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Filipe Andrade[1,2]
Akash Shukla[3]
Christophe Bureau[4]
Marco Senzolo[5]
Louis D'Alteroche[6]
Alexandra Heurgué[7]
Fanny Turon[8]
Juan-Carlos Garcia-Pagan[8]
Frédéric Oberti[9]
Dhiraj Tripathi[10]
Pierre-Emmanuel Rautou[1,11,12,*]
[1]*Service d'Hépatologie, DHU Unity, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France*
[2]*Department of Medicine, Hospital Pedro Hispano, Matosinhos, Portugal*
[3]*Department of Gastroenterology, Seth GS Medical College and KEM Hospital, Mumbai, India*
[4]*Service d'Hépato-gastro-entérologie, CHU Toulouse, Toulouse, France*
[5]*Multivisceral Transplant Unit, Department of Surgical and Gastroenterological Sciences, University Hospital of Padua, Padua, Italy*
[6]*Service Hépato-gastro-entérologie, CHU Tours, France*
[7]*Service d'Hépato-Gastro-entérologie, Hôpital Robert-Debré, Reims, France*
[8]*Barcelona Hepatic Hemodynamic Lab and Liver Unit, Hospital Clinic-IDIBAPS and CIBERehd, University of Barcelona, Spain*
[9]*University Hospital of Angers, Department of Hepatology, Angers, France*
[10]*Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK*
[11]*INSERM, U970, Paris Cardiovascular Research Center – PARCC, Paris, France*
[12]*Université Denis Diderot-Paris 7, Sorbonne Paris Cité, 75018 Paris, France*
*Corresponding author. Address: Service d'hépatologie, Hôpital Beaujon, 100 boulevard du Général Leclerc, 92100 Clichy, France. Tel.: +33 1 40 87 52 83, fax: +33 1 40 87 55 30.
E-mail address: pierre-emmanuel.rautou@inserm.fr

Prophylaxis of spontaneous bacterial peritonitis: Is there still room for quinolones?

To the Editor:

As members we are really proud of the recently published Association's Clinical Practice Guidelines (CPGs) for the management of patients with decompensated cirrhosis.[1] They offer a precise and careful dissection of the issues encountered during the management of these delicate patients and provide clear and justified indications for treatment.

Especially relevant for us are the indications provided about prophylaxis of spontaneous bacterial peritonitis (SBP). The CPGs suggest that antibiotic prophylaxis should be performed in 3 high-risk patient populations: patients with acute gastrointestinal (GI) haemorrhage, patients with low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis) and patients with a previous history of SBP (secondary prophylaxis). Whereas ceftriaxone is the antibiotic of choice in those with GI haemorrhage, norfloxacin, a molecule belonging to the class of fluoroquinolone antibiotics, is recommended for both primary and secondary prophylaxis. Norfloxacin administration must be continued until long-lasting improvement of clinical condition and disappearance of ascites in patients undergoing primary prophylaxis whilst is unclear if it can be interrupted in those receiving secondary prophylaxis. It must be noted that the American Association for the Study of Liver Disease (AASLD) Guidelines for the management of adult patients with ascites due to cirrhosis suggest a similar approach. Indeed, patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin.[2] The rationale behind the administration of fluoroquinolones in cirrhotic patients is to reduce the translocation of gram-negative bacteria from the gut lumen, as these bacteria are responsible for SBP in the majority of cases. The use of other molecules such as rifaximin, poorly absorbed in the gastrointestinal tract with high intraluminal levels, is a promising alternative but lacks sufficient evidence for use and has not been endorsed by scientific associations.[3]

On the 16th of November the European Medicines Agency (EMA) released a review on quinolone and fluoroquinolone antibiotics, recommending a restriction in these drugs use due to the possible side effects: tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste and smell.[4] The EMA document was preceded by multiple Food and Drug Administration (FDA) Drug Safety Communications suggesting that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects (07-10-2018), may lead to side effects involving the tendons, muscles, joints, nerves, and central nervous system (05-12-2016), may cause peripheral neuropathy (08-15-2013) and are associated with an increased risk of developing tendonitis and tendon rupture (Boxed Warning, 07-08-2008). Moreover, mounting evidence suggests an increased incidence of aortic aneurysm or dissection associated with use of oral fluoroquinolones.[5–7]

Uncertainties about fluoroquinolone use are not only limited to side effects, important concerns about bacterial resistance are arising. Based on the latest Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), in Europe 22.8% of *Escherichia coli* isolates and 29.7% of *Klebsiella pneumoniae* isolates were resistant to fluoroquinolones in 2015, with relevant geographical discrepancies.[8] It means that already at beginning of treatment, SBP with quinolones is ineffective in about one-fifth to one-third of patients. Without

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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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Conflict of interest

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Supplementary data

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Andrea Lombardi[1,2]
Valentina Zuccaro[2]
Stefano Fagiuoli[4]
Raffaele Bruno[2,3,*]

[1]*Department of Internal Medicine and Therapeutics, University of Pavia, Italy*
[2]*Infectious Diseases Unit, IRCCS "San Matteo", Pavia, Italy*
[3]*Department of Medical, Surgical, Diagnostic and Paediatric Science, University of Pavia, Pavia, Italy*
[4]*Gastroenterologia Epatologia e Trapiantologia, Papa Giovanni XXIII Hospital, Bergamo, Italy*
*Corresponding author. Address: Infectious Diseases Unit, Fondazione IRCCS Policlinico "San Matteo", Via Taramelli 5, Pavia 27100, Italy.
E-mail address: raffaele.bruno@unipv.it

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-