Peer Review File
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Reviewer Comments

Comment 1: What can be used as potential tools to increase the survival rate of liver transplant recipients and reduce the need for retransplantation? Is this possible with immunosuppressive therapy?
Reply 1: We agree with the reviewer that this is an important issue for this review focused on future direction of ALF. Accordingly, we included a short section discussing the possibilities of individually adapting immunosuppressive therapy to improve long-term prognosis of patients after LT (P9 L16 – P10 L9):

"ELT and liver transplantation (LT) in general have significantly improved short term survival in ALF to over 80 % after 1 year and > 70 % after 5 years. This improved outcome after LT is due to multimodal therapy concepts, standardized evaluation of organ recipients and donors, improved organ storage, optimized surgical methods and perioperative management, and development of specific immunosuppressive agents with reduced side effects. However, long term prognosis after LT is still highly variable and depends on a large variety of factors. metabolic and cardiovascular diseases, impaired renal function, infections, recurrence of the underlying disease / cause, and development of malign tumors. In addition, graft rejection remains a relevant reaction after LT limiting the prognosis, although a lot of progress has been made in recent years to optimize and individualize immunosuppressive therapy. Such reactions always require histological evaluation and should be classified following the Banff Working Group on Liver Allograft Pathology. A major challenge after LT is to adjust immunosuppression to control and avoid graft rejection. Though, immunosuppressive substances worsen factors, which determine long-term prognosis as risk for recurrence of underlying disease, development of *de novo* malignancies, and cardiovascular risk profile (increased risk for type 2 diabetes, hyperlipidemia, obesity). Most immunosuppressants are also nephrotoxic. Thus, to further improve long-term survival after LT for ALF it will be necessary to improve adaptation of immunosuppressant therapy and to identify the individually ideal therapy regimen."

Comment 2: Liver failure is a clinical syndrome that is mainly manifested by blood coagulation dysfunction, jaundice, hepatic encephalopathy and ascites caused by various causes. At present, there are still big differences in the clinical diagnosis and classification of liver failure at home and abroad. What are the consensus, differences and suggestions?
Reply 2: We thank the reviewer for this question, as definitions on acute liver failure still vary across different regions. Consensus of all the definitions throughout the different societies (EASL, AASLD, APASL) are the following

clinical features: elevated transaminases, an elevated bilirubin level, an impaired coagulopathy (INR > 1.5), and the presence of hepatic encephalopathy.
It has been suggested that a minimal hepatic encephalopathy, which can only be detected by psychometric tests in contrast to the overt forms, should also be considered as a valid criterion. We included this information in the part on definition of acute liver failure (P4 L 22 – P5 L 3):

"Although there are still differences in the detailed clinical diagnosis of ALF, there is a broad consensus among the societies EASL, AASLD and APASL that four clinical features are mandatory: elevated transaminases, an elevated bilirubin level, an impaired coagulation (INR > 1.5) and the presence of hepatic encephalopathy. Furthermore, it is widly accepted that the definition of ALF implies no previous liver injury."

Comment 3: What are the hot issues and coping strategies in the diagnosis and treatment of liver failure?
Reply 3: As we agree with the reviewer that this topic would be a good addition to our review, we included a novel section termed "What are novel developments in diagnosis and therapy of liver failure?" (Starting on page 11). Here we discuss breath tests for diagnosis of liver function, experimental therapies as plasma exchange, and stem cell therapy:

"Among the most pressing issues in the clinical handling of ALF are diagnostic options, that would give more information on remaining liver function and regenerative capacity. One method that is relatively novel is the LiMax, which can estimate liver function from a breath test. In particular, enzymatic activity of specific cytochrome c enzymes is measured by detection of their products in the breath of patients. In ALF this method seems to allow more accurate measurement of liver function than conventional serum tests and may enable monitoring of ALF course or even prediction of survival without liver transplantation.
Therapeutic options in ALF are limited to liver transplantation or are dependent on the specific causes of ALF. Experimental therapies as plasma exchange or blood purification (also termed liver dialysis) did not have significant benefits for transplant free survival or recovery time in studies performed up to date. The evidence for plasma exchange is rather limited and a clinical benefit is in question. Liver dialysis can reduce serum bilirubin and bile acid concentrations. However, it is unclear if some bile acid species might be required for liver regeneration. Thus, liver dialysis may on the one hand remove harmful bile acids while on the other hand also reducing an important signal for regeneration. One way to support liver regeneration could to supply the liver with stem cells to renew regenerative capacity. Preliminary data from adipocyte

derived stem cell transplantation in alcohol-induced ALF look promising and could be expanded for other etiologies."

Comment 4: What are the characteristics of the therapeutic effect observation and nursing methods of plasma exchange in liver failure?
Reply 4: The current situation on plasma exchange is limited by available evidence. It is to early to give a clear recommendation. We included a short part on this topic in the section on novel therapeutic options (P11 L13-18).

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Comment 5: What problems and points should be paid attention to in the clinical observation and nursing of liver failure and its complications?
Reply 5: We apologize for not including information on specific nursing and handling requirement of liver failure. As discussing this topic in all detail would probably go beyong scope and allowed length of this review, we only added a brief part in this topic (P 12 L2 – 8).

"Standard procedure for treatment of patients with ALF is intensive care with close monitoring and early continuous veno-venous haemodiafiltration in case of kidney failure. Antibiotic or antimycotic therapy should only be applied, when an infection is present. Supplementation of coagulation factors must be critically evaluated as it is usually unnecessary. This procedure is aimed to support the patient until the regenerative capacity of the affected liver can restore function. The only curative option, when recovery from ALF seems unlikely is (orthotopic) liver transplantation (LT)."

Comment 6: What are the current challenges and future directions of liver transplantation?
Reply 6: We thank the reviewer for pointing us to this omission, as we did not include a specific section on liver transplantation in ALF. According to this comment, we added the section "Challenges of liver transplantation for acute liver failure" (starting on page 12), including current situation on liver transplantation and probable future development:

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of kidney failure. Antibiotic or antimycotic therapy should only be applied, when an infection is present. Supplementation of coagulation factors must be critically evaluated as it is usually unnecessary. This procedure is aimed to support the patient until the regenerative capacity of the affected liver can restore function. The only curative option, when recovery from ALF seems unlikely is (orthotopic) liver transplantation (LT). However, LT comes with several limitations on its own. The first and most obvious problem is organ shortage on most societies, where many more patients wait for a suitable transplant liver than organs are available. For ALF there are certain criteria that allow high urgency listing, which can somewhat compensate for the organ shortage in very critical cases, though this again depends on the actual availability of donor organs. Thus it is imperative to prevent a progression of ALF into a highly critical situation and also to develop better algorithms for detection of patients, who would not require LT to recover. All currently scores in use to assess the urgency of LT in ALF (King's college criteria, Clichy criteria, MELD) lack in the identification of patients, who have sufficient regenerative capacity to recover without LT. This is a major challenge of ALF in the near future to improve on these scores or develop a new algorithm to exclude those patients from LT, who have a good prognosis. Apart from these options further improvement and research has to go into specific treatment of ALF by etiology. There are certain causes of ALF (i.e. paracetamol intoxication, autoimmune related, HBV-associated) where direct, specific treatment according to the causing agent can avoid LT and improve outcome. It would be highly desirable to develop such options for other etiologies. Finally, patients who received LT will require life-long immunosuppression, which poses a risk for infections and other complications. Current clinical research is aiming to develop personalized and well-adjusted immunosuppression therapy, which would increase long term survival and well-being of LT recipients. Taken together the major challenges in LT for ALF are identification of patients acutally not requiring LT and improving non-LT therapy for ALF to avoid this drastic option."

Comment 7: What are the clinical effects of different blood purification methods in the treatment of various types of liver failure?
Reply 7: Similar to the currently available data on plasma exchange (see reply to comment 4), evidence on blood purification in ALF is limited We included this issue in the section on novel therapeutic options (P11 L13-17; see reply to comment 4).