Abnormal polyunsaturated fatty acid metabolism is associated with a phenotype with marked sepsis-associated acute kidney injury in pediatric sepsis

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Ivan E Saraiva, MD, MS[1]; Joseph A Carcillo, MD[1]; Hernando Gomez, MD, MPH[1]
[1]Department of Critical Care Medicine, University of Pittsburgh

University of Pittsburgh

PROGRAM FOR Critical Care Nephrology

Introduction

Pediatric sepsis phenotypes have recently been described, analogous to adult sepsis[1]. Ped Sepsis A has showed low mortality (2%), followed by B and C (12 and 10%). **Ped Sepsis D is characterized by multiorgan failure and high mortality (34%).**

Several lines of evidence show that exposure to polyunsaturated fatty acids (PUFA), particularly the n6 linoleic acid (LA), as well as individual variation in LA metabolism, influence inflammation and chronic metabolic diseases. **There has been little investigation of LA metabolism in sepsis and its relationship to sepsis phenotypes.**

The first step in metabolism of LA to produce arachidonic acid involves the enzyme delta-6-desaturase (D6D), which is regulated by multiple factors including PPARs, insulin, NAD+/NADH, and variations in the *FADS* gene cluster in chromosome 11.

Hypothesis

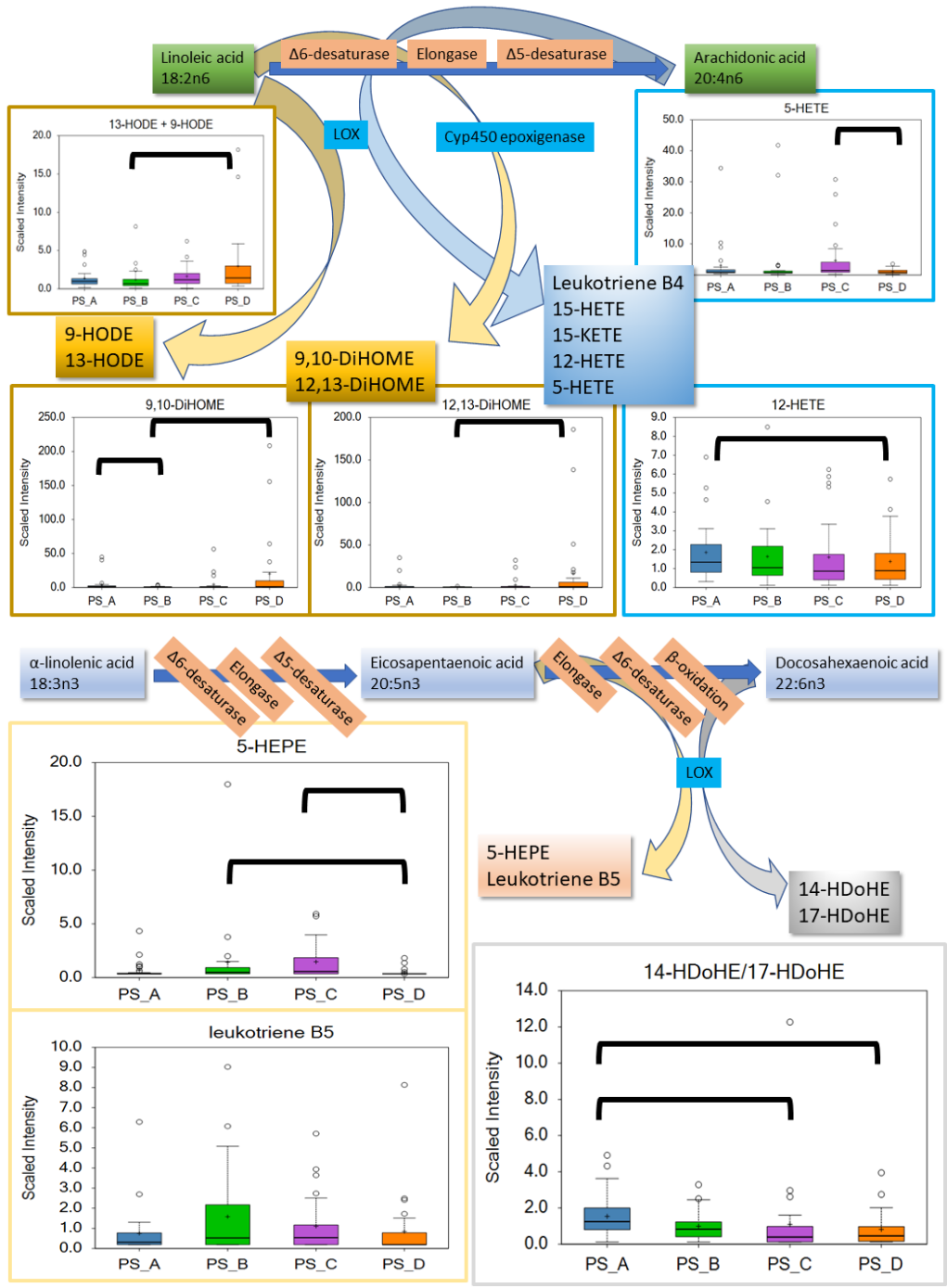
Our main hypothesis is that **higher exposure to LA dysregulates the mechanisms of inflammation and may lead to a multiorgan failure in sepsis** (corresponding to Pediatric Sepsis phenotype D).

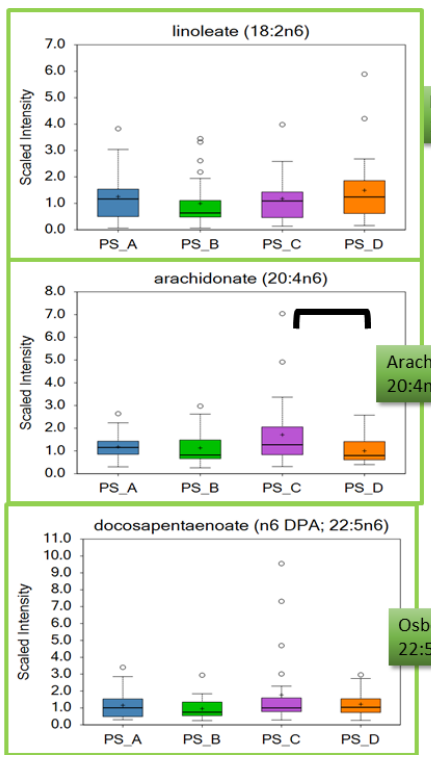
- Because of individual variation in activity of D6D, LA levels may be uninformative.
- **We expect LA-derived oxylipins,** which are associated with LA exposure[2], **to be increased in Ped Sepsis D.**
- n3 PUFA may antagonize the effect of D6D on LA through multiple mechanisms, therefore **we expect n3 PUFA to be negatively associated with Ped Sepsis D.**
- **We expect to find similar associations with creatinine levels**, as Ped Sepsis D is marked by multiorgan dysfunction and high incidence of acute kidney injury.

Methods and Materials

- Cohort of 108 pediatric patients with sepsis, classified as phenotypes A-D.
- Untargeted metabolomics by ultra-performance liquid chromatography.
- Statistical analyses:
  - Metabolite comparison between pairs of phenotypes
  - Linear regression for analysis of creatinine
  - Binary logistic regression for high-risk phenotype vs others

Results





Linear regression: Creatinine (Log)

Var	Est	SE	p
(Intrcp)	0.19	0.06	<0.01
AA	-0.28	0.19	0.14
DHA	**-0.31**	**0.14**	**0.03**
EPA	0.12	0.12	0.31
LA	**0.27**	**0.09**	**<0.01**

Var	Est	SE	p
(Intrcp)	0.19	0.13	0.15
LTB4	0.12	0.09	0.18
5-HEPE	-0.12	0.12	0.29
5-HETE	**-0.22**	**0.11**	**0.05**
9-/13-HODE	**0.15**	**0.07**	**0.03**
12-HETE	0.02	0.10	0.87
14-/17-HDoHE	-0.04	0.08	0.61

Conclusions

- LA oxylipins are increased and n3 oxylipins are decreased in Ped Sepsis D
- LA is correlated, and DHA is negative correlated, with creatinine.
- AA is decreased in Ped Sepsis D (in agreement with prior findings in adult sepsis [3])
- Future studies should estimate D6D activity to investigate relationships of LA and AA.

References

[1] Qin Y et al. Crit Care 2022, 26:128. PMID 35526000
[2] Stawarska A et al. Nutrients 2020, 12:1232. PMID 32349264
[3] Bruegel M et al. Crit Care Med 2012, 40(5):1478-86. PMID 22511130

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