Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.013.

References

[1] Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69:1047–1056.

[2] Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250–256.

[3] Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. Gut 2017;66:541–553.

[4] O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD Acute-on-Chronic Liver Failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis. Hepatology 2018, Jan 8 [Epub ahead of print].

Paul J. Thuluvath[1,3,*]
Avesh J. Thuluvath[2]
Steve Hanish[3]
Yulia Savva[1]

[1]*Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD, United States*
[2]*Johns Hopkins University School of Medicine, Baltimore, MD, United States*
[3]*University of Maryland School of Medicine, Baltimore, United States*
*Corresponding author. Address: Institute of Digestive Health & Liver Diseases, Mercy Medical Center, Baltimore, MD 21202, United States.
E-mail address: thuluvath@gmail.com

Only in the darkness can you see the stars: Severe alcoholic hepatitis and higher grades of acute-on-chronic liver failure

To the Editor:

We read with interest the recently published study by Sersté *et al.* in the *Journal*, as well as the subsequent correspondences by Forrest *et al.* and the original authors.[1,2] Both the study and subsequent correspondences agreed on to 2 important aspects in severe alcoholic hepatitis (SAH) related acute-on-chronic liver failure (ACLF): i) the benefits of corticosteroids (CS) for SAH in patients with ACLF grades 2 and 3 and ii) the dire need for new clinical trials in this difficult to treat group of patients. With this in mind, we would like to briefly discuss salient aspects in literature with regards to key studies in ACLF and provide novel insights into future prospects based on our experience with faecal microbiota transplantation (FMT) in this group of patients. Gustot *et al.* demonstrated that ACLF grade 2 and 3 patients (any cause) had a 180-day mortality approaching 79% and 96% in which, early 28-day liver transplantation (LT) improved survival in 80% at 180 days and 75% at 1 year.[3] In those without LT and <4 organ failures (OFs) and Chronic Liver Failure Consortium (CLIF-C) ACLF score <64, continuation of standard care resulted in survival in only 39% with 100% mortality in those with >4 OFs or CLIF-C ACLF score >64. Similarly, Sersté *et al.* show that ACLF in SAH is associated with a poor outcome and that the Lille response to corticosteroids was reduced in those with prevalent ACLF.[1] Forrest *et al.* reveal that for Lille-non-responders with ACLF grades 0, 1 and (2+3) the 90-day survival rates were 68.1%, 45.8% and 36.7%.[2] Corticosteroid use may also promote infections in ACLF leading to Lille non-response and worse outcomes.[4] Considering this 'catch-22' situation, we retrospectively looked at 1.5-year outcomes in patients with SAH-ACLF and infections not eligible for CS and not undergoing LT who were on salvage FMT. Written informed consent was obtained from each patient included in the study and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. From August 2016 to September 2018, 88 patients with SAH-ACLF underwent FMT as per previously described and published protocol of which 72 patients completed treatment.[5,6] The complete patient enrolment into the study along with exclusion details is shown (Fig. S1). Thirty-eight patients completed 1.5-year (548 day) follow-up, of whom 15 were excluded in view of alcohol relapse (n = 9), use of complementary and alternative medication (n = 4) and LT (n = 2). Finally, 23 patients were included in the analysis. For ease in analysis, patients with ACLF were grouped into lower (0+1) and higher (2+3) grades. All were males with mean age 46.5 ± 9.2 years; ACLF grade 0 (n = 2, 8.7%), grade 1 (9, 39%), grade 2 (9, 39%), grade 3 (3, 13%); mean CLIF-C ACLF score 93.6 ± 9.2; CLIF-C Score 11.7 ± 1.7; Child Pugh score 12.4 ± 1.2; discriminant function 78 ± 17.2 (range 53.4 to 119.4) and model for end-stage liver disease-sodium (MELD-Na) 29.5 ± 3.7. At the end of 548 days follow-up, 8 patients (overall survival rate 66%) died with overall mean survival 389.3 (95% CI 295.4 to 483.1) days. The commonest cause of death on follow-up was sepsis (n = 5/8, 62.5%). Two patients developed culture negative neutrocytic bacterascites controlled with a short course of intravenous antibiotics while another developed uncontrolled acute variceal bleeding after completion of FMT. In the lower (ACLF 0+1, n = 11) and higher grades (ACLF 2+3, n = 12), the proportion of patients surviving (Fig. 1) at the end of 548 days follow-up was 72.7% and 58.3%, respectively (χ^2 0.2761, $p = 0.59$). Hughes *et al.* demonstrated that there has been no improvement in mortality from AH because of the lack of effective treatments in this patient group.[7] We believe that healthy donor FMT may be a potential treatment option that requires further prospective high-quality studies for SAH and higher grades of ACLF. The results of ongoing randomized trial comparing CS to FMT in SAH-ACLF are highly anticipated (NCT03091010). Even though a small retrospective observation with confounding factors, following a crude protocol that requires refinement, we modestly ponder the hopeful aspect of this intervention. Many patients were excluded in

Keywords: FMT; Dysbiosis; Stool transplant; ACLF; Portal hypertension; Alcohol; Cirrhosis; Gut microbiome; Microbiota.

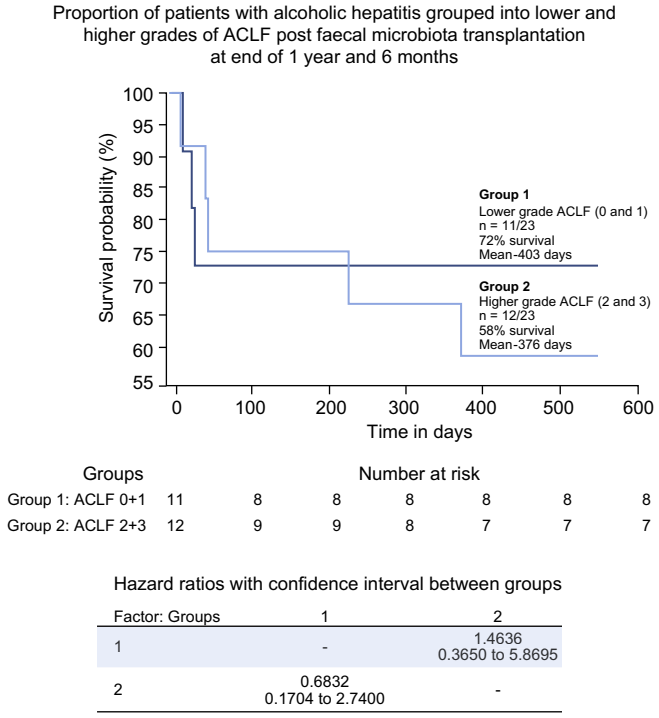

Fig. 1. Kaplan-Meier analysis. Proportion of patients with infection and SAH – ACLF (n = 23) surviving at 1.5 years post healthy donor faecal microbiota transplantation, grouped according to lower (0+1) and higher (2+3) grades of ACLF (as per CLIF – ACLF). The survival curves demonstrate better 1.5-year (548 days) transplant-free survival even in the presence of high CLIF-C-ACLF scores. ACLF, acute-on-chronic liver failure; CLIF, Chronic Liver Failure Consortium; SAH, severe alcoholic hepatitis.

our study from receiving FMT for various reasons that may have introduced a bias in their outcome. In patients with SAH-ACLF and higher CLIF-C ACLF scores and ACLF grades, in the absence of multiple organ support, before futility is decided upon, FMT may be considered as a potential safe salvage option to preserve life or as a bridge to LT because "we must accept finite disappointment, but never lose infinite hope". The strong evidence to justify use of FMT in the treatment of SAH and higher grades of ACLF is still lacking and larger randomized multi centre studies need to be undertaken to assess survival benefits beyond what the current standard(s) of care has to offer.

Financial support
The authors received no financial support to produce this manuscript.

Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
CAP designed the study and wrote the manuscript, GP, RA, AJ and SR acquired, compiled and analysed the data, CAP and PA finalized the manuscript and made critical revisions to analysis, all authors accepted to the final revision of manuscript

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.004.

References
[1] Sersté T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol 2018;69:318–324.
[2] Forrest E, Atkinson S, Richardson P, Masson S, Ryder S, Thursz M, et al. Prevalent acute-on-chronic liver failure and response to corticosteroids in alcoholic hepatitis. J Hepatol 2018, [Epub ahead of print].
[3] Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243–252.
[4] Vergis N, Atkinson SR, Knapp S, Maurice J, Allison M, Austin A, et al. In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. Gastroenterology 2017;152:1068–1077.
[5] Philips CA, Pande A, Shasthry SM, Jamwal KD, Khillan V, Chandel SS, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. Clin Gastroenterol Hepatol 2017;15:600–602.
[6] Philips CA, Phadke N, Ganesan K, Ranade S, Augustine P. Corticosteroids, nutrition, pentoxifylline, or fecal microbiota transplantation for severe alcoholic hepatitis. Indian J Gastroenterol 2018. https://doi.org/10.1007/s12664-018-0859-4, [Epub ahead of print].
[7] Hughes E, Hopkins LJ, Parker R. Survival from alcoholic hepatitis has not improved over time. PLoS ONE 2018;13 e0192393.

Cyriac Abby Philips*
Philip Augustine
Guruprasad Padsalgi
Rizwan Ahamed
Amal Jose
Sasidharan Rajesh
The Liver Unit, Cochin Gastroenterology Group, Ernakulam Medical Centre, Kochi, Kerala, India
*Corresponding author. Address: Philip Augustine Associates, Automobile Road, Palarivattom, Kochi, Kerala 682025, India.
Tel.: +91 9207745776.
E-mail address: abbyphilips@paa.org.in