Infectious Diseases: Viral Infections

Friday, August 7  2:30-4:00 pm EDT

Moderators
Suchitra Rao
Kengo Inagaki

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Note: Schedule subject to change based on presenter availability.
Background:
Testing for persistence of HIV antibodies (Ab), or seroreversion (SR) to Ab negative status in HIV exposed infants has been recommended to exclude HIV infection in those with perinatal exposure, and to diagnose HIV infection in infants without previous testing. Using older Ab assays, 25-50% of HEU reverted to seronegative status by 10-13 months of age. Past CDC guidelines suggest that HIV Ab testing after 18 months of age is sufficient to diagnose HIV infection. However, recent studies suggest that the use of newer testing platforms has led to a delay in SR among HEU. Most studies have been done in high incidence areas, where breastfeeding is common. This is the first study to look at SR among HEU in the United States using the new combined immunoassay.

Objective:
1. Among HEU non-breastfed infants, compare SR at 11-13 and 13-19 months of age when using the 4th generation HIV antigen(Ag)/Ab combined immunoassay followed by HIV 1/HIV 2 Ab supplemental test versus previous test strategies (HIV ELISA and Western Blot).
2. Assess impact of maternal viral load (VL), maternal CD4 count, maternal and infant perinatal treatment and infant factors (prematurity, birth weight, route of delivery) on time to loss of maternal HIV Ab.

Design/Methods:
This was a retrospective chart review. HEU infants born between Jan 2007 and May 2017 were eligible for inclusion. (Figure 1) Additional inclusion factors: at least two negative HIV RNA assays (with one at >4 months of age), and Ab testing between 11-13 months of age.

Results:
594 patients were eligible; 196 were excluded; 398 infants were included in the study. 52% male, 88.4% African-American, 8% born <36 weeks, 42% born via C-section, 72% of mothers diagnosed prior to pregnancy, 37% of mothers were on HAART prior to pregnancy,and 65% had VL undetectable (<75cpm) at time of delivery. At 11-13 months of age, 53% of HEU (79 of 149) were seropositive by EIA, 76% (189 of 249) by Ag/Ab (p<0.001). For 119 infants tested between 13-19 months of age, 29.1% (16/55) were positive by EIA, 50% (32/64) by Ag/Ab (p<0.03). There was no impact of maternal treatment, VL, route of delivery, or infant treatment on SR at 11-13 and 13-18 months of age.

Conclusion(s):
Use of the 4th generation combined immunoassay results in delayed seroreversion among non-breastfed HEU, and many HEU remain seropositive between 11 and 18 months of age. In areas where HEU testing consists of a single neonatal HIV plasma RNA or DNA assay, and if negative, followed by a single serologic test at 12-18 months of age, testing strategies should be adjusted.
CONTROL ID: 3376504

TITLE: Hepatitis C Screening and Infection Rate Among Pregnant Mothers with Opiate Use Disorder

PRESENTER: Jessica Snowden

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CURRENT CATEGORY: Infectious Diseases

CURRENT SUBCATEGORY: None
**SESSION TITLE:** Infectious Diseases: Viral Infections | Infectious Diseases: Viral Infections

**SESSION TYPE:** Platform/Webinar

**ABSTRACT BODY:**

**Background:** 1-4% of US pregnant women have hepatitis C virus (HCV) infection, and perinatal transmission occurs in 5-6% of their infants. Missed maternal screening poses major health risks for mothers and infants. Current guidelines recommend risk-based screening for HCV in pregnancy, but adherence is inconsistent. Despite overlapping risk factors for women with opioid use disorder (OUD) and women with HCV infection, OUD is not separately recognized as an indication for HCV screening. The increasing prevalence of OUD likely increases the frequency of those with risk factors for hepatitis C infection, and may amplify the risk of missed screening.

**Objective:** Evaluate the rate of HCV screening and infection among mothers with OUD during pregnancy and determine factors associated with the same.

**Design/Methods:** The ACT NOW Current Experience study is a cross-sectional study including 1594 mother-infant dyads with antenatal opioid exposure; infants were born July 1, 2016 to June 30, 2017 and cared for in one of 30 hospitals across the United States. Mothers were classified as HCV positive, negative, or unknown based on documentation of prenatal testing. Medical records were reviewed for demographic information, substance abuse history, and other infection risk factors. For each binary outcome (hepatitis C screening and hepatitis C infection among those screened), relationships with various maternal factors were examined using separate unadjusted logit models.

**Results:** Sixty percent (60%) of mothers with OUD had documented HCV testing (n=970/1594), and 43.8% of those tested were HCV positive (n=425/970). Race and ethnicity were significantly associated with HCV testing (34.7% of non-Hispanic black mothers with documented testing; 63.5% of non-Hispanic white mothers; 77.2% of Hispanic mothers; 58.8% of mothers of non-Hispanic other race/ethnicity; p<0.0001). Mothers with a history of heroin use (83.7%, p<0.0001) and polysubstance use (62.3%, p=0.03) were more likely to be tested during pregnancy; heroin use was also associated with positive HCV testing (68.7% of mothers with heroin use HCV positive; p<0.0001).

**Conclusion(s):** Many mothers with OUD in pregnancy had no documented HCV testing in this multi-site study of infants with antenatal opioid exposure. 43.8% of mothers tested were positive for HCV, raising the significant concern that many other at-risk women remain undiagnosed. These findings could guide efforts to improve HCV screening among women with OUD.
Objective: We tested the hypothesis that enteric zoster underlies unexplained serious abdominal pain in children.

Design/Methods: Because individuals with active VZV infection often have salivary VZV DNA, we analyzed saliva and gastric biopsies from 98 children (mean age 12; range 2-20; 60% male; mostly vaccinated) undergoing clinically indicated endoscopy. PCR amplification was used to identify VZV DNA in both saliva and mucosal biopsies. For VZV DNA to be present, biopsies would have to include a lesion and, because the mucosa contains no nerve cell bodies, VZV DNA in biopsies would indicate active mucosal infection transmitted from neurons.

Results: VZV DNA was found in saliva of 44/98 children (45%). This proportion is significantly greater than that found in severely stressed children in ICUs (7/39; p < 0.003; Fisher’s exact test) or among controls in published literature (0/139; p < 0.0001, including 0/39 children; p <0.0001). VZV DNA was present in 19/44 mucosal biopsies (43%) of the saliva positive children. In a subset of 55 patients with known diagnoses, salivary VZV DNA was far more likely to accompany endoscopy for unexplained abdominal pain (17/26; 65%) than endoscopy for other reasons, such as rectal bleeding, eosinophilic esophagitis, failure to thrive, or celiac disease (3/29;15%; p < 0.0001). VZV DNA was detected in 8/20 (40%) of the biopsies of children with salivary VZV DNA.

Conclusion(s): These data suggest that VZV is a GI pathogen and that enteric zoster may cause unexplained serious abdominal pain; moreover, salivary VZV DNA is useful in its diagnosis. VZV is unlikely to be the cause of GI problems in children without VZV DNA in either saliva or GI biopsy specimens. A controlled, double blind trial is needed to determine whether antiviral treatment is beneficial (as reported anecdotally) for children with unexplained abdominal pain and salivary VZV DNA.

(No Image Selected)
Results: In season 1, 180 infants contributed 8 influenza virus infections from 1925 child-weeks with samples tested. In season 2, 212 children contributed 22 influenza virus infections from 2759 child-weeks with samples tested. Incidence of influenza virus infections was 13.3 and 25.5 per 100 child-seasons, respectively (the number of infections divided by the number of weeks between October-April with samples tested/32 weeks). Most infections were influenza A viruses: 12 (40%) H1N1pdm09, 16 (53%) H3N2; only 2 (7%) were influenza B-Yamagata. Of the 30 detected influenza virus infections, 84% were symptomatic; overall, 64% (n=19) were medically attended (17% in the emergency department, none hospitalized). The median age of those infected was 11 months (range 3 to 23 months). No significant differences occurred in disease severity by age, influenza A sub-type or breastfeeding. Of the 30 infected, 66% had received at least one dose of influenza vaccine between 6-18 months of age at least 2 weeks prior to infection and 39% were fully vaccinated. Of the 34% unvaccinated, half were not age-eligible at the time of infection. In addition to the 19 medically-attended influenza virus infections found from weekly testing, medical record review found 5 more influenza A virus (not sub-typeable) medically-attended infections, indicating that our weekly testing protocol underestimated influenza incidence by 21%.

Conclusion(s): In PREVAIL, two-thirds of influenza virus infections in children <2 years were medically attended. Most received influenza vaccine, but many were too young to be fully vaccinated before their first influenza virus infection. Birth cohort studies of influenza virus infections should include both weekly testing and medical chart review.

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CONTROL ID: 3370499

TITLE: Pharmacologic Inhibition of the Replicative Phase of Epstein Barr Virus

PRESENTER: Sai Sudha Mannemuddhu

AUTHORS (LAST NAME, FIRST NAME): Mannemuddhu, Sai Sudha1; Bhaduri-McIntosh, Sumita2

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CURRENT CATEGORY: Infectious Diseases

CURRENT SUBCATEGORY: None

KEYWORDS: EBV, ANTIVIRAL, VIRAL RELEASE.

SESSION TITLE: Infectious Diseases: Viral Infections | Infectious Diseases: Viral Infections

SESSION TYPE: Platform|Webinar

ABSTRACT BODY:

Background: Epstein Barr Virus (EBV) is a double strand-DNA virus known to cause B- and epithelial-cell malignancies. Post-transplant lymphoproliferative disorder (PTLD) is one such condition, triggered by elevated EBV loads in the setting of transplant-related immunosuppression. With immunosuppression essential for preventing organ rejection, strategies to inhibit EBV are needed. However, anti-EBV drugs or vaccines do not yet exist. EBV replicates in B- and epithelial-cells and uses endosomal sorting complex required for transport (ESCRT) to bud from infected cells. It was recently discovered that certain FDA approved compounds impair budding of HIV by inhibiting ESCRT.

Objective: Since EBV utilizes ESCRT for budding, we asked if these compounds would inhibit virus exit, thereby reducing the number of circulating infectious viral particles.

Design/Methods: Study system: Cell culture-based model system with genetically modified HH514-16 Burkitt Lymphoma-derived cells called “CLIX-FZ” cells; treatment with doxycycline (dox) induces the EBV lytic phase. Hypothesis: Compounds T, R, and I inhibit virus egress during EBV lytic/replicative cycle by inhibiting ESCRT. We will: (Fig 1)

a. Test the effects of the 3 compounds on virus egress in lytically-activated CLIX-FZ cells, via PCR
b. Determine the IC50 for each compound
c. Ascertain whether compounds block nuclear versus cytosolic egress by electron microscopy
d. Generate ESCRT mutants able to negate effects of compounds, confirming the mechanism of action

Results: Compounds T, R and I inhibit viral egress as shown by a decrease in extracellular viral loads and cell surface staining for EBV in figures 2 and 3.
Intracellular viral loads were not inhibited; instead, loads were increased, likely due to the accumulation of intracellular viral particles, indicating that these compounds do not inhibit replication (Figure 3). Treatment of cells with compounds caused minimal toxicity as shown by a WST-1 assay (data not shown).

**Conclusion(s):** Preliminary results show that compounds T, I, and R have inhibitory effects on egress of EBV from cells. Studies to establish IC50 and mechanisms of action of the drugs are underway.

**Study Design**

Flow cytometry showing a decrease in surface staining for EBV after treatment with compounds T and I for 48 hours.

BALF5 PCR showing relative Extracellular and Intracellular EBV load after treatment with compounds T, I and R

**IMAGE CAPTION:**
Study Design

Flow cytometry showing a decrease in surface staining for EBV after treatment with compounds T and I for 48 hours.

BALF5 PCR showing relative Extracellular and Intracellular EBV load after treatment with compounds T, I and R
Children's Hospital, Columbus, Ohio, UNITED STATES;
S. Mertz, Vaccines and Immunity, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, UNITED STATES;

CURRENT CATEGORY: Infectious Diseases
CURRENT SUBCATEGORY: None
KEYWORDS: RSV, vaccine, mucosal cytokines.
SESSION TITLE: Infectious Diseases: Viral Infections | Infectious Diseases: Viral Infections
SESSION TYPE: Platform/Webinar

ABSTRACT BODY:
**Background:** RSV is the leading cause of hospitalization for infants worldwide, but the factors that determine disease severity are not well understood.

**Objective:** The objective of this study was to measure mucosal cytokine profiles and RSV loads (VL), and their potential association with RSV disease severity.

**Design/Methods:** Single-center, prospective study in previously healthy infants with mild (outpatients; OP), moderate (inpatient; IP-ward) or severe (IP-PICU) RSV infection. Mid-turbinate swabs were obtained at enrollment to measure VL by PCR and cytokine concentrations (conc.) using a 13-plex panel that included type I, II, and III interferons (IFN), and inflammatory cytokines. Cytokine conc. and VL were compared according to disease severity.

**Results:** From 2014 to 2017, we enrolled 219 infants: 78 with mild RSV infection (OP; median [IQR] 6 [3.4-10.5] mo.), 101 with moderate disease (IP-ward; 3.5 [1.3-8.3] mo.), and 40 with severe disease (IP-PICU; 2.3 [1.5-5.7] mo.). Duration of symptoms at enrollment was 4 (3-5) days and comparable between OP and IP. Median conc. of type-I (IFN-α2), type-II (IFN-γ), and mucosal IFNs (IFN-λ2/λ3) were significantly higher in OP vs IP irrespective of hospitalization unit (ward vs PICU, Table 1). On the other hand, IP-10 conc. were higher in both OP followed by ward patients vs those with severe disease requiring PICU admission (p<0.0001). In addition, higher conc. of IFN-α2 (r= -0.2; p=0.0001) and IP-10 (r= -0.3; p<0.0001) were associated with a lower clinical disease severity score. In hospitalized infants, there were modest inverse correlations between IP-10 and duration of oxygen supplementation (r= -0.2; p=0.005).

Lastly, VL were also higher in OP vs IP (8.1 [7.4-8.6] vs 7.4 [6.4-8.1] log_{10} copies/mL respectively; p<0.01) with no differences between ward and PICU infants, and significantly correlated with IP-10 (r=0.6; p<0.0001) and IFN-λ1 (r=0.3; p<0.0001) concentrations.

**Conclusion:** Infants with mild RSV infection had higher VL and more robust IP-10 and type-I, II, III IFN responses than those hospitalized with severe disease. These findings suggest that higher concentrations of IP-10 and mucosal IFNs are associated with favorable clinical outcomes and protection against severe RSV disease and could potentially be used as biomarkers in the development of a live attenuated vaccine against RSV infection.

**Table 1:** Mucosal cytokine concentrations in children with RSV infection

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>OP (n=78)</th>
<th>OP vs IP (p-value)</th>
<th>OP vs PICU (p-value)</th>
<th>IP vs PICU (p-value)</th>
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<tbody>
<tr>
<td>Type-I IFN</td>
<td>IFN-α2</td>
<td>3.8 (3.0-4.6)</td>
<td>0.0001</td>
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<tr>
<td></td>
<td>IFN-γ</td>
<td>4.2 (3.5-5.0)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Type-II IFN</td>
<td>IFN-λ2</td>
<td>1.0 (0.5-1.5)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>IFN-λ3</td>
<td>1.2 (0.8-1.7)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Type-III IFN</td>
<td>IFN-α2</td>
<td>3.5 (3.0-4.0)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>IFN-γ</td>
<td>4.2 (3.5-5.0)</td>
<td>0.0001</td>
<td>0.0001</td>
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</table>

IP: inpatients; OP: outpatients. Values represent absolute numbers and medians (25%-75% interquartile range-IQR). Cytokine conc. expressed in pg/mL. Mann-Whitney test was used to determine differences between two groups; Kruskal-Wallis was used to determine differences between three groups (p-values*).

**IMAGE CAPTION:**
P: inpatients; OP: outpatients. Values represent absolute numbers and medians (25%-75% interquartile range-IQR). Cytokine conc. expressed in pg/mL. Mann-Whitney test was used to determine differences between two groups; Kruskal-Wallis was used to determine differences between three groups (p-values*).
Background: Respiratory syncytial virus (RSV) is the leading cause of severe respiratory disease in infants. Other than age at the time of infection, the causes and correlates of severe illness in full term infants are poorly defined.

Objective: To identify gene expression correlates and mechanisms of disease.

Design/Methods: RSV infected infants were enrolled with consent. Clinical and demographic data were collected. Mild and severe illness was defined using quantitative Global Respiratory Severity Score (GRSS). Peripheral blood mononuclear cells (PBMCs) were purified from blood samples obtained during acute infection (days 1-10 of symptoms). Single cell capture and library preparation was completed on the 10X Chromium system. Sequencing was performed on a HiSeq4000 and reads were aligned to GRCh38. Gene expression data were analyzed to identify clusters, marker genes and gene expression patterns using Seurat. Functional annotation of marker genes and pathway analysis of gene sets was performed using Toppgene functional analysis software (ToppFun).

Results: In total, we generated transcriptomic profiles of 20,891 PBMCs. All major cell populations (CD4, CD8, B, NK, etc.) were represented in all subjects, but each population displayed substantial heterogeneity. We identified specific sub-populations of NK cells, CD4 T cells, and monocytes significantly associated with severe illness. We also identified a number of pathways that were significantly activated or suppressed in PBMC from infants with severe illness. Antiviral and interferon signaling pathways were suppressed in broad cell populations including NK, CD4, CD8 and B cells. This insufficiency in RSV infection-related interferon signaling is consistent with observations made from non-immune cells in these same subjects. Interestingly, we discovered activation of RBC-related pathways again in broad cell populations including NK, CD4, CD8 and B cells. This observation surprisingly included detection of high levels of HBA/B gene expression in these leukocytes. HBA/B gene expression in severely affected infant leukocytes was confirmed in sorted CD4 T cells from the same subjects.

Conclusion(s): We have generated a comprehensive single cell transcriptomic atlas for full term infants with RSV infection. We have identified cell populations and gene expression correlates of severe illness following RSV infection in infants. Our data provides insights into RSV infection and the blueprint for investigation of heterogeneous cell states in virus infection.
Background: RSV infections may occur at any time of year, but in temperate climates they are more common during winter months. For the purpose of administering prophylaxis, in 2012 we defined a fixed calendar season in BC based on 16 consecutive seasons (1994-95 to 2010-11) of RSV surveillance at BC’s Children's Hospital. This indicated that the annual RSV epidemic starts in November and, with the exception of one year, ends in April. Thus, we administer RSV prophylaxis from mid-November to March 31. However, we have not systematically studied the annual variability of the RSV epidemic. Epidemics with alternating cycles of approximately 9 and 15 months occur in many regions of Europe (Virology Journal 2009, 6:133). The annual variability of RSV seasons should better inform fixed-calendar RSV prophylaxis periods.

Objective: To determine the degree of variability in the RSV season-to-season onset, peak, and duration in BC.

Design/Methods: We studied the last six consecutive RSV seasons (2013-14 to 2018-19), by reviewing October to May weekly surveillance reports of respiratory viruses, including RSV. This was obtained using BC Children’s Hospital guidelines, consistent through the observation period.

Results: A total of 16,695 specimens were collected in Oct-May, of which 83% were obtained in Nov-Apr and 6455 (39%) were positive for RSV (RSV+) or other respiratory viruses. 96% of the 2571 RSV+ samples between Oct-May occurred between Nov and Apr. Figure 1 shows that the RSV season profile follows a biennial oscillation. Cumulatively, 97% of seasonal positives occurred between Nov-Mar in even years and 97% between Dec-Apr in odd years. The RSV epidemic in even years was more intense (Figure 2) with 30% (range: 8-65) more RSV+ samples than in odd years [median & range: 429 (397,545) vs 331 (331,369)]. In even years, 50% of all the season positives was reached by the 7.3 (5.4, 10.7) season’s week versus by the 14.2 (13.2, 15.5) season’s week in odd years. Finally, in even years the RSV season had a taller two-month peak in Dec-Jan and in odd years it had a lower three-month peak in Jan-Feb-Mar (Figure 3).

Conclusion(s): While the RSV season in BC falls within November and April, we document here its biennial oscillation between an “early”, high-intensity season with a two-month peak in even years and a “late”, lower-intensity season with a three-month peak in odd years. The impact of this oscillation on the BC immunoprophylaxis strategy needs to be reviewed.
Biennial oscillation of the RSV season in British Columbia (2013-14 to 2018-19)

Biennial variation in the median (range) intensity and rate of rise of RSV positive specimens during high and low intensity RSV seasons in British Columbia (2013-14 to 2018-19)

Cumulative season phase shift and profile during high and low intensity RSV seasons in British Columbia (2013-14 to 2018-19)

**IMAGE CAPTION:**
Biennial oscillation of the RSV season in British Columbia (2013-14 to 2018-19)

Biennial variation in the median (range) intensity and rate of rise of RSV positive specimens during high and low intensity RSV seasons in British Columbia (2013-14 to 2018-19)

Cumulative season phase shift and profile during high and low intensity RSV seasons in British Columbia (2013-14 to 2018-19)