

than conventional multivariate regression analysis. Propensity-matched analysis is generally preferred to a multivariate regression analysis when sample size is small, otherwise results are basically similar.<sup>4</sup> In our nationwide study, sample size was obviously large with 259,110 inpatients with COVID-19, including 15,476 (6.0%) patients with CLD. We relied conservatively on a propensity-matched analysis to study COVID-19 outcomes in 1,182 patients recorded with primary liver cancer, and the reduced access to mechanical ventilation was clear. By contrast, the correspondents cited 2 US studies relying on a propensity-matched analysis as sample sizes were much smaller: 363 inpatients with COVID-19 including 69 (19.0%) with CLD<sup>5</sup>; and 10,859 inpatients with COVID-19 including 192 (1.8%) with CLD.<sup>6</sup> More importantly, the correspondents may have noticed that the proportion of CLD inpatients with COVID-19 was quite different between the 2 US studies, suggesting selection bias. By contrast, our nationwide study was conducted in France, a country with universal access to hospitals, with records from all public and private hospitals. No selection procedure was applied among covariates in the multivariate regression analysis given the large sample size. In addition, issues of multicollinearity, a concern for our correspondents, were unlikely given the large sample size: the median variance inflation factor was 1.15 (range 1.00–1.44) and 1.18 (range 1.00–1.46) in the regression models regarding mechanical ventilation and 30-day mortality, respectively. As a rule of thumb, collinearity becomes an issue for values of the variance inflation factor above 5.<sup>7</sup> We agree with the correspondents that the predictive power of the 2 regression models was low, but this is expected in epidemiology and even more so with large sample sizes, although coefficients of determination are generally not reported, including in the studies cited by Dr. Zhao and colleagues. Future studies on the risks of severe COVID-19 should include measures of the therapeutic effort to adapt health policies to future pandemics. Similar studies in other geographical areas would be very interesting.

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### Conflicts of interest

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

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### Authors' contributions

VM, MS: conception of the study, analysis and interpretation of the data, draft of the manuscript. All other members of the Demosthenes group facilitated the study or took care of the reported patients.

### Supplementary data

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## Plasma and ascites pharmacokinetics of meropenem in patients with decompensated cirrhosis and spontaneous bacterial peritonitis\*

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With great interest, we read the study of Wong *et al.* who investigated risk factors for an acute-on-chronic liver failure (ACLF) in patients with decompensated cirrhosis and bacterial infections. Spontaneous bacterial peritonitis (SBP) was the most frequent site of infection and an independent risk factor for ACLF development. Moreover, ACLF was more common in patients

infected with multidrug resistant bacteria (MDRB) and those with an insufficient response to the initial antibiotic treatment.<sup>1</sup> Their study once more underlines the critical role of fast and adequate antibiotic treatment in patients with decompensated cirrhosis.

However, adequate anti-infective drug administration is challenging in these patients. Decompensated cirrhosis is often accompanied by impaired kidney function, which may cause drug accumulation and increased drug toxicity.<sup>2</sup> In contrast, ascites accumulation may enhance the volume of distribution and result in drug concentrations that are too low.<sup>3</sup> Inadequate anti-infective drug levels may lead to insufficient or delayed treatment responses, increasing the risk of MDRB or further complications such as ACLF.

Current EASL guidelines recommend using a carbapenem for treatment of nosocomial SBP (nSBP).<sup>2</sup> Of note, detailed data on pharmacokinetics of meropenem in patients with advanced liver disease, especially with regard to the ascites compartment, are lacking. Therefore, we decided to investigate the pharmacokinetics and pharmacodynamic target attainment in plasma and ascites of the current meropenem dosing practice in patients with decompensated cirrhosis and nSBP.

Patients with decompensated cirrhosis and nSBP were prospectively enrolled. Further inclusion criteria were initiation of meropenem therapy and paracenteses by transient peritoneal catheter. Exclusion criteria were age <18 years, chronic kidney failure (CKD >4), symptomatic anemia and/or a hemoglobin-level <7 g/dl, pregnancy/lactation period and missing ability to give consent. The meropenem dosing regimen was chosen by the treating physician independent of participation in the study. At

day 1 and once between treatment day 3-5, plasma and ascites samples were collected 0, 15, 30, 45, 60, 120, 480, 510, 960 minutes after meropenem infusion. On the remaining treatment days 1 plasma and 1 ascites sample were collected before the first meropenem infusion. The minimal inhibitory concentration (MIC, 2 mg/L) was defined for meropenem susceptible Enterobacterales according to "EUCAST".<sup>4</sup> All patients provided written informed consent. The study was approved by the local ethics committee (No.7912) and registered at clinicaltrials.gov (NCT03571711).

A total of 100 plasma and 110 ascites samples were collected from 7 patients. All but 1 patient received a short initial meropenem infusion (30 min), 1 patient was treated with an initial prolonged infusion (4 h). Prolonged infusion was used in 4 patients and short infusions in 3 patients during further treatment. SBP resolved in 6 patients, while a further increase of polymorphonuclear cells in the ascites was documented in 1 patient (Table 1). Trough concentration ( $C_{min}$ ) of meropenem was similar in plasma and ascites (12.4 vs. 12.2 mg/L,  $p = 0.565$ ) (Fig. S1). However, peak concentrations ( $C_{max}$ ) differed significantly between plasma and ascites (44.7 vs. 26.0 mg/L,  $p = 0.008$ ). Accordingly, the  $AUC_{0-8}$  was 178 mg\*h/L in plasma and 124 mg\*h/L in ascites. While median time to  $C_{max}$  was 30 min in blood, it was 120 min in ascites (Fig. 1). However, the MIC was exceeded in ascites within 15 min after the first infusion in all patients and remained above the MIC in both compartments at all times. Furthermore, in all patients 4\*MIC was reached in plasma and ascites at least during 44% of treatment time. The median prescribed meropenem dose was 3 g/day. Acute kidney injury was present at the time of study inclusion in 5 patients.

**Table 1. Baseline characteristics, pharmacokinetic data, and outcome of the patients.**

Variable	Median (IQR)/percentage	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex (female)	43 %	Female	Female	Male	Male	Male	Female	Male
Age (years)	51 (20)	51	56	65	37	42	62	33
MELD-score	22 (21)	33	9	22	40	14	8	31
Creatinine (μmol/L)	197 (104)	247	78	197	671	153	90	204
Bilirubin (μmol/L)	33 (267)	125	10	33	466	22	16	452
INR (Ratio)	1.44 (0.52)	2.38	1.22	1.61	1.79	1.12	1.14	1.44
eGFR (ml/min)	44 (26)	19	74	44	8	48	59	36
Meropenem dosage (g/d)	3 (0.5)	2	3	3	2	3	3	3
x-times of the standard dose	1.5 (0.5)	2	1	1.5	4	1.5	1	1.5
Prolonged application	57 %	Yes*1	No	Yes	Yes	Yes	No	No
Weight (kg)	67 (19)	66	64	63	87	93	80	67
Height (m)	1.72 (0.14)	1.68	1.65	1.75	1.87	1.92	1.67	1.72
BMI (kg/m <sup>2</sup> )	24 (2)	23	24	21	25	25	29	23
Volume of paracentesis (ml/d)	1,500 (1240)	1,060	1,500	2,300	*2	3,000	*2	980
$C_{min}$ , P (mg/L)	12.4 (15.5)	29.5	11.7	12.4	26.2	11.1	5.5	27.5
$C_{min}$ , A (mg/L)	12.2 (6.2)	15.5	12.2	12.1	20.6	9.4	6.8	18.4
$C_{max}$ , P (mg/L)	44.7 (3.6)	49.9	46.2	39.9	43.9	44.7	34.6	44.7
$C_{max}$ , A (mg/L)	26.0 (5.1)	22.7	22.2	26.0	25.0	26.8	34.9	31.0
Time to 4*MIC, A (min)	30 (15)	45	15	15	45	30	30	30
Time > 4*MIC, P (%)	100 (5)	100	44	100	100	94	*4	100
Time > 4*MIC, A (%)	100 (38)	100	44	100	100	50	*4	100
$AUC_{0-8}$ single dose, P (μg*h/ml)	178 (73)	284	242	178	187	151	93	133
$AUC_{0-8}$ single dose, A (μg*h/ml)	124 (41)	110	173	132	159	90	100	124
$AUC_{0-8}$ multiple dose, P (μg*h/ml)	174 (77)	*3	101	192	*3	156	*4	301
$AUC_{0-8}$ multiple dose, A (μg*h/ml)	125 (56)	*3	85	160	*3	101	*4	150
Death/LTx within 1 year	57 %	LTx	No	LTx/D	Death	No	No	Death

All continuous variables are displayed as medians (IQR). Percentages were calculated for dichotomous variables.

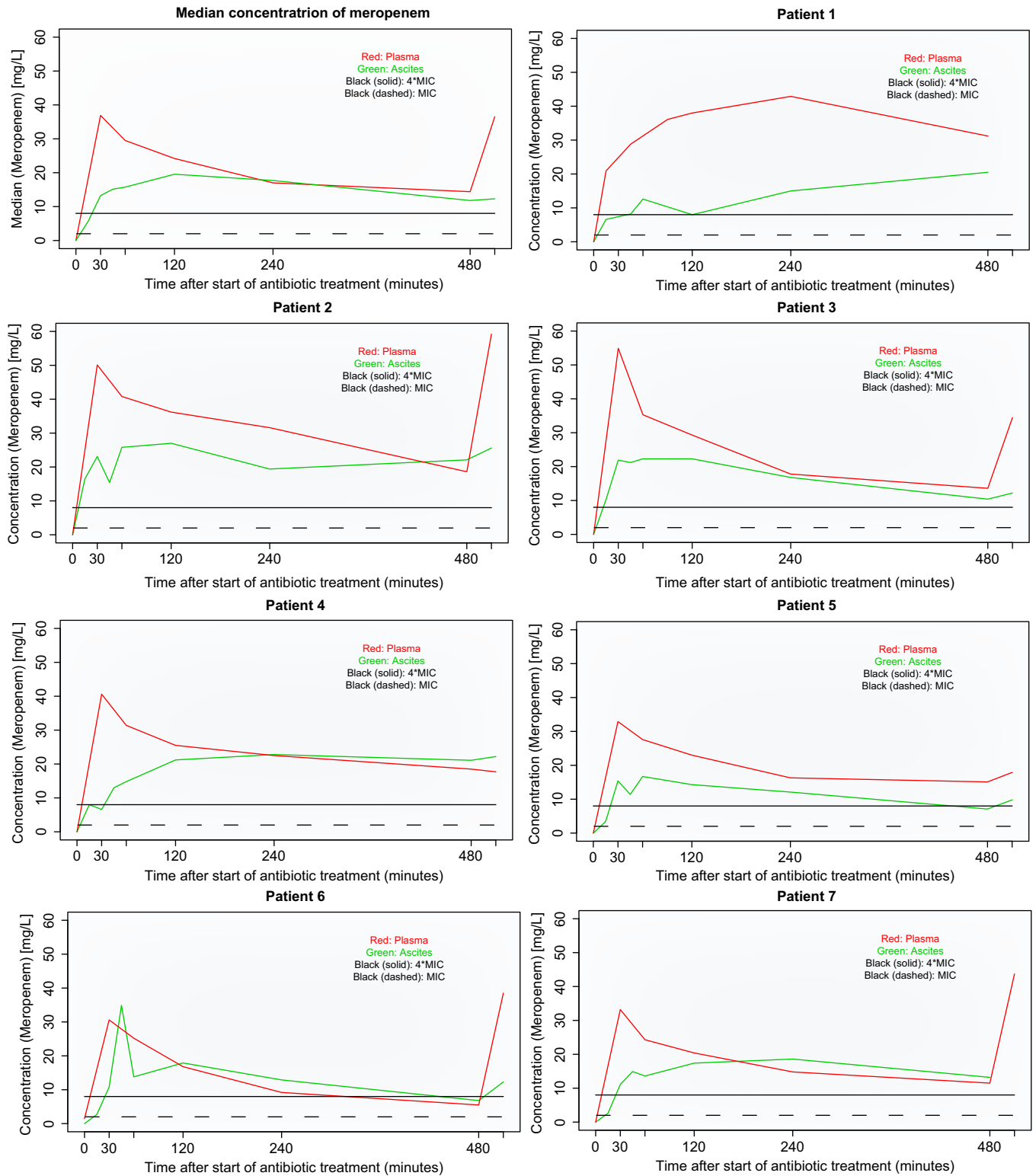
A, ascites;  $C_{max}$ , maximal concentration;  $C_{min}$ , minimal concentration; LTx, liver transplantation; MIC, minimal inhibitory concentration; P, plasma.

\*1Patient 1 also received a prolonged infusion for first application.

\*2The ascites drainage leaked. Therefore, the exact volume was not measured.

\*3The patients received meropenem only twice a day at this observation point.

\*4The patient did not complete the whole follow-up.



**Fig. 1. Plasma and ascites concentration of meropenem after single infusion.** Patient one was not taken into consideration for medium concentration as the application form differed (prolonged infusion over 4 h). Meropenem concentrations were measured using a certified HPLC method. HPLC, high-performance liquid chromatography; MIC, minimal inhibitory concentration. (This figure appears in color on the web.)

As recommended in severe infections, meropenem dosage was not strictly adjusted according to kidney function<sup>5</sup> resulting in 1.5–4x higher dosages. No meropenem-related adverse events were reported.

Early and effective anti-infective therapy is essential when managing nSBP to prevent morbidity and mortality in patients with cirrhosis;<sup>1,6</sup> therefore, early adequate drug levels at the infection site (ascites fluid) are required. While exact pharmacodynamic targets in nSBP are still unclear,  $C_{min}/MIC$  ratios of at least 4 are beneficial in severe respiratory infections.<sup>7</sup> With a median trough concentration of 12.4 mg/ml, the Tc was at least  $>4 \times MIC$  for 44% of the treatment time and  $>1 \times MIC$  for 100% of the treatment time. Although intraperitoneal application of meropenem is feasible in non-cirrhotic patients undergoing peritoneal dialysis, the fast attainment of drug concentrations above the MIC in ascites documented in our study does not implicate the need for a different route of drug administration in nSBP. Of note, only moderate dose adjustments in patients with acute kidney injury were applied in our study, as widely recommended for patients with severe illness/infections.<sup>5</sup> Despite the high trough concentration, no meropenem-associated side effects were reported. Retrospective studies associated trough concentrations of  $>64.2$  mg/L and  $>44.45$  mg/L with a 50% risk of developing neurotoxicity and nephrotoxicity events, respectively.<sup>8</sup> Here,  $C_{min}$  were clearly below these thresholds in all patients, which underlines the broad therapeutic window of meropenem.<sup>9</sup>

In summary, the current treatment practice of nSBP with meropenem provides early effective drug levels in plasma and ascites without reaching toxic concentrations.

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### Conflict of interest

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

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### Authors' contributions

B.M. and J.J.S. designed the study. M.S., B.M., D.G. and J.J.S. collected the samples and analyzed the data. All authors substantially contributed to the interpretation of the data. B.M., J.J.S., M.C. and M.S. drafted the manuscript. All authors critically revised the manuscript. All authors approved the manuscript to be published and therefore are accountable for all aspects of the work. B.M. and J.J.S. supervised the work.

### Data availability statement

To ensure the privacy of the participating patients further research data remains confidential and is not available.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.07.015>.

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