



## Week 6: Neonatal Infectious Diseases

### Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**Tuesday, Aug. 4 4:30-6:00 pm EDT**

#### **Moderators**

Jennifer Duchon

Ajay Talati

EDT	Abstract	Title	Presenting Author
4:30 pm		Introduction & General Information	
4:35 pm	3373206	The utility of the nSOFA score to predict late-onset sepsis mortality risk among VLBW infants: A retrospective international multi-center and single-center prospective study.	Noa Fleiss
4:45 pm	3384641	Serial measurement of inflammatory biomarkers to predict late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) in very low birthweight (VLBW) infants.	Rupin Kumar
4:55 pm	3376262	Shortening the Duration of Empiric Antibiotic Therapy for Possible Early-Onset Sepsis in the Neonatal Intensive Care Unit: Is 24 Hours Enough?	Pavel Prusakov
5:05 pm	3381614	Chitinase 3-Like 1 Decreases the Inflammatory Response in Chorioamnionitis	Anshu Mahadeo
5:15 pm	3373241	NICU discharge T-cell cytokine profiles predict respiratory morbidity at 1-year of life	Meagan Goates
5:25 pm		Wrap Up	

Note: Schedule subject to change based on presenter availability.

**CONTROL ID:** 3373206

**TITLE:** The utility of the nSOFA score to predict late-onset sepsis mortality risk among VLBW infants: A retrospective international multi-center and single-center prospective study.

**PRESENTER:** Noa Fleiss

**AUTHORS (LAST NAME, FIRST NAME):** Fleiss, Noa<sup>3</sup>; Coggins, Sarah<sup>1</sup>; Srinivasan, Lakshmi<sup>2</sup>; Visser, Douwe H.<sup>5</sup>; Wallman-Stokes, Aaron W.<sup>3</sup>; Polin, Richard A.<sup>3</sup>; De Jong, Brenda S.<sup>5</sup>; Wynn, James L.<sup>4</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Infectious Diseases/Immunology

**KEYWORDS:** sepsis, mortality, preterm infants.

**SESSION TITLE:** Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis |Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Sequential organ failure assessment (SOFA) scores for prediction of sepsis-related morbidity and mortality are widely used in adult and pediatric patients but not in neonates. An operational definition of organ dysfunction applicable to the preterm population (nSOFA) showed utility to predict mortality risk among preterm infants with late-onset sepsis (LOS) at a single center. The utility of the nSOFA to predict LOS mortality in other centers, as well as when used prospectively, is unknown.

**Objective:** Determine the utility of nSOFA to predict LOS-mortality in preterm VLBW (<1500g) infants.

**Design/Methods:** Multi-center retrospective case-control study conducted at Columbia University Medical Center, Children's Hospital of Philadelphia, and Amsterdam University Medical Center. Prospectively recorded nSOFA scores were collected on another infant cohort at University of Florida. The study period ranged from 2013 to 2019 and varied based on center-specific data availability. VLBWs born at <33 weeks' gestation with LOS (bacteremia/fungemia due to a single pathogen) or death due to necrotizing enterocolitis between 3-120 days of life were identified. nSOFA scores were calculated at 9 time points spanning 48 hours before and after sepsis evaluation (SE) and compared between survivors and non-survivors. The relationship between prospectively-recorded nSOFA at SE and all-cause mortality risk was determined. Descriptive statistics were performed and receiver operating curves were generated to determine the area under the curve (AUC) for mortality by nSOFA.

**Results:** 187 infants were identified (160 survivors; 27 non-survivors). Results mirrored the pilot study findings, with higher nSOFA scores among non-survivors from 6 hours prior to 48 hours following SE. Using an nSOFA cutoff >4, AUC=0.77 at SE, 0.88 at +6 hours, and 0.82 at +12 hours. Prospective nSOFA at SE and mortality risk were directly proportional among 306 LOS SEs in 157 infants (AUC=0.83).

**Conclusion(s):** This international multi-center retrospective study confirmed the utility of nSOFA to predict LOS-mortality risk among preterm VLBWs. Mortality risk was also well predicted prospectively at sepsis evaluation, using the nSOFA score.

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CONTROL ID: 3384641

**TITLE:** Serial measurement of inflammatory biomarkers to predict late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) in very low birthweight (VLBW) infants.

**PRESENTER:** Rupin Kumar

**AUTHORS (LAST NAME, FIRST NAME):** Kumar, Rupin<sup>1</sup>; Fairchild, Karen<sup>2</sup>; Sullivan, Brynne A.<sup>2</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Infectious Diseases/Immunology

**KEYWORDS:** Late onset sepsis, cytokines, biomarkers.

**SESSION TITLE:** Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis |Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Early diagnosis of LOS and NEC in VLBW infants, prior to overt deterioration, is difficult due to the non-specific nature of clinical signs and laboratory tests. Plasma cytokines change early in the immune response to infection and may be useful in decisions about therapy. Prior studies have identified cytokines associated with sepsis ruled in or out, but most have not examined baseline cytokine levels which may be elevated due to non-infectious inflammatory conditions.

**Objective:** Compare plasma cytokine levels at the time of suspected late-onset sepsis or NEC with levels at times without suspected infection.

**Design/Methods:** Remnant plasma samples and clinical data were collected prospectively from VLBW infants with parental consent. Samples were collected when a blood culture was sent for suspected sepsis or NEC, and at times when routine laboratory testing was performed. Six cytokines were measured (IL-6, IL-8, IL-10, IL-18, IP-10, and TNF $\alpha$ ) using multiplex antibody-coated bead array with dual-laser fluorometric detection. Sepsis workups were classified as sepsis ruled out (SRO, negative cultures and <5 days antibiotics), LOS including septicemia, UTI and clinical sepsis (5+ days of antibiotics), or NEC (Bell's stage 2-3). LOS was further classified as Gram-negative septicemia (GNS) or other LOS (clinical and culture-positive). Percent change in cytokine levels was compared between groups using Mann-Whitney U test, using  $p < 0.05$  as statistically significant. Sensitivity, specificity, PPV and NPV were calculated for cytokine thresholds for the combined diagnosis of GNS+NEC.

**Results:** For 78 VLBW enrolled infants, samples were collected at the time of 42 blood cultures drawn to evaluate for sepsis or NEC (Tab.1), with ultimate diagnosis of SRO (n=11), LOS (n=28; 3 GNS, 12 Gram-positive septicemia, 3 UTI, 10 clinical sepsis) and NEC (n=3). Fig. 1 shows that, compared to infants with SRO, infants with GNS or NEC had higher levels of IL-10, IL-6, and TNF $\alpha$ . We identified thresholds of these three cytokines with high sensitivity and NPV for GNS or NEC (Tab. 2). Of the 42 blood culture events analyzed, a prior remnant plasma sample was available for 39 (93%). Fig. 2 shows the percent change in cytokines at the time of diagnosis of GNS, NEC, and other LOS.

**Conclusion(s):** In this ongoing study of serial cytokine measurements, preliminary results show rises in plasma cytokines in cases of GNS or NEC but not in other cases of clinical or culture-positive sepsis.

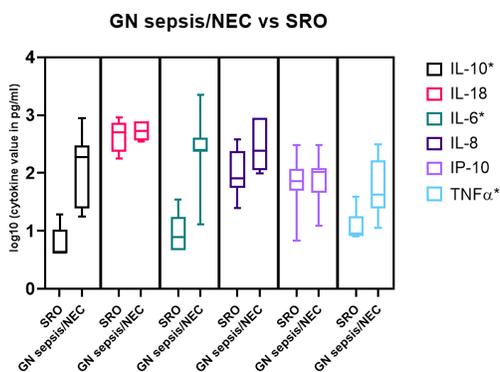


Fig 1. Cytokine levels in Gram-negative sepsis or NEC (n=6) versus SRO (n=11). \* denotes  $p < 0.05$ .

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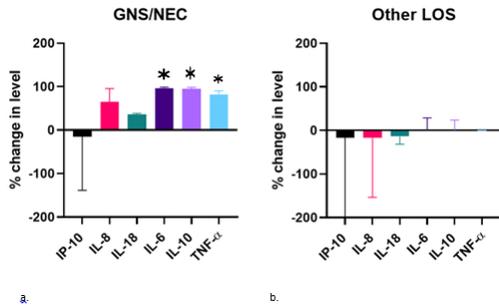


Fig 2. Percent change in cytokine levels over baseline at the time of diagnosis of all cases of (a) GNS (gram-negative sepsis) or NEC and (b) all other cases of LOS. \* denotes  $p < 0.05$ .

Variable	N (%) or median (IQR)
Subjects enrolled	78
Gestational age (weeks)	26.6 (25.3-29.2)
Birthweight (grams)	870 (690-1110)
Male sex	41 (53)
White or Caucasian race	59 (76)
Delivered by C-section	52 (67)
Mother received antenatal steroids	69 (88)
Died before NICU discharge	4 (5)
No. blood culture events analyzed	42
Age at blood culture (days)	17 (10-24)
PMA at blood culture (weeks)	28.4 (26.1-31.2)

Table 1. Demographics and characteristics of enrolled subjects.

	Sensitivity	Specificity	PPV	NPV
IL-6, > 30 pg/ml	84%	91%	27.6%	99.2%
IL-10, > 18 pg/ml	100%	91%	31.5%	100%
TNF-α, > 20 pg/ml	100%	82%	18.6%	100%
IL-8, > 100 pg/ml	83%	55%	7.1%	98.7%
IL-18, > 400 pg/ml	80%	36%	5.1%	98.1%
IP-10, > 100 pg/ml	67%	64%	7.1%	97.8%

Sensitivity, Specificity, PPV and NPV for cytokine elevation in Gram-negative sepsis and NEC.

**IMAGE CAPTION:**

Fig 1. Cytokine levels in Gram-negative sepsis or NEC (n=6) versus SRO (n=11). \* denotes  $p < 0.05$ .

Fig 2. Percent change in cytokine levels over baseline at the time of diagnosis of all cases of (a) GNS (gram-negative sepsis) or NEC and (b) all other cases of LOS. \* denotes  $p < 0.05$ .

Table 1. Demographics and characteristics of enrolled subjects.

Sensitivity, Specificity, PPV and NPV for cytokine elevation in Gram-negative sepsis and NEC.

CONTROL ID: 3376262

TITLE: Shortening the Duration of Empiric Antibiotic Therapy for Possible Early-Onset Sepsis in the Neonatal Intensive Care Unit: Is 24 Hours Enough?

PRESENTER: Pavel Prusakov

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Infectious Diseases/Immunology

**KEYWORDS:** antibiotic stewardship, newborn, early-onset sepsis.

**SESSION TITLE:** Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis |Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Antibiotic therapy in newborns is associated with both short and long term adverse consequences. On 2/15/2019, we recommended reducing empiric antibiotic therapy for possible early-onset sepsis (EOS) from 48 to 24 hours (new dosing schedule: 1 dose, gentamicin; 2 doses, ampicillin) in 6 Nationwide Children's Hospital's (NCH) neonatal intensive care units (NICU).

**Objective:** To describe the safety of providing empiric antibiotic therapy for 24 hours compared with 48 hours among high risk newborns in the NICU

**Design/Methods:** Retrospective cohort study from 12/1/2018- 7/31/2019 of all infants admitted to 6 NCH NICUs (1, level 4; 4, Level 3; 1, level 2) and received empiric antibiotic therapy (ampicillin and gentamicin) for suspected EOS. Pertinent clinical, laboratory, and microbiologic data obtained from electronic health records. Newborns who received 24 vs. 48 hours of empiric antibiotic therapy were compared. Length of therapy (LOT; days of antibiotic coverage) was obtained for first 72 hours of age and overall hospitalization. In infants <28 weeks' gestation, 1 dose of gentamicin was considered as 2 days of LOT. Safety was assessed by re-initiation of antibiotic therapy within 7 days after the initial treatment, positive bacterial cultures in the subsequent week after their discontinuation, and/or mortality (overall/sepsis-related).

**Results:** Of 441 newborns <72 hours of age (60 [14%] <28 weeks' gestation; 32 [7.3%] maternal chorioamnionitis) who received antibiotic therapy for suspected EOS, 200 (45%; 28 [14%] <28 weeks) were treated for 24 hours (1 dose, gentamicin; 2 doses, ampicillin; Table). Mean LOT for first 72 hours of age and hospitalization were significantly less among infants who received 24 hours of antibiotics (1.1 vs. 2.1 days, 1.8 vs 4.2 days, respectively; p <0.01). Antibiotics were restarted in 10 (5%) and 24 (10%) infants in the 24 and 48 hour groups, respectively. Three infants had positive blood cultures (2, *Escherichia coli* [48 hour group]; 1, *Klebsiella pneumoniae* [24 hour group]) and all survived. Time to positivity of *K. pneumoniae* blood culture was 12 hours and antibiotic therapy was continued without any missed dose. 30-day sepsis-related mortality was higher in the 48 hour (5%; n=11) vs. 24 hour (2%; n=3) group.

**Conclusion(s):** Antibiotic therapy for suspected EOS can be discontinued safely within 24 hours, decreasing antibiotic exposure among high risk infants in the NICU.

Characteristics of study population

	24 hour N(%)	48 hour N(%)	P-value
Number of infants (n)	200	241	
Outborn Age (weeks, mean ± SD)	36 ± 5	34 ± 5	0.06
Birth Weight (grams, mean ± SD)	2265 ± 667	2454 ± 820	0.15
Maternal GBS Colonization (n (%))			0.01
Positive	44 (22%)	48 (19%)	
Negative	88 (43%)	100 (41%)	
Not known	68 (33%)	93 (38%)	
Intact Membrane Antibiotics (n (%))			0.05
Yes	100 (50%)	48 (19%)	
No	67 (34%)	100 (41%)	
Unknown	66 (33%)	93 (38%)	
Chorioamnionitis (n (%))	18 (9%)	16 (7%)	0.59
Disruptive Infection (n (%))	6 (3%)	33 (13%)	<0.01
Positive Blood Culture (n (%))	1 (1%)	2 (1%)	0.67
Antibiotic Restart within 7 Days (n (%))	10 (5%)	24 (10%)	0.07
LOT in first 72 hours (days, mean)	1.1	2.1	<0.01
LOT for overall hospitalization (days, mean)	1.8	4.2	<0.01
Mortality	7 (4%)	11 (5%)	0.07
30-Day Sepsis-related Mortality	3 (2%)	11 (5%)	0.07

**IMAGE CAPTION:**

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**CONTROL ID:** 3381614

**TITLE:** Chitinase 3-Like 1 Decreases the Inflammatory Response in Chorioamnionitis

**PRESENTER:** Anshu Meenakshi Mahadeo

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Infectious Diseases/Immunology

**KEYWORDS:** Chitinase 3-Like 1, Chorioamnionitis, Inflammation.

**SESSION TITLE:** Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis |Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Chorioamnionitis is a major cause of preterm delivery and adverse neonatal outcomes. Inflammation is a key component in the induction of labor during chorioamnionitis. Regulation of the inflammatory response may be critical to stop preterm labor. Currently, there are no effective therapies to suppress inflammation in chorioamnionitis. Previous studies have shown that Chitinase 3-Like 1 (CHI3L1) plays an important role in modulating the immune response in inflammation. However, the potential role of CHI3L1 in chorioamnionitis is unexplored.

**Objective:** To assess the role of Chitinase 3-Like 1 in a mouse model of chorioamnionitis.

**Design/Methods:** Inflammation was induced by injecting 10 ng of lipopolysaccharide (LPS) into the amniotic fluid of wild-type mice on E15.5 of gestation. Control mice received normal saline (NS). To study the effects of CHI3L1 on inflammation, some mice received LPS followed by recombinant (r) CHI3L1. Experimental conditions included: NS, LPS, LPS+rCHI3L1 and rCHI3L1. Mice were sacrificed on E16.5 and samples were collected from amniotic fluid, placenta, fetal blood and lungs. Cytokine levels in amniotic fluid and fetal blood were quantified by Multiplex Immunoassay. Levels of CHI3L1 in both compartments were determined by ELISA. Immunostaining with an anti-F4/80 monoclonal rat antibody was used to identify macrophages in placental tissue. Fetal lung architecture was assessed by morphometric analysis.

**Results:** Intra-amniotic injection of LPS induced inflammation, as shown by increased IL-6, IL-18 and TNF-alpha in amniotic fluid and IL-6 in the fetal blood. The addition of rCHI3L1 significantly decreased the levels of these pro-inflammatory cytokines. Administration of rCHI3L1 only did not induce inflammation. LPS also stimulated the secretion of CHI3L1 in amniotic fluid and fetal blood when compared to controls. Immunostaining of placental tissues did not reveal any significant changes in macrophage infiltration. Fetal lung morphometric analysis showed that LPS increased fetal lung airspace fraction. The addition of rCHI3L1 did not affect airspaces when compared to LPS alone.

**Conclusion(s):** Intra-amniotic administration of LPS at E15.5 of gestation stimulates release of pro-inflammatory cytokines in the amniotic fluid and fetal blood. Interestingly, simultaneous administration of rCHI3L1 decreases inflammation in both compartments. These findings suggest that CHI3L1 may be an important modulator of the inflammatory response in chorioamnionitis.

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**CONTROL ID:** 3373241

**TITLE:** NICU discharge T-cell cytokine profiles predict respiratory morbidity at 1-year of life

**PRESENTER:** Meagan Goates

**AUTHORS (LAST NAME, FIRST NAME):** Goates, Meagan<sup>1</sup>

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**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Infectious Diseases/Immunology

**KEYWORDS:** Respiratory Morbidity, Respiratory Viral Infections, Neonatal Immunology.

**SESSION TITLE:** Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis |Neonatal Infectious Diseases/Immunology: Sepsis and Chorioamnionitis

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Premature infants have increased health care usage and rehospitalization due to respiratory viral infections. Neonatal (gestational age, oxidative stress) and post-discharge (infections, bacterial colonization) factors can alter T-cell effector function bias, which may impair their ability to protect against respiratory morbidity caused by infections.

**Objective:** To assess T-cell function across three gestational age groups by measuring T-cell effector cytokine profiles (IFN $\gamma$ , IL-4, IL-17 and IL-8) over the first year of life, and use them to predict respiratory morbidity at 1 year with other clinical variables.

**Design/Methods:** Infants of three gestational age (GA) groups [ $<29$  weeks (ELGAN, N=38), 29-36.6 weeks, (Preterm, N=46), and  $\geq 37$  weeks (Term, N=71)] were enrolled at birth in the Prematurity, Respiratory, Immune System and Microbiomes (PRISM) study. T-cells isolated from blood collected at birth, NICU discharge and 12 months were stimulated in vitro using superantigen, and intracellular cytokine production were assessed by flow cytometry. T-cell effector profiles (IFN $\gamma$ , IL-4, IL-17 and IL-8) were compared across GA groups and timepoints and then analyzed using multivariate analysis for their ability to predict the composite outcome of Persistent Respiratory Disease (PRD) at 1 year of life.

**Results:** Univariate analysis showed that, when compared to healthy term infants, ELGANs had higher IFN $\gamma$ + T-cells at discharge and 1 year, lower IL-8+ T-cells at discharge but higher at 1 year, and higher IL-17+ T-cells at discharge and 1-year. IL-4+ T-cells did not vary by GA. Logistic regression controlling for GA group, gender, and race showed that of the T-cell functions measured at discharge, IL-17 with neonatal 14-day cumulative supplemental oxygen exposure predicted PRD at 1-year (AUC=0.79). Higher IL-17+ T-cells at discharge correlated with higher illness severity scores post-discharge, but not illness frequency ( $p < 0.0001$ ,  $R^2 = 0.23$ ).

**Conclusion(s):** IL-17+ T-cells at discharge along with supplemental oxygen over the first 14 days of life predicts respiratory morbidity at 1-year of life. Further, the relationship between higher IL-17+ T-cells at discharge and respiratory morbidity may be mediated by enhanced illness severity. This study suggests that enhanced IL-17 T-cell function during respiratory illnesses after discharge may contribute to PRD in former premature infants.

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