



**HAL**  
open science

## **Closing the gap before using L-lactate to guide newborn care**

Hélène Roumes, Ifrah Omar Ibrahim, Marie-Christine Beauvieux, Chloé Perrot, Olivier Brissaud, Sophie Cramaregeas, Eric Dumas-De-La-Roque, Luc Pellerin, Jean-François Chateil, Olivier Tandonnet, et al.

### ► **To cite this version:**

Hélène Roumes, Ifrah Omar Ibrahim, Marie-Christine Beauvieux, Chloé Perrot, Olivier Brissaud, et al.. Closing the gap before using L-lactate to guide newborn care. *Pediatric Research*, 2025, Online ahead of print. <10.1038/s41390-025-04504-0>. <hal-05344158>

**HAL Id: hal-05344158**

**<https://hal.science/hal-05344158v1>**

Submitted on 3 Nov 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Copyright - All rights reserved

## Closing the gap before using L-lactate to guide newborn care

Ifrah Omar Ibrahim<sup>1,§</sup>, H el ene Roumes<sup>1,§</sup>, Marie-Christine Beauvieux<sup>1,2</sup>, Chlo e Perrot<sup>3</sup>, Olivier Brissaud<sup>4</sup>, Sophie Cramaregeas<sup>3</sup>, Eric Dumas-de-la-Roque<sup>3</sup>, Luc Pellerin<sup>5</sup>, Jean-Fran ois Chateil<sup>1</sup>, Olivier Tandonnet<sup>3</sup> and Anne-Karine Bouzier-Sore <sup>1\*</sup>

<sup>1</sup>Univ. Bordeaux, CNRS, CRMSB, UMR 5536, F-33000 Bordeaux, France. <sup>2</sup>Biochemistry Department, Bordeaux University Hospital, Bordeaux, France. <sup>3</sup>Neonatal Intensive Care Unit, Maternity, Bordeaux University Hospital, Bordeaux, France.

<sup>4</sup>Neonatal Intensive Care Unit, Children’s Hospital, Bordeaux University Hospital, Bordeaux, France. <sup>5</sup>IRMETIST, U1313, University of Poitiers and CHU of Poitiers, Poitiers, France. <sup>§</sup>These authors contributed equally.

\* corresponding author, email: akb@rmsb.u-bordeaux.fr

### RESPONSE TO COMMENTARY:

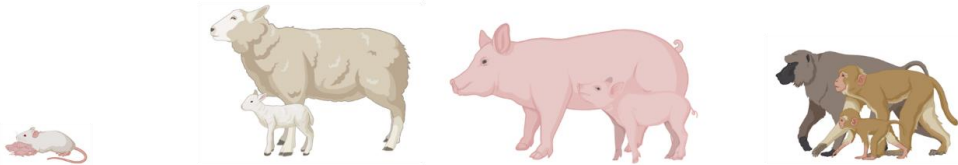
We thank the authors for their insightful commentary [1] on our article, “*Positive Impact of Sodium L-Lactate Supplementation on Blood Acid-Base Status in Preterm Newborns.*”[2]. Their response appropriately highlights the emerging recognition of lactate not merely as a byproduct of anaerobic metabolism, but as an active metabolic and signaling molecule. The commentary offers a detailed biochemical analysis of lactate metabolism and presents a comprehensive overview of its diverse physiological roles.

As highlighted in the comment, preterm neonates exhibit an increased vulnerability to metabolic stress due to immaturity of their cellular signalling pathways, limited mitochondrial capacity, and exposure to an extrauterine environment that induces oxidative stress and inflammation. Indeed, the formation of reactive oxygen species (ROS) during the transition from intrauterine to extrauterine life results from complex physiological changes associated with a shift in oxygen availability [3, 4]. Prior to birth, the foetus resides in an environment with a partial pressure of oxygen (PaO<sub>2</sub>) of approximately 20-25 mmHg [5]. During the transition to extrauterine life and the initiation of respiration, oxygen concentration doubles, initiating ROS production. As emphasized by Angelis *et al.*, postnatal inflammation plays a major role in oxidative stress, as inflammatory cells release large quantities of ROS and overproduce pro-inflammatory cytokines [5]. Our study compared the administration of sodium lactate (NaL) to sodium chloride (NaCl), via parenteral infusion, in preterm infants presenting with metabolic acidosis during the early postnatal period. The results demonstrated a significant improvement in pH and base excess in the NaL group, consistent with the metabolic conversion of lactate into bicarbonate, without causing adverse events or electrolyte disturbances. These results support its tolerability and suggest a role in stabilizing intracellular pH, promoting antioxidant enzyme activity, and potentially mitigating oxidative injury. Additionally, lactate may enhance mitochondrial bioenergetics, promote mitochondrial biogenesis via GPR81 signaling, and stimulate ATP production, offering particular benefit in the context of mitochondrial immaturity in preterms.

The commentary also highlights the potential translational relevance of NaL in the context of neonatal hypoxia-ischemia (NHI). Indeed, lactate has emerged as a key regulator of cerebral metabolism and important neuronal substrate. Therefore, its administration after an ischemic event that has deprived the brain of energetic substrate may be particularly relevant during the perinatal period. During this stage, breastfed neonates exhibit a distinct pattern of expression of monocarboxylate transporters (MCTs), which are upregulated [6] to facilitate the transport of ketone bodies—which serve in physiological condition as major energy substrates for the developing brain. MCTs also transport lactate. In addition to its neuroenergetic role, experimental data show that

lactate acts on neural cell proliferation, anti-inflammatory responses, and synaptic plasticity. As noted by the authors, lactate may also play a role in regulating gene expression, though this area still remains to be explored. In particular, lactate-induced histone lactylation—first identified by Zhang *et al.*—represents a novel epigenetic mechanism that contributes to the modulation of inflammation and the promotion of tissue repair [7]. These pleiotropic effects suggest that NaL may reduce cerebral inflammation and support recovery following NHI. However, further studies are required to completely elucidate the role of lactate in this neuroprotection. Indeed, our conclusions regarding the potential of NaL in NHI are partly supported by encouraging preclinical data from the Rice-Vannucci model in rat pups [8-10]. However, we concur with the authors that this model has notable limitations, including unilateral ischemia, variability in lesion severity, and significant anatomical differences from the human brain. To address these issues, larger animal models such as fetal sheep, piglets, and non-human primates have been developed. While the fetal sheep model is valuable for studying white matter injury, it is conducted at the fetal stage and therefore does not permit longitudinal follow-up or functional analysis. Piglet models more closely replicate human brain development, support extended hypothermia protocols, and have contributed to clinical advances, though they also lack the ability for long-term monitoring. Non-human primate models offer the closest anatomical and physiological resemblance to human neonates but are limited by ethical and regulatory constraints. Neonatal piglets [11] and primates [12], both exhibit white matter tractography much more comparable to that of human infants, making them particularly valuable for studying white matter injury; however, their use is significantly constrained by the substantial financial and logistical costs involved. As a result, the Rice-Vannucci model remains widely used due to its reproducibility, affordability, and suitability for long-term studies—though its inherent limitations must always be carefully considered. In response to the comment by Angelis *et al.*, we also acknowledge that Rice-Vannucci model is imperfect. Nonetheless, no animal model can exactly replicate the cerebral alterations observed in humans due to their complexity and uniqueness. In our previous study, we assessed the effects of lactate administration in the context of NHI [8]. This long-term study involved MRI analyses and behavioral tests. Finally, although imperfect, the Rice-Vannucci model was used to explore the therapeutic effect of hypothermia in NHI [13], which is now (after validation in piglet and lambs) use routinely in clinic. In this context, the Rice-Vannucci model was pertinent because it allowed an integrative approach, spanning from cerebral energy metabolism to functional assessments.

The comparison of the different NHI models is summarized in Table 1.



<ul style="list-style-type: none"> <li>- Well-characterized</li> <li>- Straightforward to implement</li> <li>- Low mortality rates</li> <li>- Long-term follow-up</li> <li>- Low costs</li> </ul>	<ul style="list-style-type: none"> <li>- Histopathological similarities to human neonates</li> </ul>	<ul style="list-style-type: none"> <li>- Systemic hypoxia</li> <li>- Long hypothermic periods</li> <li>- White matter tractography similar to that of human infants</li> </ul>	<ul style="list-style-type: none"> <li>- The most appropriate models for studying HI in humans</li> </ul>
<ul style="list-style-type: none"> <li>- Do not reproduce the complexity of the developing human brain</li> <li>- Variability</li> <li>- Unilateral ischemia</li> <li>- Lateralization of lesions</li> <li>- Lissencephalic cortex</li> <li>- Reduced white matter</li> </ul>	<ul style="list-style-type: none"> <li>- Advanced cerebral development</li> <li>- Only a fetal model</li> <li>- No longitudinal follow-up</li> <li>- Cost</li> </ul>	<ul style="list-style-type: none"> <li>- No longitudinal follow-up</li> <li>- Cost</li> </ul>	<ul style="list-style-type: none"> <li>- Ethical concerns</li> <li>- Cost</li> <li>- Strict authorization</li> </ul>

*Table 1: Comparison of different NHI models. In green: advantages, In orange: disadvantages.*

## Conclusion

We are grateful to the author of the commentary for enriching the discussion and supporting further investigation into NaL's therapeutic value in neonatal care. Our findings indicate that NaL is well tolerated in preterm infants with acidosis and highlight its potential as a neuroprotective agent. However, we support the call for cautious and systematic evaluation—through randomized, longitudinal studies—of its dosology, safety, and long-term neurodevelopmental effects. Comparative studies with sodium acetate (NaA), a current standard in neonatal parenteral nutrition, are also warranted. Indeed, NaA has shown benefits in correcting metabolic acidosis, reducing hyperchloremia, and is routinely recommended during the first postnatal week, particularly in very low birth weight (VLBW) infants [14]. Future studies should directly compare NaL and NaA in larger neonatal cohorts, with longitudinal assessments of clinical, metabolic, and neurodevelopmental outcomes, to determine whether NaL offers additional or superior benefits in this high-risk population. To conclude, our study by Omar Ibrahim *et al.* aimed to test the hypothesis that NaL can be administered safely without immediate metabolic risk in preterm infants experiencing acidosis. It opens promising avenues regarding its potential role in modulating cerebral metabolism under stress conditions. We fully endorse the call made by the authors for further research, ideally involving randomized, multicenter studies that include longitudinal assessments of neurodevelopment and integrated analyses of intermediary metabolism.

## References

1. Angelis, D., L.P. Brion, and L. Chalak, *L-lactate provision in preterm newborns: friend or foe?* *Pediatr Res*, 2025.
2. Omar Ibrahim, I., et al., *Positive impact of sodium L-lactate supplementation on blood acid-base status in preterm newborns.* *Pediatr Res*, 2025.
3. Shoji, H. and B. Koletzko, *Oxidative stress and antioxidant protection in the perinatal period.* *Curr Opin Clin Nutr Metab Care*, 2007. **10**(3): p. 324-8.
4. Lurie, S., et al., *Different degrees of fetal oxidative stress in elective and emergent cesarean section.* *Neonatology*, 2007. **92**(2): p. 111-5.
5. Marseglia, L., et al., *Role of oxidative stress in neonatal respiratory distress syndrome.* *Free Radic Biol Med*, 2019. **142**: p. 132-137.
6. Baud, O., et al., *Perinatal and early postnatal changes in the expression of monocarboxylate transporters MCT1 and MCT2 in the rat forebrain.* *J Comp Neurol*, 2003. **465**(3): p. 445-54.
7. Zhang, D., et al., *Metabolic regulation of gene expression by histone lactylation.* *Nature*, 2019. **574**(7779): p. 575-580.
8. Roumes, H., et al., *Neuroprotective role of lactate in rat neonatal hypoxia-ischemia.* *J Cereb Blood Flow Metab*, 2021. **41**(2): p. 342-358.
9. Tassinari, I.D., et al., *Lactate Administration Reduces Brain Injury and Ameliorates Behavioral Outcomes Following Neonatal Hypoxia-Ischemia.* *Neuroscience*, 2020. **448**: p. 191-205.
10. Tassinari, I.D. and L.S. de Fraga, *Potential use of lactate for the treatment of neonatal hypoxic-ischemic encephalopathy.* *Neural Regen Res*, 2022. **17**(4): p. 788-790.
11. Koehler, R.C., Z.J. Yang, J.K. Lee, and L.J. Martin, *Perinatal hypoxic-ischemic brain injury in large animal models: Relevance to human neonatal encephalopathy.* *J Cereb Blood Flow Metab*, 2018. **38**(12): p. 2092-2111.
12. Martin, L.J. and L.C. Cork, *The non-human primate striatum undergoes marked prolonged remodeling during postnatal development.* *Front Cell Neurosci*, 2014. **8**: p. 294.
13. Yager, J., J. Towfighi, and R.C. Vannucci, *Influence of mild hypothermia on hypoxic-ischemic brain damage in the immature rat.* *Pediatr Res*, 1993. **34**(4): p. 525-9.
14. Inder, T., J. Neil, B. Yoder, and S. Rees, *Patterns of cerebral injury in a primate model of preterm birth and neonatal intensive care.* *J Child Neurol*, 2005. **20**(12): p. 965-7.

