The Clinical and Economic Impact of Timely Diagnosis of Respiratory Virus Infections

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ID TAG™ Respiratory Viral Panel

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The following bibliography summarizes literature relevant to the burden of respiratory virus infections and the clinical and economic benefits of the timely diagnosis of these infections.

Key Points

- Respiratory viral infections are a common and major medical problem
- Clinical diagnosis is difficult because a variety of respiratory viruses can cause overlapping clinical syndromes
- Timely diagnosis of respiratory viral infections can improve the clinical management of patients and is also important for infection/outbreak control
- Diagnosis of respiratory viral infections can decrease health care costs

1. Frequency of Infections and Burden of Disease

Henrickson, K. J. (2005). "Cost-effective use of rapid diagnostic techniques in the treatment and prevention of viral respiratory infections." Pediatr Ann 34(1): 24-31.

Henrickson reviews the high burden of infections caused by respiratory viruses. The epidemiology, costs, and diagnostic methods are all reviewed. Upper respiratory viral infections are frequent, with approximately 6-9 infections per year in children, and 2-4 infections per year in adolescents and adults. There are approximately 1.5 billion upper respiratory tract infections (RTI) per year in the U.S., and although the economic costs of these infections are difficult to estimate, two costs are well appreciated: the overprescribing of antibiotics for respiratory infections unlikely to be bacterial in etiology, and the associated increased rates of bacterial resistance to antibiotics.

Although lower RTIs are less frequent, the costs of these infections are higher. 1.8 percent of schoolchildren and 13 percent of preschool children with lower RTIs are hospitalized. 11 percent of adults with lower RTIs are hospitalized, and 1.2 percent of these infections are fatal. The economic cost of viral lower respiratory infections in children was estimated in one study to be over 2.4 billion dollars annually.

Henrickson states that the early and specific identification of respiratory viruses provides many advantages to society and to individual patients. Rapid respiratory virus diagnosis of inpatients can lead to benefits in several areas: up to a 50 percent reduction in hospital days, 30 percent reduction in antibiotic use, and 20 percent reduction in unnecessary diagnostic tests and procedures. From a public health perspective, molecular assays can allow for better real time surveillance of disease in the community.

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Henrickson points out that although viral culture was the gold standard for diagnosis, it is being replaced with molecular methods. Molecular assays have high sensitivity and specificity, generally approaching 100 percent, and if a method of determining true positives is used, molecular assays can have higher sensitivity than viral culture.

Monto, A. S. (1994). "Studies of the community and family: acute respiratory illness and infection." Epidemiol Rev 16(2): 351-73.

This paper reviews several large studies that formed the basis of the then-current knowledge of the frequency, morbidity, seasonality, and transmission of respiratory infections. Respiratory infections were shown to occur in all age groups, but were especially frequent in infants and young children. Infants under one year of age had an average of 6.1 respiratory infections per year, and this frequency decreases with age to 1.3 infections per year in adults over age 60. Children age 5-9 had an average of 3.5 infections per year, and adults age 20 to 39 had an average of 2.3-2.8 infections per year. Rhinoviruses were the most common causative agents, causing 34 percent of illnesses, followed by coronaviruses, causing 14 percent of illnesses. Influenza A caused 9 percent of illnesses, bacterial infections

caused 8 percent, parainfluenza virus and RSV caused 4 percent each, and adenovirus caused 2 percent. However, RSV, bacterial infections, adenoviruses, and influenza were the most likely to result in physician contact. The seasonality of various viruses had been established with different seasons of peak incidence depending on the virus.

Makela, M. J., T. Puhakka, et al. (1998). "Viruses and bacteria in the etiology of the common cold." J Clin Microbiol 36(2): 539-42.

The frequencies of RTIs in adults with cold symptoms were analyzed over a 10 month period. Viral culture, antigen detection, PCR, and serology were used to identify the causative agents of infection. Viral etiology was established for 69 percent of the infections. The most frequent virus detected was rhinovirus, in 105 out of 200 patients. 17 patients were infected with coronaviruses (OC43 or 229E), 12 had influenza A or B infections, 7 had parainfluenza infections, 4 had RSV infections, and 1 had an enterovirus infection. 10 patients had dual infections. Bacterial infections were rare (3.5 percent of infections), confirming the concept that upper RTIs are generally caused by viruses.

Poehling, K. A., K. M. Edwards, et al. (2006). "The underrecognized burden of influenza in young children." N Engl J Med 355(1): 31-40.

The disease burden of influenza in children under five was examined with prospective surveillance of children presenting to outpatient and inpatient departments with acute RTIs and fevers. The rate of hospitalization associated with influenza in this age group was 0.9 per 1000 children, and the rate of outpatient visits was 10 to 250 times that. The burden varied with the site and year. Few influenza infections were recognized clinically: only 28 percent of inpatient children with laboratory-confirmed influenza and 17 percent of outpatient children had been given a diagnosis of influenza by the treating physician. 35 percent of children with influenza presented within 2 days of onset; this is within the window during which antiviral treatment could shorten the duration of illness and lessen its severity.

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2. Clinical Impact of Rapid Diagnosis

Bonner, A. B., K. W. Monroe, et al. (2003). "Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial." Pediatrics 112(2): 363-7.

The impact of timely diagnosis of influenza was examined in patients aged 2 months to 21 years in a prospective study. After screening for influenza symptoms, patients were randomized to one of two groups: in the first group, the treating physician was aware of the rapid influenza test results, and in the second group, the physician was unaware of the results. Results were available to the physician prior to examination of the patient. There were statistically significant decreases in antibiotic use, number of other tests performed and the charges associated with these, and length of stay in the emergency department among patients whose physicians were aware of their test results, compared to patients whose physicians were not aware. In addition, there was a statistically significant increase in antiviral use among patients whose physicians were aware of their test results.

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Byington, C. L., H. Castillo, et al. (2002). "The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital." Arch Pediatr Adolesc Med 156(12): 1230-4.

The effect of DFA test results for respiratory viruses on antibiotic administration was examined in a retrospective study in 229 patients over 2 winter seasons. A negative DFA result was found to be significantly associated with an increase in antibiotic administration: patients with negative DFA results were 2.3 times more likely as compared to with positive results to receive intravenous antibiotics. In patients with positive DFA results receiving antibiotic therapy, the duration of therapy was significantly shorter (2.5 days versus 4.0 days).

Rocholl, C., K. Gerber, et al. (2004). "Adenoviral infections in children: the impact of rapid diagnosis." Pediatrics 113(1 Pt 1): e51-6.

The clinical impact of the use of timely immunofluorescence testing for adenovirus was investigated with a retrospective chart review. Out of 1901 patients with respiratory infections, 143 tested positive for adenovirus. Thirty-six percent of patients had a change in management based on their positive test results. The most common changes were discontinuation of antibiotics and patient discharge.

Adcock, P. M., G. G. Stout, et al. (1997). "Effect of rapid viral diagnosis on the management of children hospitalized with lower respiratory tract infection." Pediatr Infect Dis J 16(9): 842-6.

The effect of rapid viral tests on patient management was studied in a prospective study at a children's hospital. Two types of tests were done, a rapid

enzyme immunoassay for RSV, and a shell vial culture immunofluorescence assay for multiple pathogens (viral respiratory panel). The results of the rapid tests were generally available within hours of hospital admission, but the results of the viral respiratory panel were generally not available for several days often after discharge. The rapid test results did alter patient management, whereas the results of the viral panel did not. Positive rapid RSV results decreased the duration of antibiotic therapy: the median duration of therapy was 2 days in patients with positive test results, and 3 days in patients with negative tests results. 73 percent of physicians surveyed stated that the results of the RSV rapid test changed their patient management.

Sharma, V., M. D. Dowd, et al. (2002). "Effect of rapid diagnosis of influenza virus type A on the emergency department management of febrile infants and toddlers." Arch Pediatr Adolesc Med 156(1): 41-3.

A retrospective study evaluated the effect of rapid diagnosis of influenza A on the management of children aged 2 to 24 months. Two groups of children with positive influenza enzyme immunoassays (EIA) were compared: the first group received EIA results before discharge from the emergency department (early diagnosis group), and the second group received EIA results after discharge (late diagnosis group). There was a significant decrease in the use of ancillary tests and antibiotic therapy in the early diagnosis group. 2 percent of patients in the early diagnosis group received antibiotics, compared to 24 percent in the late diagnosis group. 2 percent of patients had urinalyses and 17 percent had complete blood counts in the early diagnosis group, compared to 24 percent and 44 percent in the late diagnosis group.

2a. Impact on Appropriate Therapeutic

Aoki, F. Y., M. D. Macleod, et al. (2003). "Early administration of oral oseltamivir increases the benefits of influenza treatment." J Antimicrob Chemother 51(1): 123-9.

The benefit of early treatment of influenza with oral oseltamivir was investigated in a multicenter, open-label trial. 1426 patients aged 12 to 70 years received treatment for influenza within 48 hours of illness onset. The duration of illness was found to be shorter the earlier treatment began: initiation of treatment within the first 12 hours after the onset of fever resulted in a decrease of median illness duration by 74.6 hours (41 percent) compared to treatment at 48 hours. For every six hours earlier treatment was initiated, the duration of illness was 10 hours shorter. Earlier treatment was also associated with reduced duration of fever, reduced severity of symptoms, and shorter time to return to baseline normal health and activities.

Edell, D., V. Khoshoo, et al. (2002). "Early ribavarin treatment of bronchiolitis: effect on long-term respiratory morbidity." Chest 122(3): 935-9.

The long term respiratory morbidity of RSV bronchiolitis in infants is high: up to 70 percent of infants will have increased reactivity and/or impaired pulmonary function for up to 10 years after RSV bronchiolitis. This study addressed whether early treatment with ribavirin can reduce the respiratory morbidity following RSV bronchiolitis. 49 previously healthy infants with severe RSV bronchiolitis received either conservative treatment or ribavirin therapy. The incidence and severity of reactive airway disease (RAD) decreased in the ribavirin-treated infants compared to the control infants. 80.9 percent of control infants had RAD versus 62.5 percent of ribavirin-

treated infants. During the one year follow-up period, the ribavirin-treated infants had significantly fewer episodes of RAD (2.7/patient/year) compared to the control infants (6.4/patient/year). Ribavirin treatment also decreased respiratory-illness related hospitalizations: the treated infants had 25 days in hospital/100 patients/year compared to the control infants, who had 90 days in hospital/100 patients/year.

Schuh, S., A. L. Coates, et al. (2002). "Efficacy of oral dexamethasone in outpatients with acute bronchiolitis." J Pediatr 140(1): 27-32.

A randomized, double-blind, placebo controlled trial examined the efficacy of one dose of oral corticosteroids administered in the emergency department, early in the course of bronchiolitis. The single dose of corticosteroids significantly decreased the rate of hospitalization. 19 percent of children receiving steroid therapy were hospitalized, compared to 44 percent of children receiving placebo.

2b. Impact on Unnecessary Antibiotic Use

Gonzales, R., D. C. Malone, et al. (2001). "Excessive antibiotic use for acute respiratory infections in the United States." Clin Infect Dis 33(6): 757-62.

Gonzales et. al. examined antibiotic use for respiratory infections in 1998 in the U.S. Based on bacterial prevalence rates for otitis media, sinusitis, pharyngitis, bronchitis, and upper respiratory infection, the "ideal" antibiotic prescription rates were estimated. Out of 41 million antibiotic prescriptions, 22.6 million (55 percent) were estimated to have been prescribed for infections unlikely to have a bacterial etiology. The cost of antibiotic prescriptions was 1.32 billion dollars, 726 million of which was likely not necessary considering the likely cause of the infection. This paper suggests that overuse of antibiotics is substantial and has a high economic cost. The authors state that accurate diagnosis of the cause of respiratory infections would likely decrease excessive antibiotic prescribing and its associated costs.

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Noyola, D. E. and G. J. Demmler (2000). "Effect of rapid diagnosis on management of influenza A infections." Pediatr Infect Dis J 19(4): 303-7.

The impact of rapid diagnosis of influenza A on patient management was studied retrospectively. Management of patients with positive influenza A enzyme immunoassays (EIAs) was compared to management of control patients with culture-confirmed influenza A. For patients discharged from the emergency department, patients with positive EIAs were less likely to receive antibiotics: only 20 percent of patients received antibiotics compared to 53 percent of control patients. For patients admitted to the hospital, the likelihood of receiving antibiotics was the same for EIA-diagnosed patients and control patients, but the duration of antibiotic therapy was shorter for EIA-diagnosed patients (3.5 days compared to 5.4 days for control patients). In addition, patients with positive EIA results were more likely to receive antiviral therapy.

2c. Impact on Surveillance and Infection Control

Leonardi, G. P., H. Leib, et al. (1994). "Comparison of rapid detection methods for influenza A virus and their value in health-care management of institutionalized geriatric patients." J Clin Microbiol 32(1): 70-4.

A retrospective survey of influenza infections in geriatric institutionalized patients was performed to compare the morbidity between institutions using culture alone for diagnosis, versus institutions using rapid (EIA) diagnosis plus culture. Institutions using culture alone for diagnosis did not implement antiviral prophylaxis. Using the projected attack rate, the preventable morbidity was estimated to be 9 to 38 percent of influenza cases, if prophylaxis had been used in these institutions. Rapid diagnosis was recommended to permit timely administration of antiviral therapy and infection control.

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Loeb, M., A. McGeer, et al. (2000). "Surveillance for outbreaks of respiratory tract infections in nursing homes." Cmaj 162(8): 1133-7.

The impact of outbreaks of respiratory infections in long-term care facilities for older people was examined both retrospectively and prospectively. Outbreaks accounted for a large proportion of all respiratory illnesses at 24 percent during the prospective period, and 19 percent during the retrospective period. Morbidity was high, with 12 percent of patients requiring transfer to the hospital, and an 8 percent case fatality rate. The clinical findings were non-specific and could not be used to distinguish the causative agent, and a variety of pathogens were responsible for illness including influenza virus, parainfluenza virus, RSV, Legionella sainthelensi, and Chlamydia pneumoniae. Early identification of the causative agent would allow for implementation of measures to interrupt transmission and optimization of therapy, and could potentially decrease the burden of outbreaks in this setting.

3. Economic Impact of Rapid Diagnosis

Barenfanger, J., C. Drake, et al. (2000). "Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study." J Clin Microbiol 38(8): 2824-8.

Barenfanger et. al. assessed the impact of rapid diagnosis of influenza A and B, RSV, parainfluenza virus, and adenovirus on patient care and costs. During year 1 of the study, the average turnaround time for the diagnostic techniques used was 4.5 days, and during year 2, rapid detection resulted in an average turnaround time of 0.9 days. The mean length of stay in the hospital in year 1 was 10.6 days, and in year 2 was 5.3 days. Patients with positive test results were more likely to have antibiotics discontinued in year 2, with 28.6 percent discontinuing in year 2 versus only 9.1 percent discontinuing in year 1. The mean variable costs per patient were $7893 for year 1, and $2177 for year 2. After subtracting costs associated with rapid testing, the savings in variable costs were $144, 332 per year. Although the differences in length of stay, antibiotic use, and cost did not reach statistical significance due to small sample sizes, they did approach statistical significance. A larger study should confirm the decrease in duration of hospital stay, antibiotic use, and costs associated with rapid respiratory virus detection suggested by this study.

Woo, P. C., S. S. Chiu, et al. (1997). "Cost-effectiveness of rapid diagnosis of viral respiratory tract infections in pediatric patients." J Clin Microbiol 35(6): 1579-81.

The impact of rapid diagnosis of respiratory virus infections on clinical care was examined in a retrospective study. During year 1 of the study, diagnosis of viral RTIs except for RSV took a median of 8 days, using conventional culture. During year 2, diagnosis by immunofluorescence for influenza, parainfluenza, and adenovirus had a median turnaround time of 24 hours. RSV test results were available within 24 hours during both years. A decrease in the duration of hospital stay, days of antibiotic use, and number of additional microbiological investigation was seen for year 2 compared to year 1. The mean reduction in duration of stay was 0.9 days, and the mean reduction duration of antibiotic use was 2.6 days. The mean reduction in number of other investigations was 1.7 fewer investigations for year 2. The reduction in duration of hospital stay alone was estimated to save 18 percent of the pediatric hospital costs.

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Langley, J. M., E. E. Wang, et al. (1997). "Economic evaluation of respiratory syncytial virus infection in Canadian children: a Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study." J Pediatr 131(1 Pt 1): 113-7.

The costs and distribution of health care resources spent on RSV infections were examined in a prospective study in Canada. Costs are given in U.S. dollars. The annual cost (direct and indirect) of RSV-associated illness was 18 million dollars. 62 percent of these costs were for inpatient care, and 38 percent were for ambulatory care. The average length of hospital stay of children in the study was 6.7 days. The investigators concluded that the greatest

reductions in cost would come from interventions that prevent or shorten the hospital stay. Decreasing the duration of hospital stay by 1 day would decrease the annual direct costs by 5 percent. Ribavirin was used in only 7 percent of the hospitalized children, although under the guidelines for ribavirin use in RSV from the American Association of Pediatrics, 39 to 82 percent of children could have received ribavirin.

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Serwint, J. R. and R. M. Miller (1993). "Why diagnose influenza infections in hospitalized pediatric patients?" Pediatr Infect Dis J 12(3): 200-4.

Nosocomial influenza infections were examined during one winter season at a children's hospital. 74 patients had positive influenza cultures, and 11 of these cases were nosocomial in origin. In 64 percent of the nosocomial cases a roommate exposure or potential index case was identified, and none of these had influenza considered as the admission diagnosis. The burden of nosocomial influenza was high: hospitalization was extended for 55 percent of patients, and additional costs were incurred for diagnostic tests. The total financial burden of all additional costs related to these 11 nosocomial influenza cases was in excess of $83,000. The paper concludes that rapid diagnostic tests for influenza are needed to identify patients with influenza at admission, in order to prevent nosocomial transmission by facilitating isolation and cohorting decisions.

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Gupta, A. G., C. A. Moyer, et al. (2005). "The economic impact of quarantine: SARS in Toronto as a case study." J Infect 50(5): 386-93.

The economics costs and benefits associated with quarantine during a SARS outbreak were estimated based on the experience with SARS in Toronto in 2003. Two hypothetical outbreak models were generated. In the first, spread of SARS was unchecked by any public health intervention, and infected patients were isolated and treated. In the second, quarantine was implemented early on in the epidemic. Depending on the transmission rate of the virus, the costs of the epidemic, including lost productivity due to illness and mortality, ranged from millions to billions of dollars. The costs of quarantine were estimated at 42.2 million dollars, suggesting that quarantine would be cost-effective. In addition, in the model where quarantine was used to contain the virus, it was estimated that quarantine would be an effective measure to drastically limit the number of infections.

Halasa, N. B., J. V. Williams, et al. (2005). "Medical and economic impact of a respiratory syncytial virus outbreak in a neonatal intensive care unit." Pediatr Infect Dis J 24(12): 1040-4.

The impact of an outbreak of RSV in an NICU was examined through a retrospective chart review. Nine infants were infected with RSV during this outbreak, which had significant medical and economic costs. The morbidity of infection ranged from moderate to high, with 5 infants requiring mechanical ventilation and one requiring extracorporeal membrane oxygenation. The cost of the outbreak was high: over 1.15 million dollars in hospital charges were attributable to the outbreak. There was a delay in identification of the cause of the outbreak. The first infants diagnosed with RSV were not diagnosed until day 9. After recognition of the outbreak, the attack rate decreased and further spread was contained. The paper concludes that the key to outbreak control is early detection of RSV and strict infection control.

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