Letter to the Editor

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Normothermic liver machine perfusion as a dynamic platform for assessment and treatment of organs from septic donors

To the Editor:

It was with great interest that we read the review published by Lascaris *et al.*[1] in the *Journal of Hepatology*, which nicely summarizes the potential for normothermic liver machine perfusion (NLMP) as a dynamic platform for regenerative purposes. The authors rightly stress that NLMP promises to narrow the gap between organ supply and demand. NLMP permits longer preservation times and viability testing and thereby aids in the utilization and selection of liver grafts. This is ultimately expected to increase graft utilization.[2,3] Many of the approaches cited in the article by Lascaris *et al.*, including the possibility to treat donor livers for hepatitis C during NLMP, are still in an experimental phase and have yet to show clinical applicability. While the possibility to apply antiviral treatment to increase organ utilization is mentioned, the option to use antimicrobial therapy during NLMP was not addressed. Treating potentially contaminated organs from septic donors with the goal of preventing donor-derived infections could increase the safety profile of such transplantations and thus the number of potential donor organs available for transplantation.[4] The Zurich group has recently published their experience of using NLMP as a platform for treating the liver *ex situ* with antimicrobial agents during an extended period of normothermic perfusion. This was done in an organ carrying a tumor of unclear nature retrieved from a donor with sepsis caused by multidrug-resistant micro-organisms.[5] In light of this observation, we would like to add our own experience, where we used NLMP as a platform to treat organs originating from septic donors.

A liver from a standard criteria donor with pneumonia (positive bronchoalveolar lavage) and sepsis was offered to our center. The donor received antibiotic therapy with piperacillin/tazobactam before and during donor surgery. The liver was put on NLMP (OrganOx® metra®) and targeted antibiotic treatment was applied. Viability assessment and SeptiFast (SF) testing were done prior to the decision to go ahead with liver transplantation (LT). The SF test (Roche Diagnostics, Mannheim, Germany), a commercially available multiplex PCR assay, is designed to detect the DNA of 25 clinically important bacteria and fungi in the blood. SF test results are available within 6 hours.[6] However, in contrast to blood cultures, no antimicrobial susceptibility testing is available. In response to donor blood culture findings the antimicrobial regimen was extended with ceftazidime/avibactam as well as fluconazole. Viability assessment performed during NLMP exhibited good graft performance (bile pH >7.4, bile glucose 2 mg/dl, perfusate pH ≥7.2 without the need for excessive HCO_3^- substitution, falling glucose levels beyond 2 hours, peak lactate fall >40 mg/dl, alanine aminotransferase <6,000 U/L at 2 hours).[2,7] After 12 hours of NMLP, perfusate samples were taken for SF testing. Following negative SF test results, we went ahead with LT. The patient did not experience reperfusion syndrome and no donor-derived infection was observed. Blood cultures from the perfusate during NLMP remained negative.

We compared the clinical course with that of two other cases, in which the perfusate cultures taken at the end of NMLP were positive for *Klebsiella pneumoniae* and *Staphylococcus aureus*. Since no clinical information suggestive of bacteremia in the donors was available and perfusate analyses were completed only days after the LT, a standard antimicrobial regimen (cefuroxime) was administered during NLMP. After transplantation, both recipients experienced severe reperfusion syndrome, displayed exceptionally high peak IL-6 values and developed severe sepsis (Table 1). The possibility to apply antimicrobial therapy during NLMP and to monitor the treatment response via SF testing deserves recognition. Applying this concept in a liver from a septic donor resulted in successful transplantation of an organ, which otherwise would most likely have been discarded. Of note, both kidneys were retrieved but ultimately discarded in light of concerns about a donor-derived infection and the lack of a normothermic kidney machine perfusion platform.

In contrast to cold storage, normothermic machine perfusion creates an environment for microorganisms to grow. While this poses both a threat and an opportunity, the combination of SF testing and antimicrobial treatment during normothermic machine perfusion means that transplantation can be considered with organs that would otherwise be declined. This exemplifies the possibilities arising from the clinical introduction of NLMP as a platform for organ assessment, reconditioning and ultimately repair.

Table 1. Antimicrobial and reperfusion characteristics.

Case	#1	#2	#3
Perfusate cultures	Positive	Positive	Negative
Recipient blood cultures/IV catheter cultures	Positive	Positive	Negative
Microorganisms cultured	*Klebsiella pneumonia*	*Staphylococcus aureus*	None
Reperfusion syndrome	Yes	Yes	No
IL-6 peak in recipient	330,717 ng/L	169,433 ng/L	651 ng/L
CRP in recipient	27 mg/dl	12 mg/dl	15 mg/dl
PCT in recipient	53 μg/L	68 μg/L	140 μg/L

CRP, c-reactive protein; IL-6, interleukin-6; IV, intravenous; PCT, procalcitonin.

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Authors' contributions

The authors declare that they have participated in the preparation of the manuscript and have seen and approved the final version. FJK was involved in acquisition of data, analysis and interpretation of data and drafting of the manuscript. RO was involved in study design, analysis and interpretation of data and drafting of the manuscript. RB was involved in study design and critical revision of the manuscript. GW was involved in interpretation of data and critical revision of the manuscript. SS was involved in study concept and design, analysis and interpretation of data, critical revision of manuscript and overall study supervision.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.10.033.

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Author names in bold designate shared co-first authorship

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