Hepatology International (2019) 13:395–398
https://doi.org/10.1007/s12072-019-09961-4

COMMENTARY

The first Chinese guidelines on the Management of Ascites and its Related Complications in Cirrhosis: a great goal for a great country

P. Angeli[1]

Received: 31 March 2019 / Accepted: 14 June 2019 / Published online: 16 July 2019
© Asian Pacific Association for the Study of the Liver 2019

Introduction

The guidelines developed by scientific societies and associations make sense if they can be interpreted and contextualized in the real-life conditions of different geographical areas and countries. For this to happen, they must bear in mind that: (a) the clinical characteristics of the same disease (liver cirrhosis in the case in point) can vary due to genetic, ethnic, and environmental factors and (b) many aspects of disease management strongly depend on how different health systems are organized. The Chinese Society of Hepatology takes credit for achieving this goal. The methodology adopted by the Society and its working team was rigorous and multidisciplinary. The final document may seem rather long and difficult to consult in clinical practice. The same criticism was voiced over the European Association for the Study of the Liver (EASL) guidelines [1], too. However, the topic is very broad and such guidelines should be used like a manual, ready to hand, that deals separately with specific issues under separate headings. This commentary is on "Chinese guidelines on the management of ascites and its related complications in cirrhosis" published in Hepatology International 2019;13(1):1–21. https://doi.org/10.1007/s12072-018-09923-2.

Ascites

The main issue in the Chinese Society's Guidelines is "ascites". With regard to the pathogenesis of ascites, the authors seem to have overlooked the latest developments of research in this field. They focus only on portal hypertension [2], which is the core process, of course, but fail to mention other key processes such as systemic inflammation and oxidative stress [3], which are at the center of the scientific debate today (Fig. 1). The role of albumin is also discussed only in terms of its oncotic properties, although this molecule's non-oncotic properties seem to be gaining importance.

Moving from the pathogenic to the clinical sphere, the one third of the 14 recommendations concern the criteria for diagnosing refractory ascites. The authors did not adopt the recommendations of the EASL [1], or American Association for the Study of the Liver (AASLD) [4], which were largely based on the results of two consensus conferences organized by the International Ascites Club (ICA) in 1996 and 2003 [5, 6]. Instead, they opted for those arbitrarily proposed by Zhang et al. in 2014 [7]. We probably do need a new, treatment-driven classification of ascites, considering not only the two categories (responsive and refractory ascites) currently envisaged, but also a third category—recurrent ascites—for which a definition already exists [1]. That said, this should be done through a process of consensus to avoid a fragmentation of the science and expertise on these aspects of ascites, which would hinder further advances in this field. As for the treatment of ascites, the authors have not accurately quoted the results of the ANSWER study [8], and the MACTH study [9] both of which were published in 2018, on the effect of long-term infusions of 20% human albumin (HA) solution on the prognosis of patients with ascites. As a consequence, the dosage of HA suggested in their Recommendation 9 is again arbitrary. The same can be said of the dose of 4 g of HA per liter of ascitic fluid removed by means of a therapeutic paracentesis, as suggested in Recommendation 10. This suggestion is based on a small randomized controlled study (RCT) [10] and disregards the findings of larger RCTs and meta-analyses [11]. There is not enough evidence as yet to support the use of tolvaptan or terlipressin to manage refractory ascites, as suggested in Recommendations 5 and 6, respectively. Reports on the efficacy of tolvaptan are still conflicting [7, 12–14], and there is only

✉ P. Angeli
pangeli@unipd.it

[1] Internal Medicine and Hepatology Unit (UIMH), Dept of Medicine (DIMED), Padova University-Teaching Hospital, Padua, Italy

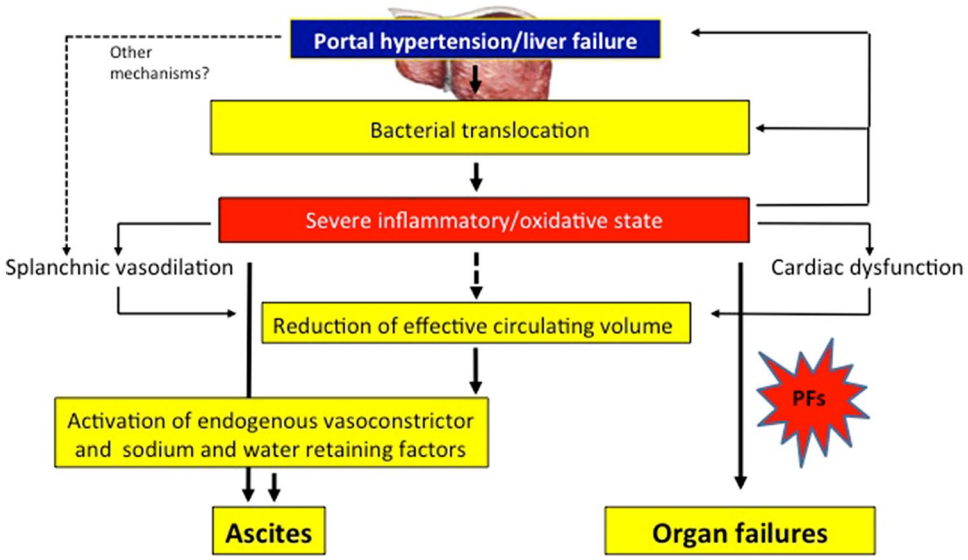

Fig. 1 New theory on the pathogenesis of decompensation and organ failure/s in patients with cirrhosis

little, and time-limited evidence of the role of terlipressin in patients with normal renal function [15]. The use of terlipressin in patients with type 2 hepatorenal syndrome (HRS), who often have refractory ascites, has been disappointing, with high rates of HRS recurrence and no survival benefit [16, 17]. Therefore, some RCTs on tolvaptan and vasoconstrictors, including midodrine, would be needed before any such recommendations can be made. While on the subject of tolvaptan, a paragraph in the guidelines dedicated to hyponatremia would have been valuable, for three main reasons: first, hyponatremia is the commonest electrolyte disturbance in patients with cirrhosis and ascites; second, China and Japan are the only countries in the world to use tolvaptan for the treatment of fluid retention and hyponatremia in patients with cirrhosis; and third, the potentially positive effect of tolvaptan on survival for patients with cirrhosis and refractory ascites seems to relate to an improvement in the serum concentration of sodium [15]. Recommendation 11 on the use of TIPS suffers from the previously mentioned arbitrary definition of refractory ascites. Finally, it is impossible to comment on Recommendation 14, concerning the potential role of Traditional Chinese Medicine, as this requires specific expertise in a field peculiar to the culture and organization of China's health system that the authors of the Guidelines naturally could not ignore.

Spontaneous bacterial peritonitis

The discussion of the topic of spontaneous bacterial peritonitis (SBP) and the recommendations on the management of this complication are some of the best parts of the Guidelines as a whole. This is particularly true considering that, at the time of their writing, the authors had yet to benefit from the data of the GLOBAL study on the epidemiology and clinical assessment of bacterial infections in various parts of the world, including China [18].

That said, first, in the background, the authors often refer to the severity of the infection, and to sepsis in particular, without mentioning the diagnostic tools used to define them—although they exist and have been validated in such patients [19]. Second, there is no adequate recommendation on the use of HA in the prevention of acute kidney injury (AKI) in patients with SBP, though this was mentioned in the background. Third, the recommendation on SBP primary and secondary prophylaxis is rather weak and insufficient: the authors mention rifaximin "that can help to prevent the recurrence of SBP", but not norfloxacin, which can be used to prevent SBP in patients at high risk of developing it [20, 21], as well as for treating cases of recurrent of SBP [22], improving survival as a result [20, 21]. Their failure to consider norfloxacin may have to do with concerns that long-term prophylaxis with quinolones may favor the onset of infections supported by multi-drug resistant bacteria, but recent findings in cirrhotic patients did not confirm as much [23, 24].

Hepatorenal syndrome

Without repeating the previous comments on pathogenesis, there is a new theory (Fig. 1) that the pathogenesis of HRS cannot just be attributed to kidney hypoperfusion. A more complex pathophysiological background than circulatory

dysfunction alone may induce renal damage through other mechanisms, including inflammation, microvascular dysfunction, or direct tubular damage. In their diagnostic considerations, the authors could have adopted a more coherent sequence for their recommendations, because once the KDIGO criteria have been accepted for the diagnosis of Acute Kidney Injury (AKI) (as proposed by the ICA in 2015), it is no longer possible to go on using the old definition of type 1 HRS, which has been replaced with HRS-AKI, as the authors argued [24]. As a result, there is no longer any cutoff for serum creatinine (sCr) beyond which AKI (and, therefore, also HRS-AKI) has to be diagnosed, and the final cutoff for sCr has no place in the new definition of HRS-AKI [25]. This is crucial, because the efficacy of treatment for HRS-AKI is strongly related to baseline sCr: the higher the baseline sCr, the lower the likelihood of a response to the treatment [26]. Finally, a stage-driven algorithm for managing AKI and HRS-AKI as proposed by the ICA [1, 25] is lacking. In addition, there is no mention of the well-known advantages of administering terlipressin by continuous iv. infusion [27], while the use of tolvaptan is recommended, though it has never been tested in patients with HRS-AKI and hyponatremia.

Conclusions

The Chinese Society of Hepatology is to be congratulated for taking the initiative and for its methodological approach. These are the first Chinese Guidelines on the "Management of Ascites and Its Related Complications", and this in itself suffices to lend prestige and honor to what has been done. Like the results of all human efforts, these Guidelines can be improved, but they represent a valid starting point for providing patient care and developing research in the near future. This will hopefully be done by maintaining a solid and active interaction with other international scientific associations to avoid a fragmentation of science and expertise, which is an enemy of scientific progress. Focusing on furthering research, the aims of the document are clearly defined and this will contribute to making it a milestone for the development of hepatology in China, adding to this great country's contribution to global science and medical understanding.

References

1. EASL Clinical Practice Guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 53:397–417
2. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodes J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151–7
3. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272–84
4. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline. Management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57: 1651–1653
5. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–66
6. Arroyo V, Gines P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatology 1996;23:164–76
7. Zhang X, Wang SZ, Zheng JF, Zhao WM, Li P, Fan CL, et al. Clinical efficacy of tolvaptan for treatment of refractory ascites in liver cirrhosis patients. World J Gastroenterol 2014;20:11400–5
8. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417–29
9. Solà E, Solé C, Simón-Talero M, Martín-Llahí M, Castellote J, Garcia-Martínez R, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. J Hepatol 2018;69:1250–9
10. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417–29
11. Alessandria C, Elia C, Mezzabotta L, Risso A, Andrealli A, Spandre M et al. Prevention of paracentesis-induced circulatory dysfunction in cirrhosis: standard vs half albumin doses. A prospective, randomized, unblinded pilot study. Dig Liver Dis 2011;43:881–6
12. Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012;55:1172–81
13. Rai N, Singh B, Singh A, Vijayvergiya R, Sharma N, Bhalla A et al. Midodrine and tolvaptan in patients with cirrhosis and refractory or recurrent ascites: a randomised pilot study. Liver Int 2017;37:406–14
14. Jia JD, Xie W, Ding HG, Mao H, Guo H, Li Y, et al. Utility and safety of tolvaptan in cirrhotic patients with hyponatremia: a prospective cohort study. Ann Hepatol 2017;16:123–32
15. Wang S, Zhang X, Han T, Xie W, Li Y, Ma H, et al. Tolvaptan treatment improves survival of cirrhotic patients with ascites and hyponatremia. BMC Gastroenterol 2018;18(1):137. https://doi.org/10.1186/s12876-018-0857-0
16. Fimiani B, Guardia DD, Puoti C, D'Adamo G, Cioffi O, Pagano A, et al. The use of terlipressin in cirrhotic patients with refractory ascites and normal renal function: a multicentric study. Eur J Intern Med 2011;22:587–90
17. Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. Eur J Gastroenterol Hepatol 2002;14:1363–8
18. Rodriguez E, Henrique Pereira G, Solà E, Elia C, Barreto R, Pose E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. Liver Transpl 2015;21:1347–54

19. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J. et al. on behalf of International Club of Ascites Global Study Group. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2018
20. Piano S, Bartoletti M, Tonon M, Baldassarre M, Chies G, Romano A, et al. Assessment of Sepsis-3 criteria and quick SOFA in patients with cirrhosis and bacterial infections. Gut 2018;67:1892–9
21. Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24
22. Moreau R, Elkrief L, Bureau C, Perarnau JM, Thévenot T, NORFLOCIR Trial Investigators et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology 2018;155:1816–27
23. Gines P, Rimola A, Planas R, Vargas V, Marco F, Almela M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology 1990;12:716–24
24. Angeli P, Bernardi M. Reply to: prophylaxis of spontaneous bacterial peritonitis: is there still room for quinolones? J Hepatol 2019;5:25. https://doi.org/10.1016/j.jhep.2019.01.011 **(Epub ahead of print)**
25. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. J Hepatol 2015;62:968–74
26. Piano S, Schmidt HH, Ariza X, Amoros A, Romano A, Hüsing-Kabar A et al. on behalf of EASL CLIF Consortium, European Foundation for the Study of Chronic Liver Failure (EF Clif). Association Between grade of acute on chronic liver failure and response to terlipressin and albumin in patients with hepatorenal syndrome. Clin Gastroenterol Hepatol 2018;16: 1792–1800
27. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatology 2016;63:983–92

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.