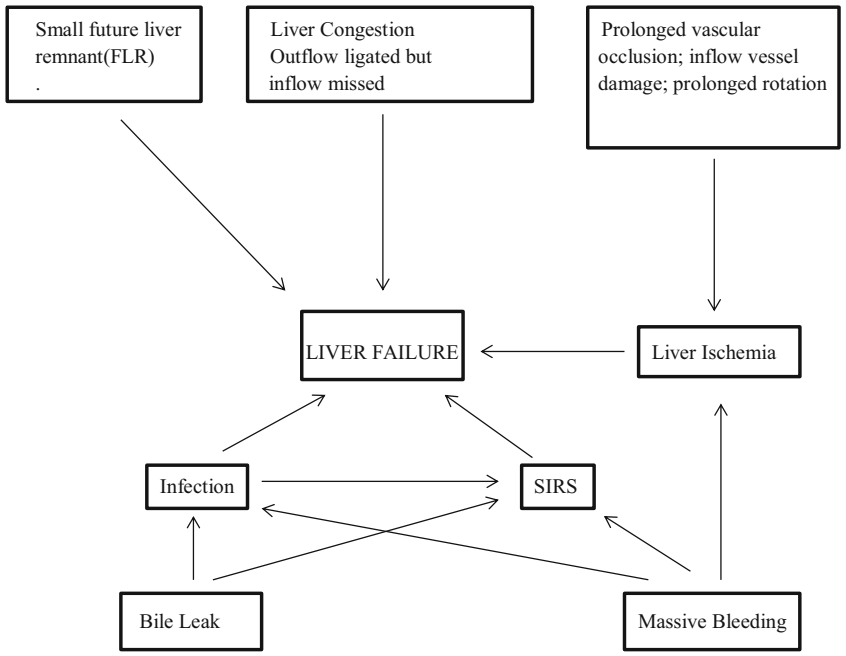

Fig. 1 Pathophysiology of PHLF

transplantation [23, 24]. Patients with cirrhosis and acute viral hepatitis have even higher mortality [8].

4. Preoperative chemotherapy: in patients with colorectal liver metastasis, hepatic parenchymal injury occurs in 78 % of patients receiving oxaliplatin and is addressed as the sinusoidal obstruction syndrome [25]. Irinothecan results in chemotherapy-associated steatohepatitis (CASH) which negatively affects 90-day mortality rate [26]. Though there is no good level evidence for preoperative transarterial chemoembolization (TACE), now major hepatectomy is also performed in setting of preoperative TACE. Chemoembolization can aggravate impairment of liver function and severity of cirrhosis. It makes operation more difficult, risky, and may affect postoperative outcomes, though increased mortality has not been reported [27, 28].

(B) Intraoperative:

1. FLR: FLR is standardized to total liver volume (TLV). PHLF is related to volume and function of the remaining liver. Recommended FLR are:

   (a) Normal liver: safe FLR is >26.5 % [29]. According to consensus statement published in 2006, safe limit of FLR for hepatectomy for colorectal metastasis is >20 % [30].

   (b) Cholestatic liver: patients with cholangiocarcinoma are more frequently associated with cholestasis, and they are also subjected to more major hepatectomy to achieve R0 resection. Extent of liver resection is limited even after cholestasis has been relieved. Limit of liver resection in setting of cholestatic liver disease is not well established. Recommendations by Ferrero et al. and Suda et al. of safe FLR are 35 % [31, 32].

   (c) Steatosis: safe limit is not established; but as per data in literature, safe limit of FLR in mild steatosis should be 30–35 % and in sever steatosis should be 40 % [33].

   (d) Postchemotherapy liver: consensus statement published in 2006 advises safe FLR for postchemotherapy hepatectomy as >30 % [30].

Table 1 Grades of steatosis

Grade 1:	<33 % of hepatocytes affected.
Grade 2:	33 to 66 % of hepatocytes affected
Grade 3:	>66 % of hepatocytes affected

Table 2 Child-Pugh classification

Measure	1 point	2 points	3 points	Units
Bilirubin	<2	2–3	>3	mg/dl
Serum albumin	>3.5	2.8–3.5	<2.8	g/dl
INR	<1.7	1.7–2.2	>2.2	No unit
Ascites	None	Suppressed with medication	Refractory	No unit
Encephalopathy	None	Grade I–II	Grade III–IV	No unit

Class A, 5–6 points; Class B, 7–9 points; and Class C, 10–15 points

(e) Cirrhotic liver: Shirabe et al. after analysis of 80 patients with chronic liver disease (50 % cirrhotics) who underwent major liver resection concluded safe FRL volume as <250 mL/m^2 [34]. The reported safe FLR range was from 30 to 40 %. Ferrero A et al. considered FLR of >31 % as a safe limit of hepatectomy in diseased liver and the consensus safe FLR for hepatectomy in cirrhotic liver is 40 % [30, 31].

2. Blood loss: >1,000 ml increases the risk of PHLF as a result of fluid shift following excessive blood loss and systemic inflammation because of bacterial transmission[3, 15]. Coagulopathy following blood loss also increases the risk of intra-abdominal hematomas and bacterial infections. Blood transfusions exert an immunosuppressive effect.

(C) Postoperative:

1. Sepsis: risk factors associated with infection include obesity, blood transfusion, comorbidities (diabetes, chronic obstructive pulmonary disease), and bile leak.

Manifestations of PHLF

PHLF is a fatal but potentially reversible condition owing to the enormous regenerative capacity of the liver. To conquer such a dreaded complication, it must recognize the enemy at the earliest. It usually manifests as multiorgan failure. Clinical manifestations are not different from other causes of acute liver failure and include jaundice, coagulopathy, ascites, edema, and/or HE [35]. Serum bilirubin and prothrombin time have been validated as predictive for liver failure by postoperative day 5, the time at which PHLF may be advanced and difficult to treat [9, 12]. Yuichiro Otsuka et al. proposed that patients with significant abnormalities in platelet count (<100,000), INR (>2.0), and/or total bilirubin (6.6 mg/dL) on postoperative day 2 are at significantly increased risk for developing irreversible PHLF and patients not developing PHLF had total bilirubin <2 mg/dL in 98 % of cases, INR <2 in 97 % of cases, and prothrombin time <19 s in all cases [36]. Rahman et al. showed that patients developing PHLF had a significant lower CRP level on POD 1 than patients without PHLF [37]. Systems most hit in liver failure manifest as below:

1. Circulatory system: resembles circulatory failure in septic shock as progressive hypotension, peripheral vasodilation, and disseminated intravascular coagulopathy [38].
2. Kideny: urea synthesis is impaired. Postoperative renal failure may be caused by parenchymal renal disease, administration of nephrotoxic drugs in the perioperative period, hypovolemia, and hepatorenal syndrome (HRS). HRS is precipitated by infection or hypovolemia and is characterized by oliguria and low urine sodium concentration. Type 1 HRS is a rapidly progressive decline in renal function, leading to a doubling of the initial serum creatinine to>2.5 mg/dL, or a 50 % reduction of creatinine clearance to<20 mL/min within 2 weeks. Type 2 HRS is renal failure not fulfilling the parameters outlined above.
3. Respiratory system: gradually progressing insults are pulmonary edema; acute lung injury, and acute respiratory distress syndrome.
4. Hepatic encephalopathy (HE): hyperammonemia is central in causation of hepatic encephalopathy [39]. West Haven criteria grades HE from I to IV according to severity (Table 3) [40].

Prevention

Improving preoperative variables: accurate assessment of hepatic anatomy and reserve is the key principle (Table 4).

1. Small FLR: manifest as small for size graft i.e., <0.6 % body weight. Small liver volume is not able to compensate for liver functions. If FLR is below the critical values as described earlier, then strategies to improve FLR should be adopted.

(a) Accurate calculation of FLR: CT volumetry by automated software is most commonly used. FLR volume=(remnant liver volume×100)/(total liver volume−tumor volume)

(b) Portal vein embolization (PVE): depending on extent of liver function, volume can be increased from 31 to 47 % [41]. Many institutes also incorporate Indocynanin Green Clearance (IGC) along with FLR to select patients for PVE. Indications for PVE should be carefully selected and includes: (1) in normal liver FLR<20 % and (2) in diseased liver (indocyanin green (ICG) retention at 15 min >15 %) when FLR<40 % [41–43]. If ICG R15 exceeds

Table 3 Grades of hepatic encephalopathy

HE grade	Mental state
1	Mild confusion, slowing of ability to do mental tasks
2	Drowsiness, inappropriate behavior
3	Somnolent but rousable, marked confusion
4	Coma

Table 4 Measures to assess hepatic reserve

Anatomical	Functional
• CT volumetry	• Child-Pugh criteria • Indocyanin green clearance • Hepatic steatosis

20 %, major hepatectomy is contraindicated even after PVE (Fig. 2) [44]. Absolute contraindications to PVE are: (1) extensive ipsilateral tumor thrombus and (2) portal hypertension [45]. Post resection morbidity are similar to non PVE patients. Surgery can be done by 3–4 weeks.

(c) Two stage hepatectomy: studies reported feasibility and success of two stage hepatic resection in initially unresectable bilobar colorectal liver metastasis; however, additional studies are required [46, 47].

(d) Downstaging by TACE.

2. Preoperative percutaneous transhepatic biliary drainage (PTBD) for cholestasis: different studies showed advantages of PTBD, but never a significant improvement in outcome. PTC-related complications led to an increase in overall complications [48]. PTBD selectively reduces the morbidity rate when intrahepatic segmental cholangitis accompany biliary carcinoma [49].

Improving intraoperative variables:

1. Central venous pressure ≤5 mmHg during parenchymal transection limits intraoperative blood loss without deterioration of renal function [50]. Low CVP with continuous or intermittent portal triad clamping is advantageous for the prevention of excessive intraoperative blood loss [51]. The latter procedures are equally effective but total vascular exclusion leads to more hemodynamic changes and higher complication rates [52].
2. Ischemic preconditioning: temporal clamping of the portal triad before a prolonged clamping has been shown to reduce hepatocyte damage but there was no influence on PHLF [53].

Improving postoperative variables:

1. Postoperative liver enzymes albumin, creatinine, INR, SIRS criteria, and signs of encephalopathy should be regularly monitored along with regular clinical reevaluation
2. Postoperative sepsis: meticulous surgical techniques with minimal blood loss; short operative time, and avoiding bile spillage are the key. Early postoperative mobilization and physiotherapy should be instituted. It is utmost important to recognize postoperative infection early, prompt institution of broad-spectrum antibiotics, and aggressive source control to win the battle against sepsis and its sequel. A study by Garwood et al. found that the delay in antibiotic therapy was associated with increased infectious mortality [54].

Treatment

Management principles are same as those applied to acute liver failure and the main focus is to provide support to the

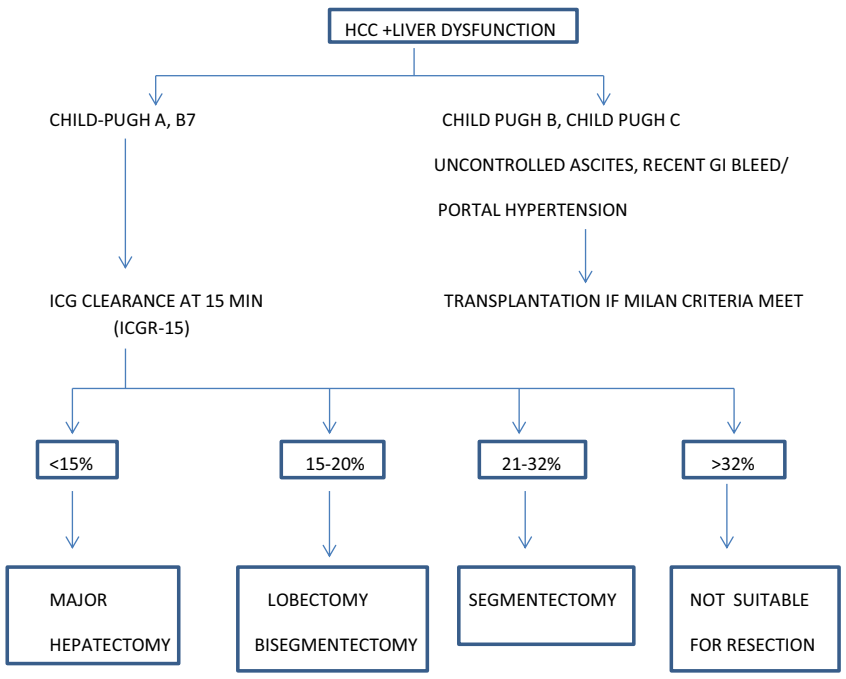

Fig. 2 Liver resection tailored on the basis of ICG clearance

liver and end organs. PHLF should be graded according to ISGLS (Table 5). Bilirubin and INR levels can normally rise 48–72 h postresection.

1. Circulation: monitor CVP, arterial pressure, and support with vasopressor accordingly.
2. Renal: maintain urine output at least 0.5 ml/kg/h.
3. Respiratory system: monitor arterial oxygen saturation and ventilator support as required.
4. Coagulation: monitor INR; platelets, and support with FFP as required.
5. Neurological: hyperammonemia plays a central role in its development. Commence lactulose and consider neuroprotective strategies like hyperventilation, hypertonic saline, mannitol, and cooling to 32–24 °C.
6. Rule out treatable conditions:
   (a) Portal vein thrombosis: give rise to ischemia. The diagnosis can be made using either ultrasound Doppler or CT scan. It can be managed by surgical removal or anticoagulation.
   (b) Venous outflow obstruction: can be due to the rotation of the remnant liver segment, surgical intervention is indicated. Endovascular stenting also improve venous outflow.
7. Nutritional support: early enteral nutrition is preferred and preserve the integrity of the gut barrier and reduce postoperative infection rates. It can be supplemented with parenteral nutrition if required. Supplementation with branched chain amino acids may be useful in liver with cirrhosis [55]. Protein intake should not exceed 60 g/day in patients with encephalopathy.
8. Liver function support:
   (a) Hepatoprotection: experimental studies suggest that N-acetylcysteine (NAC) administration may reduce the ischemic reperfusion injury, including restore glutathione, reduced free radical formation, reduced bacterial translocation from the gut, less microcirculatory disturbance, and less hepatic necrosis [56]. In nonparacetamol-induced causes of acute liver failure, both intravenous and oral NAC has been shown to improve transplant-free survival and appear safe and well tolerated [57, 58]. N-acetylcysteine is infused for 72 h, 150 mg/kg loading dose over 1 h, 12.5 mg/kg/h for 4 h, and 6.25 mg/kg/h

Table 5 Criteria for grading of PHLF

	Criteria for PHLF Grade A	Criteria for PHLF Grade B	Criteria for PHLF Grade C
Specific treatment	Not required	Fresh-frozen plasma Albumin, Daily diuretics Noninvasive ventilation Transfer to intermediate/intensive care unit	Transfer to the intensive care unit, Circulatory support (vasoactive drugs) Need for glucose infusion Hemodialysis Intubation and mechanical ventilation Extracorporeal liver support Rescue hepatectomy/liver transplantation
Hepatic function	Adequate coagulation (INR <1.5) No neurological symptoms	Inadequate coagulation (INR≥ 1.5<2.0) Beginning of neurologic symptoms (ie, somnolence and confusion)	Inadequate coagulation (INR ≥2.0) Severe neurologic symptoms/ hepatic encephalopathy
Renal function	Adequate urine output (>0.5 mL/kg/h) BUN <150 mg/dL No symptoms of uremia	Inadequate urine output (≤0.5 ml/kg/h) BUN <150 mg/dL No symptoms of uremia	Renal dysfunction not manageable with diuretics BUN ≥150 mg/dL Symptoms of uremia
Pulmonary function	Arterial oxygen saturation >90 % May have oxygen supply via nasal cannula or oxygen mask	Arterial oxygen saturation <90 % despite oxygen supply via nasal cannula or oxygen mask	Severe refractory hypoxemia (arterial oxygen saturation ≤85 % with high fraction of inspired oxygen)
Additional evaluation	Not required	Abdominal ultrasonography/CT Chest radiography Sputum, blood, urine cultures Brain CT	Abdominal ultrasonography/CT Chest radiography/CT Sputum, blood, urine cultures Brain CT ICP monitoring device

Table 6 King's College criteria

Indicators of a poor prognosis in non-acetaminophen acute liver failure
Prothrombin time >100 s or INR >6.7
Acute presentation of Wilson disease
Any three of the following:
• Unfavorable etiology (seronegative hepatitis or drug reaction)
• Age <10 years or >40 years
• Acute or subacute categories (e.g., jaundiced >7 days)
• Serum bilirubin >300 μmol/L
• Prothrombin time >50 s or INR >3.5

INR international normalized ratio

subsequently. Stuart M. Robinson et al. were not able to demonstrate any advantage in the routine administration of perioperative NAC in patients undergoing a liver resection [59].

(b) Liver support systems: Cochrane database systematic review of artificial and bioartificial liver system concluded that artificial liver systems seem to improve the mortality in acute-on-chronic liver failure; artificial and bioartificial support systems did not appear to affect mortality in acute liver failure [60]. Additional randomized clinical trials are needed before any support system can be recommended for routine use.

(c) Rescue hepatectomy and liver transplantation: patients uncommonly fit for criteria of liver transplantation. Orthotopic liver transplantation (OLT) should be restricted to groups of patients with PHLF, who meet pretreatment Milan's criteria, and R0 resection. In these patients, OLT provide survival advantages not met by any other mean [36]. King's college criteria may be applied in these selected patients in identifying candidates for transplantation (Table 6).

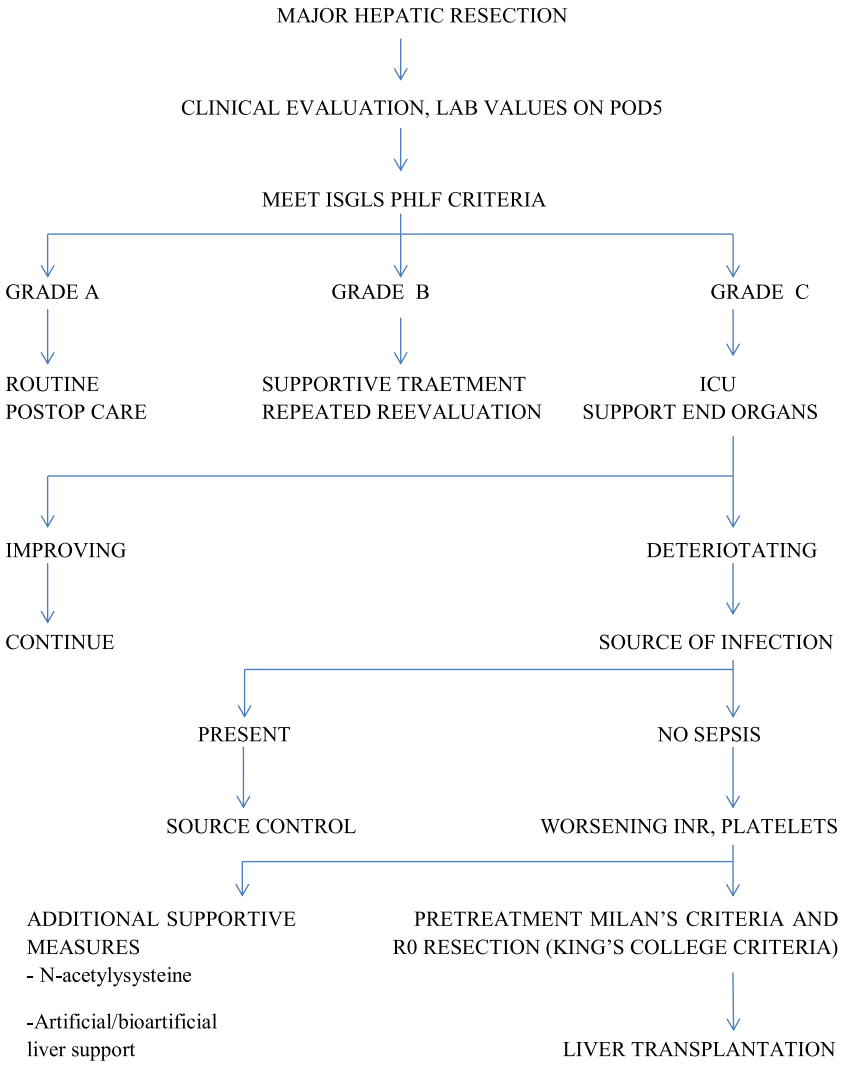

Fig. 3 Treatment algorithm PHLF

Future Directions

Early experimental study includes encapsulated hepatocytes transplanted intraperitoneally, avoiding the need for immunosuppressive therapy to help treat postoperative liver failure [61]. Extracorporeal hepatic support systems show promise, but efficacy data are still missing. Novel systems for in vivo and in vitro expansion of human hepatocytes are still early in development.

Conclusion

From this review of available evidence, we formulated a treatment algorithm for PHLF as shown in Fig. 3.

Conflict of Interest There is no conflict between authors regarding any issues

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