

Incidence of respiratory syncytial virus infection in infants and young children referred to the emergency departments for lower respiratory tract diseases in Italy

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Abstract. *Background:* Respiratory Syncytial Virus (RSV) is the leading cause of emergency visits and hospitalization for acute lower respiratory tract infections (LRTI) in infants and young children worldwide. To collect specific epidemiological data on the incidence of RSV infection among infants referred to Emergency Departments (ED) for LRTI in a Mediterranean country, an Italian multicenter epidemiological surveillance program was established. *Methods:* Eight pediatric centers throughout Italy participated in this study. The study population included 272 children ≤ 4 years of age, admitted to the ED between October 2000 and April 2001 for respiratory problems that might be possibly related to LRTI. 152 children were < 1 year of age, 50 between 1 and 2 years, and 70 > 2 years of age. Data regarding medical history and physical examination were recorded for each child, whereas an immunoenzymatic RSV test (TestPack RSV[®], Abbott) was performed on nasal and pharyngeal secretions. *Results:* Out of 272 tested children, 85 were positive for RSV. The peak of the RSV epidemic occurred in February, with an earlier start and end of the RSV season in the northern and central regions, compared to the southern regions. Major risk factors for RSV infection were younger age ($p < 0.05$) and low weight at birth ($p < 0.05$). Among children positive for RSV infection, 55.2% were < 1 year of age, 18.3% were between 1 and 2 years, and 25.7% were > 2 years of age. RSV positivity was associated with a higher rate of hospitalization in the whole study population ($p < 0.01$) and especially in the children ≤ 12 months of age ($p < 0.01$). Clinical evidence of lower respiratory tract involvement, was also more frequently observed in RSV positive than in RSV negative children, both in the whole study population ($p < 0.01$) and in the ≤ 12 months of age subgroup ($p < 0.01$). *Conclusion:* These data confirm that the patterns of RSV infection in Italy are similar to those reported for other countries in the northern hemisphere: RSV is associated with a higher risk of hospitalization and clinically evident LRTI involvement than respiratory infections of other etiologies, especially in infants.

Key words: Respiratory syncytial virus, epidemiological surveillance, lower respiratory tract infections, infants, young children, hospitalization

Introduction

Respiratory Syncytial Virus (RSV) is the leading cause of respiratory infections and hospitalization in infants and young children. RSV is identified as the etiologic agent in 60–90% of the patients with bron-

chiolitis and in 25–50% of those with pneumonia (1, 2).

The peak incidence of the infection is between the second and the sixth month of age. At the time of their first RSV infection more than one third of the children develop lower respiratory tract infections

(LRTI) (1-4). Serologic studies indicate that half of the children are infected during the first year (2, 5) and nearly all children have antibodies against RSV by the end of the second year of life (1-6). Premies with or without chronic lung diseases and infants with congenital heart diseases or immunodeficiency, are particularly prone to RSV infection and they are frequently admitted to the hospital or to the Intensive Care Unit (ICU) for severe impairment of lung function. Data collected in different parts of the world demonstrate that half of the children hospitalized for RSV infections do not have any of the risk factors predisposing to severe RSV disease (7-9). However, other factors, such as age, prematurity, underlying pathological conditions, hypoxemia on admission, evidence of lung involvement on chest X-ray and the individual characteristics of each hospital, have been associated with length of stay (7-11). Despite administered treatments, mortality for RSV infection remains high and ranges between 0.5 and 4%.

Most of the available epidemiological data on RSV infection come from studies performed in the USA and Canada (4-9). However, multicenter studies on health care utilization of infants and children with chronic lung diseases that included centers outside North America have shown that the management of children with RSV differs markedly countries to countries, even in the industrialized nations, and is strongly influenced by the type of institution where a patient is hospitalized (7, 12-14). In this context, little information is available on the rate of hospitalization for LRTI in children, with or without RSV infection, in southern Europe (7, 14, 15).

With this background, we designed a multicenter, national, epidemiological, observational study with the objectives to collect specific epidemiological data on the incidence of RSV infection among infants referred to Emergency Departments (ED) for acute respiratory tract infections, assessing the seasonal and geographical distribution of RSV in Italy, and to characterize the risk factor profile of children with RSV infection requiring or not requiring hospital admission. The study lasted 1 year (October 2000-September 2001), but data showed in this report refer only to the epidemic season (October 2000-April 2001).

Materials and Methods

Study design and patient population

The study population consisted of children, ≤ 4 years of age, referred to the ED with acute respiratory tract diseases (wheezing bronchitis or pneumonia), possibly related to RSV infection between October 1, 2000 and April 30, 2001. Eight tertiary care pediatric centers throughout Italy participated in the study, covering the epidemic season (October 2000 to mid April 2001). For practical and convenience reasons, only children evaluated on Tuesday of each week, between 8 a.m. and 2 p.m. were enrolled into the study.

Before the beginning of the study, written informed consent, consistent with local requirements, was sought from the parents by study personnel, in each hospital. After collection of demographic and medical information, the physicians treated the patients according to their symptoms and disease severity. No follow-up was foreseen. There were no restrictions on prior or concomitant therapy. Since the patients did not enter specific treatment protocols, no randomization was applied.

Basic demographic information and data on the family and patient's past medical history collected included: gestational age of the child, body weight at birth; presence of chronic heart or lung diseases (including chronic lung disease of the new-born), cystic fibrosis, immunodeficiency, personal or family history of atopy, previous respiratory infections, use of systemic or inhaled corticosteroids and/or bronchodilators in the last 3 months, current respiratory infection in the household, day-care attendance birth order, number of children in the family, age of mother and father, educational level of the parents, social status score (based on father's educational level, mother's age and number of children in the family) and number of smokers in the household. Following the clinical assessment, nasopharyngeal specimens were obtained, for viral detection, according to the usual protocol at each hospital. The samples were sent to the microbiology laboratory of each hospital, to evaluate them for the presence of RSV by the immunoenzymatic test

(TestPack®RSV, Abbott) within 24 hours from sampling. No other respiratory viruses were tested for.

At the end of the enrollment to the study the patients were treated according to existing protocols and hospitalized or sent home, based on the severity of their disease and/or response to initial therapy.

Data analysis

The primary outcome was the percentage of children with and without RSV infection, i.e. the incidence of RSV infection in the studied population. All the other parameters collected in the study (secondary variables) were used to stratify the patients in order to assess the seasonal, geographical and epidemiological distribution of the disease and the associated risk factors in children requiring or not requiring hospital admission.

The primary outcome variable (percentage of patients with and without RSV infection) was evaluated for the whole study period, for each month of the study and separately for each of the three geographic areas (northern, central, southern Italy). Comparison of the distribution of RSV negative and RSV positive children was made by a Chi-square test. Secondary outcomes (all the other variables assessed in the study) were determined in all patients and separately for patients with and without RSV infection. In the groups with or without RSV infection, variables were listed according to age, gestational age and birth weight. The variables were again considered based on gestational age (≤ 28 , 29-32, 33-35 and ≥ 35 months) and birth weight (≤ 1000 , 1001-1500 and ≥ 1501 grams) within each age category (0-3, 3-6, 6-12 months, 1-2, 2-3 and 3-4 years). Additional analyses included computation of: 1) the percentage of children aged ≤ 4 years; 2) the monthly distribution of lower respiratory tract diseases in all subjects and separately for each national area; 3) monthly distribution of the number of children in the family and current respiratory infections in the household in children positive for RSV infection; 4) classification on the basis of all the demographic and clinical data collected.

When indicated, between-group comparisons were assessed by a Chi-square test (categorical varia-

bles) or by a Student t-test (continuous variables). Seasonal trends were assessed by Chi-square test. For all statistical tests a value of $p < 0.05$ was considered as significant.

Results

Demographic and clinical characteristics of the study population

In the period October 2000–April 2001 a total of 4765 children were evaluated in the EDs of the 8 pediatric hospitals participating in the study. A total of 272 (5.7%) individuals, whose demographic and clinical characteristics are illustrated in Table 1, were tested for a possible RSV infection. 152 children were < 1 year of age, 50 between 1 and 2 years, and 70 > 2 years of age. Independently from the etiology of the infection, 40.4% of children were admitted to the hospital based on the severity of symptoms or lack of response to therapy.

Incidence of RSV infection in the study population

Results of the immunoenzimatic test demonstrated that out of the 272 children, 186 (68.0%) were RSV negative and 86 (31.9%) were positive. While the

Table 1. Demographic and clinical data of the 272 children tested for a possible RSV infection (data are shown as percentage or means \pm SD)

Male (%)	51.8
Age (months)	15.7 \pm 15.1
Gestational age (months)	38.3 \pm 2.4
Low gestational age (≤ 35 weeks, %)	10.9
Weight at birth (gr)	3167.0 \pm 611.1
Low weight at birth (< 1500 gr, %)	2.2
Chronic Lung Disease (CLD, %)	16.5
Previous RSV infection (%)	23.5
Use of corticosteroids or bronchodilators (%)	48.5
Smokers in the household (%)	51.1
Hospitalized children during the visit in the ED (before knowing the result of the RSV detection test, %)	40.4

overall number of females and males included in the study was similar, the percentage of female children positive to RSV test was slightly higher than that of male children (53.6 vs. 46.4%), but the difference did not reach statistical significance ($\chi^2=1.544$; $p=NS$). Among children positive for RSV infection, 55.2% were <1 year of age, 18.3% were between 1 and 2 years, and 25.7% were > 2 years of age. When the monthly distribution of RSV positive children in the whole population was considered, the peak of infection was in February ($p<0.01$ vs. preceding and following months) (Figure 1). When seasonal trends of RSV infection were analyzed separately for the three Italian areas, an earlier occurrence and disappearance of the infection were observed in the northern and central regions, as compared to the southern regions (North: December to February, $\chi^2=2.961$, $p<0.01$; Center: January and February, $\chi^2=7.234$, $p<0.01$; South: February to April, $\chi^2=7.025$, $p<0.01$) (Figure 1).

Risk factors for RSV infection

Two third of the 272 children included in the study did not have identifiable risk factors predisposing to severe RSV disease, with no differences between RSV positive and RSV negative children (not shown). Major risk factors for RSV infection were young age (13.3 ± 13.9 months in RSV positive vs.

17.0 ± 15.7 months in RSV negative children; $p<0.05$), low birth weight (<1500 gr.) (6.0% in RSV positive and 0.5% in RSV negative children; $p<0.01$). Other major risk factors possibly associated with RSV positivity, but not reaching statistical significance in our study population because of the uneven distribution of patients and/or low numbers in the subgroups, were low gestational age, large number of siblings and high birth order ($p>0.05$ each comparison). The presence of chronic lung diseases and day-care attendance, were also found to be risk factors for development of RSV infection, though only when associated with the presence of major risk factors, in particular young age and low gestational age.

Previous RSV infection or bronchiolitis

Almost one fourth (23.5%) of the children included in the study had a positive history for RSV infection. 28.1% of these children suffered of a RSV re-infection, i.e. were positive to the RSV test and represented the 21.2% of all the children positive to the RSV test. As expected, the older the patient, the higher was the chance of having a positive history for RSV infection (17.1% for age ≤ 1 year, 26% for age 1-2 years and 35.7% for age >2 years) ($\chi^2=9.432$; $p<0.01$).

Use of systemic or inhaled corticosteroids and/or bronchodilators in the last 3 months

Information for this variable was available in all children. A high percentage (48.5%) of children had a positive history of corticosteroid or bronchodilator use in the 3 months preceding the study. While no significant differences between groups were found in recent corticosteroid use, RSV negative children had a higher frequency of recent bronchodilator use, as compared to RSV positive children (74.6% vs. 25.4% of RSV positive, $\chi^2=4.320$, $p<0.05$).

Rate of hospitalization

The rate of hospitalization was higher for RSV positive than for RSV negative children ($p<0.01$) (Fi-

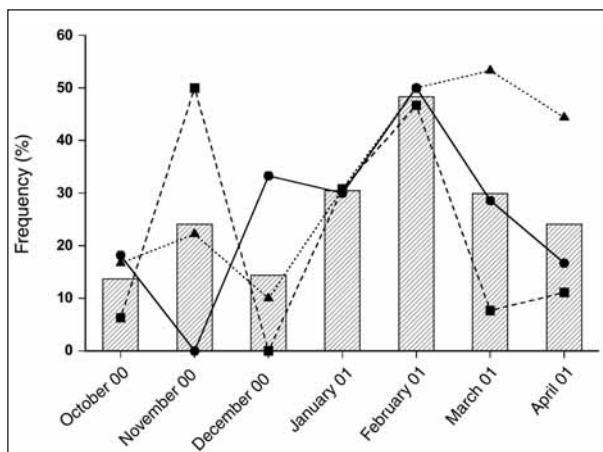


Figure 1. Monthly distribution of RSV infection in the three national areas (North=continuous line, Center=dashed line and South=dotted line) and in the whole country (striped bars)

figure 2, panel A). When the patient population was arbitrarily classified on the basis of age, low weight at birth, and gestational age, we found that younger children, i.e. ≤ 12 months of age, had a higher risk for hospitalization for RSV infection ($p < 0.01$) (Figure 2, panel B). Because of the uneven distribution of patients and/or low numbers in the subgroups no significant differences were observed between low and normal weight at birth and low and normal gestational age populations (not shown).

Lower respiratory tract involvement

A LRTI was diagnosed in 87.5% of RSV positive children and in 71.1% of RSV negative children ($p < 0.01$) (Figure 3, panel A). In the younger group, the presence of LRTI was more frequently observed in the RSV positive children subgroups, as compared to the RSV negative subgroups ($p < 0.01$) (Figure 3, panel B). Because of the uneven distribution of patients and/or low numbers in the subgroups no significant differences were observed between groups of low and normal weight at birth and low and normal gestational age (not shown).

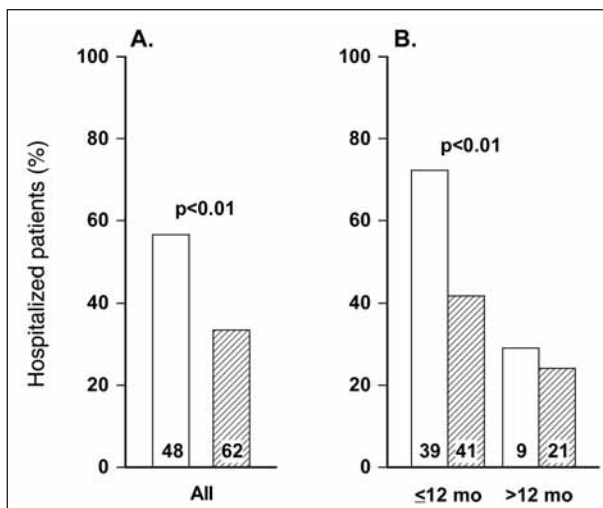


Figure 2. Rate of hospitalization in the children positive (clear bars) or negative (hatched bars) to RSV test. Data are summarized for all children (panel A) and for children ≤ 12 months or > 12 months of age (panel B). Numbers at the bottom of each bar refer to the number of patients in each group. P values indicate the level of the statistical significance of the differences

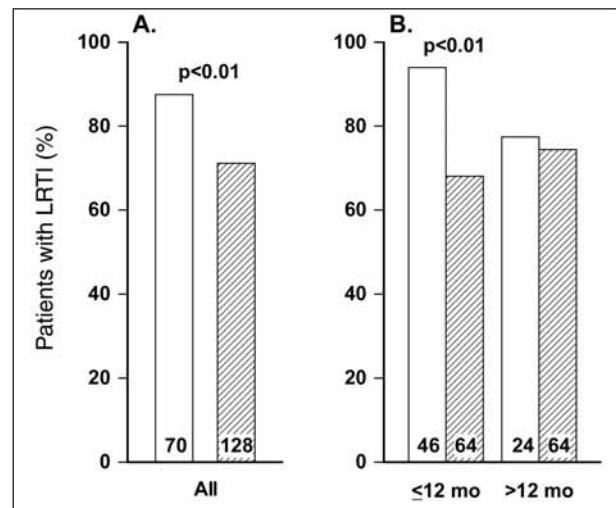


Figure 3. Rate of LRTI in the children positive (clear bars) or negative (hatched bars) to RSV test. Data are summarized for all children (panel A) and for children ≤ 12 months or > 12 months of age (panel B). Numbers at the bottom of each bars refer to the number of patients for each group. P values indicate the level of the statistical significance of the differences

Discussion

Collection of data on the prevalence of RSV infection in Italy among children referred to EDs with LRTI in the epidemiological season October 2000–April 2001, has shown that 1) out of a total of 272 tested children, 85 (31.9%) were positive for RSV; 2) the peak of the RSV epidemic occurred in February, with an earlier occurrence and disappearance in the northern and central regions, compared to the southern regions; 3) major risk factors for RSV infection in this population were younger age and low weight at birth; 4) RSV positivity was associated with a higher hospitalization rate and more frequent LRTI involvement than RSV negativity, this being particularly evident in young infants.

The percentage of children found to be positive for RSV in our study is relatively low, compared with data reported in northern European and American countries (7–13). This difference may be related to differences in climatic conditions, in environmental factors and/or in severity of RSV epidemics from one year to another. In comparison with northern European countries and north America, Italy has fall-win-

ter seasons characterized by relatively warm not favoring the survival and the spreading of respiratory viruses (16, 17). The possibility that this may indeed be true also for RSV epidemics in the "real worlds" is supported by the recent observation of negative correlations between higher monthly mean temperature and RSV infection in tropical regions (18).

In agreement with previous observations which suggested that the management of children with RSV may differ among industrialized countries (7, 12-14), we observed a high rate of hospitalization for RSV infection in the eight tertiary care pediatric centers in Italy. The finding that almost 60% of RSV positive patients evaluated in the EDs were hospitalized may partially reflect the severity of the disease in the study population. In a high proportion of the children a LR-TI was confirmed by chest x-ray. This figure is substantially higher than that reported in studies performed in North America and in other developed nations. Most of the published studies on the management of infants hospitalized with RSV infections include heterogeneous study populations with different demographic characteristics, severity of respiratory symptoms and incidence of underlying risk factors, different type of medical care preceding hospital evaluation and admission, different median duration of pre-admission respiratory symptoms and hospitalization. However, when comparing different nations, the discrepancy in hospitalization rate may also reflect the degree to which medical resources are rationed by the country's healthcare system, the therapeutic preferences of local physicians and the availability of beds in the wards, the population served by a given hospital. Indeed, international comparison in the management of RSV patients clearly showed differences between continental European hospitals (i.e. Belgium, France, Germany, the Netherlands and Italy) and Australian, northern American and northern European hospitals (7, 15, 19). In Italy, the vast majority of children referred to the EDs are those previously evaluated by their pediatricians and sent to the hospital because of the severity of the disease. This approach results in a more severely ill childhood population. In addition parental factors or doctor-related factors, such as the inter-observer variability in the decision of whether a

patient has to remain hospitalized or not, may play an important role.

Finally, the results of the present study may also be biased by the epidemic season, i.e. the period October 2000-April 2001, which appeared somehow longer and associated to a greater morbidity, as compared with the previous season October 1999-April 2000 (14).

The greatest morbidity for RSV infection occurs among high risk children, including preterm infants who are less than six months old and young children with underlying pulmonary or cardiac diseases (20-25). Consistent with data published by other groups, we demonstrated that a great proportion of our children had no risk factors predisposing to severe RSV disease (7, 12-15, 20). Our study also confirms what is shown by previous reports, i.e. that younger age and low weight at birth are significantly associated with lower respiratory tract symptoms related to RSV infections. We could not demonstrate a significant association between low gestational age or high birth order and RSV positivity, possibly because of the small number of children included in the different subgroups.

The finding that RSV positivity was associated with a higher rate of hospitalization and increased roentgenographic evidence of lower respiratory tract involvement is in agreement with our understanding that RSV positive children require more frequent and longer admissions to general pediatric wards and intensive care units, more outpatient attendances and general practitioner consultations for respiratory related disorders and a higher total cost of care (15, 26). A recent study on the use of health care resources and associated costs by infants with chronic lung disease showed that RSV positivity was associated with higher costs of care including not only costs of hospital admission and outpatient attendances, but also costs of primary care respiratory related consultations and therapeutic pharmacologic agents (15).

In summary we showed that in a mediterranean country (Italy) RSV infection causes major morbidity, as indicated by high hospitalization rate due to lower respiratory tract involvement in an unselected pediatric population. This information should be conside-

red in estimating the cost-effectiveness of RSV prophylaxis, including screening programs and passive immunizations.

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