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Interdisciplinary Discussion

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Acute-on-Chronic Liver Failure

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Question 1: Systemic inflammation is a hallmark of (acutely) decompensated liver cirrhosis and in particular of acute-on-chronic liver failure (ACLF). Frequently, it is challenging to discriminate infection from sterile inflammation in these patients. Which patient – in the absence of proven infection – do you treat with antibiotics in these scenarios, and are there any preferred antibiotic regimens?

Bechstein: Patients have developed ACLF either because of community-acquired or nosocomial infection including so-called spontaneous bacterial peritonitis (SBP) or because of gastrointestinal bleeding or encephalopathy. In the former case, the focus of infection should be identified and organisms isolated with immediate subsequent empiric calculated antibiotic therapy. In patients with ACLF following gastrointestinal bleeding or encephalopathy, the high risk of subsequent sepsis justifies prophylactic antibiotics. The choice of antibiotics depends upon previous isolates from the patient and the spectrum of organisms and antibiotic resistances typically encountered in the specific local setting (intensive care unit (ICU), hospital) – in other words: consult with local microbiology and infectious disease colleagues to draw up local standard operating procedures for these cases.

Berg/Engelmann: Currently there are no valid diagnostic means to identify the presence of bacterial infections in ACLF early and with a high level of certainty, apart from the direct proof with standard cultural methods. Making a sepsis diagnosis is also challenging. Criteria to define ACLF overlap substantially with the sepsis criteria, as they are both based on the SOFA (Sequential Organ Failure Assessment) score. Conventional biomarkers of bacterial infections such as C-reactive protein (CRP) and procalcitonin (PCT) have in combination a positive predictive value of >90% (CRP of 24.7 ng/ml and PCT of 0.49 µg/l) and might help to make decisions about the indication for antibiotic treatment.

Although bacterial infections are the most common triggers for ACLF, the precipitating event remains unclear in more than 40%. It is tempting to hypothesize that unrecognized bacterial infection is also involved in these instances.

As the intestinal bacterial translocation is also increased in patients with ACLF, with circulating bacteria and bacterial products maintaining the systemic inflammatory response, the threshold for a pre-emptive antibiotic treatment, especially if the above-mentioned predictors are present, should be low. This is also supported by the fact that every hour of delay of antibiotic treatment is associated with a significant increase in mortality. However, if started pre-emptively, the necessity to continue antibiotic treatment should be reassessed after 48 h to avoid unnecessary therapy and the risk for selecting multiresistant bacteria.

Bruns: Bacterial infections are considered the major precipitating events of acute decompensation and ACLF. As almost none of the available biomarkers reliably discriminates sterile inflammation driven by tissue damage and nonviable bacterial translocation from infection-driven inflammation, we perform a thorough diagnostic workup for bacterial infections. There is no evidence sup-

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porting routine antibiotic prophylaxis in acute decompensation and ACLF. However, potential factors that may support antibiotic use in the absence of clinical, microbiological or imaging signs of infection are: the progression of ACLF (development of novel organ failures), the dynamics of systemic inflammation (sudden increase in white blood cells, acute-phase proteins, or PCT), excessive immune responses (disproportionally high biomarkers), and vasopressor use for septic shock. As in the case of proven bacterial infections, we select empiric antibiotic therapy according to the suspected site of infection, considering individual and local risk factors for antimicrobial resistance.

Trebicka: There is evidence that infections do not only trigger ACLF but also develop in ACLF patients [1, 2] and that infections are associated with increased mortality. There is no published evidence that prophylactic antibiotics improve survival in ACLF patients, at least to my knowledge, but in high-risk patients, e.g. to prevent SBP, it is already accepted and recommended by the current guidelines. The prevention of SBP and also other infections in decompensated cirrhosis might also be the rationale for the improved survival after prophylactic norfloxacin treatment in patients with Child C cirrhosis, as shown in a French multicenter study [3]. Whether this can be extrapolated to ACLF is not yet shown, but logical.

Question 2: Which patient with ACLF do you consider to be a good candidate for liver transplantation?

Bechstein: Ideally, a patient with ACLF should have been listed for liver transplantation before ACLF occurs. If this is the first patient contact with the transplant center, abbreviated listing examinations should be carried out with infectious disease screening, imaging to rule out cancer, and confirmation of portal vein patency as well as cardiovascular risk assessment. Obtaining fully informed consent poses additional challenges in this situation. Liver transplantation in the setting of the patient being on the ventilator, depending on dialysis, and needing vasopressor support should be avoided – the lethal triad of liver transplantation. Perhaps the window of opportunity for a successful liver transplant is missed if a graft does not become available within 1 week of the patient being in the ICU.

Berg/Engelmann: Even patients with ACLF grade 3 are potential candidates for orthotopic liver transplantation (OLT), as it has been recently demonstrated in an important series from France. Although the risk for postoperative complications was significant, the 1-year post-OLT survival rate was >80%, hence nearly equivalent to the outcome seen in patients with less severe conditions. Therefore, we consider every patient with ACLF as OLT candidate as long as potential infections are well controlled and no other contraindications are present. However, there are certainly negative predictors which speak against OLT. Patients with prolonged disease course and ongoing multiple organ failure with continued vasopressor support have a high likelihood for peri- and postoperative complications. Moreover, there are patients with a rapidly progressing ACLF and high CLIF-C ACLF score (>70) after 48 h of maximal support who have a mortality rate of nearly 100% (Engelmann et al., unpublished data). To date, it is unclear as to whether those patients are good candidates for OLT, considering that the risk for complication is presumably high and the time for assessment and organ allocation is short. The listing of these patients should be discussed on an individual basis.

Bruns: Against a background of a 'sickest first' policy for organ allocation, careful selection is crucial to identify patients with ACLF who still qualify for liver transplantation. Retrospective analyses suggest that the duration and severity of extrahepatic organ failure, particularly hemodynamic instability and severe respiratory failure, are associated with poor post-transplant outcomes whereas improvement of ACLF prior to transplant is associated with a favorable prognosis. However, the 'window for transplantation' in patients with advanced ACLF seems small and needs to be defined.

Moreau: One could consider patients with ACLF too sick to receive a liver transplant. However, this opinion has recently been challenged. We know that patients with 4 organ failures or more (assessed 3–7 days after diagnosis of ACLF) have a 'spontaneous' 28-day mortality of 100%. In other words, standard medical treatment seems to be futile in these patients. This is why some investigators have suggested that salvage liver transplantation could be the only option to treat patients with high-grade ACLF. There are two studies [4, 5] suggesting that salvage liver transplantation could be beneficial in patients with high-grade ACLF. These results should be confirmed because if they are affirmed the management of ACLF would be markedly changed.

Trebicka: As suggested by Moreau, ACLF might become an indication for special and urgent selection for liver transplantation. More importantly, these data clearly show that ACLF per se is not a contraindication for liver transplantation.

Question 3: How do you handle the coagulopathy of advanced liver cirrhosis and ACLF before invasive procedures or in the case of bleedings?

Bechstein: Usually, even in decompensated cirrhosis there is a balance between coagulation and fibrinolysis. If anything, the scale may be slightly tipped towards a procoagulatory state. This changes dramatically when bleeding occurs, either spontaneously as in the context of upper gastrointestinal bleeding or following injury (invasive procedures, surgery). Before invasive procedures, component therapy is essential, international normalized ratio should be below 1.8 (Quick > 40%), and platelets should be above 50,000/μl. In case of bleeding in cirrhotics, dependent upon circulation and fluid balance, red blood cells and fresh frozen plasma should be administered in a 1:1 ratio with early platelet transfusion in case of thrombocytopenia < 50,000/μl. In case of potential fluid overload, prothrombin complex concentrates may be necessary.

Bruns: It has been increasingly recognized that traditional coagulation tests are often inadequate to assess the meticulous balance of pro- and antihemostatic factors in patients with advanced cirrhosis. Experiences from some centers suggest that rotational thrombelastometry (RTE) can be successfully applied to reduce the use of coagulation factor concentrates in patients with cirrhosis and ACLF undergoing invasive procedures or liver transplantation. Although thrombelastometry as a global coagulation measure accounts for the interplay of all blood components and seems to be a promising tool, it is not universally available and requires some experience in interpretation.

Canbay: One major difficulty in the clinical management of patients with cirrhosis is impaired coagulation with high risk for bleeding. It is well known that bleeding and impaired coagulation contribute significantly to the prognosis of patients with acutely decompensated cirrhosis. In these patients, even minor interventions may be associated with significant risk due to bleeding diathesis, which is usually corrected by administering coagulation factors to adjust classical parameters of coagulation (i.e., 50×10^9 platelets/l or prothrombin time of 50%). However, transfusion of coagulation factors is costly and may also induce complications such as portal vein thrombosis and other thrombotic events. To improve clinical management of patients with advanced cirrhosis, RTE may be used for assessing coagulopathy. Indeed, it has already been shown that this method can improve management in a surgical setting. Supplementation of coagulation factors according to RTE assessment of coagulopathy significantly reduced transfused coagulation factors compared with conventional methods. Moreover, this procedure was not associated with any bleeding or thrombotic complications and reduced the effective cost in patient management [6].

Question 4: Do you consider extracorporeal liver support devices as beneficial in patients with ACLF? Are there specific situations or indications in which you would recommend to use them? Do you believe that the specific type of device (or plasmapheresis) matters?

Bechstein: Currently available evidence does not support the use of extracorporeal liver support devices in the setting of ACLF (nor in any other setting for that matter).

Moreau: The answer is: 'It is not so clear.' The published results of randomized controlled trials (RCTs) of extracorporeal liver support in ACLF are not encouraging. However, these RCTs have been performed during the 'pre-CANONIC' era, using poor criteria for ACLF. One should have in mind that preliminary results of a meta-analysis of MARS trials show beneficial effects on survival of high doses (more than 4 MARS sessions) in patients with ACLF (reclassified according to CANONIC criteria). The paper is under evaluation. MARS may be resuscitated in the future.

There are sporadic case reports suggesting beneficial effects of plasma exchange in patients with ACLF. A large European trial of plasma exchange in patients with ACLF will start this year (APACHE study; sponsor: European Foundation for the Study of Chronic Liver Failure (EF Clif)) and should clarify the use of this approach.

Trebicka: Besides the previously discussed studies, there is a large H2020-funded project called ALIVER, which, also using a specific device (DIALIVE), aims to treat ACLF patients. The rationale is to remove dysfunctional albumin and endotoxins and to simultaneously replace it with functional albumin in one unit. The expected benefits lie in the decreased levels of inflammatory and oxidative stress mediators, which are thought to be responsible for the development and aggravation of ACLF.

Question 5: ACLF is defined by specific organ failures in patients with acute decompensation of liver cirrhosis. As a consequence, patients with ACLF are heterogeneous, e.g. with respect to the underlying liver disease or to the precipitating event of ACLF. In your opinion, should this patient heterogeneity have an impact on the design of clinical intervention trials for the treatment of ACLF?

Bechstein: While it seems obvious for the clinician treating these patients that there are inherent differences, e.g. when comparing a relatively young male patient with biliary sepsis and primary sclerosing cholangitis as opposed to an elderly male patient with SBP, alcoholic cirrhosis, obesity, diabetes, and cardiovascular comorbidity, current data from prospective studies do not yet allow meaningful stratifications on which interventions could be based. However, this does not impede the design of carefully planned interventional trials. Post-hoc exploratory data analysis will then lead to meaningful hypotheses for further studies.

Berg/Engelmann: This is a tremendously important issue that has to be considered in every future clinical study. To us, there are three different aspects that majorly define the heterogeneity.

First, the disease severity and number of organ failures, which define the ACLF grade. Patients with ACLF grade 3 are already excluded in most clinical trials as they often show a rapidly progressing liver disease with high death rates and low regenerative capacity.

Second, the prognosis of ACLF is worse if triggered by infections in comparison to other precipitating events. This means that stratification according to the precipitating event should be considered in future trials.

Third, it becomes more and more apparent that individual pathomechanism patterns, such as inflammation, translocation, apoptosis, etc., are evident in a varying degree in individual patients with ACLF. To date it is unclear whether patients with e.g. predominant inflammation or rather apoptosis require different types of treat-

ments. However, it is conceivable that future trials need to consider these patterns as this might determine treatment responses.

Bruns: ACLF is a very heterogeneous syndrome in terms of underlying disease, precipitating events, consecutive immune response, and type and severity of organ failures, all of which are determining course and outcome. As a consequence, treatment strategies may substantially differ e.g. between patients with sterile and infection-driven inflammation, those with severe inflammatory and hyporesponsive states of the innate immune system, or those patients with hepatic or extrahepatic organ failures. In addition, the timing of the intervention is critical. In my opinion, it is virtually impossible to design trials with exhaustive stratification or conclusive subgroup analysis for this broad range of possible confounders. Given the urgent need for effective therapies, clinical trials should therefore pragmatically define those ACLF patients who will likely benefit the most from the particular intervention but without losing the representative character of the population and still allowing for a feasible recruitment of participating centers.

Moreau: The answer is yes. For example, future interventional studies should be contextual, aiming to improve care of patients with severe sepsis or septic shock or of those patients with steroid-resistant severe alcoholic hepatitis (SAH). Actually, bridge therapies should be developed in patients with ACLF because of the perspective of liver transplantation. A better understanding of molecular networks underlying context-dependent severity could help identify novel therapies.

Another point is prevention. For a given environmental stimulus (infection, excessive alcohol drinking) not all patients develop ACLF. Future studies should identify: i) patients at risk of developing sepsis-related ACLF or SAH, and ii) therapies which could prevent the development of these forms of ACLF.

Prevention of infection is a major issue in patients who survive an episode of ACLF. Indeed, infection develops in 50% of these. Currently, we do not know how to identify patients at risk and which prophylaxis to use. Future studies are needed.

Trebicka: The patients' heterogeneity is important to be considered, and personalized medicine is needed in all areas of medicine and especially in ACLF. Still, ACLF grades were chosen based on the mortality of the respective combination of organ failures and dysfunction, and therefore are a good tool of stratification (first step in the direction of personalized medicine) of the patients. Moreover, despite the heterogeneity of the ACLF patients, the mortality rates are very homogeneous and confirmed in different studies. Of note, ACLF is a heterogeneous group of patients with one surprisingly homogeneous feature, i.e. massively and extensively increased systemic levels of inflammatory markers, which is the reason for or consequence of development of organ failure. This is another topic requiring further studies, which are only possible if we consider ACLF a syndrome with some homogeneous features, as defined in the CANONIC study and recently in the EASL Clinical Practice Guidelines.

Question 6: Do you apply any experimental drugs such as N-acetylcysteine (NAC) or granulocyte-colony stimulating factor (G-CSF) outside of clinical studies for the treatment of patients with ACLF?

Bechstein: Both substances are not being used in the setting of ACLF outside of clinical trials.

Berg/Engelmann: G-CSF has the potential to become an effective treatment approach in patients with ACLF. An impressive survival benefit was observed; however, only in several small and monocentric studies which were nearly exclusively performed in India. Hence, the broad application of G-CSF in ACLF can currently not be recommended, as confirmation of these results in larger multicenter studies is required. Moreover, it is still unclear in which situation G-CSF, which actually is an immune stimulator, unfolds its regenerative capacities in a disease characterized by systemic inflammation. In Germany, we are running a multicenter clinical trial supported by the German research foundation, the GRAFT-Study, which actively recruits patients to evaluate the effect of G-CSF in ACLF. Outside of clinical trials, individual treatments should only be performed in cooperation with clinicians experienced in identifying patients who might benefit from this type of therapy.

Bruns: Currently, we are applying G-CSF for ACLF only in the context of a multicenter clinical trial led by the University Hospital Leipzig. We do not use NAC in cirrhotic patients with ACLF.

Moreau: The answer is no for the following reasons:

G-CSF has been evaluated in the context of SAH in two RCTs performed in India [7, 8]. There were limitations: open label, corticosteroids were not used, the presence of ACLF was not assessed, and the RCTs have been performed in a single center (Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh), raising the question of generalizability.

There is only 1 RCT of G-CSF in patients with ACLF. Limitations were: mixed patient population (hepatitis B virus-related and alcoholic liver disease), open label, single center (Institute of Liver and Biliary Sciences (ILBS) in New Delhi), no trial in Europe.

NAC has been evaluated in the context of SAH. There was only a marginal effect of NAC in a French multicenter trial in patients with SAH treated with corticosteroids (not all had ACLF) [9]. In one of the two Indian RCTs (see above), survival was lower among patients receiving G-CSF plus NAC than among those who received G-CSF alone [8].

Trebicka: There is evidence that G-CSF may be a relevant treatment in ACLF, as outlined above. Especially the multicenter German study GRAFT is not only expected to demonstrate that G-CSF is safe but also that it might improve mortality in ACLF patients. By contrast, while NAC in acute liver failure induced by acetaminophen protein adducts is standard, the evidence for NAC in ACLF is conflicting; therefore, its use is not evidence-based.

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References

1 Moreau R, Jalan R, Gines P, et al: Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–1437, 1437.e1–9.
2 Fernández J, Acevedo J, Wiest R, et al.; European Foundation for the Study of Chronic Liver Failure: Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2017;DOI: 10.1136/gutjnl-2017-314240.
3 Moreau R, Elkrief L, Bureau C, et al: A randomized trial of 6-month norfloxacin therapy in patients with Child-Pugh class C cirrhosis. J Hepatol 2017;66 (suppl):S1.
4 Gustot T, Fernandez J, Garcia E, et al.; CANONIC Study Investigators of the EASL-CLIF Consortium: Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243–252.
5 Artru F, Louvet A, Ruiz I, et al: Liver transplantation in the most severely ill cirrhotic patients: a multicentre study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708–715.
6 Bedreli S, Sowa JP, Gerken G, Saner FH, Canbay A: Management of acute-on-chronic liver failure: rotational thromboelastometry may reduce substitution of coagulation factors in liver cirrhosis. Gut 2016;65:357–358.
7 Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R: Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. Am J Gastroenterol 2014;109:1417–1423.
8 Singh V, Keisham A, Bhalla A, Sharma N, Agarwal R, Sharma R, Singh A: Efficacy of granulocyte colony-stimulating factor and N-acetylcysteine therapies in patients with severe alcoholic hepatitis. Clin Gastroenterol Hepatol 2018;DOI: 10.1016/j.cgh.2018.01.040.
9 Nguyen-Khac E, Thevenot T, Piquet MA, et al: Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365:1781–1789.