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Detection of multiple respiratory viruses associated with mortality and severity of illness in children

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Abstract

Objective—Respiratory viral infection is a common source of morbidity and mortality in children. Co-infection with multiple viruses occurs frequently; however, the clinical significance of concomitant viral pathogens is unclear. We hypothesized that presence of more than one respiratory virus is associated with increased morbidity and mortality when compared to children with a single respiratory virus.

Design—Retrospective cohort study.

Setting—A tertiary care hospital.

Patients—All children at Duke Children's Hospital over a two year period with isolation of a virus on an extended viral respiratory panel (EVRP) result. Demographic data, co-morbidities, and details of hospital encounter were recorded.

Interventions—None

Measurements and Main Results—235 hospital encounters demonstrated positive EVRPs. Immunocompromised status (37%) and respiratory comorbidities (23%) were common. 28 patients (12%) tested positive for multiple viruses, with adenovirus (23/28) and respiratory syncytial virus (15/28) most prevalent in patients with multiple viruses. Viral co-detection was associated with increased use of non-invasive ventilation (p=0.02), extracorporeal membrane oxygenation (p=0.02), increased likelihood of moderate or severe illness (p=0.005) and increased mortality (p=0.01). Subgroup analysis demonstrated that this mortality association persisted for children with normal immune function (p=0.003) and children with no comorbidities (p=0.007).

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Conclusions—Children with multiple respiratory viruses may be at increased risk of moderate or severe illness and mortality, with previously healthy children potentially being at greatest risk. Further studies are indicated to determine the significance and generalizability of this finding and to better understand the pathophysiology of viral co-infection.

Keywords

pediatric; virus; severity of illness; respiratory; adenovirus; influenza; human metapneumovirus; respiratory syncytial virus; parainfluenza

Introduction

Viral respiratory infections are a common source of disease burden in young children worldwide[1–9]. Respiratory viruses such as influenza, respiratory syncytial virus and human metapneumovirus each individually account for annual hospitalization rates of more than 1 per 1000 children, with higher rates for children less than 12 months of age[2,3,6]. Hospitalization is a small portion of the overall societal burden of these diseases, as they also account for substantial number of outpatient visits, emergency room visits, parental absence from work, and cost [10,11].

Simultaneous co-infection with more than one respiratory virus in children is relatively common, with reported rates in symptomatic children of 10 to 40%[12–18]. While bacterial co-infection with a respiratory virus clearly increases morbidity and mortality[19], the impact and clinical implications of co-infection with multiple viral pathogens is unclear. Conceptually, multiple pathogens should increase risk of severe illness; however, the inflammatory response generated by one virus may not be significantly increased by the presence of a second or third virus[8]. The published data regarding the outcomes associated with respiratory viral co-infection are mixed[14,15,20–22].

When compared to children with a single respiratory virus, we hypothesized that children with isolation of multiple respiratory viral pathogens would have increased hospital mortality. We also hypothesized that multiple respiratory viral pathogens would increase severity of illness, as indicated by more frequent need for intensive therapies.

Methods

Duke University Medical Center began offering an extended viral respiratory panel (EVRP) for clinical testing in February 2011. Real-time polymerase chain reaction testing was performed on nasal washings from patients. This extended panel (Prodesse, Waukesha, WI) tested for adenovirus, human metapneumovirus (HMPV), influenza A and B, parainfluenza 1, 2, and 3, and respiratory syncytial virus (RSV). Use of this test was at clinician discretion and not restricted to any specific population, nor was it protocolized within the institution. There was a separate rapid screen for influenza and RSV which was also available for clinicians. EVRP positivity rate at our institution ranges between 10% and 30%, displaying seasonal variation for individual viruses.

Duke Children's Hospital is a 190 bed institution affiliated with Duke University Medical Center, and accounts for almost 200,000 pediatric outpatient visits, 15,000 emergency department visits, and 5,000 inpatient visits annually. Included in the 190 inpatient beds are 50 neonatal intensive care beds, 29 pediatric critical care beds, and a 16 bed bone marrow transplant unit capable of providing non-invasive bi-level positive airway pressure (BiPAP).

With institutional review board approval, we completed a retrospective chart review of all patients ≤ 18 years of age with a positive EVRP result at Duke University Medical Center from introduction of clinical testing through the next two respiratory viral seasons (through June 2013). Demographic data collected included age, race and ethnicity, presence of comorbidities, and immunocompromised status. Encounter data included location (inpatient, emergency department, or outpatient) and details of visit including length of stay, therapies administered, and certain diagnoses (sepsis, shock, pneumonia, bronchiolitis, and/or bacteremia).

Definitions

An encounter was defined as the provider visit in which the positive EVRP was collected. 'Hospital' encounters included inpatient admissions and emergency department (ED) visits. Outpatient encounters were excluded from analysis. If the patient was seen in two different hospital or clinic visits separated by less than 48 hours, these visits were considered part of the same encounter. Viral co-detection was defined as separate viruses detected on the same EVRP.

For hospital encounters, mortality was measured by survival to encounter discharge. Surrogates for severity of illness included therapies provided to the patient during that encounter, including intensive care unit (ICU) admission, assisted ventilation (non-invasive or invasive), use of inotropes, or use of extracorporeal membrane oxygenation (ECMO). "Moderate disease" was defined as receiving non-invasive ventilation, while "severe disease" was defined as receiving intubation and mechanical ventilation, ECMO, and/or inotropic support. Diagnoses of shock, sepsis, bronchiolitis, and pneumonia were based on physician note documentation. Bacteremia was recorded only in the presence of a blood culture positive for a pathogen during that encounter. Typical contaminants, such as *staphylococcus epidermidus*, were excluded.

Respiratory comorbidities and immunocompromised states were identified during chart review of provider notes and diagnoses. Respiratory comorbidities included clinical diagnoses of asthma, cystic fibrosis, chronic lung disease, bronchopulmonary dysplasia, interstitial or restrictive lung disease, recurrent aspiration, subglottic stenosis, or laryngo-, tracheo- or bronchomalacia. Patients were classified as immunocompromised if they had received chemotherapeutic agents for cancer treatment in the six months prior to encounter date, were on chronic glucocorticoid therapy with ≥ 14 days of steroids in the six months prior to encounter date, were currently receiving immunomodulants for auto-immune disease, had any history of a solid organ or hematopoetic stem cell transplant (HSCT), or had been diagnosed with primary immunodeficiency. Complex congenital heart disease was defined as cyanotic heart disease or left-sided obstructive lesions. Prematurity was defined as birth prior to 37 weeks gestational age.

For therapies, non-invasive mechanical ventilation was defined as continuous positive airway pressure (CPAP), BiPAP, or high-flow nasal cannula ≥ 5 Lpm in infants (≤12 months of age) or ≥ 8 Lpm in older children. Use of inotropes included any use of epinephrine, dopamine, dobutamine, norepinephrine, or vasopressin infusions for blood pressure support.

Statistical Analysis

For univariate analysis, continuous variables were compared using Wilcoxon's Rank Sums Test; dichotomous variables were compared using chi-squared analysis. Multivariable logistic regression was then performed to evaluate the association between viral co-detection and the development of moderate to severe disease when controlling for other factors. Univariate analysis was performed using JMP v. 11 (SAS, Inc., Cary, NC), while STATA 13 (College Station, TX) was used for multivariable analyses. P values ≤ 0.05 were considered significant.

Results

Positive EVRP results were found in 235 encounters for 202 individual patients. Table 1 summarizes the demographics for the patients included in the study. Most patients in this series (178 of 235; 76%) had at least one underlying comorbidity.

EVRP detected 264 viruses during these 235 encounters. Table 2 summarizes EVRP results. In 207 of 235 encounters (88%), EVRP samples were sent within the first 72 hours of admission to the hospital. Viral co-detection was present in 28 encounters (12%), with one patient testing positive for three separate viruses. Adenovirus was isolated in 23 of the 28 (82%) patients with viral co-detection, RSV was isolated in 15 of 28 (54%), and either adenovirus or RSV were isolated in 27 of these 28 (96%) patients.

There was no statistical difference in viral co-detection rates based on patient demographics including age, race, ethnic group, or gender, nor was there a difference in viral co-detection rates based on prematurity, immunocompromised status, respiratory comorbidity, or complex congenital heart disease.

Patient Outcomes by Viral Co-Infection

Table 3 compares the clinical findings for those patients with multiple viral isolates to those with a single respiratory virus. For the diagnoses and treatment modalities reported in Table 3, there was no difference attributable to race or ethnicity. Of note, presence of viral co-detection was associated with increased likelihood of moderate or severe illness and with hospital mortality.

Among all children with isolation of viruses, patients who were premature at birth were more frequently admitted to the ICU (67% vs. 46%, p=0.003), receive invasive (35% vs. 21%, p=0.03) and non-invasive (50% vs. 26%, p=0.001) ventilation, and have moderate or severe illness (59% vs. 36%, p=0.002), but did not have increased mortality compared to full-term children. Patients with respiratory comorbidities were more frequently diagnosed with pneumonia (36% vs. 18%, p=0.005), but otherwise did not differ statistically from the

remainder of the cohort in terms of therapies or survival. Similarly, patients with complex congenital heart disease did not differ from the remainder of the cohort for any therapies or survival.

Presence of viral co-detection was not associated with hospital mortality for immunocompromised patients (20% vs. 8%, p=0.26). When compared to immunocompetent patients, a greater proportion of immunocompromised patients died during the encounter for all hospitalized patients (9% vs. 2%, p=0.01) and for patients admitted to the ICU (28% vs. 2%, p < 0.0001). However, immunocompromised patients were less frequently admitted to the ICU (34% vs. 60%, p<0.0001). A smaller proportion of immunocompromised patients received invasive (16% vs. 28%, p=0.03) or non-invasive (22% vs. 37%, p=0.02) ventilation, or demonstrated moderate to severe illness (29% vs. 48%, p=0.005), despite being more frequently diagnosed with sepsis (23% vs. 7%, p=0.0003) or exhibiting documented bacteremia (20% vs. 5%, p=0.0006).

For patients with normal immune function, patients with viral co-detection more frequently received ECMO support (11% vs. 1%, p=0.02) and more frequently died during that encounter (11% vs. 1%, p=0.003). For the 57 previously healthy patients (i.e. no associated comorbidities) seen in hospital encounters, viral co-detection was also associated with increased mortality (15% vs. 0%, p=0.007).

Associations by virus

RSV isolation was associated with younger age (median 22 vs. 29 months, p=0.02), diagnosis of bronchiolitis (43% vs. 12%, p<0.0001) and use of NIV (46% vs. 25%, p=0.002). RSV was less frequently associated with a diagnosis of sepsis (4% vs. 16%, p=0.01), but was associated with moderate or severe disease (52% vs. 36%, p=0.02). Patients with adenovirus were less likely to carry a diagnosis of bronchiolitis (11% vs. 27%, p=0.002). Patients with influenza were likely to be older (median 39 vs. 26 month s, p=0.01) and were less frequently diagnosed with bronchiolitis (0% vs. 23%, p=0.002). Individual viruses were not associated with mortality, ICU admission, bacteremia, intubation, ECMO use, or diagnoses of pneumonia or shock.

Multivariate analysis

Multivariable analysis demonstrates that isolation of two or more viruses increases the odds of moderate or severe disease when adjusted for patient age and the presence of any comorbidity (OR 2.59; 95% CI 1.12, 5.96). This analysis also indicates that older age (> 3 months), regardless of viral isolation or comorbidity, protects against moderate or severe disease when compared to age < 3 months (OR 0.44; 95% CI 0.29, 0.67). Mortality was not included in multivariable analysis due to overall numbers of patients.

Discussion

While prior studies have demonstrated association between viral co-detection and diagnosis of viral pneumonia[23], hospitalization rates[12,15], and the severity of illness[14], this is the first study to demonstrate both an increased severity of illness and mortality in children presenting to the hospital with isolation of viral co-pathogens. This finding is of particular

import as some studies have demonstrated no worsening in clinical outcomes in the presence of multiple respiratory viruses[20–22]. Increased mortality was associated with viral co-detection for this entire cohort, as well as patients with normal immune function, and for children without any previously existing comorbidities. The association between viral co-detection and moderate or severe illness also persisted in multivariable analysis.

The cohort reported in this study had a high prevalence (76%) of comorbidities and/or immunocompromised status. Given the additional cost of the EVRP testing and the availability of separate rapid RSV and influenza testing, use of the panel was often reserved for patients either presenting with a high severity of illness or at high risk of critical illness, with more than half of the inpatients in this cohort (119/235, 51%) being admitted to the ICU during their hospital admission. The baseline risk of severe illness for this cohort may have increased the likelihood of being able to demonstrate an association with mortality, when compared to prior studies evaluating the impact of viral co-detection on severity of illness[20–22].

For inpatients, it is counterintuitive that immunocompromised patients with positive viral testing were less frequently admitted to the ICU; however, this may be secondary to increased use of the EVRP for screening in immunocompromised children with mild symptoms. Similarly, immunocompromised patients may have been more likely to receive therapies to treat viral infection. Our data was incomplete regarding these therapies, but selected immunocompromised patients received cidofivir, ribavirin, foscarnet, ganciclovir, or intravenous immunoglobulins, all of which are not typically used when respiratory viruses are detected in immunocompetent patients. Finally, Duke Children’s Hospital has a Bone Marrow Transplant Unit which is able to care for many HSCT patients at a higher level of care than the general wards, and patients admitted to the Bone Marrow Transplant Unit were not included as ICU admissions.

While hospitalized immunocompromised patients demonstrated a higher overall mortality than immunocompetent patients, their mortality risk was not increased in the presence of viral co-detection. Contrarily, the subset of patients in this cohort who appeared to be at greatest risk of death secondary to viral co-pathogens were immunocompetent patients and patients without comorbidities. This association may be related to a vigorous inflammatory response to viral infection, which is responsible for many of the symptoms and illness severity in these patients[8]. The increased frequency of death in patients able to generate an adequate immune response to viruses supports the concept that multiple viral co-pathogens may exacerbate the inflammatory response, and subsequently, increase the severity of illness[24,25]. While immunocompromised patients demonstrated increased mortality with any viral detection, their reduced ability to generate a strong immune response may have been protective from increased severity of respiratory illness in the presence of multiple viral pathogens. While these data do not support firm conclusions regarding this finding, the discrepant outcomes in the immunocompetent vs. immunocompromised patients could provide an area for further investigation of treatment of respiratory viral infection through modulation of the immune response[26].

This study has all of the inherent limitations of a retrospective review, including selection bias from a lack of prospectively determined inclusion and exclusion criteria and the lack of EVRP testing guidelines, along with the inability to control for many variables. Reliance on physician documentation for certain clinical diagnoses may be unreliable, therefore we chose more clear dichotomous outcomes (use of specific therapies) as surrogates for severity of illness. Routine viral screening was available for influenza and RSV, so to avoid unnecessary cost, many patients testing positive for one of these viruses may not have received EVRP testing and may not have been captured in this study. Also, the EVRP at Duke University Medical Center during this study period did not test for every potential respiratory virus, most notably rhinovirus, nor did we collect serum testing for non-respiratory viruses. We, therefore, may have underestimated the overall number of patients with respiratory viruses, including those with co-pathogens. However, presence of untested viruses among our single virus cohort would reduce differentiation between cohorts and therefore be more likely to produce a null effect, rather than the mortality difference we observed. Also of note, the data collection period for this study preceded the recent outbreak of enterovirus D68.

While this study evaluates the impact of isolation of respiratory viruses, it was not powered to evaluate the interactions of specific viruses. Just as certain individual viruses may be more virulent, it is possible that possible that specific virus combinations may be associated with worsened clinical outcomes[18,27]. The interactions between specific viruses are another area for further investigation with appropriately powered prospective studies.

Despite these limitations, this study demonstrates an association between viral co-detection and both severity of illness and mortality for children presenting for care at a tertiary medical center. While no causality may be inferred, awareness of this association may assist providers in both prognosis and identifying children at risk for critical illness. More so, this study supports the need for further research into the immune response to respiratory viruses, potential therapies to optimize that immune response, and evaluation of the complex interactions between respiratory viruses.

Conclusion

Isolation of two or more respiratory viral pathogens is associated with moderate or severe illness and death in children cared for in the hospital setting. Larger prospective studies are needed to clarify patients at greatest risk and to evaluate interactions between specific viruses.

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Table 1

Cohort demographics

	Patients N=202	Encounters N=235
Median age in months (IQR)	24 (9,55)‡	26 (12, 53)
Race / Ethnicity		
-Asian	2 (1%)	2 (<1%)
-Black or African American	73 (36%)	88 (37%)
-Hispanic or Latino	36 (18%)	42 (18%)
-White or Caucasian	83 (41%)	96 (41%)
Male	111 (55%)	105 (45%)
Prematurity (<37 weeks GA)	44 (22%)	54 (23%)
Respiratory comorbidity	50 (25%)	55 (23%)
-Asthma	22 (11%)	23 (10%)
-Cystic fibrosis	8 (4%)	8 (3%)
-Chronic lung disease	10 (5%)	10 (4%)
-Bronchopulmonary dysplasia	2 (1%)	2 (<1%)
-Malacia*	2 (1%)	6 (3%)
-Other#	6 (3%)	6 (3%)
Complex congenital heart disease	14 (7%)	19 (8%)
Immunocompromised	73 (36%)	86 (37%)
-Primary immunodeficiency	4 (2%)	8 (3%)
-Cancer receiving chemotherapy	10 (5%)	15 (6%)
-Hematopoetic stem cell transplantation	16 (8%)	22 (9%)
-Solid organ transplant	20 (10%)	40 (17%)
-Other immunomodulants$	1 (<1%)	1 (<1%)

‡Age of patient at first encounter during study period

*Includes laryngo-, tracheo-, and bronchomalacia

#Includes interstitial lung disease, restrictive lung disease, recurrent aspiration, and subglottic stenosis

$Includes mycophenylate and chronic steroid use

Table 2

Identified viral pathogens

Virus	**N=264**
Adenovirus	**85 (32%)**
Human metapneumovirus	**48 (18%)**
Influenza	**19 (7%)**
-Influenza A	−7 (3%)
-Influenza B	−12 (5%)
Parainfluenza	**44 (17%)**
-Parainfluenza 1	−9 (3%)
-Parainfluenza 2	−9 (3%)
-Parainfluenza 3	−26(10%)
Respiratory syncytial virus	**69 (26%)**
Co-infections*	**N=28**
ADV + FLU	1 (4%)
ADV + HMPV	7 (25%)
ADV + PARA	4 (14%)
ADV + RSV	10 (36%)
FLU + RSV	1 (4%)
HMPV + PARA	1 (4%)
HMPV + RSV	1 (4%)
PARA + RSV	2 (7%)
ADV + PARA + RSV	1 (4%)

*ADV = adenovirus, FLU = influenza, HMPV = human metapneumovirus, PARA = parainfluenza, RSV = respiratory syncytial virus

Table 3

Univariate analysis of single respiratory virus detection vs. viral co-detection.

	Single respiratory virus N=207	Respiratory viral co-detection N=28	P value
Demographics			
Median age in months (IQR)	28 (12, 55)	18 (10, 48)	0.27
Male	114 (55%)	16 (57%)	0.83
Prematurity	46 (22%)	8 (29%)	0.48
Respiratory comorbidity	50 (24%)	5 (18%)	0.45
Complex congenital heart disease	18 (9%)	1 (4%)	0.30
Immunocompromised	76 (37%)	10 (36%)	0.92
Hospital stay			
Hospital length of stay (days; median, IQR)	8 (4,20)	11 (3,42)	0.61
ICU admission required	103 (50%)	16 (57%)	0.46
ICU length of stay (days; median, IQR)	5 (2,17)	9 (1, 18)	0.92
Therapies and severity of illness			
Non-invasive ventilation	60 (29%)	14 (50%)	**0.02**
Invasive mechanical ventilation	48 (23%)	8 (29%)	0.53
Extracorporeal membrane oxygenation	2 (1%)	2 (7%)	**0.02**
Inotropes	25 (12%)	6 (21%)	0.17
Moderate or severe illness	79 (39%)	17 (61%)	**0.02**
Death during encounter	7 (3%)	4 (14%)	**0.01**
Diagnoses during encounter			
Diagnosis of sepsis	28 (14%)	2 (7%)	0.34
Diagnosis of shock	13 (6%)	1 (4%)	0.57
Bacteremia (culture positive)	22 (11%)	3 (11%)	0.99
Pneumonia (clinical diagnosis)	47 (23%)	6 (21%)	0.88
Bronchiolitis (clinical diagnosis)	43 (21%)	7 (25%)	0.61