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Poor Outcome of Acute Respiratory Infection in Young Children with Underlying Health Condition in Brazil

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SUMMARY

Objectives: It is well established that respiratory viruses are an important cause of hospitalizations in young children worldwide, but data are limited on the contribution of specific viruses to severe illness in South America. We describe clinical and laboratory findings from prospective surveillance for acute respiratory infections at a tertiary hospital in São Paulo, Brazil.
Methods: We screened children < 2 years old with acute respiratory tract infections admitted to an urban tertiary hospital for respiratory viruses from March 2008 through February 2010, using polymerase chain reaction assays.
Results: Respiratory viruses were identified in 378 (53%) of the 715 samples analyzed. Respiratory syncytial virus was the most commonly identified virus (52%), followed by adenovirus (27%) and Human metapneumovirus (12%). More than one virus was identified in 19% of specimens. Almost half of the samples (46%) were from children with underlying health conditions. We demonstrated that compared to the previously healthy group, those with comorbidities had a worse outcome in terms of severity, with prolonged hospital stay and more need of intensive care.
Conclusion: Identification of this high-risk population along with strategies for fast diagnosis might each help to reduce morbidity and mortality in this group.

1. Introduction

It is well established that respiratory viruses are an important cause of morbidity in young children worldwide.[1] While respiratory syncytial virus (RSV) remains the leading cause of lower respiratory tract infection (LRTI) in young children, especially those under 12 months,[2] other viruses, such as human metapneumovirus, influenza, parainfluenza and adenovirus, are also associated with LRTI.[3] Great effort has been done to improve viral diagnostic methods in an attempt to identify the causative agents of the most common clinical syndromes, such as bronchiolitis and pneumonia. In this scenario of multiple viruses causing the same spectrum of disease, diagnostic tests are helpful for identifying possible etiologies, which may ultimately help target prevention and treatment strategies. In addition to the agent, the host also plays an important role in determining outcomes.[4,5]

Therapeutic and preventive strategies available nowadays against respiratory viruses are still limited. Influenza vaccines

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and passive immunization with monoclonal antibodies against RSV (palivizumab) can help to reduce influenza and RSV infection and morbidity, but still leaves uncovered most of the acute respiratory virus infection burden. Moreover it's been demonstrated that influenza vaccine's efficacy is lower than desirable in young infants[6,7] and that palivizumab is cost-effective mostly in high-risk population.[8] Antivirals used for influenza treatment, such as neuraminidase inhibitors, can shorten the duration of symptoms and help to reduce related complications, but have their efficacy linked to the timing of drug prescription.[9]

Young children with underlying diseases or risk factors, with emphasis on those with a history of premature birth, congenital heart and lung disease, are at greater risk for unfavorable outcomes when infected with a respiratory virus.[10] Therefore, most of available preventive and treatment drugs are directed to this special population, although the majority of these strategies have high cost and /or limited efficacy. Active virus surveillance allowing good seasonality planning and accessible virus detection tools for etiological definition of the respiratory syndromes can lead to a more rational usage of these strategies.

We describe clinical and laboratory findings from a prospective surveillance of hospitalizations due to acute respiratory infection in young children at a tertiary hospital in São Paulo, Brazil, comparing outcomes in infants with underlying disease to those previously healthy.

2. Patients and Methods

2.1. Study design

In 2008, we started a prospective surveillance system of acute respiratory infections (ARI) in children under two years of age at a university hospital in São Paulo city, Brazil. This analysis includes clinical, epidemiological and laboratory data collected during the two-year time period from March 1, 2008 through February 28, 2010.

Surveillance was conducted in the Pediatrics Department of Santa Casa de Misericórdia Hospital; a tertiary care center that receives patients referred from other centers and serves as a primary hospital for surrounding communities. Enrollment and sample collection was performed Monday through Friday from 8:00 a.m. to 12:00 p.m. Children under two years-old were eligible for enrollment if they were admitted to the hospital and had acute respiratory symptoms of cough and/or difficult breathing or had an admitting diagnosis of bronchiolitis, pneumonia, wheezing, croup, pertussis, paroxysmal cough, apnea and cyanosis. An illness was considered associated with a specific pathogen if it was detected by polymerase chain reaction assays (PCR) as described below. The unit of analysis was hospitalizations, so individuals may be enrolled more than once over the surveillance period.

Information regarding symptoms, history of underlying health conditions and immunization status, were collected from parent/guardian interview and medical records. Antibiotic use, length of hospital stay, oxygen use, need for intensive care and mechanical ventilation data were retrieved from medical records.

After obtaining consent for enrollment and specimen collection from parents/guardians, a single nasopharyngeal aspirate (NPA) was obtained during each hospitalization by a respiratory technician. NPAs were kept under refrigeration at 4-6 °C within one to five hours and were then divided into three cryotubes per sample and stored in liquid nitrogen. Weekly, specimens were sent to the virology laboratory of the University of São Paulo for detection of respiratory viruses by PCR. All samples were tested for the following: respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza virus 1, 2 and 3 (PIV1-3), influenza virus A and B (IA, IB) and adenovirus (ADV). 2009 pandemic influenza A H1N1 (IA-pH1N1) was tested in samples obtained during the months of January 2009 through February 2010. PCR and reverse transcription (RT)-PCR assays were developed using Gene Scan analysis with primers previously described.[11–15] IA-p H1N1 was detected by real time PCR assay developed by the Center for Disease Control and Prevention (CDC RT-qPCR Swine Flu Panel).[16] The protocol specified that samples should be collected within 24 h of admission. If ordered by a clinician, the results of blood cultures were also recorded.

Vaccination in Brazil is public and accessible to all citizens. Private clinics are permitted and can provide vaccines and other prophylaxis not included in the National Immunization Program (NIP). The Brazilian NIP provides influenza vaccine to all children from 6 months to 5 years of age and all age groups with underlying conditions or risk factors.[17] There is a recent federal recommendation for RSV prophylaxis. Nevertheless, some states, including São Paulo where this study was carried out, have specific recommendations regarding RSV prophylaxis and provide, free of charge, palivizumab with 5 doses during the seasonality for infants born premature, under 12 months if $\leq$ 28 weeks of gestational age (WGA) and all children $<$ 2 years of age with chronic lung disease or severe congenital heart disease since 2007.[18] The Brazilian Pediatric Society[19] recommends universal influenza vaccination to all children older than 6 months and extends RSV prophylaxis to premature infants born $\leq$ 31 weeks and 6 days, infants with neuromuscular diseases, severe immunosuppression, and congenital abnormalities of the airways. Palivizumab should also be considered in a 3 doses regimen for those premature infants born with a gestational age of 32 weeks to 34 weeks and 6 days with at least one risk factor and born 3 months before or during RSV season.[19]

The study was approved by the Research Ethics Committee of Santa Casa de Misericórdia Hospital and by the University of São Paulo. Written informed consent was obtained from the parent or guardian of each child enrolled in the study.

2.2. Data analysis

Data analysis was limited to enrolled children who had a respiratory specimen collected according to the study protocol criteria. Categorical variables were compared using χ^2 test or Fischer's exact test, when appropriated. Student t test, Mann-Whitney test or the One-way ANOVA were used for the continuous variables. Odds ratio was determined to associate underlying conditions with hospitalization by specific respiratory virus. A multivariate logistic regression model was performed to take into account the other known risk factors for severe disease and need of intensive care. Age and hospital days were not normally distributed. Mann-Whitney U test was used to compare age and hospital days in the group of healthy versus underlying disease. All the analyses were performed with SPSS software, version 17.0. Statistical significance was considered when $p < 0.05$.

3. Results

3.1. Surveillance population and laboratory analysis

During the surveillance period, there were 760 hospitalized patients who met the eligibility criteria. Of those eligible, all had an NPA obtained, but 41 specimens were obtained >24 hours after admission and 4 specimens were excluded due to inadequate sample collection. Therefore, we included 715 (94%) specimens from all eligible patients, adding up to a total of 622 individuals.

Respiratory viruses were identified in 378 (53%) of the 715 specimens. RSV was the most commonly identified virus (52% of positive specimens), followed by adenovirus (27%), hMPV