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**Session:** 280. Viral Pathogenesis  
**Saturday, October 5, 2019: 12:15 PM**

**Background:** Enterovirus (EV) and human Parechovirus (PeV) cause a range of illness including asymptomatic to systemic infections. The host immune response in children, especially the one induced by PeV, is largely unknown. The aim of this study was to determine the immune response induced by EV and PeV in cerebrospinal fluid (CSF) and plasma obtained from children with systemic infection.

**Methods:** Left-over CSF and paired blood samples collected from children with laboratory confirmed EV and PeV central nervous system-infection were enrolled in this study. EV/PeV-negative CSF and paired plasma from children were used as controls. Level of cytokines and chemokines were measured using a customized 21-plex ELISA panel that included 16 cytokines and 5 chemokines (Millipore, CA). Additionally, clinical characteristics of all the patients were collected to determine the potential association between the immune response and pathogenicity.

**Results:** Total of 74 samples were enrolled and divided into 3 groups, EV ( $n = 27$ ), PeV ( $n = 23$ ) and control group ( $n = 24$ ). Median age of all the three groups was 2 weeks (IQR 2–4 weeks). The key analytes which had a significant difference between each groups are shown in the Table. In general, EV induced more robust cytokine secretion than PeV and control group. Anti-viral response such as IFN- $\gamma$  was remarkably absent in both CSF and plasma in PeV group compared with EV group ( $P < 0.05$ ). Only IL-8 was significantly higher ( $P < 0.05$ ) in EV CSF group compared with any other groups or sample types. Level of all the chemokines measured were much higher in all the three groups but significant difference was found between PeV CSF and plasma for IP-10 and MCP-1 chemokines ( $P < 0.05$ ).

**Conclusion:** In this study, we demonstrate that EV and PeV induces distinct immune response in children with systemic infections. While EV induces more robust inflammation, PeV-induced inflammation appears to be either weak or absent in CSF, but robust in plasma. The suppressed pro-inflammatory response might facilitate PeV growth and proliferation in CSF and might play a role in disease severity. Further studies are needed to fully understand the differential immune response induced by these two viruses.

**Table.** Comparison of cytokine levels (pg/ml) in different groups and sample types.

Analytes (pg/ml)	EV CSF (n=23) Mean $\pm$ STD	EV Plasma (n=10) Mean $\pm$ STD	PeV CSF (n=27) Mean $\pm$ STD	PeV Plasma (n=14) Mean $\pm$ STD	Control CSF (n=24) Mean $\pm$ STD	Control Plasma (n=13) Mean $\pm$ STD
IFN- $\gamma$	26.8 $\pm$ 34.83	25.1 $\pm$ 27.39	2.09 $\pm$ 1.06	11.5 $\pm$ 7.8	6.6 $\pm$ 16.3	21.4 $\pm$ 18.8
IL-6	435.5 $\pm$ 696.8	40.5 $\pm$ 65.6	3.07 $\pm$ 2.15	21.4 $\pm$ 14.9	111.3 $\pm$ 403.04	36.3 $\pm$ 18.5
TNF- $\alpha$	11.7 $\pm$ 13.8	94.1 $\pm$ 46.5	1.7 $\pm$ 1.78	84.2 $\pm$ 15.5	1.66 $\pm$ 1.7	74.4 $\pm$ 51.9
IL-1Ra	869.4 $\pm$ 1421.08	1119.6 $\pm$ 874.7	36.4 $\pm$ 32.18	3499.9 $\pm$ 2291.4	129.3 $\pm$ 331.7	811.9 $\pm$ 1335.5
Fractalkine	176 $\pm$ 1.62	76.3 $\pm$ 34.24	154.6 $\pm$ 17.67	442.4 $\pm$ 562.3	132.2 $\pm$ 22.9	214.8 $\pm$ 326.9
IL-8	1292.3 $\pm$ 1760.4	31.9 $\pm$ 43.3	113.2 $\pm$ 53.6	31.9 $\pm$ 13.5	164.5 $\pm$ 235.6	38.09 $\pm$ 76.9
IP-10	11521.8 $\pm$ 5570.6	3900 $\pm$ 4121.2	9474.1 $\pm$ 3911.7	9765.8 $\pm$ 2229.2	2953.7 $\pm$ 4576.4	2600.6 $\pm$ 3320.9
MCP-1	6344.2 $\pm$ 6332.3	2580.3 $\pm$ 2344.8	3838.8 $\pm$ 2192	7254 $\pm$ 5021.7	1770.9 $\pm$ 1174.7	1185.4 $\pm$ 857.4
RANTES	339.1 $\pm$ 621.6	4187.3 $\pm$ 1830.6	147.3 $\pm$ 312.3	3806 $\pm$ 2166.5	227.6 $\pm$ 472.9	5816.3 $\pm$ 3390.0

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### 2783. Expansion of Monocytic Myeloid-Derived Suppressor Cells in Infants with Severe Respiratory Syncytial Virus (RSV) Infection

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**Background:** RSV remains a leading cause for hospitalization of infants. The mechanisms associated with the ability of RSV to suppress the induction of an adequate immune response are not well understood and represent a challenge for vaccine development. Myeloid-derived-suppressor cells (MDSCs) have been shown to suppress CD8<sup>+</sup> T cells in patients with malignancies. These immature myeloid cells are divided into three groups: granulocytic, monocytic, and undifferentiated. Of those, monocytic MDSCs (M-MDSCs) are considered to be key regulators of inflammatory responses during acute infections. Their potential role in the immunopathogenesis of RSV infection in infants is yet to be defined.

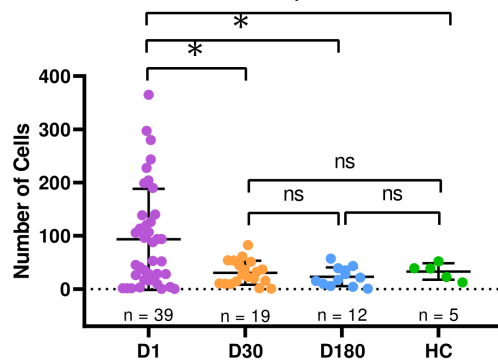
**Methods:** Single-center, prospective cohort study in previously healthy infants hospitalized with severe RSV lower respiratory tract infection (LRTI) and age-matched healthy controls (HC). Nasopharyngeal swabs for RSV detection and blood samples for cell immunophenotyping were analyzed at enrollment (D1), 1-month (D30), and 6-months (D180) follow-up visits. Disease severity was assessed using a clinical disease severity score (CDSS), duration of supplemental O<sub>2</sub>, and duration of hospitalization.

**Results:** We enrolled 39 infants with RSV LRTI (median [IQR] age: 3.3 [1.5–5.2] months) and 5 HC (5.9 [4.5–7.2] months). Infants with RSV infection demonstrated an expansion of M-MDSCs during the acute infection (D1) that resolved to numbers

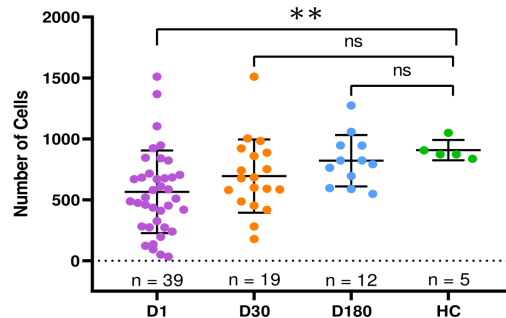
comparable to those in HC at follow-up visits (Figure 1A). In addition, numbers of CD8<sup>+</sup> T cells were significantly reduced during the acute infection (D1) in RSV-infected infants, but also returned to the HC baseline on D30 and D180 (Figure 1B). Finally, the increase in M-MDSCs numbers and decrease in CD8<sup>+</sup> T-cell numbers were associated with worse clinical outcomes as defined by duration of supplemental oxygen (>1 day), hospitalization (>48 hours), and clinical disease severity score (CDSS, > 9) (Figure 2).

**Conclusion:** These findings suggest that an expansion of M-MDSCs may play a role in T-cell suppression in children with severe RSV disease. As new vaccines are being developed, it is critical to elucidate the immune suppressive mechanisms associated with RSV infection.

### A. Monocytic MDSCs by Visit in RSV Infants

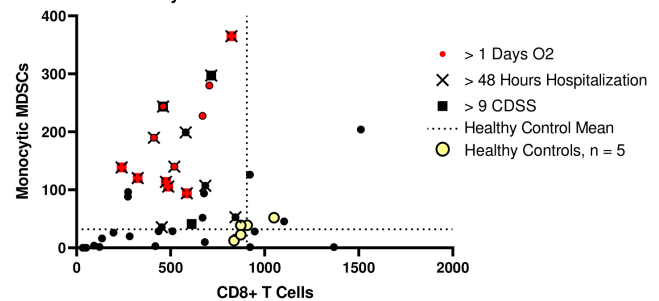


### B. CD8+ T Cells By Visit in RSV Infants



**Figure 1.** Number of (A) monocytic myeloid-derived suppressor cells (M-MDSCs) and of (B) CD8<sup>+</sup> T cells in infants hospitalized with RSV LRTI (D1), and at follow up of 1-month (Day 30) and 6-months (Day 180) post hospitalization, and healthy controls (HC). ( $p < 0.05$ ).

### Association of Clinical Outcomes by Monocytic MDSCs and CD8+ T Cells



**Figure 2.** RSV infants profiled by numbers of monocytic myeloid-derived suppressor cells (M-MDSCs) and CD8<sup>+</sup> T cells. Stratified by the mean number of CD8<sup>+</sup> T cells and M-MDSCs of age-matched healthy controls (HC, dotted lines). RSV infants with higher number of M-MDSCs and lower number of CD8<sup>+</sup> T cells (left upper quadrant) showed worse parameters of clinical disease severity. Healthy controls are plotted as a reference (yellow dots).

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### 2784. Increased Frontal Lobe Volume and Density in Macaques Exposed to Zika Virus In Utero

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**Background:** In utero Zika virus (ZIKV) infection causes birth defects and neurodevelopmental deficits in neonates. We reasoned that a translational macaque model of congenital ZIKV infection could define disease pathophysiology not possible in human clinical studies.

**Methods:** We inoculated 5 pregnant rhesus macaques with a Puerto Rican isolate of ZIKV (ZIKV-PRVABC59) during the first trimester, monitored infection with plasma viral RNA (vRNA) loads, and evaluated infants for birth defects and neurodevelopmental deficits during their first week of life. Assessments included neurobehavioral assessments, ophthalmic examinations, optical coherence tomography, electroretinography with visual evoked potentials, hearing examinations, brain magnetic resonance imaging (MRI), and tissue histopathological analyses.

**Results:** All five pregnant dams demonstrated plasma viremia and seroconversion following ZIKV inoculation. One of the five pregnancies resulted in a stillbirth. All liveborn infants had decreased feeding volumes and weight gain compared with control infants. A comprehensive voxel-based morphometric comparison of ZIKV-exposed and control infant brain MRIs identified increased gray matter volume and density in the frontal lobe in the ZIKV-exposed infant group, which corresponds to the pharyngeal motor cortex responsible for coordinating swallowing. Ocular studies identified differences between ZIKV-exposed and control infants in retinal layer thicknesses (inner plexiform, outer nuclear layers, photoreceptor outer segment) and visual evoked potentials (increased amplitude of waveforms). While ZIKV vRNA was detected in the decidua of 2/5 pregnancies, no ZIKV vRNA was identified in infant tissues and none of the infants developed an anti-ZIKV IgM response.

**Conclusion:** In utero ZIKV exposure resulted in decreased feeding volumes and weight gain, which may be related to the gray matter changes identified in the pharyngeal motor cortex. Changes in retinal layer thicknesses and increased cortical visual pathway waveform amplitude suggest vision may be impaired. These changes occurred despite the lack of evidence of vertical transmission, suggesting that ZIKV exposure without measurable vertical transmission affects fetal brain development.

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#### 2785. Respiratory Viral Panel Testing in Intensive Care Units: Effects on Outcomes

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**Background:** Acute respiratory viral illnesses cause significant morbidity and mortality leading to high healthcare costs. Delayed viral pathogen diagnosis likely contributes to increases in morbidity and mortality. We aimed to analyze: (1) the use of respiratory viral panel (RVP) testing in adults hospitalized to intensive care units (ICUs) with acute respiratory illness (ARI) during flu season; and (2) if RVP testing is associated with improved outcomes.

**Methods:** Data from adults hospitalized to the ICU with ARI during the 2015–2016, 2016–2017, and 2017–2018 influenza seasons at 3 hospitals participating in the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) study was analyzed. Details of disease severity, underlying health status, and vaccination status were obtained through enrollment interviews and medical records. Clinical RVP results were recorded. Research swabs for influenza (CDC PCR) were performed in all patients who did not have a clinical sample. Multivariate regression was used to estimate the associations between RVP and in-hospital complications.

**Results:** 397 patients were enrolled; 263 (66%) had a clinical RVP done. 25% of patients with  $\geq 1$  CDC-defined high-risk condition for influenza complications did not have an RVP. 36 (9%) of patients had a positive RVP for flu (1 H1N1, 28 H3, 1 A no subtype, and 6 B). Mean time from onset of symptoms to RVP was  $2.25 \pm 2.24$  days and mean time from ICU admission to RVP was  $0.85 \pm 1.27$  days. 11 (8%) of patients who had only a research swab were positive for flu (1 A no subtype, others H3). 4 (36%) of

these patients received oseltamivir. Use of antivirals was significantly more common in patients who had RVPs (68 vs 1%, p

**Conclusion:** One-third of patients admitted to the ICU with ARI during the flu season did not have an RVP, including 25% of patients with  $\geq 1$  high-risk condition for influenza complications. Influenza was present in 8% of patients who did not undergo clinical testing and 64% of these patients did not receive antivirals. There is room for improvement in ordering of RVPs in ICUs.

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#### 2786. The Role of Respiratory Panel PCR in Decreasing Antibiotic Exposure in Patients Diagnosed With a Respiratory Viral Infection

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**Background:** Respiratory viral infections (RVI) are becoming increasingly recognized as an important cause of pneumonia. There is limited data regarding the role of rapid PCR testing for RVI and its effect on antibiotic duration and length of stay (LOS).

**Methods:** We performed a single-center, retrospective chart review in adult patients who were admitted and underwent evaluation with the FilmArray Multiplex Respiratory Panel (RP) (Biomerieux™) using a random sample from July 1, 2016 through April 1, 2018. Patient clinical and virologic characteristics, LOS, antibiotic use, and duration of treatment were collected. A Student's *t*-test was performed for all comparisons.

**Results:** We identified 540 patients who were admitted and underwent RP testing. The mean age was 57.1 years (range 19–99), 50.2% were immunocompromised, 23.8% were transplant recipients, 70.4% had respiratory symptoms, and 35.7% had an admitting diagnosis of pneumonia. 55.6% required supplemental O<sub>2</sub> and 24.6% had an ICU admission that required either noninvasive or mechanical ventilation. 22.6% (*N* = 122) of these patients were diagnosed with an RVI, of which 15 were co-infected with two or more respiratory viruses. There were 41 (34%) rhinovirus/enterovirus, 41 (34%) influenza (Types A/H1, A/H3, A/H1-2209, and B), 16 (13%) RSV, 15 (12%) coronavirus (Types NL63, OC43, 229E, and HKU1), 13 (11%) metapneumovirus, and 7 (5%) parainfluenza (Types 2, 3, and 4). 85.2% (104/122) of patients with an RVI received antibiotics. The mean LOS and antibiotic duration were 9.07 days and 7.31 days for patients with an RVI when compared with 11.5 days and 10.4 days for patients without an RVI (*P* = 0.098; *P* = 0.032), respectively. In patients with an RVI and negative bacterial cultures, the mean LOS was 8.4 days and mean antibiotic duration was 5.9 days when compared with 16.4 days and 15.5 days for all patients with positive bacterial cultures (*P* = 0.003; *P* < 0.0001), respectively. The mean time from available results of + RP to antibiotic discontinuation was 5.1 days in the setting of negative bacterial cultures.

**Conclusion:** Although antibiotic exposure and time to discontinuation still remained significant in patients diagnosed with an RVI, there was a marked reduction in LOS and antibiotic duration in the subset of patients with an RVI and negative bacterial cultures.

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#### 2787. Respiratory Syncytial Virus in Elderly Adults

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**Background:** The role of respiratory viruses other than influenza in acute respiratory tract infections (ARTI) among elderly adults has probably been underestimated. Recent advances in molecular diagnosis have made the rapid identification of RSV infection possible. The aim of our study was to assess the role of RSV in patients older than 65 years.

**Methods:** Prospective observational study (April 2018–February 2019) conducted in a 137-bed institution in Buenos Aires, Argentina. All consecutive elderly patients (>65 years) admitted with ARTI were included. Clinical and laboratory parameters as well as nasopharyngeal swab for respiratory viruses were obtained. Blood cultures and sputum collection, were analyzed. Viral detection was performed according to CDC real-time RT-PCR assay. All patients underwent clinical follow-up during hospitalization and up to 30 days after discharge.

**Results:** A total of 124 patients were recruited (mean age 82 years; range: 65–98) 58% female. Clinical diagnosis at admission were: community-acquired pneumonia 90 (72%), COPD exacerbation 11 (9%), acute bronchitis 10 (8%), healthcare-associated pneumonia 8 (7%) influenza like syndrome 5 (4%). Blood cultures were obtained in 92 patients: 4 positives for *Streptococcus pneumoniae*, 3 *E. coli*, 2 SAMS, 1 *Klebsiella pneumoniae*. Sputum was obtained in 20 patients, none were positive. The viral results of the 124 samples were: RSV 13 (10.4%), Influenza B 9 (7.2%), Influenza A 8 (6.4%). Regarding RSV positive patients, the mean age was 87 years and 69% were female. 30% had history of heart failure and 30% had history of COPD. Clinical diagnosis on