Acetaminophen Prescribing and Pharmacokinetic Analysis in Children, Adolescents, and Young Adults with Cancer

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Introduction:

~52% of children with cancer develop chronic and/or acute liver complications; further it has been estimated that >70% of children with cancer receive hepatotoxic Acetaminophen (**APAP**).[1,2] There is an urgent need to understand how cancer physiology and polypharmacy interact to alter APAP metabolism, which is integral to reducing drug-induced liver injury (**DILI**) risk. To understand APAP-DILI risk in children with cancer, we must first measure APAP exposure and metabolite formation. We hypothesize that children with cancer will have increased cytochrome P450 (CYP)-mediated APAP metabolism compared to their cancer-free peers.

Goal of Research: To quantify initial APAP exposure and metabolite formation in children with cancer.

Methods:

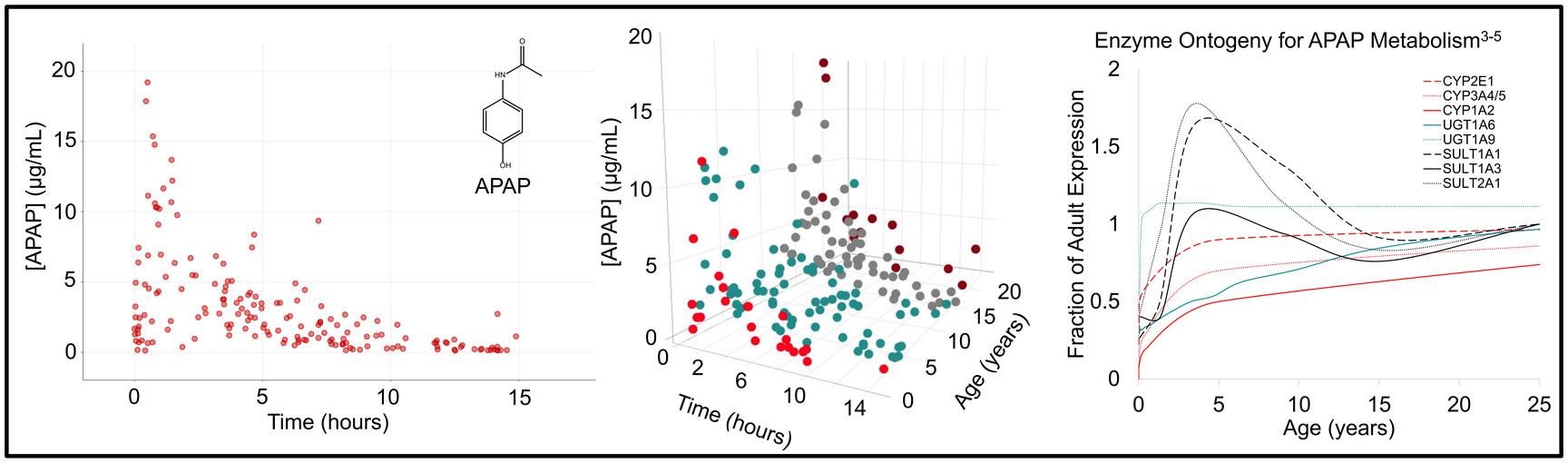
- National-level data were obtained from the Pediatric Health Information System ® (**PHIS**); regional data were obtained from Intermountain Healthcare's Primary Children's Hospital (**PCH**).
- Inclusion: 28 days – 26 years old; cancer diagnosis, inpatient:

Demographic	All Patients	- APAP	+ APAP
N	4,631	231	4,400
Male, N (%)	2,473 (53.4%)	126 (54.5%)	2,347 (53.3%)
Race/ ethnicity			
Asian	57 (1.2%)	2 (0.9%)	55 (1.3%)
Hispanic	606 (13.1%)	24 (10.4%)	582 (13.2%)
Non-Hispanic	3,214 (69.4%)	137 (59.3%)	3,077 (69.9%)
Native American	48 (1.0%)	1 (0.4%)	47 (1.1%)
African American	70 (1.5%)	3 (1.3%)	67 (1.5%)
White	4,052 (87.5%)	199 (86.1%)	3,853 (87.6%)
Other	325 (7.0%)	24 (10.4%)	301 (6.8%)
Pacific Islander	57 (1.2%)	0 (0.0%)	57 (1.3%)
Age at first cancer diagnosis			
0 to <28 d	65 (1.4%)	7 (3.0%)	58 (1.3%)
28 d to <2 yr	683 (14.7%)	40 (17.3%)	643 (14.6%)
2 to <12 yr	2,414 (52.1%)	119 (51.5%)	2,295 (52.2%)
12 to <18 yr	1,221 (26.4%)	56 (24.2%)	1,165 (26.5%)
18 to <27 yr	248 (5.4%)	9 (3.9%)	239 (5.4%)
APAP admin./ 24h encounter, median (IQR)	-N/A-	-N/A-	4 (2, 10)

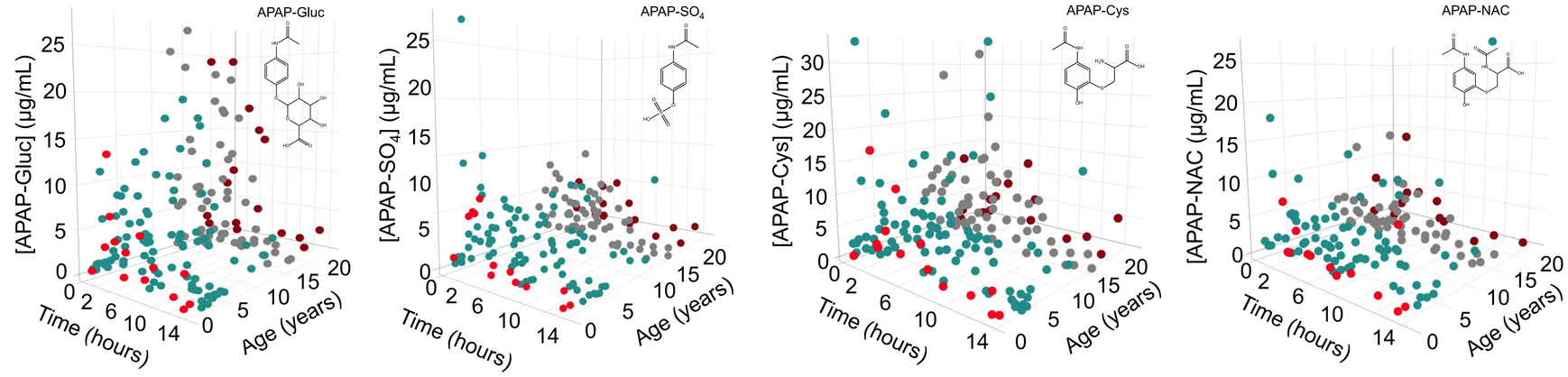
- Parent APAP and metabolites (glucuronide, sulfate, cysteine, N-Acetylcysteine) were quantified using a Waters Micromass LC-MS/MS and validated with deuterated internal standards.
- 3D Plots: Red (Infants), Blue (Children), Gray (Adolescents), Burgundy (Young Adults).

Abbreviations: Acetaminophen (**APAP**), Drug-Induced Liver Injury (**DILI**), Cytochrome P450 (**CYP**), Pediatric Health Information System (**PHIS**), Primary Children's Hospital (**PCH**), Glucuronide (**Gluc**), Sulfate (**SO_4**), Cysteine (**Cys**), *N*-Acetylcysteine (**NAC**).

Approach: LC-MS/MS Metabolite Concentration & Ratio Quantification



- Using a conditional weighted residual approach, no outliers were identified for the parent APAP data set (threshold: >6).
- Age-based changes in APAP concentration *vs.* time are likely related to enzyme ontogeny, for example, glucuronidation yielding APAP-Gluc (leftmost plot):



- APAP-Cys and APAP-NAC are formed following glutathione conjugation (detoxification) of the reactive CYP intermediate, *N*-acetyl-p-benzoquinoneimine. This intermediate is also responsible for the formation of APAP-protein adducts known to promote cell death and DILI.

Time (h)	µMolar Ratio: APAP	APAP-Gluc	APAP-SO_4	APAP-Cys	APAP-NAC
1	0.67 ± 0.25	0.20 ± 0.13	0.15 ± 0.06	0.01 ± 0.01	0.0 ± 0.01
4	0.32 ± 0.12	0.40 ± 0.17	0.26 ± 0.09	0.02 ± 0.01	0.01 ± 0.01
8	0.30 ± 0.15	0.43 ± 0.16	0.22 ± 0.06	0.04 ± 0.03	0.01 ± 0.02
12	0.31 ± 0.07	0.39 ± 0.14	0.24 ± 0.07	0.04 ± 0.03	0.02 ± 0.03
15	0.22 ± 0.17	0.47 ± 0.20	0.19 ± 0.16	0.08 ± 0.09	0.04 ± 0.07
Slope	-0.028	0.024	0.004	0.003	0.002

- The ability to compare metabolite ratios over time may allow for a more granular assessment of metabolic trends in children with cancer moving forward, for example, how the apparent increase in CYP metabolism (APAP-Cys & APAP-NAC) relates to pathway saturation or cofactor depletion.

Conclusions:

- An estimated 95% of children with cancer receive APAP at PCH.
- Our pilot study of 200 PK samples revealed no children exceeded the APAP therapeutic range between 0-6 hours; however, only 13/ 98 patients met a therapeutic concentration (10-20 ug/ mL).
- Although APAP metabolism varies with age, across all groups levels of APAP-Cys and APAP-NAC consistently increase over time (8x, 4x). Additional work is needed to relate oxidative metabolism to APAP protein adducts.

References:

1.) *Cochran Data. Sys. Rev.* **2019**, *4*, CD008205; 2.) *Leuk. & Lymph.* **2020**, *61*, 1920; 3.) *Drug. Metab. Disease* **2017**, 181; 4.) *Clin. Pharmackinet.* **2019**, *58*, 189; 5.) *Drug Metab. Dispos.* **2019**, *47*, 831.

Acknowledgements:

This project was funded by the generous support of: NIH1K22CA258671-01A1 (JEC) and NIH NCATS CCTS-PCHF-002580 (JEC).