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Predictive Value of Testing Nasopharyngeal Samples for Respiratory Viruses in the Setting of Lower Respiratory Tract Disease

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To determine the predictive value of nasopharyngeal (NP) sample testing for respiratory viruses (RVs) in suspected lower respiratory tract disease, 72 paired NP and bronchoalveolar lavage (BAL) fluid specimen sets, mostly from transplant recipients or patients with hematologic malignancies, were analyzed. Overall, 31.3% of the specimens tested positive for an RV. In 19 sets (26.4%), the NP and BAL fluid specimens were both positive for an RV; in 3 sets (4.2%), the NP specimens were positive but the BAL fluid specimens were negative; and in 3 other sets, the NP specimens were negative but the BAL fluid specimens were positive. The positive and negative predictive values of the NP specimens were 86.4% and 94%, respectively.

Improved detection of respiratory viruses (RVs) with PCR-based diagnostics has increased the understanding of the morbidity and mortality associated with these pathogens (1–3). Specimens obtained from the upper airway, including by nasopharyngeal (NP) swabbing or washing, are often used for RV testing in the setting of lower respiratory tract disease (LRTD), due in large part to the ease of specimen collection compared to that of lower respiratory tract sampling by bronchoscopy (3, 4). Indeed, using bronchoscopy to test for possible LRTD after the detection of certain RVs in NP samples has become increasingly uncommon in certain patient populations (5). However, the utility of PCR-based RV testing on NP samples is not clear, since the predictive value for an RV in LRTD is poorly defined. Existing studies were limited to specific pathogens, such as influenza (6–8), or patient populations, such as lung transplant recipients (9), pediatric patients (4), or patients with severe community-acquired pneumonia who required admission to an intensive care unit (10, 11). The purpose of this retrospective study was to determine the correlation of PCR-based testing for RVs between NP and bronchoalveolar lavage (BAL) fluid samples in all patients for whom RV testing was performed during evaluation for LRTD.

Adult patients who had NP specimens (obtained by nasal swabbing or washing) and BAL fluid specimens submitted for RV testing between 1 June 2010 and 15 June 2014 were included if the BAL fluid and NP samples were collected and submitted for RV testing within 7 days of each other. Clinical and microbiologic information was obtained by chart review. All the samples were analyzed using the xTAG respiratory viral panel (RVP) (Luminex) (12). Approval from the Institutional Review Board of the Oregon Health and Science University (OSHU) was obtained prior to beginning this work.

A total of 72 sets of paired NP and BAL fluid samples were obtained from 71 patients (Table 1). One patient had two sets of paired NP and BAL fluid samples submitted 17 days apart. The majority of patients who were tested had undergone a hematopoietic stem cell transplant (HSCT) or had an underlying hematologic malignancy. Most of the patients were adults; only three patients were younger than 18 years. A minority of the patients had symptoms of upper respiratory tract disease (URTD), whereas most of them had fever, cough, or hypoxemia. All episodes in which radiography was performed (71 of 72) were associated with radiographic evidence of LRTD at the time of bronchoscopy.

A total of 144 individual specimens from the 72 paired NP and BAL fluid sets were analyzed; the median time between the NP and BAL fluid specimen collections was 2 days (range, 0 to 7 days, where 0 indicates that the samples were collected on the same day) (Table 2). The NP sample was submitted before the BAL fluid sample for all but one case. Forty-five specimens (31.3%) from 25 patients (35.2%) tested positive for an RV. This rate of RV detection was consistent with the incidence of URTD symptoms in these patients (Table 1) and was similar to those in comparable studies (10, 11, 13, 14). Rhinovirus (RhV) was the most common virus identified. Two RVs were identified in the same sample in one patient whose BAL fluid sample was positive for parainfluenza virus type 3 (PIV3) and RhV. The NP sample from this patient was positive for PIV3 only; for purposes of this analysis, this paired set was considered discordant (the NP sample was negative [NP^-] for RhV, and the BAL fluid sample was positive [BAL $fluid^+$] for RhV), as described in the results below.

In 47 sets (65.3%), the samples were NP^-/BAL $fluid^-$ for an RV, while in 19 sets (26.4%), the samples were NP^+/BAL $fluid^+$ for an RV. The same RV was detected in the NP and BAL fluid samples in all 19 paired NP^+/BAL $fluid^+$ sets. Six paired NP/BAL sets (8.3%) had discordant results. Three were NP^+ but BAL $fluid^-$ for RhV. The interval between the NP and BAL fluid sample collections was 1 day in all three cases. One of these patients was felt by the managing medical teams to have RhV as an LRTD based on clinical assessment and lack of any other pathogen identified in the BAL fluid sample. Of the other two cases, one had documented *Streptococcus pneumoniae* pneumonia and one had aspiration pneumonia. Three paired NP/BAL fluid sets were NP^- but BAL $fluid^+$ for human metapneumovirus (hMPV), respiratory syncy-

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TABLE 1 Patient and disease characteristics

Characteristic	Patient data
Underlying disease[a,b]	
Allogeneic HSCT	29 (40.8)
Hematologic malignancy[c]	20 (28.2)
Autologous HSCT	5 (7.0)
Tandem autologous/allogeneic HSCT	1 (1.4)
Solid organ transplant	4 (5.6)
Solid tumor	3 (4.2)
HIV	2 (2.8)
Other[d]	7 (9.9)
Median (range) age[a]	54 yr (4 mo to 78 yr)
Gender[a]	
Male	50 (70.4)
Female	21 (29.6)
Clinical findings[e]	
Fever	47 (65.2)
Cough	54 (75)
URTD symptoms[f]	23 (31.9)
Hypoxemia	53 (73.6)
Radiographic abnormalities[g]	71 (100)
Lobar	12
Multilobar/diffuse	59
Median (range) symptom duration (days)[h]	5 (1–74)

[a] $n = 71$.
[b] One underlying disease state per patient.
[c] Hematologic malignancies were acute myeloid leukemia ($n = 9$), acute lymphocytic leukemia ($n = 5$), lymphoma ($n = 2$), chronic lymphocytic leukemia ($n = 2$), acute promyelocytic leukemia ($n = 1$), and myelodysplastic syndrome ($n = 1$).
[d] Other disease states were congenital immunodeficiency, pregnancy, Crohn's disease, systemic lupus erythematosus, cardiomyopathy, diabetes, or none.
[e] Reported on a total of 72 RV episodes.
[f] Symptoms were rhinorrhea, congestion, and sore throat.
[g] Abnormalities occurred at any time from initial presentation through bronchoscopy; in one case, radiography was not performed.
[h] Duration of symptoms was measured at the time of NP sample collection.

TABLE 2 Results of RV testing on paired NP and BAL fluid sample sets

Sample set variable	No. (%)
Samples positive for RV[a]	45 (31.3)[b]
Rhinovirus	22
Parainfluenza virus 3	8
Human metapneumovirus	5
Adenovirus	4
Respiratory syncytial virus	3
Influenza A	2
Parainfluenza virus 1	2
Underlying disease in patients with positive samples	25 (35.2)
Allogeneic HSCT	10
Hematologic malignancy	5
Autologous HSCT[c]	3
Solid organ transplantation	2
Other[d]	5
Median time from NP to BAL fluid testing (days)	2
Concordant paired NP^-/BAL $fluid^-$ sets	47 (65.3)
Concordant paired NP^+/BAL $fluid^+$ sets	19 (26.4)
Discordant paired NP/BAL fluid sets	6 (8.3)
NP^+/BAL $fluid^-$[e]	3
NP^-/BAL $fluid^+$[f]	3
Copathogen in BAL fluid sample testing positive for an RV[g]	6 (27.2)

[a] Out of a total of 144 samples from 72 paired sets.
[b] One sample tested positive for two RVs.
[c] Hematologic malignancies were acute myeloid leukemia ($n = 2$), chronic lymphocytic leukemia ($n = 1$), acute lymphocytic leukemia ($n = 1$), and lymphoma ($n = 1$).
[d] Other underlying diseases were congenital immunodeficiency, pregnancy, HIV, diabetes, or none.
[e] All accounted for by RhV.
[f] hMPV, RSV, and RhV.
[g] Five bacterial and one bacterial and galactomannan positive.

tial virus (RSV), and RhV. The intervals between the NP and BAL fluid sample collections were 3, 7, and 2 days, respectively. These three patients were felt to have a clinical syndrome consistent with an RV in the setting of LRTD. A clinically relevant copathogen was found in 6 (27.2%) of the 22 BAL fluid samples that tested positive for an RV.

Using RV PCR testing of BAL fluid as the microbiologic diagnostic gold standard for an RV in LRTD (15), the sensitivity of NP testing was 86.4% (95% confidence interval [CI], 65.1% to 96.9%), the specificity was 94% (95% CI, 83.4% to 98.7%), the positive predictive value was 86.4% (95% CI, 65.1% to 96.9%), and the negative predictive value was 94% (95% CI, 83.4% to 98.7%). For RhV, the positive predictive value of NP testing was lower (75% [95% CI, 42.8% to 94.2%]).

The data presented here demonstrate a high negative predictive value of NP sample testing, consistent with previously published data, but less NP^+/BAL $fluid^-$ discordance and, consequently, a higher positive predictive value (4, 9, 11). The higher positive predictive value may be due to several differences between this study and those cited for the positive predictive value data that relate to the pretest probability of a positive result in a BAL fluid sample for an RV. Patients with hematologic malignancies or HSCT recipients, who comprised a majority in this study, may be more likely to have an RV in LRTD than, for example, patients admitted to an intensive care unit with community-acquired pneumonia (10, 11). Also, comparable studies in lung transplant and pediatric populations have included patients without evidence of LRTD or without acute lower respiratory syndromes (4, 9), thereby potentially reducing the likelihood of RV detection in a BAL fluid sample while at the same time detecting RVs in NP samples due to coincident upper respiratory tract infections or asymptomatic shedding (3, 16).

Interestingly, all the discordant NP^+/BAL $fluid^-$ specimens in this study were accounted for by RhV. Others have noted similar discordance, specifically with RhV (4, 9), and indeed, RhV results in LRTD less frequently than do many other RVs (16, 17), perhaps due to suboptimal replication at temperatures found in the lower airways (18).

The retrospective nature of this study precluded obtaining paired NP and BAL fluid samples contemporaneously. However, the relatively brief interval (median, 2 days) between sample collections makes this limitation unlikely to have significantly impacted our findings. Whether these results can be extrapolated to viruses that were present in a minority of samples, such as influenza (6–8), is not clear. Finally, the relatively small sample size at a single institution mandates validation of these results with additional studies.

In conclusion, we found that PCR-based NP sample testing for RVs in patients with clinical evidence of LRTD has a high negative predictive value and a variable virus-specific positive predictive value, which was lower for RhV than for other RVs. The data presented here may be useful to the clinician in determining the need for additional diagnostics after initial RV testing on an NP sample. Such decisions should take into account underlying patient characteristics, clinical presentation, the specific RV identified, and the rate of coinfection with other pathogens in this study and others involving similar patient populations (1). Larger studies are needed to confirm these findings and to determine when invasive procedures, such as bronchoscopy, are unlikely to be of added benefit in patients with LRTD given the results of NP sample testing for RVs.

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