taking into account the fact that cirrhotic patients are experienced to health care structures, and thus carry a higher probability of being colonized by multidrug resistant germs. Furthermore, fluoroquinolone exposure increases the rate of resistant microorganism isolation beside the enteric microbiota. Tacconelli *et al.*[9] showed that quinolone use was associated with a risk ratio of 3 of acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the highest across different class of antibiotics, with relevant consequences in infections other than SBP.

Taken together, all these data suggest that we have to rethink the use of quinolones and fluoroquinolones for SBP prophylaxis. Despite the laudable service rendered, evidence is shifting the balance toward a prevalence of negative consequences. If we want to continue to use these drugs for SBP prophylaxis, proof showing their impact on both side effects and antimicrobial resistance in this specific setting are demanded. Moreover, also in this setting, antibiotic stewardship programmes should be implemented: they consist of a series of policies aimed at the appropriate use of antimicrobial drugs in order to reduce microbial resistance and decrease the spread of multidrug resistant organisms.[10]

Otherwise, alternative/new regimens must be sought: in the meantime, prophylaxis with trimethoprim/sulfamethoxazole can be considered a safe and effective alternative and it has already been endorsed by AASLD guidelines. Rifaximin, with its peculiar pharmacokinetic properties limiting the systemic values of the drug, and thus the side effects, is a promising alternative. However, larger and well-conducted randomised controlled trials are needed to establish the non-inferiority of rifaximin compared to systemic antibiotics for SBP prophylaxis.

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Supplementary data

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Reply to: "Prophylaxis of spontaneous bacterial peritonitis: is there still room for quinolones?"

To the Editor:

We read with great interest the Letter by Lombardi *et al.* on "Prophylaxis of spontaneous bacterial peritonitis: Is there still room for quinolones?" First, we would like to offer a few words of sincere gratitude for the kind words that the authors used in evaluating the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines (CPGs) that we recently had the burden and the honor of publishing.[1]

That said, it is our wish to directly address the main comment of Lombardi *et al.* related to the use of norfloxacin in primary and secondary prophylaxis of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis, which is the follow-

ing: "data suggest that we have to rethink the use of quinolones and fluoroquinolones for SBP prophylaxis". The authors based their conclusion on 3 main issues: a) the side effects of fluoroquinolones recently referred to by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), b) the high resistance profile to fluoroquinolones and c) the contribution of fluoroquinolones in generating multidrug resistant (MDR) and extensively drug resistant (XDR) bacteria.

Regarding the adverse effects, we would like to recall that some of them, that is those involving the osteo-muscular apparatus and the central and peripheral nervous system,[2] have long been recognised while others, such as the possible hypoglycaemic effect of norfloxacin or its possible contributory role in the pathogenesis of aortic aneurysms, were only recently reported, after the publication of the CPGs.[3–5]

We do not intend to underestimate the relevance of the FDA and EMA documents mentioned by the authors, but it must be recognised that no report on the significant adverse effects of norfloxacin is currently available from randomised clinical trials (RCTs) or in studies of "real clinical practice" with norfloxacin as prophylaxis for SBP.

Moving to the high resistance profile of isolates of *Escherichia coli* and *Klebsiella pneumoniae* to fluoroquinolones reported by the European Antimicrobial Resistance Surveillance Network in 2015,[6] we agree with Lorenzi *et al.* that this problem opens the discussion on how to prevent a relapse of SBP when the index episode was sustained by a quinolone-resistant bacterium. Thus, we agree that alternative regimens must be sought and tested in RCTs, particularly in secondary prophylaxis of SBP, while, in the meantime, rifaximin could be used empirically.[7] But, we do not agree with the use of trimethoprim/sulfametoxazole in the prophylaxis of SBP, since it must be remembered that the prevalence of trimethoprim/sulfametoxazole-resistant microorganisms isolated from patients with cirrhosis is at least as high as that of quinolone-resistant strains.[8] Nevertheless, we would like to point out that, even in the context of secondary prophylaxis, the problem of the resistance of gram-negative bacteria to quinolones is far more complex than it may appear. In fact, a) there are either some doubt on the invasive capacity of quinolone-resistant gram-negative bacteria,[9] or some evidence that sub-minimum inhibitory concentrations of norfloxacin are able to reduce the *in vitro* adherence on epithelial cells by *E. Coli* strains from patients with cirrhosis, a capability not affected by the resistance to quinolones;[10] b) it is not known how long a quinolone-resistant strain of a gram-negative bacterium, responsible for an episode of SBP can maintain its profile of resistance in the microbiome of a patient with cirrhosis.

All this makes it possible to explain why in a recent multicentre French RCT, long term norfloxacin prophylaxis was able to reduce the rate of infections sustained by gram-negative bacteria and improve survival in patients with Child-Pugh class C cirrhosis at high risk of developing SBP.[11]

Finally let us comment on the potential role of prophylaxis of SBP with norfloxacin in the selection of MDR or XDR bacteria. This is a very common belief among hepatologists, but again not supported by the most recent data, that Lorenzi *et al.* did not mention. In fact, this belief was not confirmed by the French RCT previously quoted[11] and by the largest prospective, observational study conducted worldwide on the epidemiology of bacterial infections in patients with cirrhosis hospitalised for a bacterial infection or developing a bacterial infection during their hospital stay.[12] In these patients, the incidence of infections caused by MDR bacteria was not higher among those who received norfloxacin than among those who did not.[12]

So, on clinical grounds, while waiting for new options for SBP prophylaxis, the most important message that can also be drawn from the most recent findings[11,12] is that patients with an indication for primary or secondary prophylaxis of SBP should continue to receive quinolones with few exceptions, raising the level of clinical monitoring for the potential development of adverse effects.

In conclusion, the most recent finding,[11,12] added to those already existing,[13,14] justify, on the methodological level, the recommendations on the prophylaxis of SBP reported in the EASL CPGs for the management of patients with decompensated cirrhosis. Indeed, recommendations should be based on evidence and not on considerations or speculations, which may certainly be valid and shareable, at least in part as in this case, but have the limit of remaining what they are.

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Supplementary data

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Is *ex vivo* liver resection and autotransplantation a valid alternative treatment for end-stage hepatic alveolar echinococcosis in Europe?

To the Editor:

The authors of the article "*Ex vivo* liver resection and autotransplantation (ELRA) as alternative to allotransplantation for end-stage hepatic alveolar echinococcosis" describe an overall mortality rate of 12% after a mean follow-up of 22 months.[1] The authors come to the conclusion that ELRA is an effective alternative to liver transplantation and is a feasible surgical option for patients with end-stage alveolar echinococcosis (AE).

The contents of article have to be regarded with caution, especially by European clinicians, given that essential information is missing. Although the selection process used to propose this procedure to patients, with very advanced AE, is properly described, comparison of its outcome with that of patients from the same center with standard *in situ* resection, and with anti-infective treatment, without surgery, is not available in this article. The conclusions are based on the assumption that liver transplantation is the only therapeutic alternative to resection in these patients and that such high mortality is acceptable. Results after allotransplantation are indeed associated with significant mortality, recurrence of disease, and the procedure is limited by the organ shortage that affects all countries, including China.[2,3] However, indications for liver allotransplantation for AE have considerably decreased in the European endemic areas of AE (only 1/111 in Bern [Switzerland] and 2/172 since 2000 in Besançon [France]), and the results of non-surgical treatment strategies in Europe are far better than presumed by the authors. Long-term treatment using albendazole alone or in conjunction with perendoscopic biliary stenting is a

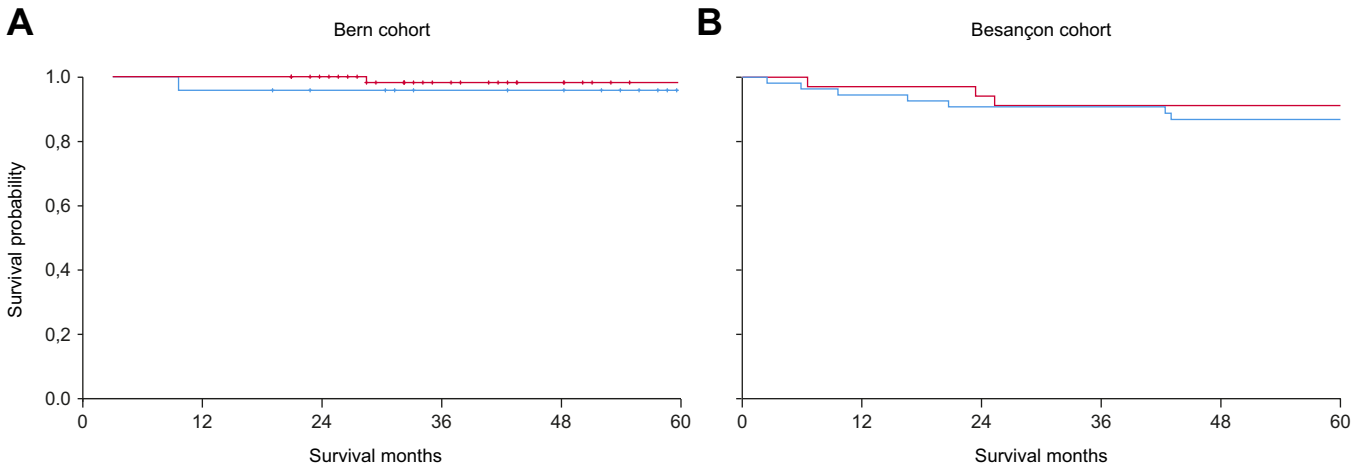

Fig. 1. Survival after conservative (blue curves) and surgical treatment (red curves) in Europe. (left panel) Bern, Switzerland and (rigth panel) Besançon, France. 5 yr-survival in 67 patients with diagnosis and follow-up in Bern from 1 Jan 1993 to 31 Dec 2015; 68.7% of patients had radical surgery; no deaths were related to AE. 5 yr-survival in 85 patients with diagnosis and follow-up in Besançon from 1 Jan 2003 to 31 Dec 2011; 38% of patients had radical surgery; only 1 death (1.2%) was related to AE. No death was directly related to the surgical procedure in either center, and all other deaths were related to associated conditions. AE, alveolar echinococcosis. (This figure appears in colour on the web.)