MSPR Plenary III - Bowel / Gut; Liver / Kidney; Neurological; Miscellaneous

Thursday, October 8 4:45-6:15 PM CDT

Moderators
Katherine Satrom – University of Minnesota
Steven McElroy - The University of Iowa Hospitals and Clinics Department of Pathology
Lyndsay Harshman - The University of Iowa Stead Family Department of Pediatrics
Ulrike Mietzsch – University of Washington School of Medicine

CDT	Abstract	Title	Presenting Author
4:45 PM		Introduction & General Information	
4:50 PM	3475999	Effects of caffeine maintenance dosing on renal tissue oxygenation in preterm neonates	Amy Rothwell
5:00 PM	3473606	The hidden consequence of intraventricular hemorrhage: persistent cerebral desaturation after IVH in preterm infants	Zachary Vesoulis
5:10 PM	3476295	Gut Mycobiome Maturation During Infancy and its Clinical Determinants	Timothy Heisel
5:20 PM	3476276	Complement Receptor C3AR1 regulates pathophysiology of fibrosing cholangiopathies of biliary atresia and primary sclerosing cholangitis	Unmesha Thanekar
5:30 PM	3473817	Early Body Composition and Prefrontal Cortex Development in Preterm Infants	Erin Morris
5:40 PM	3476634	A critical evaluation of current NEC definitions using statistics and machine learning	Shiloh Lueschow
5:50 PM	3471570	Hospital bed days and medical technology use as a proxy for cost comparison of resuscitation between 22-, 23-, and 24-week gestation infants	Leah Thomas
6:00 PM	3475847	Early-life antibiotics disrupted postnatal development and phagocytic function of neutrophils in neonatal mice.	Natsumon Udomkittivorakul
6:10 PM		Wrap Up	

Note: Schedule subject to change based on presenter availability.

CONTROL ID: 3475999

TITLE: Effects of caffeine maintenance dosing on renal tissue oxygenation in preterm neonates

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Amy Rothwell

AUTHORS/INSTITUTIONS: A. Rothwell, M. Harer, Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, UNITED STATES|

CURRENT CATEGORY: Clinical Investigation

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Caffeine is most commonly used for apnea of prematurity, but administration in neonates is also associated with reduced incidence and severity of acute kidney injury (AKI). The mechanism of this protection remains unproven, but is thought to be mediated by increased renal blood flow. Near infrared spectroscopy (NIRS) is a non-invasive monitor used to continuously measure somatic tissue oxygenation, such as Renal regional tissue oxygenation ($RrSO_2$). When used with continuous pulse oximetry, renal fractional tissue oxygenation extraction (rFTOE) can be calculated. The effects of caffeine on $RrSO_2$ and rFTOE in preterm neonates have not been well described.

Objective: To evaluate changes in $RrSO_2$ and rFTOE following caffeine maintenance dosing in preterm neonates.

Design/Methods: A secondary retrospective analysis of a prospective NIRS study was performed. Invos NIRS sensors were placed on eligible neonates <32 weeks' gestation within 48 hours of age. Continuous $RrSO_2$ data was collected until 7 days of age, and 20-minute means were determined immediately prior to caffeine administration (baseline), and at 0.5, 1, 2, 3, 4, 6, and 12 hours after dose completion. Caffeine dose (mg/kg), administration time (T_0), and oxygen saturations were extracted from chart review. Subgroups were determined by baseline $RrSO_2$ values and post-dose $RrSO_2$ and rFTOE values were compared to baseline.

Results: Of 35 total infants, 31 received caffeine and were included for analysis (mean gestational age 28.1 ± 0.4 weeks, mean birth weight 1,056 ± 77 g). A total of 156 maintenance doses were analyzed, mean dose 7.9 ± 0.1 mg/kg, of which 37 (23.7%) were oral. Subgroup analysis demonstrated increases in $RrSO_2$ from baseline median in the 20-29.99% subgroup (Table 1A), with significant increases at 1, 2, 3, 4, 6, and 12 hours (Figure 1A). Decreases in rFTOE from baseline median were observed in the 20-29.99% subgroup (Table 1B), with significant decreases at 1, 2, 3, 4, 6, and 12 hours (Figure 2B).

Conclusion(s): In preterm neonates receiving caffeine, significant increases in $RrSO_2$ and decreases in rFTOE were observed in those whose baseline $RrSO_2$ values were in the range of 20-29.99%. This preliminary analysis suggests that caffeine may be an effective therapy to increase renal perfusion and oxygenation, potentially explaining its association with reduced incidence of AKI in preterm neonates. Future studies assessing changes in $RrSO_2$ and rFTOE following bolus caffeine administration are needed to fully characterize the effects of caffeine in this context.

(no table selected)

IMAGE CAPTION:

Table 1

A

$\Delta RrSO_2$ from baseline median post-caffeine

Subgroup	+0.5 hr	+1 hr	+2 hr	+3 hr	+4 hr	+6 hr	+12 hr
<20% (n=12)	1.50	0.85	0.91	2.07**	1.74	0.16	0.12
20-29.99% (n=16)	4.51	5.90**	13.74***	9.20***	12.72****	8.26*	13.87**
30-39.99% (n=18)	6.14	8.06*	2.94	4.29	6.60	4.51	2.37
40-49.99% (n=13)	1.36	0.62	1.35	1.98	-0.15	1.35	0.83
50-59.99% (n=21)	3.81	-0.10	1.40	3.64	3.37	1.39	-0.06
≥ 60% (n=76)	-1.53	-2.53	-4.57*	-6.53**	-1.89	-2.99	-4.38*

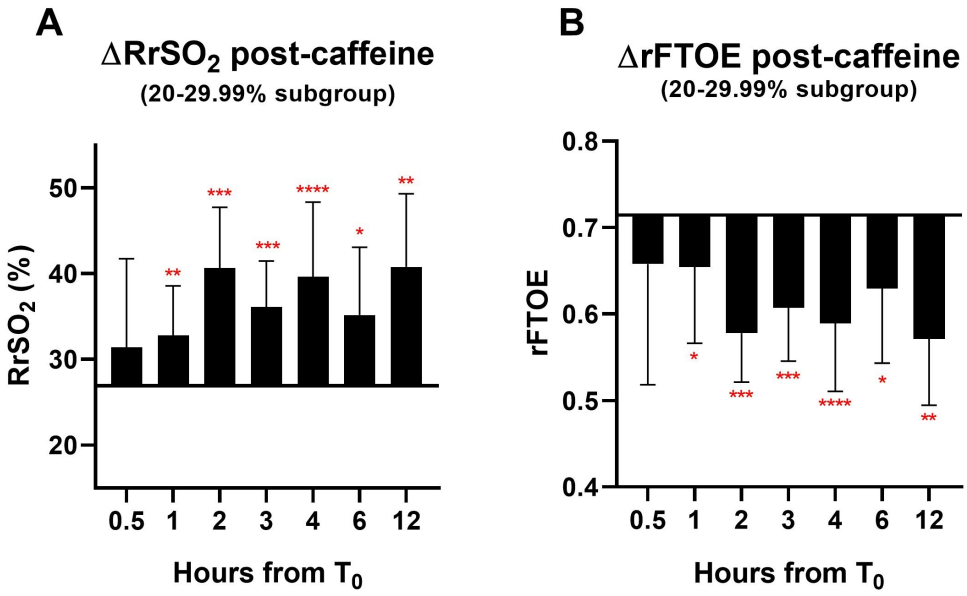
B

ΔrFTOE from baseline median post-caffeine

Subgroup	+0.5 hr	+1 hr	+2 hr	+3 hr	+4 hr	+6 hr	+12 hr
<20% (n=12)	-0.021	-0.008	-0.011	-0.021*	-0.017	0.005	0.002
20-29.99% (n=16)	-0.057	-0.060*	-0.137***	-0.108***	-0.126****	-0.085*	-0.144**
30-39.99% (n=18)	-0.052	-0.073*	-0.037	-0.047	-0.062	-0.029	-0.016
40-49.99% (n=13)	-0.020	-0.023	-0.045	-0.042	-0.012	-0.019	-0.020
50-59.99% (n=21)	-0.024	-0.003	0.001	-0.028	-0.029	-0.001	-0.001
≥ 60% (n=76)	-0.013	0.030	0.041*	0.070**	0.031	0.037	-0.034

*** p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001**

Figure 1



* p < 0.05, ** p< 0.01, *** p < 0.001, **** p < 0.0001

CONTROL ID: 3473606

TITLE: The hidden consequence of intraventricular hemorrhage: persistent cerebral desaturation after IVH in preterm infants

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Zachary Andrew Vesoulis

AUTHORS/INSTITUTIONS: Z.A. Vesoulis, H.V. Whitehead, S.M. Liao, Pediatrics, Washington University in Saint Louis School of Medicine, Saint Louis, Missouri, UNITED STATES|A.M. Mathur, Pediatrics, Saint Louis University School of Medicine, Saint Louis, Missouri, UNITED STATES|

CURRENT CATEGORY: Clinical Investigation

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Previous studies describe a short-term decrease in cerebral oxygen saturation (StO_2) after intraventricular hemorrhage (IVH) in premature infants. Systemic hypoxia has previously been linked to the development of IVH, but the impact of IVH on regional oxygenation in the brain is understudied. This is particularly problematic as IVH quickly evolves into a chronic condition-- the implications of this prolonged insult are not known. In this study, we hypothesized that IVH induces persistent, long-term alterations in cerebral oxygenation, inducing chronic cerebral hypoxia independent of other causes of chronic hypoxia, namely anemia of prematurity.

Objective: To evaluate the longitudinal impact of IVH on cerebral oxygenation and fractional tissue oxygen extraction for preterm infants born before 30 weeks gestation.

Design/Methods: Infants born < 30 weeks gestational age (GA) were included. Clinical characteristics, hemoglobin measurements, highest grade of IVH, and white matter injury (WMI) were noted.

NIRS monitoring occurred daily or every other day for four weeks; weekly through 36 weeks GA. Recordings were error-corrected before calculation of mean StO_2 and fractional tissue oxygen extraction (FTOE). Smoothed conditional means were calculated using ggplot2 in R. When datasets were > 1000 elements, modeling was done using generalized additive models (GAM) with integrated smoothness estimation; those < 1000 elements were modeled using locally estimated scatterplot smoothing (LOESS).

For this analysis, infants were first divided as those with and without IVH. The line of best-fit and the 95% confidence interval were estimated. A similar approach was used to model the relationship between longitudinal FTOE and white matter injury where infants were clustered by presence or absence of WMI on neuroimaging.

Results: 1237 recordings from 185 infants were included with a mean length of 6.5 hours. The mean GA was 26.3 weeks and the mean birth weight was 951 grams. The overall incidence of IVH was 29%, the incidence of severe IVH was 8%, and white matter injury was noted in 16%. IVH was independently associated with an acute drop in StO_2 which remained lower for 68 days (beyond the 95% CI). Severe IVH was associated with lower StO_2 values than mild IVH. WMI was associated with early and persistent elevation of FTOE.

Conclusion(s): IVH of any grade is associated with a prolonged cerebral desaturation, WMI is associated with prolonged elevation of FTOE. This finding is exacerbated for infants with severe IVH.

(no table selected)

IMAGE CAPTION: **Figure 1:** StO_2 by Postnatal Age (PNA), IVH vs. no IVH. Each point represents a single recording, plotted by PNA in days on the x-axis and StO2 on the y-axis. Infants without IVH are blue, infants with IVH are black. Best-fit lines by LOESS non-linear regression are solid lines, bounded by the 95% CI shown in gray shading. For infants with IVH, cerebral desaturation occurs soon after birth and is distinct from infants without IVH until postnatal day 68. **Figure 2:** Cerebral Fractional Tissue Oxygen Extraction (FTOE) by Postnatal Age (PNA), WMI vs. no WMI. Each point represents a single recording, plotted by PNA in days on the x-axis and FTOE on the y-axis. Infants without WMI are blue, infants with WMI are black. Best-fit lines by LOESS non-linear regression are solid lines, bounded by the 95% CI shown in gray shading. For infants with WMI, elevated extraction occurs soon after birth and is largely distinct from infants without WMI until postnatal day 45.

Figure 1: StO_2 by Postnatal Age (PNA), IVH vs. no IVH. Each point represents a single recording, plotted by PNA in days on the x-axis and StO2 on the y-axis. Infants without IVH are blue, infants with IVH are black. Best-fit lines by LOESS non-linear regression are solid lines, bounded by the 95% CI shown in gray shading. For infants with IVH, cerebral desaturation occurs soon after birth and is distinct from infants without IVH until postnatal day 68.

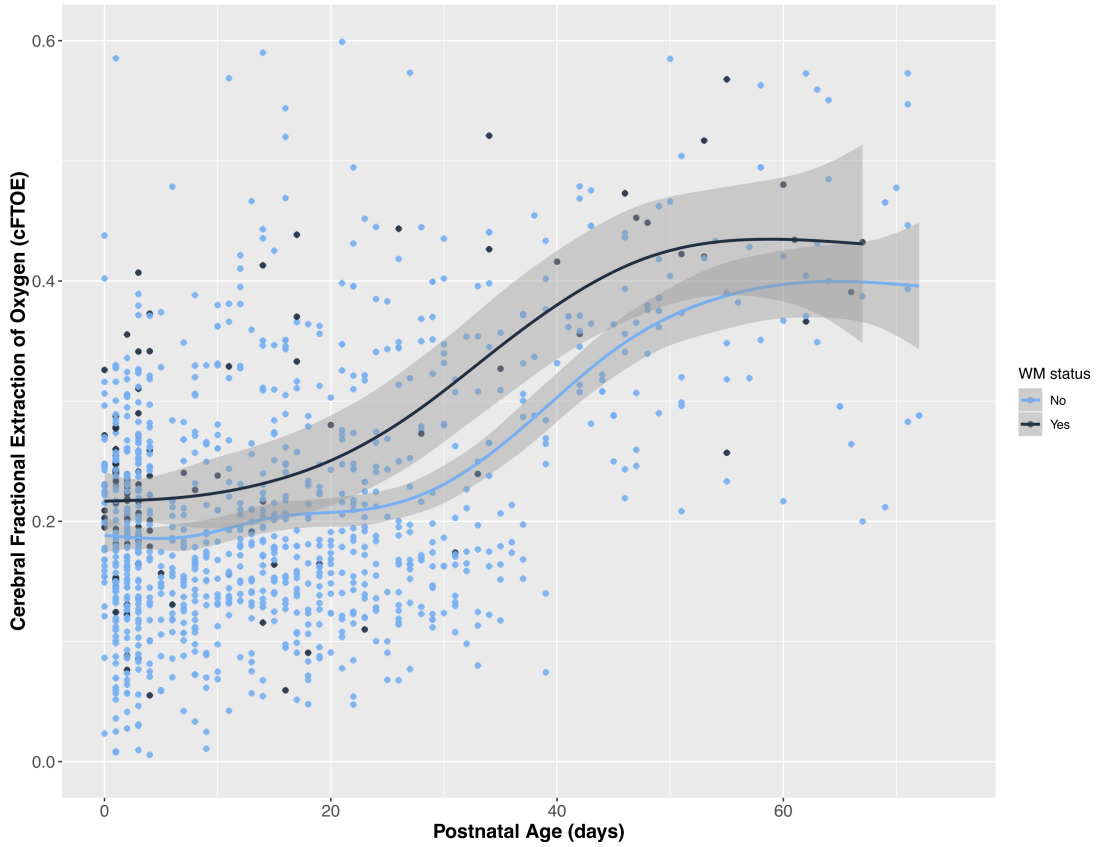


Figure 2: Cerebral Fractional Tissue Oxygen Extraction (FTOE) by Postnatal Age (PNA), WMI vs. no WMI. Each point represents a single recording, plotted by PNA in days on the x-axis and FTOE on the y-axis. Infants without WMI are blue, infants with WMI are black. Best-fit lines by LOESS non-linear regression are solid lines, bounded by the 95% CI shown in gray shading. For infants with WMI, elevated extraction occurs soon after birth and is largely distinct from infants without WMI until postnatal day 45.

CONTROL ID: 3476295

TITLE: Gut Mycobiome Maturation During Infancy and its Clinical Determinants

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Timothy Heisel

AUTHORS/INSTITUTIONS: T. Heisel, S. Gonia, C.A. Gale, Pediatrics, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|A. Johnson, S. Hoops, D. Knights, Computer Science and Engineering, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|S. Mukhopadhyay, Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, UNITED STATES|P. Kennedy, College of Biological Sciences, University of Minnesota, St. Paul, Minnesota, UNITED STATES|M.J. Sadowsky, Soil, Water, and Climate, University of Minnesota, St. Paul, Minnesota, UNITED STATES|K.M. Puopolo, J. Gerber, Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Gut microbes contribute to human health, with early-life colonization being particularly important for the development of metabolism, immunity and the brain. Fungi and bacteria both colonize the infant gut and modulate immune responses at this site. Despite this importance, there has been a lack of studies examining early-life fungal community (mycobiome) development and clinical determinants of its composition and function within the host.

Objective: The goal of this study was to characterize mycobiome maturation during the first two years of life and to determine if early-life mycobiomes are modulated by birth mode, sex, and antibiotic exposure. In addition, because fungi represent a small population relative to the gut bacteria, we used two complementary mycobiome characterization approaches (amplicon and metagenomic sequencing).

Design/Methods: Longitudinal infant fecal samples (n=1034) from 187 unique infants and associated clinical metadata were obtained from the MAGIC study (Children's Hospital of Philadelphia). Metagenomic libraries and fungal ITS2 amplicons were generated from fecal DNA and then sequenced on Illumina NovaSeq and MiSeq systems, respectively.

Results: Both ITS2 and metagenomic datasets contained high abundances of Candida albicans and Saccharomyces, as well as high prevalences of Malassezia restricta and S. cerevisiae. A total of 59 fungal taxa were shared, and these accounted for the majority of abundant phylogenetic groups in both datasets. For both datasets, species counts increased over time (t-test $p<0.001$). Neonatal samples (<1 month of age) had different mycobiomes as compared to samples from older infants (>1 month) (beta diversity, PERMANOVA $p<0.05$), particularly in abundances of M. restricta (higher in neonates, Wilcoxon rank-sum test, FDR-corrected $p<0.25$). Birth mode (43% C-section) was associated with mycobiome differences across all ages as well as when grouped by neonatal and older infant cohorts (beta diversity $p<0.05$ for all three tests). Sex (44% female) and infant antibiotic exposure (35% of infants) were associated with differences in abundances of specific fungal phylogenetic groups (Wilcoxon, FDR-corrected $p<0.25$) as well as whole community composition (beta diversity, PERMANOVA $p<0.05$ for both clinical factors).

Conclusion(s): Infant gut mycobiomes exhibit dynamic maturation that is affected by birth mode, sex, and antibiotics. Further, the primary result trends were shared between amplicon and metagenomic approaches, thus, our results are robust to sequencing methodology.

(no table selected)

(No Image Selected)

CONTROL ID: 3476276

TITLE: Complement Receptor C3AR1 regulates pathophysiology of fibrosing cholangiopathies of biliary atresia and primary sclerosing cholangitis

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Unmesha Thanekar

AUTHORS/INSTITUTIONS: U. Thanekar, R. Mourya, A. Malik, P. Shivakumar, Gastroenterology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, UNITED STATES|G.N. Matos Ortiz, Department of Biology, Pontifical Catholic University of Puerto Rico Mayaguez Campus, Mayaguez, PUERTO RICO|P. Shivakumar, Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Fibrosing cholangiopathies of biliary atresia (BA) and primary sclerosing cholangitis (PSC), are characterized by cholangiocyte injury, immune cell infiltrations and obstruction of the biliary tree. Recent evidence suggests that the complement receptor C3AR1 negatively regulates neutrophil mobilizations, cellular tight junctions and elaboration of proinflammatory cytokines in several diseases.

Objective: To investigate C3AR1-dependent regulation of biliary disease pathogenesis in the context of BA and PSC.

Design/Methods: Experimental BA was induced in newborn mice by i.p. injection of $1.0X10^6$ ffu of rhesus rotavirus (RRV). Knockout mice were generated by superimposing C3AR1 deficiency on an MDR2–/– background. Liver biochemistry was assessed by plasma bilirubin, ALT and AST levels. Histology of extrahepatic bile ducts (EHBDs) and livers was evaluated by H&E staining and cytokeratin (CK)+ bile duct profiles. Liver immune cells were phenotyped using flow cytometry and gene expressions were determined by qRT-PCR.

Results: Expressions of C3AR1, CXCR4 and CXCL12 were elevated in livers of human (2.5–7.3 fold above normals $P \leq 0.0003$) and EHBDs of experimental BA (RRV: 1.3–6.3 fold above controls, $P<0.02$). Serum levels of C3, C3a and C3adesArg also increased in BA patients (1.2–1.4 fold above controls, $P<0.03$, Fig 1). RRV infection of C3AR1–/– mice resulted in severe EHBD atresia, liver inflammation, early mortality by day 10 (77%) vs WT mice (0%, $P<0.0001$), elevated bilirubin (25.7±3.9; WT: 13.1±1.9 mg/dL) and ALT (354±158; WT: 128±16 IU/L) levels ($P<0.0001$) (Fig 2). Hepatic expressions of Tnf α, IL1 β and IL6 and Nkg2d+ CD4+/CD8+, NK, pDCs, macrophage and neutrophils were elevated (2.6– 6.3 fold, $P<0.01$–<0.0001) in C3AR1–/– mice. RRV infection suppressed C3AR1 expression on hepatic CD45+Lin+ and increased on CD45–Lin– cells. MDR2 deficiency significantly suppressed hepatic C3AR–expressing CD3+CD314+CD4+/CD8+, CD11b+Gr1+, pDC and NKp46+CD314+ cells. C3AR1–/–MDR2–/– mice showed enhanced onion skin fibrosis (Fig 4), dilatation of intrahepatic ducts resembling large-duct PSC and an inflamed and tortuous extrahepatic common duct (Fig 3). Sirius red areas increased significantly in C3AR1–/–MDR2–/– (1.6E+05±4.4E+04) compared to MDR2–/– mice (7.4E+04±3.3E+04) (Fig 3).

Conclusion(s): C3AR1 regulates the fibroinflammatory and proliferative responses in BA and PSC. C3AR1 agonism may therefore be a novel therapeutic intervention in pediatric and adult cholestatic liver diseases.

(no table selected)

IMAGE CAPTION:

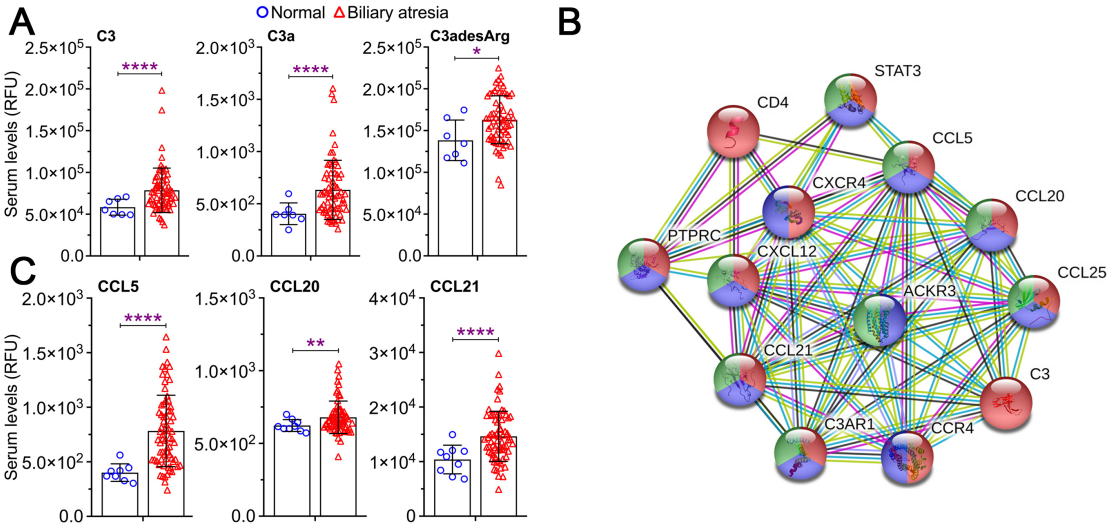


Fig. 1. (A) Patients with BA show elevated levels of serum C3, C3a, C3adesArg indicating detectable levels of complement molecules in systemic circulation. (B) STRING protein-protein network shows interaction of C3AR1, CXCR4 and CXCL12 with critical chemokines in biological processes [Red: defence response, Blue: regulation of locomotion, and Green: cell migration], that were increased in serum from BA patients (C). ****=P<0.0001, Student's t-test.

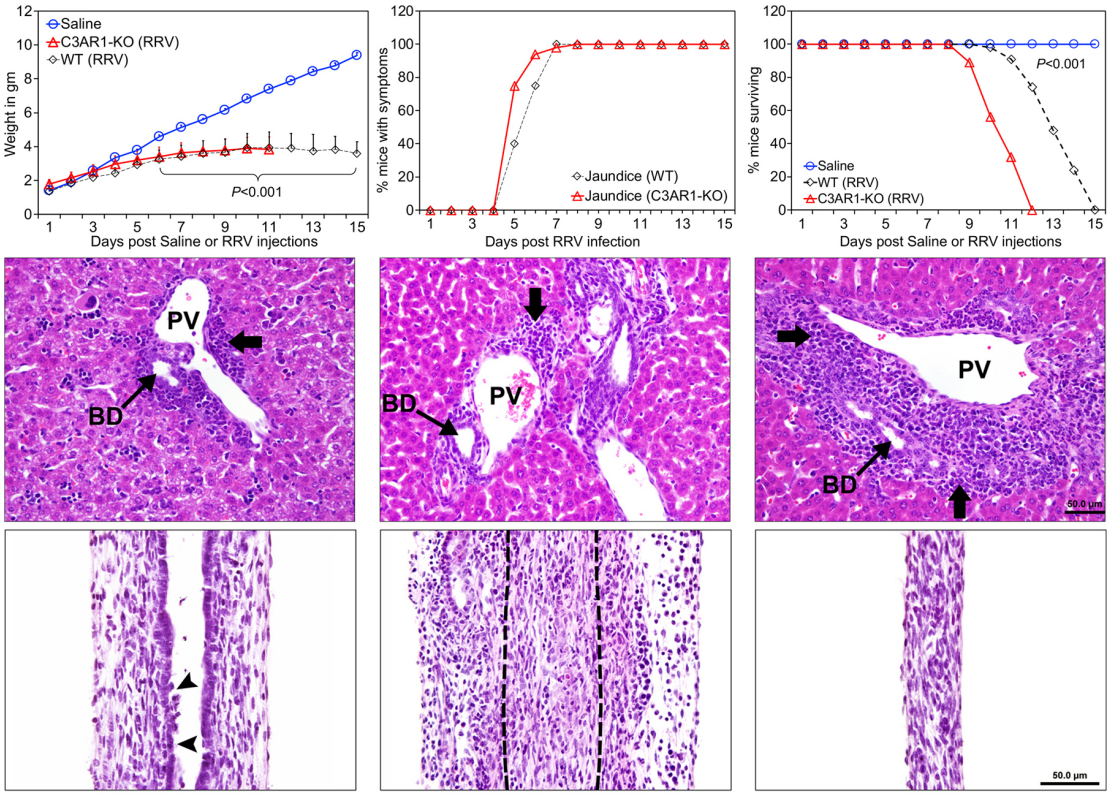


Fig. 2. Top Panel: RRV infection of WT and C3AR1–/– mice shows severe growth failure compared to saline-injected mice. Both WT and C3AR1–/– mice infected with RRV show persistence jaundice until 2 weeks post challenge. Kaplan-Meier survival analysis shows early mortality in RRV-C3AR1–/– compared to WT mice. N=25-40 mice/group. Middle Panel shows histology of livers at days 3, 7 and 14 post RRV infection in C3AR1–/– mice associated with severe portal inflammation, expansion and cholangitis. Bottom panel shows progressive injury, inflammation and atresia of extrahepatic bile ducts at days 3, 7 and 14 from RRV infected C3AR1–/– mice. N=25-30/timepoint.

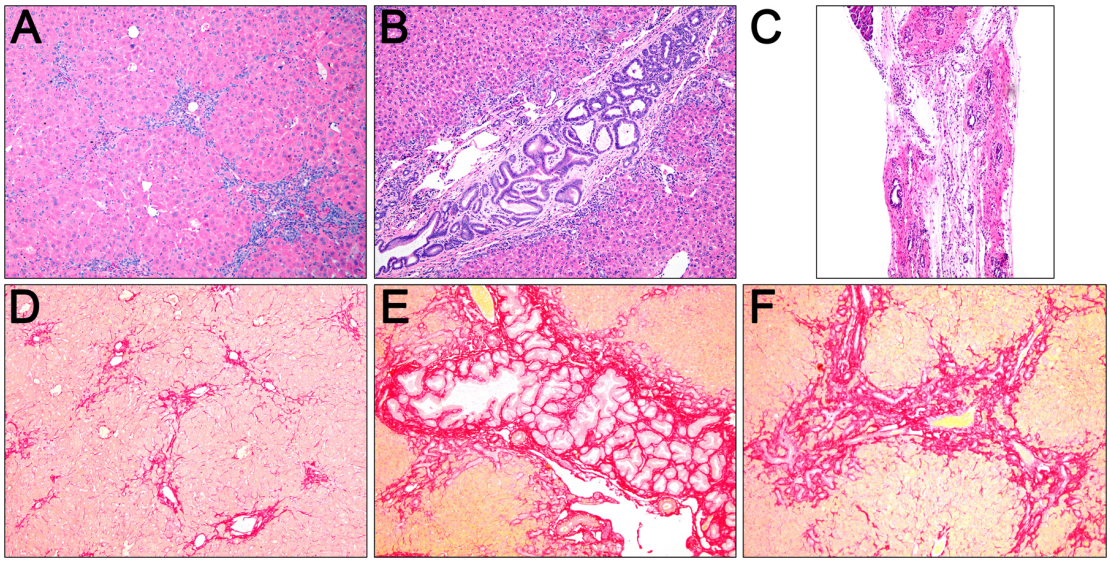


Fig. 3. Panel (A) shows bridging fibrosis and inflammation in MDR2 –/– mice. (B) Intrahepatic bile ducts in MDR2 –/–C3AR1–/– mice show significant expansion of medium and large ducts with features of large-duct PSC. (C) H&E stained EHBD sections show severe inflammation, cholangitis, and ductal strictures impeding bile flow. (D) Sirius Red stained sections show progressive fibrosis in MDR2 –/– mice with portal and bridging fibrosis, while panel (E) shows severe forms of medium and large intrahepatic ducts. (F) depicts severe portal and bridging fibrosis of the intrahepatic ducts. Magnification: 100X.

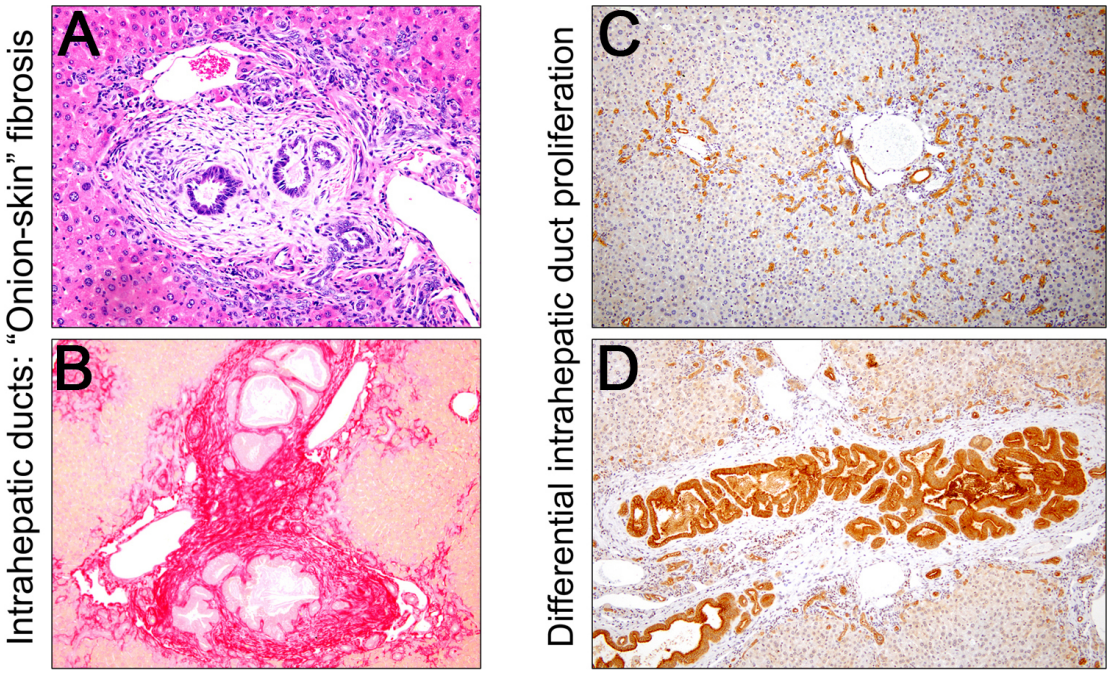


Fig. 4. H&E (A) and Sirius Red (B) staining of livers from MDR2 –/–C3AR1–/– mice shows increased severity of cholangitis and spontaneous development of onion skin-like periductal fibrosis of medium and large sized intra-hepatic bile ducts. Panel (C) depicts increased CK19+ bile duct profiles and reactive duct proliferation in MDR2 –/– mice. (D) Livers from MDR2 –/–C3AR1–/– mice show significant expansion of CK19+ large ducts ducts with severe fibroinflammation of the surrounding region.

CONTROL ID: 3473817

TITLE: Early Body Composition and Prefrontal Cortex Development in Preterm Infants

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Erin Elizabeth Morris

AUTHORS/INSTITUTIONS: E.E. Morris, M.K. Georgieff, S. Ramel, Neonatology, University of Minnesota, Roseville, Minnesota, UNITED STATES|N.C. Miller, M.K. Georgieff, Center for Neurobehavioral Development, University of Minnesota, Minneapolis, Minnesota, UNITED STATES|J.L. Haapala, HealthPartners Institute, Minneapolis, Minnesota, UNITED STATES|

CURRENT CATEGORY: Clinical Investigation

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Development of the prefrontal cortex (PFC) is of particular interest in premature infants due to their risk of later difficulties with attention, social, and communication skills. Altered body composition in preterm infants is associated with risk to cognitive development, but its effect on PFC development is unknown.

Objective: Evaluate the relationship between early body composition and behavioral indices of PFC development, specifically self- regulation, reactivity, and ability to modulate arousal in early childhood.

Design/Methods: Prospective observational trial of 103 appropriate for gestational age infants (birth weight < 1500g) recruited from the neonatal intensive care unit at University of Minnesota Masonic Children's Hospital from 2012 to 2016. Fat mass (FM) and fat free mass (FFM) were measured using air displacement plethysmography (ADP) at discharge and 4 months corrected age (CA). The Infant Behavior Questionnaire (IBQ) was completed at 12 months CA, and the Early Childhood Behavior Questionnaire (EBQ) was administered at 24 months CA. Statistical analysis was completed using a standard regression analysis, with significance declared at $P \leq 0.05$.

Results: Fifty-two infants had at least one body composition measurement. Increased FM at discharge was associated with maternal report of increased fear, distress to limitations, and decreased soothability at 12 months CA ($P \leq 0.05$ for all). Increased FM at 4 months CA was associated with increased activity level at 12 months CA and decreased inhibitory control at 24 months CA ($P < 0.03$ for all). Increased FFM at 4 months CA was associated with increased impulsivity and decreased low intensity pleasure ($p < 0.04$ for all) at 24 months.

Conclusion(s): Increased FM gains out to 4 months CA are associated with more difficult temperament at 12 and 24 months CA. FFM gains after discharge were associated with increased impulsivity and decreased pleasure with low intensity stimuli; this may reflect that rapid FFM gains after discharge do not fully compensate for FFM deficits prior to discharge. We speculate excessive FM gains may contribute to a pro-inflammatory state detrimental to PFC development, while inpatient, rather than late, FFM gains are important to the development of gray matter and connectivity. Further research into relationships between body composition and temperament among preterm infants may allow targeted strategies to improve later behavioral issues in this vulnerable population.

(no table selected)

IMAGE CAPTION:

Table 1: Associations between FFM and FM z-scores at discharge with IBQ and ECBQ

Outcome		FFM Model 1 *Adjusted for age at visit, GA at birth, IVH (grade 2+)*			FM Model 1 *Adjusted for age at visit, GA at birth, IVH (grade 2+)*		
		N	β (SE)	P-value	N	β (SE)	P-value
Infant Behavior Questionnaire (IBQ), 12 months	Activity Level	23	0.185 (0.113)	0.12	23	0.143 (0.111)	0.22
	Distress to Limitations	23	0.227 (0.188)	0.24	23	0.347 (0.169)	**0.05**
	Fear	23	0.134 (0.178)	0.46	23	0.384 (0.149)	**0.019**
	Duration of Orienting	23	0.027 (0.140)	0.85	23	0.157 (0.130)	0.24
	Low Intensity Pleasure	23	-0.114 (0.131)	0.40	23	-0.147 (0.124)	0.25
	Soothability	23	-0.233 (0.157)	0.16	23	-0.462 (0.118)	**0.001**
	Perceptual Sensitivity	23	-0.066 (0.196)	0.74	23	0.011 (0.190)	0.95
	Approach	23	0.127 (0.108)	0.25	23	-0.055 (0.107)	0.61
Early Childhood Behavioral Questionnaire (ECBQ), 24 months	Attentional Focusing	33	-0.053 (0.153)	0.73	33	-0.029 (0.135)	0.83
	Attentional Shifting	33	-0.121 (0.115)	0.30	33	-0.100 (0.102)	0.34
	Frustration	33	0.015 (0.165)	0.93	33	0.206 (0.140)	0.15
	High-Intensity Pleasure	33	-0.000 (0.174)	0.99	33	0.086 (0.153)	0.58
	Impulsivity	33	0.094 (0.154)	0.55	33	0.189 (0.132)	0.16
	Inhibitory Control	33	-0.195 (0.124)	0.13	33	-0.170 (0.109)	0.13
	Soothability	33	-0.083 (0.119)	0.49	33	-0.045 (0.106)	0.68
	Low-Intensity Pleasure	33	-0.289 (0.147)	0.06	33	-0.189 (0.133)	0.17

Abbreviations:
FFM: fat free mass, FM: fat mass, IBQ: infant behavior questionnaire, ECBQ: early childhood behavioral questionnaire, GA: gestational age, IVH: intraventricular hemorrhage

Table 2: Associations between FFM and FM z-scores at 4 mo. with IBQ and ECBQ

Outcome		FFM Model 1 *Adjusted for age at visit, GA at birth, IVH (grade 2+)*			FM Model 1 *Adjusted for age at visit, GA at birth, IVH (grade 2+)*		
		N	β (SE)	P-value	N	β (SE)	P-value
Infant Behavior Questionnaire (IBQ), 12 months	Activity Level	25	0.187 (0.092)	0.06	25	0.305 (0.104)	**0.008**
	Distress to Limitations	25	0.203 (0.122)	0.11	25	0.256 (0.149)	0.10
	Fear	25	0.095 (0.127)	0.47	25	0.159 (0.154)	0.31
	Duration of Orienting	25	0.088 (0.123)	0.48	25	-0.025 (0.152)	0.87
	Low Intensity Pleasure	25	-0.087 (0.103)	0.41	25	-0.013 (0.129)	0.92
	Soothability	25	-0.162 (0.116)	0.18	25	-0.181 (0.143)	0.22
	Perceptual Sensitivity	25	0.068 (0.134)	0.62	25	0.145 (0.162)	0.38
	Approach	25	0.041 (0.083)	0.63	25	0.061 (0.102)	0.56
Early Childhood Behavioral Questionnaire (EBQ), 24 months	Attentional Focusing	33	-0.146 (0.124)	0.25	33	0.039 (0.152)	0.80
	Attentional Shifting	33	-0.116 (0.101)	0.26	33	-0.225 (0.116)	0.06
	Frustration	33	-0.048 (0.145)	0.74	33	-0.254 (0.167)	0.14
	High-Intensity Pleasure	33	0.199 (0.122)	0.11	33	0.000 (0.153)	0.99
	Impulsivity	33	0.276 (0.123)	**0.033**	33	0.024 (0.159)	0.88
	Inhibitory Control	33	-0.090 (0.102)	0.39	33	-0.265 (0.114)	**0.027**
	Soothability	33	-0.167 (0.093)	0.08	33	-0.077 (0.117)	0.51
	Low-Intensity Pleasure	33	-0.260 (0.114)	**0.030**	33	-0.200 (0.144)	0.18

Abbreviations:
FFM: fat free mass, FM: fat mass, IBQ: infant behavior questionnaire, ECBQ: early childhood behavioral questionnaire, GA: gestational age, IVH: intraventricular hemorrhage

CONTROL ID: 3476634

TITLE: A critical evaluation of current NEC definitions using statistics and machine learning

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Shiloh R Lueschow

AUTHORS/INSTITUTIONS: S.R. Lueschow, T.J. Boly, Pediatrics, The University of Iowa Hospitals and Clinics, Iowa City, Iowa, UNITED STATES|R. Patel, Department of Pediatrics, Emory University, Atlanta, Georgia, UNITED STATES|K. Ryckman, Public Health, University of Iowa, Iowa City, Iowa, UNITED STATES|S.J. McElroy, Pediatrics, The University of Iowa Hospitals and Clinics Department of Pathology, Iowa City, Iowa, UNITED STATES|S.R. Lueschow, Microbiology, University of Iowa Carver College of Medicine, Iowa City, Iowa, UNITED STATES|

CURRENT CATEGORY: Clinical Investigation

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Necrotizing Enterocolitis (NEC) was first described in the 1960s, but despite being the leading cause of gastrointestinal mortality (30-50%) in premature infants, its etiology and pathophysiology remain unclear. This ambiguity has resulted in difficulty diagnosing and defining NEC. The most commonly used definition is the Modified Bell's staging system, but six new definitions of NEC have been developed (Fig 1). However, the efficacy, sensitivity, and specificity of these new definitions to identify true NEC has not been evaluated or compared.

Design/Methods: To examine this knowledge gap, we performed a retrospective, 10-year cohort analysis including 220 VLBW infants from the University of Iowa hospital diagnosed with NEC, intestinal perforation, or both. The presence of NEC was determined by a single-blinded investigator from clinical diagnosis independent of NEC definitions. Sensitivity and specificity were evaluated using standard statistics and then classification supervised machine learning was applied. Six different classifiers were used to evaluate all NEC definitions. For each definition, the data was split into a training and test set and the classifiers were evaluated on sensitivity, specificity, accuracy, and Area Under the Receiver Operating Curve (performance). Finally, after evaluating all classifiers, feature importance evaluation was performed on each decision tree classifier to determine the most important criteria.

Results: Using standard statistics, the Modified Bell and UK definitions had high sensitivity but poor specificity for diagnosing NEC, while all other definitions had high specificity and low sensitivity (Fig 1). Applying machine learning to our data showed all newer definitions had greater sensitivity and specificity than Modified Bell criteria in most classifiers and of all classifiers, the decision tree performed the best. In addition, machine learning identified six criteria (pneumatosis, GI bleeding, apnea, lethargy, gestational age, and postnatal age at NEC onset) critical for definitions in diagnosis.

Conclusion(s): This study is the first to use a retrospective cohort of VLBW infants to compare classical and newly suggested NEC definitions. Our data shows that newer definitions of NEC are superior to the classic Modified Bell's criteria using standard statistics and machine learning techniques. Although preliminary, this study could eventually lead to a more efficient and effective NEC diagnosis and ultimately a better prognosis for patients who acquire NEC.

(no table selected)

IMAGE CAPTION:

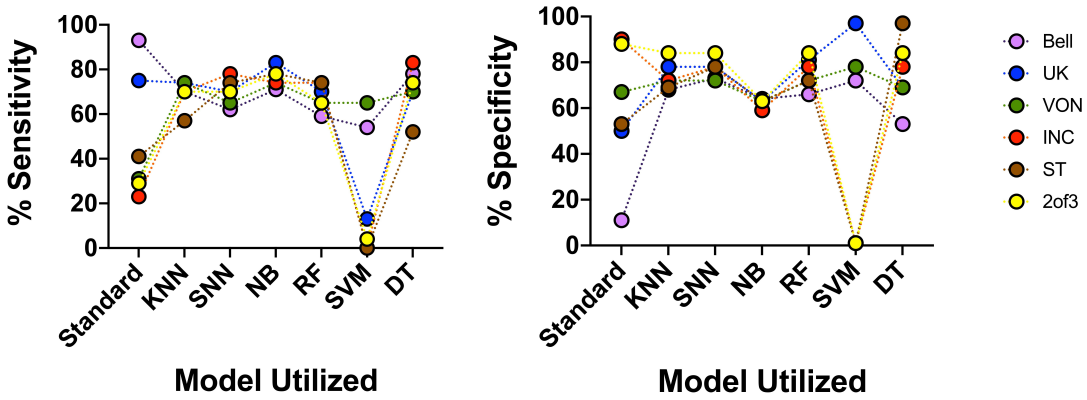


Figure 1: A) Sensitivity and B) Specificity of various definitions of NEC including Severe Bell (Bell), United Kingdom (UK), Vermont Oxford (VON), 2of3, Stanford (ST), and International Neonatal Consortium (INC) based on standard statistics (standard), K nearest neighbors (KNN), simple neural network (SNN), Naive Bayes (NB), random forest (RF), support vector machine (SVM), and decision tree (DT) modeling.

CONTROL ID: 3471570

TITLE: Hospital bed days and medical technology use as a proxy for cost comparison of resuscitation between 22-, 23-, and 24-week gestation infants

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Leah Thomas

AUTHORS/INSTITUTIONS: L. Thomas, University of Chicago Pritzker School of Medicine, Chicago, Illinois, UNITED STATES|A. Schuh, C. Carlos, B. Andrews, Neonatology, UChicago Medicine, Chicago, Illinois, UNITED STATES|S. Millikan, Pediatrics, UChicago Medicine, Chicago, Illinois, UNITED STATES|

CURRENT CATEGORY: Clinical Investigation

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Many physicians refuse to resuscitate infants born at 22 weeks gestational age (GA), citing reasons such as low chance of survival, quality of life, and resource burden. A barrier to offering resuscitation is that studies have shown that resuscitation is not cost-effective. However, some neonatologists have observed that fewer 22-week infants survive than 23- and 24-week infants, and those that do survive do not stay significantly longer.

Objective: We aim to compare the number of bed days and medical technologies used in the NICU and in rehospitalizations one year from NICU discharge between 22-, 23-, and 24-week GA infants. If the use of bed days and technologies, as a proxy for cost of resuscitation, is not significantly higher for 22-weeks GA infants, this is one fewer reason for physicians to not offer resuscitation to parents.

Design/Methods: This was a retrospective, single-center chart review at a pediatric academic tertiary care center from 2016 to 2018. Bed days were determined for each 22-, 23-, and 24-week infant born alive and resuscitated. Because Illinois Medicaid and other insurers reimburse per bed day, cost of an inpatient stay can be estimated from the length of stay and technologies used.

Results: The total days spent inpatient in the NICU plus rehospitalizations one year from discharge were not significantly different between GA, nor were rates of medical technology usage (gastrostomy tube, tracheostomy, ventriculoperitoneal shunt, home oxygen). Over 3 years, 5,508 of 63,598 NICU bed days, or 8%, were utilized by caring for 22-, 23-, and 24-week infants at a large academic tertiary care center, with 22-week infants alone utilizing 1.6%.

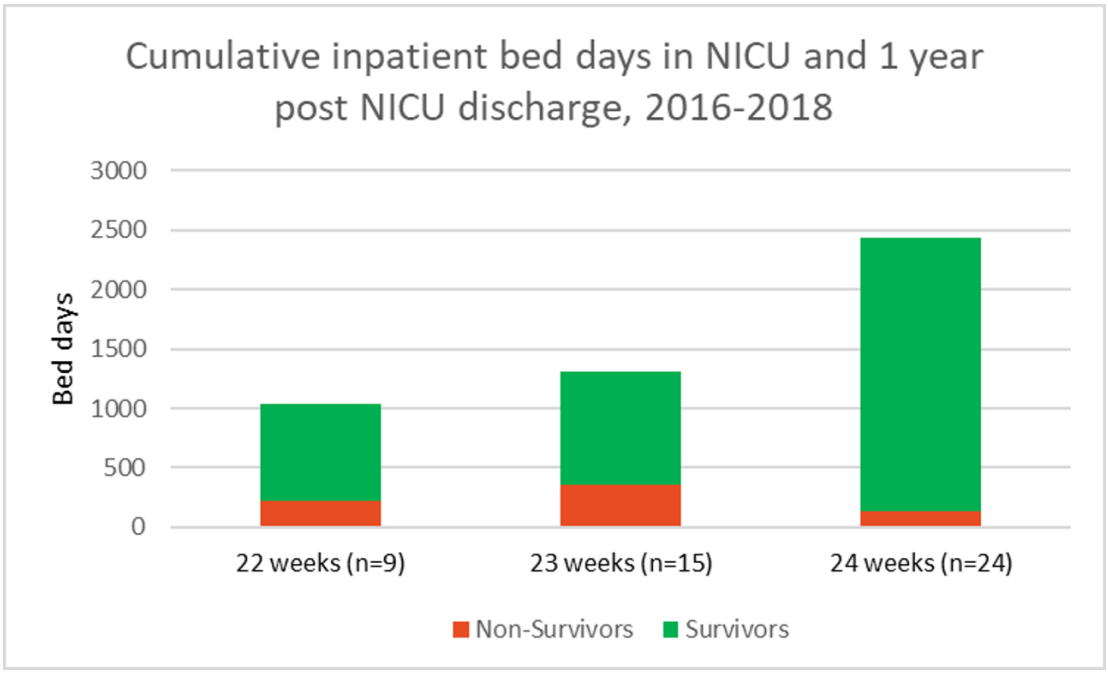
Conclusion(s): On average, resuscitated, inborn, 22-week infants did not use significantly more bed days in the NICU and inpatient one year after NICU discharge than 23 and 24-weeks infants and did not require medical technology at higher rates. Thus, 22-week infants that survived did not have significantly more comorbidities requiring hospitalization than 23- and 24-week infants. Most care and resources in the NICU are allocated to infants of increasing GA. Resource usage related to NICU bed days, rehospitalizations bed days, and medical technology should not be a deterrent to offering resuscitation at 22 weeks in tertiary care centers.

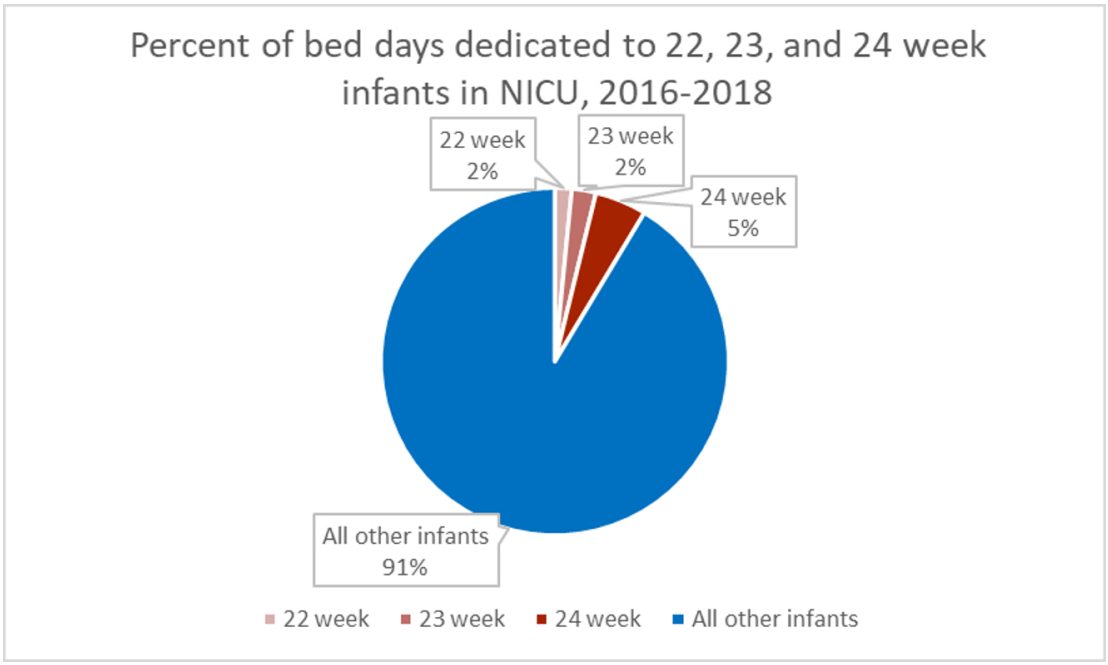
(no table selected)

IMAGE CAPTION: Table 1: Population characteristics

Gestational Age	**22 0/7-6/7 (N=19)**	**23 0/7-6/7 (N=17)**	**24 0/7-6/7 (N=24)**
Born alive and resuscitated	9	16	24
Sex, Male	6 (67%)	12 (75%)	13 (42%)
Mean Birth Weight (SD)	467 g (72)	545 g (86)	670 g (155)
Vaginal Delivery	9 (100%)	12 (75%)	9 (38%)
Cesarean Delivery	0	4 (25%)	15 (62%)
Mean APGAR, 1 min (SD)	2 (1.3)	2 (1.2)	3.1 (1.9)
Mean APGAR, 5 min (SD)	3.7 (2.8)	4 (2.1)	5.9 (2.3)
Medical Technology Use in Survivors	**22 0/7-6/7 (N=4)**	**23 0/7-6/7 (N=6)**	**24 0/7-6/7 (N=16)**
Home Oxygen	4 (100%)	5 (83%)	12 (75%)
Gastrostomy Tube	2 (50%)	0	4 (25%)
Tracheostomy	0	0	1 (6%)
Ventriculoperitoneal Shunt	1 (25%)	0	2 (13%)

Table 1: Population characteristics


Cumulative inpatient bed days in NICU and 1 year post NICU discharge, 2016-2018
Bed days
3000
2500
2000
1500
1000
500
0
22 weeks (n=9)
23 weeks (n=15)
24 weeks (n=24)
Non-Survivors
Survivors


Percent of bed days dedicated to 22, 23, and 24 week infants in NICU, 2016-2018
22 week 2%
23 week 2%
24 week 5%
All other infants 91%
22 week
23 week
24 week
All other infants

CONTROL ID: 3475847

TITLE: Early-life antibiotics disrupted postnatal development and phagocytic function of neutrophils in neonatal mice.

DIGITAL OBJECT IDENTIFIER (DOI):

ABSTRACT STATUS: Sessioned

PRESENTER: Natsumon Udomkittivorakul

AUTHORS/INSTITUTIONS: N. Udomkittivorakul, A. Nadeem, M. Bonfield, J. Gray, T. Wang, J. Stevens, H. Deshmukh, Neonatology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, Ohio, UNITED STATES|

CURRENT CATEGORY: Basic Science

CURRENT SUBCATEGORY: None

ABSTRACT BODY:

Background: Neutrophils are critical in host defense against bacteria in neonates. We previously demonstrated that early-life antibiotic (ABX) exposure interrupted postnatal granulocytosis and rendered neonatal mice susceptible to bacterial sepsis.

Objective: We aimed to understand how early-life ABX use disrupts postnatal development and functions of neutrophils.

Design/Methods: We treated pregnant mice (C57BL/6J) starting from gestational day 15 with drinking water containing 3 antibiotics (ampicillin, gentamycin, and vancomycin). Multipotent hematopoietic stem cell (LSK), common myeloid progenitor (CMP), and granulocyte monocyte progenitor (GMP) populations in blood, bone marrow (BM) and spleen were identified by flow cytometry across different neonatal and adult time points. We quantified neutrophil development ex vivo using low-density BM culture. Neutrophil extracellular trap (NET) formation and phagocytic ability were determined by neutrophil elastase and using pHrodo E. coli BioParticles, respectively. We inoculated the mice with E. coli via intraperitoneal infection for a mortality study.

Results: We observed a significantly higher percentage of both proliferative (bone marrow and spleen) and circulating (peripheral blood) neutrophils in neonatal mice at postnatal days 1-3. Interestingly, increased neutrophils in early life correlated with the expansion of LSK, CMP, and GMP populations. ABX-treated neonatal mice had a global decrease of neutrophil frequencies in blood, bone marrow, and spleen, while LSK, CMP and GMP fractions in the bone marrow remained unchanged (Figure 1). However, BM cells from ABX-treated neonatal mice had significantly decreased LSK and GMP expansion ability compared to controls (Figure 2). Neonatal mice had impaired NET formation with marked susceptibility to E. coli sepsis, while ABX-treated neonatal mice also demonstrated reduced phagocytic ability.

Conclusion(s): Increased neutrophils in early life correlated with the expansion of the progenitors. ABX exposure disrupted postnatal granulocytosis, diminished the capacity of BM neutrophil progenitors to expand, and reduced phagocytic ability in neonatal mice.

(no table selected)

IMAGE CAPTION:

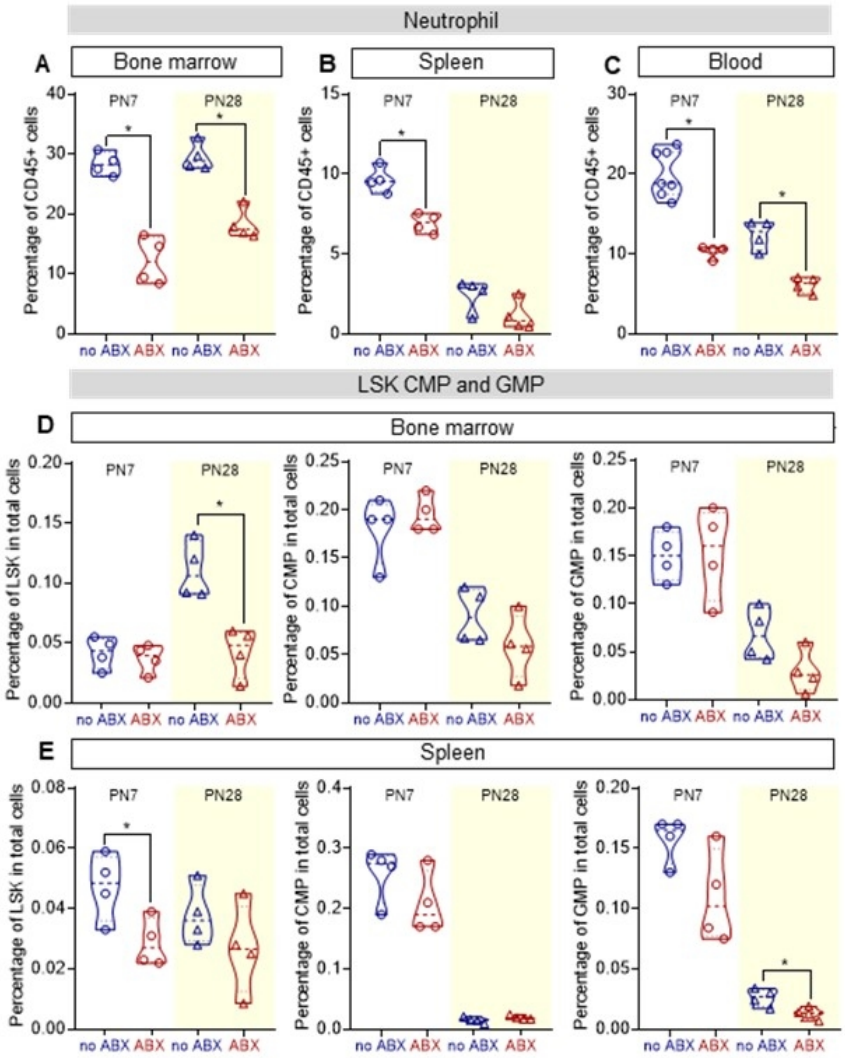


Figure 1: Effect of antibiotics exposure on neutrophil, LSK, CMP, and GMP populations. Percentage of neutrophil in **A)** bone marrow **B)** spleen and **C)** blood and percentage of LSK/CMP/GMP in **D)** bone marrow and **E)** spleen of ABX-free or ABX-treated neonatal (PN7) and adult (PN28) mice. Results are shown as individual values with median and quartiles in violin plots (Student's t-test, *P $\leq$ 0.05).

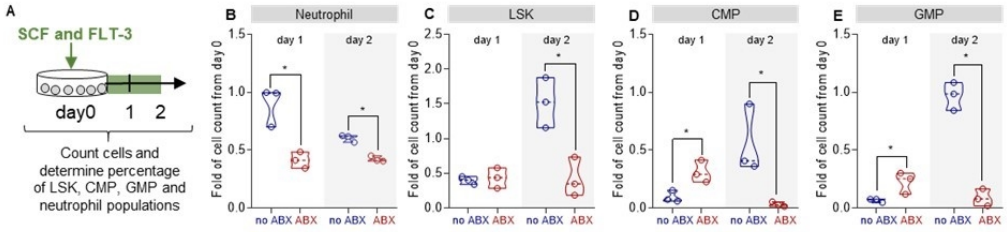


Figure 2: Low-density bone marrow neutrophil culture. A) Low-density bone marrow cells were cultured with supplementation of SCF and FLT-3 on day 0. Cultured cells were counted and the percentage of neutrophil and LSK/CMP/GMP populations was determine by flow cytometry on day 0, 1 and 2. Fold change difference of **B)** neutrophil **C)** LSK **D)** CMP, and **E)** GMP cell count from day 0 of ABX-free or ABX-treated neonatal (PN7) mice. Fold difference of cell count was determine by total cell count x percentage of each cell population from flow cytometry analysis. Results are shown as individual values with median and quartiles in violin plots (Student's t-test, *$P \leq 0.05$).