

In recent years, various immune checkpoint inhibitors have been extensively studied in various types of tumor [1]. In the phase I/II HCC nivolumab trial [2,3], the results were encouraging as objective response rate (ORR) of 20% with manageable safety profile in advanced HCC. In the open-label phase 2 pembrolizumab trial [4], 18 of 104 (17%) patients who had previously been treated with sorafenib experienced objective response with tolerable adverse effects. These trials showed significant potentiality of PD-1/PD-L1 inhibitor in treating HCC.

Furthermore, the combination of sorafenib and PD-1 blockade may provide synergic effects through relieving cell-intrinsic and cell-extrinsic inhibitions of effector T cells or the affection of vascular endothelial growth factor (VEGF), [5,6] indicating the combination therapy might become a prospective trend of immunotherapy. The recent phase I open-label study of SHR-1210 and apatinib combination therapy, starting from 2016, showed promising efficacy (ORR: 50%) in 16 patients with advanced HCC [7], which inspired us to administrate this particular treatment plan.

With the experience of the first case of successful combination therapy in early stage HCC, we have reasons to expect more patients with early-stage HCC could benefit from this combination therapy, which brings the question of whether we should expand the indication for immunotherapy. Future studies should be performed to answer this question.

#### Conflict of interest

None declared.

#### Guarantor of the article

The corresponding author is accessing to the data and have control of the decision to publish and accepting full responsibility for the conduct of the study.

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Zeyu Zhang  
Yufan Zhou  
Kuan Hu  
Zhecheng Li  
Zhiming Wang  
Yun Huang\*

Department of Hepatobiliary Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, China

\* Corresponding author.

E-mail address: [huangyun-1002@163.com](mailto:huangyun-1002@163.com) (Y. Huang)

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#### Sodium load and intravenous antimicrobials in patients with cirrhosis



Strong evidence indicates that reduction of salt intake lowers blood pressure and reduces the risk of cardiovascular disease and all-cause mortality [1]. This issue has also been deeply investigated in patients with decompensated cirrhosis. In fact, the guidelines of the European Association for the Study of the Liver (EASL) recommend a salt intake of 4.6–6.9 g/daily, corresponding to 1.84–2.76 g of sodium/daily, for patients with cirrhosis and ascites.[2] In the advanced stage of cirrhosis, splanchnic vasodilation causes a marked arterial underfilling that induces the maximum activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the arginine vasopressin release. All these activated systems would entail a reduced renal perfusion with consequent further retention of sodium and water, ultimately leading to the onset of hypervolemic hyponatremia and refractory ascites. The degree of activation of these neurohumoral mechanisms and renal impairment directly correlate with the degree of portal hypertension.[3] Consequently, hyponatremia represents a parameter indirectly reflecting the severity of portal hypertension, and it is strongly associated with an increased risk of liver-related mortality.[4] Furthermore, it has to be noted that any sodium intake (i.e., with food, or administered with fluid therapy such as balanced crystalloids, normal saline, colloids) in patients with cirrhosis may negatively affect the sodium retention being responsible for hyponatremia and worsening of ascites.[1]

Advanced stages of chronic liver disease favor the development of sepsis due to hepatic dysfunction, presence of porto-systemic shunts, intestinal dysbiosis, increased bacterial translocation, and immune dysfunction.[5] Therefore, the strategy to deal with the sepsis by extensive use of antibiotics treatment is mandatory in cirrhotic patients.[6] However, sodium is included in the preparation of the injectable antibiotics to stabilize the pH of the solutions, in varying amount according to the different classes of antibiotics.

Since sodium is the solute contained in the greatest quantity in the extracellular space, only 25–30% of the infused sodium remains in the intravascular space for 1–2 hours, whereas 70–75% very quickly flows into the interstitial space, contributing to maintenance of ascites and of peripheral edematous status.

Only a few, non-recent studies have taken into consideration the amount of sodium contained in the antibiotic solutions infused in patients with microbial infections and heart disease, and the possible impact of such unintentional administration of sodium on the heart failure.[7,8] This aspect has never been considered in the subset of patients with cirrhosis. In this regard, analyzing the amount of sodium contained in the antibacterial and antifungal treatments commonly recommended in patients with liver cirrhosis and microbial infections [5,9], a sodium concentration ranging from 12.05 mg to 7,680 mg was identified (Table 1).

**Table 1**  
Sodium concentrations in infusion antimicrobial solutions recommended for bacterial and fungal infections in cirrhotic patients.

Community Acquired Bacterial Infection	Antibiotics	Daily dosage in mg, range	Sodium concentration in mg, range
SBP, spontaneous bacterial empyema, spontaneous bacteraemia	cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	250 - 2,000 1,000 - 4,000 1,000/200 - 3,000/600	12.05 - 96.4 83 - 332 62.9 - 188.7
UTI Uncomplicated	ciprofloxacin or cotrimoxazole	200 - 1,200 400/80 - 1,600/320	900 - 5,400 34 - 136
UTI Complicated with sepsis	cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	250 - 2,000 1,000 - 4,000 1,000/200 - 3,000/600	62.9 - 188.7 83 - 332 62.9 - 188.7
Pneumonia	amoxicillin/clavulanic acid or ceftriaxone + gentamicin	1,000/200 - 3,000/600 1,000-4,000 + 80-240	62.9 - 188.7 83-332 + 283- 849
Cellulitis	amoxicillin/clavulanic acid or ceftriaxone + oxacillin	1,000/200 - 3,000/600 1,000-4,000 + 250-3,000	62.9 - 188.7 83-332 + 50-3,000
Nosocomial Bacterial Infection			
SBP,spontaneous bacterial empyema and spontaneous bacteremia	piperacillin/tazobactam or meropenem ± glycopeptide (vancomycin or teicoplanin) or daptomycin or linezolid	4,000/500 - 2,000/1,500 500 - 3,000 ± 200 - 800 4-6 /kg 600 - 1,200	216 - 648 90 - 270 ± 23 - 92 8.2 - 10.8/kg 114 - 228
Uncomplicated UTI	fosfomycin	2 - 24	640 - 7,680
UTI Complicated with sepsis	piperacillin/tazobactam or meropenem ± glycopeptide (vancomycin or teicoplanin) or linezolid	4,000/500 - 2,000/1,500 500 - 3,000± 200 - 800 600 - 1,200	216 - 648 90 - 270± 23 - 92 114 - 228
Pneumonia	piperacillin/tazobactam or meropenem ceftazidime ciprofloxacin ± glycopeptide (vancomycin or teicoplanin) or linezolid	4,000/500 - 2,000/1,500 500 - 3,000 5000 + 9,000 200 - 1,200 ± 200 - 800 600 - 1,200	216 - 648 90 - 270 58 - 1,044 900 - 5,400 ± 23 - 92 114 - 228
Cellulitis	meropenem or ceftazidime oxacillin or glycopeptides (vancomycin or teicolplanin) daptomycin or linezolid	500 - 3,000 500+9,000 250 - 3,000 200 - 800 4-6 /kg 600 - 1,200	90 - 270 58 - 1,044 50 - 600 23 - 92 8.2 - 10.8/kg 114 - 228
Fungal Infection	Antifungal Agents		
SFP, fungemia, disseminated fungal infections	casprofungin anidulafungin fluconazole voriconazole amphotericin b	Loading dose 70; 50 Loading dose 200; 100 50 - 800 Loading dose 800; 400 50 - 2,500	23;23 700; 350 450 - 7,200 870.4 - 435.2 31.6 - 1,580

SBP, spontaneous bacterial peritonitis; UTI, Urinary tract infection; SFP: Spontaneous fungal peritonitis

Microbial infections represent a main cause of a worsening of clinical outcome in patients with cirrhosis, therefore antimicrobial therapy is mandatory in infected cirrhotics. However, physicians should be aware that in these patients any excess sodium might worsen the hemodynamic, hypervolemic status potentially contributing to the decompensation of the liver disease. Thus, the sodium amount infused with the antibacterial/antifungal treatments should be carefully taken into consideration in the evaluation of the daily balance of sodium in cirrhotic patients, preventing – or at least reducing – the risk of the aforementioned maintenance of the general edematous status.

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Maimone S.\*

*Division of Clinical and Molecular Hepatology,  
University Hospital of Messina, Messina, Italy*

Mazzeo A.T.

*Department of Surgical Sciences, Anesthesia and  
Intensive Care, University of Turin, Azienda*

*Ospedaliera Città della Salute e della Scienza di  
Torino, Presidio Molinette, Turin, Italy*

Squadrito G. <sup>a,b</sup>

Raimondo G. <sup>a,b</sup>

<sup>a</sup> *Division of Clinical and Molecular Hepatology,  
University Hospital of Messina, Messina, Italy*

<sup>b</sup> *Department of Clinical and Experimental Medicine,  
University of Messina, Messina, Italy*

\* Corresponding author.

E-mail address: [smaimone@unime.it](mailto:smaimone@unime.it) (S. Maimone)

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