Why Making a Diagnosis of Respiratory Syncytial Virus Should Matter to Clinicians

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Respiratory Syncytial Virus (RSV) is an important cause of lower respiratory infections, with severe disease affecting primarily infants and older adults. RSV infections are common during the winter, occurring at an annual rate of 2-10% in older adults and attack rates can exceed those of influenza in this population.[1,2] In adults ≥60 years of age, there are an estimated 700,000 to 2 million cases annually.[2-5] Moreover, approximately 12% of all medically attended acute respiratory illnesses (ARI) in older adults[3,6] and approximately 200,000 hospitalizations annually are associated with RSV infection compared to 300,000 hospitalizations secondary to influenza in the same population.[7,8] The incidence of RSV associated hospitalization increases with age; one study reported that 30% of hospitalizations of adults older than 75 years admitted for ARI were due to RSV infection.[3,8]

Like influenza, RSV mortality disproportionately affects the elderly, with 78-82% of all RSV-associated deaths occurring in persons ≥65 years of age in the US.[4,5] Population based reports estimate 6-8% mortality or 11,000-17,000 RSV associated deaths in older adults each year in the United States (US).[4-6] Moreover, an estimated 1-2% of all cardio-respiratory deaths are attributed to RSV.[4,5] However, perhaps more significant than the limited mortality data is what we know about RSV associated morbidity. First, RSV infection can exacerbate chronic underlying cardiac and pulmonary conditions and antecedent RSV infection may be a trigger for hospitalization for these conditions.[9] Falsey et al estimated that among patients ≥65 years of age hospitalized with laboratory confirmed RSV infection, RSV infection accounted for 11% of hospitalizations for pneumonia, 11% of hospitalizations for chronic obstructive pulmonary disease (COPD), 5% of hospitalizations for congestive heart failure (CHF), and 7% of hospitalizations for asthma.[2] In a recent study 445 subjects age ≥ 50 years with COPD and/or CHF were followed prospectively, 22% diagnosed with RSV infection over a 2-3 year period suggesting higher attack rates in this population.[10] Other studies have also found a significant association between RSV infection and

exacerbation of other cardiovascular conditions in older adults demonstrating that when patients with underlying cardiac disease are infected with RSV they generally have higher healthcare utilization and worse outcomes.[11]

Despite these previously published findings, the burden of RSV infection in older adults may actually be underestimated for several reasons. To begin with, RSV testing is not routinely performed. Secondly, low awareness of RSV infection in adults among providers leads to a low index of suspicion and clinical diagnosis. Thirdly, RSV is either not suspected or may no longer be detectable when it results in an exacerbation of an underlying chronic cardiac or pulmonary condition. The authors of this important study add to the body of literature which demonstrates the burden of RSV infection in older adults. They correctly conclude that this is one of the largest studies to compare outcomes from infection with RSV to influenza in this population and astutely surmise that a comparison with a more widely recognized cause of severe morbidity and mortality may increase provider awareness of the potential of RSV to cause severe disease in older adults and trigger more routine testing for RSV.

But why should clinicians be concerned about making a diagnosis of RSV in this patient population? Previous arguments in favor of routine testing for RSV and more comprehensive population based characterization of infection and disease in older adults have included the support of antimicrobial stewardship efforts, the timely and appropriate isolation of infected subjects in acute care settings and to inform the evaluation of antiviral and vaccines candidates in development. However, there is an even more direct benefit to knowing an elderly patient has an RSV infection: to better care for the patient and understand their risk for, and perhaps prevent, serious clinical outcomes.

In this observational retrospective cohort study conducted at the Kaiser Permanente southern California healthcare system which provides care and access to 4.4 million patients at 15 large community hospitals, Ackerson et al. were able to evaluate a wide range of clinical outcomes for adults hospitalized with RSV infection. During the study period 645 adults ≥ 60 years were hospitalized with RSV and 1878 patients with influenza. Patients with RSV were slightly older with a higher proportion of adults ≥85 years hospitalized compared to influenza. Interestingly and consistent with previous reports, subjects with RSV were more likely to have CHF (35.3% vs. 24.5%, p< 0.001), COPD (29.8% vs. 24.3%, p- 0.006) and asthma (26.6% vs. 18.6%, p =0.12) than those with influenza. Patients with RSV were also more likely to have received oseltamivir prior to hospitalization, likely reflecting the failure of outpatient providers to recognize and diagnosis RSV infection and more likely to receive antibiotics and treatment with inhaled, oral or intravenous steroids in the hospital. The latter findings can probably be explained by the higher incidence of complications related to the exacerbation of underlying cardiopulmonary disease in RSV patients compared to those with influenza.

Other clinical outcomes in this study included healthcare utilization measures such as length of stay, use of mechanical ventilation or other respiratory support and intensive care unit (ICU) admission. Previously, healthcare utilization for older patients hospitalized with RSV has been reported to be similar or higher when compared to patients hospitalized with influenza. In one study at a single large academic institution 94% of older adults diagnosed with RSV in the emergency department required hospitalization.[12] Increased disease severity has also been demonstrated for older adults by longer lengths of hospital stay (6 vs. 3.6 days) and increased need for mechanical ventilation (16.7% vs. 7.2%) resulting in mean adjusted costs for RSV hospitalizations more than double ($38,828) those for influenza ($14,519). [13] Additionally in a recent review of the epidemiology of medically attended RSV infection in

older adults, 10-30% of patients required ICU care and 3-17% mechanical ventilation.[6] Similarly, Ackerson and colleagues reported higher lengths of stay among patients with RSV compared to those with influenza (OR 1.5, 95% CI 1.2-1.7), more frequent respiratory complications (OR 2.7, 95% CI: 2.2-3.2), greater oxygen supplementation among other clinical parameters (OR 1.6, 95% CI: 1.0-1.6) and higher incidence of ICU admission (OR 1.3, 95% CI: 1.0-1.7). But perhaps the most consequential finding and novel information pertains to long-term morbidity and mortality. The authors of this paper report that one-third more adults infected with RSV required home health service after discharge compared to those with influenza (OR 1.3, 95% CI:1.0-1.6). Moreover, one year survival after admission was significantly lower in older adults hospitalized with RSV compared those with influenza (74.2% vs. 81.2%, p = <0.001). This is the first study which has assessed the long-term impact of RSV hospitalization and the conclusions are important: not only can RSV infections result in severe acute illnesses for older adults, but may also have a lasting and prolonged impact on long-term functional status and mortality. This may, as the authors point out, reflect the ability of RSV to drive chronic inflammation associated with persistent and progressive pulmonary disease but may also be related to loss in functional status due to prolonged hospitalization that may in part result from the failure to recognize and diagnose RSV infection early.

There are more than 50 therapeutic and vaccine agents currently being developed which makes this an ideal time to conduct studies that collect data on the incidence of RSV infection in older adults and characterize the extent of RSV-associated complications and health care resource utilization. Ultimately, these data will help to prioritize and assess the benefits of RSV prevention and treatment strategies. The authors of this paper have provided an important update to what has previously been reported but more importantly demonstrate a significance finding on the long-term impact of RSV in this population.

Awareness of the burden of RSV infection in older adults may be starting to improve. Pastula and colleagues conducted a retrospective review of the National Inpatient Sample data from 1997-2012 and noted increased RSV hospitalization rates from 0.5 to 4.6 per 100,000 for older adults likely due to increased testing and recognition.[13] Conversely, in a recent survey of the diagnostic testing practices for RSV of infectious disease physicians nationwide, 80% of physicians that cared for patients with ARI felt being able to diagnose RSV in adults was either very or somewhat important but only 48% reported that they were likely to order RSV testing for older adult patients or those with COPD exacerbation.[14] The primary reason given for respondents who reported that diagnosing RSV was not very important was the lack of antiviral treatment or current vaccines and 63% of physicians surveyed were not aware that RSV candidate vaccines for older adults were in development. While developing protective vaccines and effective antiviral agents is an important goal, I propose that making a diagnosis of RSV infection in older adults is in itself a worthwhile pursuit. RSV is not just one the non-influenza viral infections without a specific treatment but rather is a viral infection with serious potential long-term clinical consequences for a growing older population. Knowing that an elderly patient has RSV early in their hospital course might allow clinicians to implement early interventions such as chest physiotherapy, bronchodilators and anti-inflammatory treatments as well as physical therapy to get the patient moving and prevent deconditioning. Or perhaps a diagnosis of RSV and understanding of the potential functional decline associated with infection in older adults can be used to better counsel patients and their families about overall prognosis and the need for post hospitalization rehabilitation services. For those reasons, making a diagnosis of RSV should be very important to all clinicians.

Potential conflicts of interest

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References

1. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiology and infection.* Feb 1996;116(1):51-63.

2. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *The New England journal of medicine.* Apr 28 2005;352(17):1749-1759.

3. McClure DL, Kieke BA, Sundaram ME, et al. Seasonal incidence of medically attended respiratory syncytial virus infection in a community cohort of adults >/=50 years old. *PloS one.* 2014;9(7):e102586.

4. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. *Influenza and other respiratory viruses.* Sep 2014;8(5):507-515.

5. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *Jama.* Jan 8 2003;289(2):179-186.

6. Colosia AD, Yang J, Hillson E, et al. The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: A systematic review. *PloS one.* 2017;12(8):e0182321.

7. Malosh RE, Martin ET, Callear AP, et al. Respiratory syncytial virus hospitalization in middle-aged and older adults. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology.* Nov 2017;96:37-43.

8. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of hospitalization attributable to influenza and RSV in the US during 1997-2009, by age and risk status. *BMC public health.* Mar 21 2017;17(1):271.

9. Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *The Journal of infectious diseases.* Jun 15 2014;209(12):1873-1881.

10. Falsey AR, Walsh EE, Esser MT, Shoemaker K, Yu L, Griffin MP. Respiratory syncytial virus-associated illness in adults with advanced chronic obstructive pulmonary disease and/or congestive heart failure. *Journal of medical virology.* Aug 21 2018.

11. Ivey KS, Edwards KM, Talbot HK. Respiratory Syncytial Virus and Associations With Cardiovascular Disease in Adults. *Journal of the American College of Cardiology.* Apr 10 2018;71(14):1574-1583.

12. Binder W, Thorsen J, Borczuk P. RSV in adult ED patients: Do emergency providers consider RSV as an admission diagnosis? *The American journal of emergency medicine.* Aug 2017;35(8):1162-1165.

13. Pastula ST, Hackett J, Coalson J, et al. Hospitalizations for Respiratory Syncytial Virus Among Adults in the United States, 1997-2012. *Open forum infectious diseases.* Winter 2017;4(1):ofw270.

14. Allen KE, Beekmann SE, Polgreen P, et al. Survey of diagnostic testing for respiratory syncytial virus (RSV) in adults: Infectious disease physician practices and implications for burden estimates. *Diagnostic microbiology and infectious disease.* Dec 21 2017.