723. Validation of a Wild-Type Influenza A/Texas-Like H3N2 Human Challenge Model with Comparison to the Validated A(H1N1)pdm09 Model

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Session: 69. Respiratory Infections: Viral
Thursday, October 4, 2018: 12:30 PM

Background. Healthy volunteer challenge studies provide an opportunity to better understand influenza pathogenesis and correlates of protection. The development of vaccines and therapeutics has relied on these studies as will future universal vaccine candidates. The first fully validated wild-type human infection model with A(H1N1) pdm09 was developed at the NIH Clinical Center (CC) in 2012 and this study represents the first validation of a wild-type seasonal H3N2 human infection model. The objective of this study was to characterize a wild-type Influenza A/Texas-like H3N2 challenge virus in healthy volunteers.

Methods. Healthy volunteers were isolated at the NIH CC for a minimum of 9 days. Subjects received a single dose of a reverse genetics, cell-based, GMP, wild-type A H3N2 virus intranasally. Dose escalation was performed from 10^4 to 10^7 $TCID_{50}$. Viral shedding and clinical disease were evaluated daily, including clinician assessments and a validated patient-reported outcome tool, FLU-PRO©.

Results. A total of 37 subjects were challenged. Sixteen (43%) subjects had viral shedding and 27 (73%) developed influenza symptoms, with 12 subjects (32%) experiencing mild-to-moderate influenza disease (MMID) defined as symptoms and shedding. Only subjects receiving the 10^6 and 10^7 $TCID_{50}$ doses experienced MMID at 44% and 40%, respectively. Nose and throat symptoms were most common and peaked by Days 2–3 post-challenge. Although serum antibody responses were observed, many of these responses were limited in a significant number of subjects.

Conclusion. The A/Texas-like H3N2 Influenza challenge virus safely induced MMID in healthy volunteers, but was less effective than the A(H1N1)pdm09 challenge virus. This lower MMID rate of 40% was observed at the 10^7 $TCID_{50}$ dose and was driven by less detection of shedding as the incidence of symptoms was similar to A(H1N1)pdm09. The limited serum antibody responses observed demonstrate that preexisting immunity in healthy volunteers against the seasonal H3N2 lineage may limit shedding compared with the more recently emerged seasonal A(H1N1)pdm09 lineage. The successful characterization of this H3N2 model makes future studies using this model to explore viral pathogenesis or evaluate vaccines possible.

This research was supported by the Intramural Research Program of the NIH, NIAID.

Disclosures. **All authors:** No reported disclosures.

724. Neurologic Complications in Hospitalized Pediatric Patients with Influenza Infection, A Multicenter Retrospective Study in Korea

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Session: 69. Respiratory Infections: Viral
Thursday, October 4, 2018: 12:30 PM

Background. The aim of the study was to evaluate the incidence and characteristics of influenza associated neurologic complications (IANCs) in hospitalized pediatric patients in Korea.

Methods. We performed retrospective review of hospitalized cases of confirmed influenza infection from October 2010 to April 2017. Patient's data were collected from three referral hospitals in different regions of the country.

Results. A total 2,002 laboratory confirmed influenza cases were identified. The median age was 3.3 years old (range 0.0–18.9 years) and 1,003 patients were male (54%). Influenza A was diagnosed in 1,357 cases (68%), influenza B in 624 (31%) and both influenza A and B in 21 (1%). Other combined respiratory virus infection was detected in 104 (5.2%) cases. Out of 2,002 cases, IANCs were identified in 167 cases (8.3%); influenza virus A was detected in 116 (69.4%), B in 50 (29.9%) and both A and B in one case (0.6%). Of 167 cases with IANCs, 25 patients (15%) had underlying neurologic diseases. Eleven patients (11/167, 6.5%) had combined respiratory viral infection (Rhinovirus = 5; respiratory syncytial virus = 3; coronavirus = 2; and bocavirus = 1). The most common diagnosis was a simple febrile seizure (112/167, 67.1%), followed by other seizures (26/167, 15.6%), encephalopathy/encephalitis (17/167, 10.2%), meningitis (7/167, 4.2%), meningism (4/167, 2.4%) and acute ataxia (1/167, 0.6%). In two patients with encephalitis/meningitis, one patient had influenza A and the other patient had influenza B detected by PCR in cerebrospinal fluid. Most of the patients were fully recovered (162/167, 97%) and no neurologic complication occurred in patients who had only initial manifestation of simple febrile seizure. Ten patients (10/167, 6.0%) required hospitalization in intensive care unit. Three patients (3/167, 1.8%) died of encephalopathy ($n = 1$) and combined encephalopathy/myocarditis ($n = 2$). Pre-existing neurologic disease was a risk factor of IANCs with an odds ratio of 3.94 (95% confidence interval 2.37 to 6.56, $P < 0.0001$).

Conclusion. IANCs is not rare and may cause serious outcome including death. Clinicians should be aware of the increased risk for IANCs in certain patients with neurologic diseases.

Disclosures. **All authors:** No reported disclosures.

725. Clinical Outcomes of Elderly Individuals Presenting with Acute Respiratory Infections

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Session: 69. Respiratory Infections: Viral
Thursday, October 4, 2018: 12:30 PM

Background. Elderly individuals experience increased morbidity and mortality from acute respiratory infections (ARI), which are complicated by difficulties defining etiologies of ARI and risk-stratifying patients in order to guide care. A number of scoring tools have been developed to predict illness severity and patient outcome for proven pneumonia, however less is known about the use of such metrics for all causes of ARIs.

Methods. We analyzed risk factors, clinical course and major outcomes of individuals ≥60 years of age presenting to the emergency department with a clinical diagnosis of ARI over a 5-year period.

Results. Of the enrolled individuals 40 had proven viral infection and 52 proven bacterial infections, but 184 patients with clinically adjudicated ARI (67%) remained without a proven microbial etiology despite extensive workup. Age (71.5 vs. 65.9 years, $P < 0.001$) and presence of cancer and heart failure were strongly predictive of illness severe enough to require hospital admission as compared with treatment in the outpatient setting. Of those with proven etiology, individuals with bacterial infection were more likely to require hospital and ICU admission ($P < 0.001$). When applied to this study, a modified PORT score was found to correlate more closely with clinical outcome measures than a modified CURB-65 (r, 0.54 vs. 0.39). Jackson symptom scores, historically used for viral illness, were found to inversely correlate with outcomes (r, −0.34) and show potential for differentiating viral and bacterial etiologies ($P = 0.02$). Interestingly, a multivariate analysis showed that a novel scoring tool utilizing sex, heart rate, respiratory rate, blood pressure, BUN, glucose and presence of chronic lung disease and cancer was highly predictive of poor outcome in elderly subjects with all-cause ARI.

Conclusion. Elderly subjects are at increased risk for poor clinical outcomes from ARI and their clinical management remains challenging. However, modified PORT, CURB-65, Jackson symptom score, and a novel scoring tool presented herein all offer some predictive ability for all-cause ARI in elderly subjects. Such broadly applicable scoring metrics have the potential to assist in treatment and triage decisions at the point of care.

Disclosures. **All authors:** No reported disclosures.

726. Viral Genomic Load, Cytokine Profiles and Life-Threatening Respiratory Syncytial Virus Infection in Previously Healthy Infants

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Session: 69. Respiratory Infections: Viral
Thursday, October 4, 2018: 12:30 PM

Background. Data are controversial regarding the role of viral load and the host immune response in the severity of respiratory syncytial virus (RSV) infection. The objective of this study was t. o analyze the relationship between viral load (VL) and host cytokine responses with RSV life-threatening disease (LTD).

Methods. Prospective cohort study including previously healthy infants <12 months, hospitalized with a first RSV infection in 2017. Viral titers were assessed by qPCR and cytokine levels measured in nasopharyngeal aspirates obtained on admission. All patients with LTD were admitted to the intensive care unit.

Results. Fifty-one patients, median age 3 months (IQR 2–4), 29(56.9%) male. Eight developed LTD (1,569 LTD cases/10,000 RSV-hospitalizations/year [95% CI 702–2.859]). Antibiotic prescription was significantly higher (42.9 vs. 87.5%, $P < 0.001$) and length of hospitalization significantly prolonged (5.2 ± 1.9 vs. 16.1 ± 12.7 days, $P < 0.001$) in infants with LTD. No differences were seen in the number of amplification cycles needed for a positive qPCR test (CT) nor in the viral titers of patients with LTD compared with those with better outcome ($P = 0.71$), Figure 1. VL was not a predictor of LTD (AUC = 0.53); however, no LTD was seen with ≤159,200 copies/mL. CT/VL did not correlate with other outcomes (Figure 2). IFN-γ levels (Th1 response) were significantly lower in infants with LTD ($P = 0.034$). We detected no differences in TNF-α (pro-inflammatory), IL-9, IL-13 (Th2), IL-10 or IL-17 (regulatory) levels from