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.[4] 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[5]; and 10,859 inpatients with COVID-19 including 192 (1.8%) with CLD.[6] 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.[7] 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.

Financial support
The authors received no financial support to produce this manuscript.

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

Please refer to the accompanying ICMJE disclosure forms for further details.

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
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.09.022.

References
Author names in bold designate shared co-first authorship

[1] Long J, Sang X, Zhao H. Association of chronic liver disease with the prognosis of COVID-19 patients. J Hepatol 2022;76:228–229.
[2] **Williamson EJ**, **Walker AJ**, **Bhaskaran K**, **Bacon S**, **Bates C**, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–436.
[3] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73(5):1063–1071.
[4] Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69(3):345–357.
[5] Hashemi N, Viveiros K, Redd WD, Zhou JC, McCarty TR, Bazarbashi AN, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. Liver Int 2020;40(10):2515–2521.
[6] Satapathy SK, Roth NC, Kvasnovsky C, Hirsch JS, Trindade AJ, Molmenti E, et al. Risk factors and outcomes for acute-on-chronic liver failure in COVID-19: a large multi-center observational cohort study. Hepatol Int 2021;15(3):766–779.
[7] Fox J, Monette G. Generalized collinearity diagnostics. J Am Stat Assoc 1992;87(417):178–183.

Vincent Mallet[1,*]
Michaël Schwarzinger[2,3], for the Demosthenes research group
[1]*AP-HP.Centre Université de Paris, Groupe Hospitalier Cochin Port Royal, DMU Cancérologie et spécialités médico-chirurgicales, Service d'Hépatologie, Paris, France*
[2]*Department of Methodology and Innovation in Prevention, Bordeaux University Hospital, 33000 Bordeaux, France*
[3]*University of Bordeaux, Inserm UMR 1219-Bordeaux Population Health, 33000 Bordeaux, France*
[*]Corresponding author. Address: 27 rue du Faubourg Saint Jacques 75014, Paris. France.
E-mail address: vincent.mallet@aphp.fr (V. Mallet)

Plasma and ascites pharmacokinetics of meropenem in patients with decompensated cirrhosis and spontaneous bacterial peritonitis☆

To the Editor:

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

Received 9 June 2021; received in revised form 13 July 2021; accepted 15 July 2021; available online 24 July 2021
https://doi.org/10.1016/j.jhep.2021.07.015

infected with multidrug resistant bacteria (MDRB) and those with an insufficient response to the initial antibiotic treatment.[1] 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.[2] In contrast, ascites accumulation may enhance the volume of distribution and result in drug concentrations that are too low.[3] 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).[2] 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".[4] 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^2)	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.

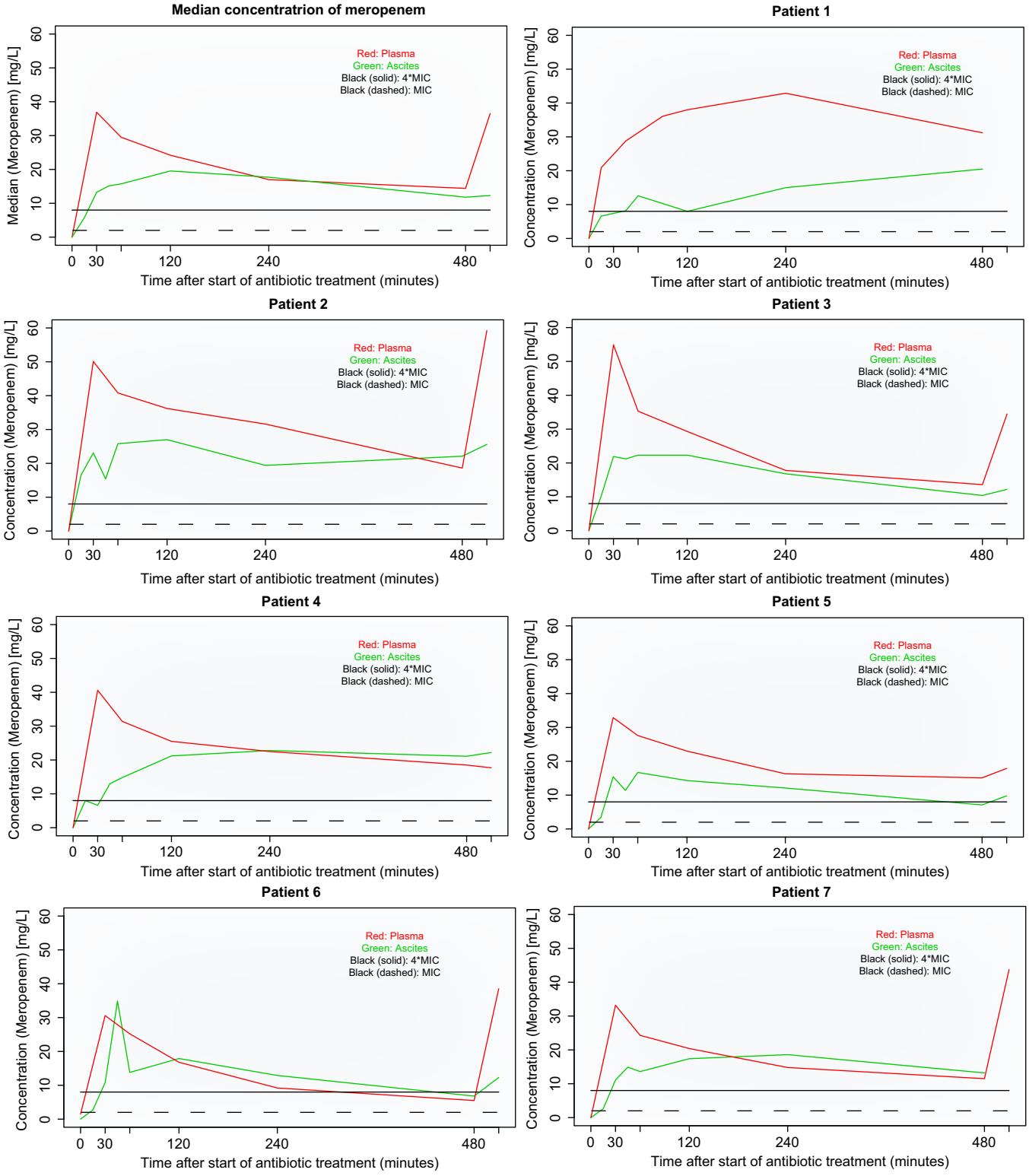

Fig. 1. Plasma and ascites concentration of meropenem after single infusion. Patient one was not taken into consideration for medium concentration as the application form differed (prolonged infusion over 4 h). Meropenem concentrations were measured using a certified HPLC method. HPLC, high-performance 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[5] resulting in 1.5–4x higher dosages. No meropenem-related adverse events were reported.

Early and effective anti-infective therapy is essential when managing nSPB to prevent morbidity and mortality in patients with cirrhosis;[1,6] 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.[7] With a median trough concentration of 12.4 mg/ml, the Tc was at least >4*MIC for 44% of the treatment time and >1*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.[5] 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.[8] Here, C_{min} were clearly below these thresholds in all patients, which underlines the broad therapeutic window of meropenem.[9]

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

Financial support

MS and this work were supported by the 'KlinStrucMed Programm – Promotionskolleg' funded by the Else Kröner-Fresenius-Stiftung. BM was supported by the "Clinician Scientist"-program (Junge Akademie) of Hannover Medical School.

Conflict of interest

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

Please refer to the accompanying ICMJE disclosure forms for further details.

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.

Acknowledgement

We thank the patients participating in the study.

Supplementary data

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

References

[1] Wong F, Piano S, Singh V, Bartoletti M, Maiwall R, Alessandria C, et al. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. J Hepatol 2021;74(2):330–339.
[2] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018 Aug;69(2):406–460.
[3] Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64(12):1147.
[4] Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0 [Internet]. 2020 [cited 13.02.2020]. Available from: http://www.eucast.org.
[5] Matzke GR, Aronoff GR, Atkinson Jr AJ, Bennett WM, Decker BS, Eckardt K, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: improving Global Outcomes (KDIGO). Kidney Int 2011;80(11):1122–1137.
[6] Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Am J Gastroenterol 2014 Sep;109(9):1436–1442.
[7] Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51(5):1725–1730.
[8] Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of β-lactam concentration–toxicity relationships. J Antimicrob Chemother 2017;72(10):2891–2897.
[9] Fachinformation Meronem [Internet]. 2018 [updated 10/; cited 25.02.2020]. Available from: https://www.pfizermed.de/fileadmin/produktdatenbank/pdf/016053_freigabe.pdf.

Marie Griemsmann[1]
Denis Grote-Koska[2]
Markus Cornberg[1,3]
Julius J. Schmidt[4,†]
Benjamin Maasoumy[1,*,†] for the CirPK - Study Group[#]
[1]*Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Carl-Neuberg-Str.1, 30625 Hannover, Germany*
[2]*Department of Clinical Chemistry, Hannover Medical School, Carl-Neuberg-Str.1, 30625 Hannover, Germany*
[3]*Centre for Individualised Infection Medicine a joint venture of Helmholtz Centre for Infection Research and Hannover Medical School, Hannover, Germany*
[4]*Department of Nephrology, Hannover Medical School, Carl-Neuberg-Str.1, 30625 Hannover, Germany*
[*]Corresponding author. Address: Carl-Neuberg-Straße 1, 30625 Hannover, Germany; Tel.: 0049-5115326814, fax: 0049-5115324896.
E-mail address: maasoumy.benjamin@mh-hannover.de (B. Maasoumy)

[#] CirPK – Study Group: Thorsten Book, Birgit Bremer, Benjamin Schulte, Michael P. Manns, Heiner Wedemeyer, Korbinian Brand
[†] JJS and BM contributed equally.
[☆] Guest Editor: Dominique Valla