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Risk Factors for Respiratory Failure Associated with Respiratory Syncytial Virus Infection in Adults

Coley B. Duncan[1,2], **Edward E. Walsh**[1,2], **Derick R. Peterson**[3], **F.Eun-Hyung Lee**[4], and **Ann R. Falsey**[1,2]

[1]Department of Medicine, Rochester General Hospital, University of Rochester School of Medicine and Dentistry, Rochester, New York

[2]Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

[3]Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester, New York

[4]Division of Pulmonary and Critical Care Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York

Abstract

Risk factors associated with respiratory failure during respiratory syncytial virus (RSV) infection have not been assessed in adults. We identified RSV by quantitative reverse transcription polymerase chain reaction in 58 adults during the 2007–2008 winter. Clinical variables and respiratory secretion viral loads were compared in 26 outpatients and 32 inpatients. Cardiopulmonary diseases were more common among inpatients than outpatients (91% vs 31%, $P = .0001$), whereas mean RSV load was similar. Nasal viral load was higher in ventilated vs nonventilated hospitalized patients ($\log_{10}$ 3.7 ± 1.7 plaque-forming units (PFUs)/mL vs 2.4 ± 1.1 PFUs/mL, $P = .02$), and high viral load was independently associated with respiratory failure.

Respiratory syncytial virus (RSV) is an important pathogen in young children and older adults [1,2]. Although severe disease has been linked to prematurity, low birth weight, and cardiopulmonary conditions, the majority of children who are hospitalized for RSV are healthy infants in whom pathogenesis is likely due to the immune response and viral cytotoxicity [3, 4]. Some investigators find high viral load to be a risk factor for severe disease, including respiratory failure in infants [5–8]. Disease pathogenesis in adult reinfection may be considerably different from primary infection in childhood. Illness severity in adults is likely mutifactorial; underlying pulmonary disease, poor functional status, and low levels of serum neutralizing antibody are potential indications for hospitalization in adults [9]. Although largely unexplored, age-related cellular immune dysregulation resulting in ineffective viral clearance may also play a role in disease pathogenesis. Currently, to our knowledge there are no data in adults on the relationship of disease severity and viral load. In this report we describe

Reprints or correspondence: Dr. Ann R. Falsey, Rochester General Hospital, 1425 Portland Ave, No. 246, Rochester, NY 14621-3001 (ann.falsey@rochestergeneral.org)..

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risk factors associated with RSV-related respiratory failure in adults, including viral load in respiratory secretions.

Methods

During the winter of 2007–2008, awareness among physicians of RSV infection in our medical intensive care unit was heightened due to an ongoing study of RSV disease pathogenesis. Thus, viral diagnostic testing identified RSV infection in 11 patients with respiratory failure. This circumstance allowed analysis of risk factors associated with severe disease and respiratory failure during this winter season.

The study was conducted between 1 December 2007 and 30 April 2008 in Rochester, New York. RSV illnesses were identified in 3 groups: a cohort of independently living adults, hospital employees with acute respiratory tract illnesses (ARTIs), and adults with ARTIs evaluated in the Rochester General Hospital (RGH) emergency department and/or admitted to the hospital. All participants or guardians provided informed consent. The University of Rochester Research Subjects Review Board and the RGH Clinical Investigation Committee approved the study.

Prospective subjects with illness characterized by sore throat, nasal congestion, new or worse cough, sputum production, or dyspnea were evaluated within 48 hours of our notification. Hospitalized patients with diagnoses of upper respiratory infection, bronchitis, pneumonia, chronic obstructive pulmonary disease (COPD), asthma, viral illness, or respiratory failure were evaluated within 48 hours of admission. Evaluations consisted of a medical history, chart review, and physical examination.

Nasal samples were obtained from all participants by 1 of 4 study team members by rubbing the nasal turbinates for 5 s with a cotton swab [10]. Swabs were placed in 3 mL of sterile water and transported to the laboratory on ice. Reverse transcription polymerase chain reaction (RT-PCR) was performed within 24 hours of collection. Study subjects who tested positive for RSV were visited daily. Among individuals who underwent RSV testing as part of routine care, only 1 nasal sample was collected. Expectorated sputum and endotracheal aspirated secretions were obtained if possible; however, sputum was not induced. Serum was collected on the first day possible after RSV was identified. Respiratory specimens were collected daily Monday through Friday for the first 7 days of illness and every other day thereafter until negative RT-PCR results were obtained on 2 consecutive samples.

RNA was extracted into 12 μL of water from 250 μL of respiratory specimen. Sputum was diluted with an equal volume of distilled water and vigorously mixed with a vortex mixer before extraction. RSV RNA was detected in single runs by using real-time multiplex RT-PCR. For reverse transcription, 5.25 μL of RNA was incubated at 42°C for 30 minutes with 10 U of Avian Myeloblastosis Virus reverse transcriptase, 10 U of RNasin, at a concentration of 200uM dNTPs, and a forward common group A and B RSV primer (5′-ATGCAGGTGTAACAACACCTTTAAGCACTTACATGTTAAC) at a concentration of 200nM. The amplification mixture contained 5 μL of cDNA, 6mM $MgCl_2$, 500uM dNTP (dUTP replacing dTTP), 5 U of Taq polymerase and 1 U of uracyl DNA-glycosylase (UNG), 200nM of RSV group A forward primer (5′-CACCCTGTTGGAAAC) , group B forward primer (5′-CACCTTGCTGGAAAT), a common reverse primer (5′-CTCTGTCAGTTCTTG), and group-specific probes (Intergrated DNA Technologies); group A (5′-FAM-ATGTTGGACCCTTCTTTTGTGTTGGTTGTA); and group B (5′-TR-ATATTTGATCCTTCTTTGATGTTGGTGGTG). Amplification was performed on a BioRad iCycler for 42 cycles of 95°C for 5 s, 42°C for 40 s, and 68°C for 10 s. The cycle threshold

(Ct) was defined when the relative fluorescent units (RFUs) exceeded 15% of the highest RFU value for the positive control.

RNA was quantified for RSV A by using a published assay [11]. The group B assay used the reverse primer (5′-TCCTCTATCAGTCCTTGTT) with the above forward primer and probe. A standard curve was run for each assay by using 10-fold dilutions of stock RSV A2 and B1 [10^6 plaque-forming units (PFUs)/mL] and Ct values for samples converted to PFUs per milliliter equivalents.

The titer of serum immunoglobulin G and nasal immunoglobulin A to purified RSV F and G glycoproteins was determined using established methods [11,12]. Nasal titers were standardized to a total protein of 100 μg/mL nasal secretion.

Neutralization titers were determined with a microneutralization assay as previously published [13].

Differences in categorical and continuous distributions were evaluated with the Fisher Exact test and the Wilcoxon test, respectively. The Spearman rank correlation was used to quantify the monotonic association between continuous variables. Multiple logistic regression analysis was used to model the relative odds of being an inpatient versus outpatient, and of undergoing ventilation versus not undergoing ventilation, as a function of continuous $\log_{10}$ (viral load +1), COPD, diabetes mellitus, any cardiac condition (coronory artery disease, congestive heart failure, or both), steroid use, and continuous age. Likelihood ratio tests were used to analyze the independent contribution of each predictor, and 95% Wald-type confidence intervals were computed for the odds ratios. Except for viral load, covariates failing to meet the 2-tailed 0.10 level of significance were omitted from the final models. Final models were refitted excluding the immunocompromised subjects to verify that results were not driven by these patients.

Results

Overall, 58 subjects with RSV infection were identified; 26 were cared for as outpatients and 32 were hospitalized. Of the 32 inpatients, 11 (34%) required admission to the intensive care unit (ICU); 9 of the 11 developed respiratory insufficiency requiring mechanical ventilation. Although the other 2 patients had respiratory symptoms, ICU admission was unrelated to respiratory infection (ie, myocardial infarction, *Clostridium difficile* colitis). Thus, these 2 patients were included with nonventilated patients for analysis. RSV B strains were identified in 83% of infections (48 cases), but there were no significant differences between ventilated patients, nonventilated patients, and outpatients.

The mean age of hospitalized patients was 71 years, and many had underlying cardiopulmonary diseases (Table 1). Two patients receiving ventilation were considered to be immunocompromised: one had metastatic, poorly differentiated adenocarcinoma and had received radiation therapy and chemotherapy, and the other had myelodysplastic syndrome with possible transformation to acute leukemia.

Overall, most radiographic abnormalities associated with respiratory failure were relatively subtle. The 2 immunocompromised patients had definite pulmonary infiltrates, described as patchy bilateral interstitial and airspace opacities. Of the other 7 patients, 2 had radiographs that were clear, 1 had a radiograph that showed a small subpulmonic effusion, and 4 had radiographs that showed minimal basilar changes. One patient had bacterial infection at the time of respiratory failure with 4+ *Haemophils influenzae* cultured from an endotrachealsuctioned sputum sample. A second patient developed *Serratia marcesens* ventilator-associated pneumonia and bacteremia 1 week after ICU admission. Five of 9 (56%) patients who developed respiratory failure died, including both immunocompromised patients.

In 52 subjects (91%), the first or second nasal sample contained the highest viral load; there was no significant difference between inpatients and outpatients. Inpatients shed virus for a slightly longer time than did outpatients (9.8 ± 5.8 days vs 8.6 ± 3.6 days, $P = .36$). Although age was not significantly correlated with nasal viral load, 7 of 8 (88%) subjects with nasal viral loads of $\geq 10^{4.0}$ PFUs were older than 65 years.

Underlying cardiopulmonary diseases were more common among inpatients than outpatients (91% vs 31%, $P = .0001$), while age, steroid use, and nasal and sputum viral loads were not significantly different between inpatients and outpatients (Table 1). Outpatients were evaluated earlier in their illness than hospitalized patients (3.9 ± 1.4 days vs 6.6 ± 3.7 days), possibly biasing results toward higher peak viral loads in out-patients. Thus, a second analysis was restricted to samples collected ≥6 days of illness. Hospitalized patients had only slightly higher peak viral loads than outpatients (2.6 ± 1.1 days vs 2.5 ± 1.1 days, $P = .72$). Acute serum-neutralizing antibody titers against group A2 or B1 RSV were not significantly different between inpatients and outpatients, although nasal immunoglobulin A (IgA) titers to F and G proteins were significantly lower in hospitalized patients. Nasal viral titers inversely correlated with nasal IgA F and IgA Gb ($r = -0.24$, $P = .09$, and $r = -0.43$, $P = .002$, respectively).

Ventilated patients were older than nonventilated patients (79 vs 68 years, $P = .04$), but rates of chronic medical conditions and corticosteroid use were similar in the 2 groups (Table 2). Peak nasal viral load was significantly higher in ventilated patients ($\log_{10}$ 3.7 ± 1.7 PFUs/mL vs 2.4 ± 1.1 PFUs/mL, $P = .02$), and ventilated patients were more likely to have viral loads $\geq 10^{4.0}$ PFUs than were nonventilated subjects [5/8 (63%) vs 1/23 (4%), $P = .002$]. Of the 5 ventilated patients with nasal viral loads $\geq 10^{4.0}$ PFUs, 1 was immunocompromised and 1 received oral corticosteroids prior to admission. In the other immunosupressed patient, RSV was identified at the clinical microbiology laboratory, and quantitative RT-PCR was not performed.

The presence of COPD (odds ratio [OR] 4.6, [95% confidence interval {CI} 1.2–17.7], $P = .02$), any cardiac disease (OR 7.5 [95% CI 1.3–43.6], $P = .01$), or diabetes (OR 5.0 [95% CI 1.0–25.8], $P = .04$) were found to be independent predictors of hospitalization, whereas viral load was not ($P = .91$) (Table 3). Peak viral load (OR 2.7 [95% CI 1.0–7.0], $P = .01$) and the presence of COPD (OR 8.9 [95% CI 0.7–111.3], $P = .04$) were independently associated with respiratory failure and use of mechanical ventilation (Table 4). Age was not significant in either model.

Discussion

This analysis revealed that high nasal viral load is an independent risk factor for respiratory failure in adults with RSV infection. Although viral load has been shown to be a risk factor for severe disease in infants, this is the first report to our knowledge of a similar association in adults [5,6]. RSV infection of lower airways of immunocompromised patients has been demonstrated by others, and the need for effective antiviral therapy is well accepted [14]. However, pathogenesis is less well defined in older adults. Immunosenescence resulting in poor viral clearance and greater inflammation is a plausible explanation for severe disease in the elderly. Although age did not correlate with viral load in this small study, 88% of the patients with very high nasal loads were over 65 years.

The presence of cardiopulmonary diseases was strongly associated with risk of hospitalization during RSV infection, thus confirming earlier work in which chronic lung disease and poor functional status were associated with risk of hospitalization in adults [9]. Unlike findings in our previous studies, low serum-neutralizing antibody titer was not associated with a risk of hospitalization. However, sera in the current analysis were obtained ~1 week after symptom

onset, when antibody levels had likely begun to rise. Viral load in nasal secretions of inpatients was not significantly different than that of outpatients, thus suggesting that need for hospitalization was driven primarily by underlying chronic diseases. In contrast, viral load was highest in patients with respiratory failure. A trend toward higher viral load was noted for sputum samples from ventilated patients, but statistical significance was not achieved, likely due to fewer samples available.

Our findings associating viral load and respiratory failure suggest several avenues of further study. RSV rapid antigen tests, which are generally insensitive in adults, may be of value for patients with respiratory failure. Additionally, if our findings are confirmed in larger studies, older adults with respiratory failure might be considered a target group for studies of antiviral therapy. Effective therapy could be important, as we observed a mortality rate of 56%, similar to the 40% death rate noted by Guidry et al in RSV-infected patients who required mechanical ventilation [15]. Clearly, once respiratory failure develops in RSV-infected adults, outcome is poor with supportive treatment alone.

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Table 1

Characteristics of Outpatients and Inpatients with Respiratory Syncytial Virus Infection

Variable	Outpatients (*n* = 26)	Inpatients (*n* = 32)	*P*
Age, mean ± SD	65 ± 14	71 ± 13	.06
Male sex, no.(%)	11 (42)	21 (66)	.11
Medical conditions, no. (%)			
COPD	6 (23)	18 (56)	.02
Asthma	1 (4)	7 (22)	.06
CAD	2 (8)	8 (25)	.16
CHF	0	9 (28)	.003
DM	3 (12)	11 (34)	.06
Any cardiopulmonary disease	8 (31)	29 (91)	.0001
Receipt of oral steroids, no. (%)	1 (4)	6 (19)	.12
Death, no (%)	0	6 (19)	.03
Peak nasal RSV load $\geq 10^4$, No. (%)	2 (8)	5 (16)[a]	.27
Peak nasal RSV load, $\log_{10}$, mean ± SD	2.9 ± 0.9	2.7 ± 1.4)[a]	.59
Peak sputum RSV load, mean ± SD	2.4 ± 1.8[b]	2.7 ± 2.0[a]	.71
MNA, $\log_2$, mean ± SD	11.1 ± 1.7	11.4 ± 1.8[c]	.60
MNB, $\log_2$, mean ± SD	11.4 ± 1.6	11.5 ± 1.8[c]	.97
IgA F, $\log_2$, mean ± SD	3.4 ± 0.9	2.7 ± 1.0[d]	.01
IgA Gb, $\log_2$, mean ± SD	3.6 ± 1.5	2.8 ± 1.2[d]	.03

NOTE. CAD, coronory artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IgA, immunoglobulin A; SD, standard deviation.

[a] $n = 31$.

[b] $n = 12$.

[c] $n = 27$.

[d] $n = 28$.

Table 2

Characteristics of Nonventilated and Ventilated Patients with Respiratory Syncytial Virus Infection

Variable	Nonventilated (*n* = 23)	Ventilated (*n* = 9)	*P*
Age, mean ± SD	68 ± 14	79 ± 6	.04
Male sex, no. (%)	14 (61)	7 (78)	.44
Medical conditions, no. (%)			
COPD	11 (48)	7 (78)	.23
Asthma	7 (30)	0	.15
CAD	7 (30)	1 (11)	.39
CHF	7 (30)	2 (22)	.99
DM	10 (44)	1 (11)	.11
Any cardiopulmonary disease	21 (91)	8 (89)	>.99
Oral steroids, no. (%)	3 (13)	3 (33)	.31
Death, no. (%)	1 (4)	5 (56)	.003
Peak nasal RSV load 10^4, no. (%)	1 (4)	5 (63)[a]	.002
Peak nasal RSV load (mean ± SD)	2.4 ± 1.1	3.7 ± 1.7[a]	.02
Peak sputum RSV load (mean ± SD)	2.4 ± 2.1[b]	3.6 ± 2.1[c]	.34
MNA (mean ± SD)	11.3 ± 1.8[d]	11.6 ± 1.7[e]	.71
MNB (mean ± SD)	11.4 ± 1.6[d]	11.8 ± 2.4[e]	.88
IgA F (mean ± SD)	2.6 ± 1.0[d]	2.7 ± 1.0[e]	.98
IgA Gb (mean ± SD)	2.9 ± 1.3[d]	2.6 ± 1.0[e]	.61

NOTE. CAD, coronory artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; IgA, immunoglobulin A; SD, standard deviation.

[a] *n* = 8.

[b] *n* = 15.

[c] *n* = 4

[d] *n* = 21.

[e] *n* = 6.

Table 3

Multiple Logistic Regression Model for Inpatients (n = 31) vs Outpatients (n = 26)

Variable	OR	95% CI	*P* value
Viral load $\log_{10}$ (value +1)	1.0	0.5–1.7	.91
COPD	4.6	1.2–17.7	.02
Any cardiac disease[a]	7.5	1.3–43.6	.01
DM	5.0	1.0–26.0	.03

Notes. Neither age nor steroid use made a statistically significant contribution to the model ($P > .25$ for each). One of the 32 inpatients was omitted due to missing viral load information, and this patient was 1 of the 2 immunocompromised patients; further omitting the 1 other immunocompromised patient did not substantially impact the above results. COPD, chronic obstructive pulmonary disease.

[a] Any cardiac disease is a binary variable indicating coronory artery disease (CAD), congestive heart failure (CHF), or both (vs neither CAD nor CHF).

Table 4

Multiple Logistic Regression Model for Ventilated (n = 8) vs Nonventilated (n = 23)

Variable	OR	95% CI	*P* value
Viral load $\log_{10}$ (value +1)	2.7	1.0–7.0	.01
COPD	8.9	0.7–111.3	.04

NOTES. Age, any cardiac disease (coronory artery disease, congestive heart failure, or both), diabetes mellitus, and steroid use did not make statistically significant contributions to the model (P > .10 for each) and were removed in order to improve stability, given the small sample size (n = 31). One of the 9 ventilated inpatients was omitted due to missing viral load, and this patient was 1 of the 2 immunocompromised patients; further omitting the 1 other immunocompromised patient did not substantially impact the above results. COPD, chronic obstructive pulmonary disease.