410. Influence of Pre-season Antibody Titers to Influenza Infection Risk in a Cohort of Healthcare Personnel

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**Background.** Influenza (flu) and other respiratory viruses circulate regularly throughout healthcare systems, often placing healthcare personnel (HCP) at high risk for illness. Hemagglutination inhibition (HAI) titers are associated with protection from flu illness, though few studies have characterized HAI in HCP. The Respiratory Protection Effectiveness Clinical Trial (ResPECT), provided HAI titers and data to assess infection risk based on four flu seasons. Participants from multiple outpatient settings were respiratory protection within six feet of symptomatic patients.

**Methods.** Serological samples obtained at the beginning and end of each season and anterior nasopharyngeal swabs were taken randomly and when participants reported respiratory symptoms were assessed. Our primary outcome was PCR-confirmed influenza.

**Results.** During 5,180 participant-seasons of observation, 128 PCR-confirmed influenza A infections (20 H1N1, 108 H3N2) and 34 PCR-confirmed influenza B infections. 4,041 (98%) reported receiving an annual influenza vaccine. Each log₂ base 2 increase in titer subtype-specific titer reduced the hazard of influenza infection with A/ H3N2 by 18% (Relative Risk RR = 0.82; 95% CI 0.72–0.94), by 28% for influenza B (RR = 0.72; 95% CI 0.56–0.92) and by 25% for influenza A H1N1 (RR = 0.75; 95% CI 0.57–1.0). After adjusting for HAI titers, age was not significantly associated with risk for any of the subtypes.

**Conclusion.** In this prospective cohort of monitored HCPs, these findings support the current literature demonstrating that HAI titers are associated with protection from influenza infection. The relationship between HAI titers, influenza, and vaccination is complex, however. Vaccination was not shown to be associated with influenza infection. The relationship between HAI titers, influenza, and vaccination is complex, however.

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411. Does an Early Cytokine Response During Ebola Virus Disease Improve the Duration of Survival in Rhesus Macaques?

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**Background.** Ebola virus disease results in a severe cytokine release resulting in organ failure and disseminated intravascular coagulation, often leading to death. An early post-exposure immune response may improve outcomes but that remains poorly characterized. Therefore, we evaluated select serum cytokine markers of immune activation in nonhuman primates (NHPs) for their association with duration of survival.

**Methods.** This was a post-hoc analysis of an interventional supportive care NHP study in which 13 rhesus macaques were inoculated intramuscularly with a target dose of 1000 PFU Zaire ebolavirus (Kikwit). We measured cytokines with a Luminex MAGPIX panel at baseline and daily starting day 3 post-exposure until euthanasia.

Based on human clinical data, 10 cytokines and proteins were included in our analysis: IL-1α, IL-6, IL-10, GM-CSF, MCP-1, MIP-1α, IFN-γ, TNF-α, and C-reactive protein levels. After NHPs were divided into two groups by k-means clustering, we developed Kaplan–Meier curves for time to death (Figure 1). We visually explored Pearson’s correlation and kinetics of serum cytokines and log₂ viral load (Figure 1; Figure 2). We fitted cox regression models with each cytokine to evaluate the risk of early disease for each cytokine log₂ level or log₂ fold change. We performed a sensitivity analysis for MIP-1β centering the data at dpe 0.

**Results.** Among NHPs with temperature data, 83% (N = 10) developed fevers (>3 SD base line) from dpe 3 to 4. The macrophage marker MIP-1β was associated with an increased risk of early death (per log₂ pg/ml increase, HR = 52.83 at dpe 3, adjusted P = 0.045). Surprisingly, this association was also observed at dpe 0 (HR = 36.88 at dpe 0, adjusted P = 0.044). Other cytokine levels or changes were not associated with an increased hazard of death.

**Conclusion.** Our findings did not support a role for early systemic cytokine release in improving survival. However, elevated baseline levels of the MIP-1β may predispose NHPs to early death from EVD. This finding could represent a target for therapeutic strategies and should be further researched.

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412. Host Response Biomarkers Predict Clinical Failure in Patients with Staphylococcus aureus Bacteremia (SAB) Treated with Flucloxacinillin (FLU) or Vancomycin (VAN)

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**Background.** Imbalance among innate mediators such as IL-1β, IL-10, and TNF-α portends poor outcomes of persistence and death in patients with SAB. Previous studies did not consider the role of antibiotic treatment in this important host–pathogen relationship. In this study of SAB, we determined cytokine signatures that correlate with the composite endpoint of clinical failure (bacteremia duration >4 days or 30-day mortality) in Australian patients treated with FLU or VAN.

**Methods.** Sera from 86 patients with SAB (24.4% MRSA) were obtained from a clinical study of patients treated with FLU or VAN. All of the patient samples were collected at clinical presentation (day 0 or day 1 of infection) and were treated with FLU or VAN throughout. Patients were classified into either clinical success (CS = 68) or clinical failure (CF = 18), defined as death or prolonged bacteremia >4 days. Patients were characterized by serum concentrations of 17 pro-inflammatory cytokines and protein markers using Luminex and BioPlex technology. Logistic regression analysis was performed to determine the cytokine signature predictive of clinical failure.

**Results.** Among 86 patients with SAB (24.4% MRSA), 35 patients (40.7%) were classified as clinical failure. Patients with clinical failure showed a significantly higher concentration of IL-1β, IL-6, IL-10, TNF-α, and GM-CSF compared to patients with clinical success (Figure 1). Multivariate logistic regression analysis identified IL-6 (OR = 1.47, P = 0.03) and IL-10 (OR = 1.46, P = 0.03) as independent predictors of clinical failure.

**Conclusion.** Host response biomarkers such as IL-6 and IL-10 are independent predictors of clinical failure in patients with SAB treated with FLU or VAN. These findings highlight the importance of early identification and management of patients at high risk of clinical failure.

**Disclosures.** No reported disclosures.

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Background. More than 350 genetic disorders cause immune deficiencies; given the rarity of these conditions, in-depth study of infections associated with primary immune deficiencies (PID) requires extremely large sample sizes from broad populations. Using a large electronic health record (EHR) dataset, we linked clinical and microbiologic data to develop digital phenotypes for PID.

Methods. Using the Cerner HealthIntelligence EHR dataset from 2009 to 2017 we extracted clinical and microbiologic data for hospitalizations from patients <18 years old with ICD9/10 PID diagnoses and ≥1 positive culture for infection. Machine learning models were used to identify key features to predict PID diagnosis. Features included patient and hospitalization characteristics; infectious agent and infection site; and selected comorbidities. Model validation was done using the area under the receiver operating characteristic (AUC) curve.

Results. Overall 1316 patients with a PID were identified (Table 1). The 10 most common pathogens identified by PID are listed in Table 2. The models classified DiGeorge syndrome (positive predictive value 49%), functional disorders of polymorphonuclear neutrophils (PMN) (PPV 43%), and common variable immunodeficiency (CVID) (PPV 47%) better than combined immunodeficiency (CID) (PPV 20%); the overall true positive rate was 47% with an AUC of 0.73. Predictive features for each PID were as follows: CVID—having enteritis, hypertension, and pneumonia (Figure 1a); PMN—having hypoxia and hypertension (Figure 1b); DiGeorge syndrome—having congenital deformities and not having hypertension (Figure 1c); CID—finding Staphylococcus aureus in a wound or Escherichia coli in the blood were predictive of CID (Figure 1d).

Conclusion. Early models demonstrate some discrimination, specifically for more common PIDs (CVID) and those with highly identifying factors (DiGeorge syndrome). These models can be improved by including a wider array of clinical data, and they provide a first look at a new methodology to digitally phenotype PIDs for future diagnostic use.

Table 1. Patient counts by PID diagnosis

| PID Diagnosis                  | Number of Patients | Percentage of Patients |
|-------------------------------|--------------------|------------------------|
| Common Variable Immunodeficiency | 450                | 36.9%                  |
| DiGeorge Syndrome             | 141                | 20.6%                  |
| Functional Disorders of Polymorphonuclear Neutrophils | 307          | 15.7%                  |
| Combined Immunodeficiency— Unspecified | 182         | 13.3%                  |
| Total                          | 1316               | 100.0%                 |

Table 2. Two most frequent infections per PID diagnosis

| PID Diagnosis                  | Infections |
|-------------------------------|------------|
| Common Variable Immunodeficiency | 1.16         |
| DiGeorge Syndrome              | 1.16         |
| Functional Disorders of Polymorphonuclear Neutrophils | 1.16       |
| Combined Immunodeficiency— Unspecified | 1.16     |

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413. Differences in Inflammatory Mechanisms in Pseudomonas aeruginosa and Staphylococcus aureus Infections in Cystic Fibrosis

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Background. Chronic bacterial lung infections are the primary cause of morbidity and mortality in cystic fibrosis (CF). The most common CF pathogens, Pseudomonas aeruginosa (P. aeruginosa) or Staphylococcus aureus (S. aureus), are common communal or environmental organisms that adapt to the CF lung. We sought to investigate whether adaptation from early lung colonizer to chronic pathogen alters the bacterial effects on host inflammation.

Methods. P. aeruginosa (n = 25) and S. aureus (n = 25) isolates from CF patients with early and chronic infections were acquired from Seattle Children’s CF Environmental (n = 8) and clinical, non-CF P. aeruginosa (n = 8) isolates were obtained from the University of Ottawa. P. aeruginosa reference strain PA14 and PA14 transposon mutants for TSS and flagellin were used to observe the relationship between cell death and cytokine production. We infected THP-1-derived macrophages with reference strain PA14 and PA14 transposon mutants for TSS and flagellin in vitro for 3 hours with various MOIs. We subsequently measured cell death of THP-1-derived macrophages using neutral red assay and cytokine production using ELISAs.

Results. Infections with PA14 mutants and non-CF P. aeruginosa isolates demonstrated that rapid cell death of THP-1-derived macrophages caused a reduction in cytokine production relative to strains that did not cause as much cell death. At 10 MOI, early P. aeruginosa isolates from CF patients induced more THP-1-derived macrophage cell death compared with clinical isolates (P < 0.0001). Chronic P. aeruginosa isolates induced greater production of TNF, IL-8, and IL-6 (P < 0.001), and P < 0.0001, respectively) compared with early strains. No difference in IL-1β production was observed. When controlling for cell death between the two groups by heat-killed bacteria, the only difference maintained was in TNF production (P < 0.01). Between early and chronic S. aureus isolates, the one difference observed was greater IL-8 production among early isolates (P < 0.01).

Conclusion. Chronic P. aeruginosa isolates from CF patients induce less cell death relative to more TNF, IL-8, and IL-6 production compared with early isolates. This suggests that P. aeruginosa producing chronic infections induce inflammatory signals that may contribute to increased morbidity among CF patients.

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414. Developing Digital Phenotypes of Primary Immune Deficiencies Using Machine Learning on a Large Electronic Health Record Database

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