
Respiratory repercussions in adults with a history of infantile bronchiolitis

Roberto Gómez, MD, PhD*; Carlos Colás, MD, PhD*; Antonio Sebastián, MD, PhD*; and Jesús Arribas, MD, PhD†

Background: Viral bronchiolitis in infancy has been identified in previous studies as a potential precursor to the development of lower respiratory tract illness in later childhood and beyond.

Objective: To evaluate the long-term respiratory repercussions of acute infantile viral bronchiolitis.

Methods: We studied 71 individuals aged 19 to 24 years with a history of a viral bronchiolitis in infancy and 32 controls. All participants underwent the following evaluation: medical history, forced spirometry, methacholine challenge, and skin prick testing.

Results: The bronchiolitis group had a higher prevalence of respiratory symptoms ($P = .03$) and bronchial hyperresponsiveness ($P = .003$) than controls. The bronchiolitis group also had a lower peak expiratory flow rate ($P = .02$). Skin prick test responses were similar in both groups.

Conclusions: The findings from this study support and extend those from previous studies by suggesting that viral bronchiolitis may be a predisposing factor for lower respiratory tract problems in young adulthood.

Ann Allergy Asthma Immunol. 2004;93:447–451.

INTRODUCTION

Acute infantile viral bronchiolitis (AIVB) is an infectious condition that primarily affects the terminal and respiratory bronchioles, causing fibrinoid necrosis and desquamative epithelial changes.¹ Many infectious agents are known to cause AIVB: adenovirus, rhinovirus, paramyxovirus, influenza virus, parainfluenza virus, and *Mycoplasma pneumoniae*. However, respiratory syncytial virus is the most commonly involved agent. It can be found in approximately 50% of all cultures performed in children younger than 2 years who have AIVB.² The diagnosis is based mainly on clinical criteria, assisted by a series of complementary tests, such as chest radiography, serologic tests, and the epidemiologic features of the disease. Serologic tests have not been available until the past 2 decades, and, therefore, diagnosis was previously based on clinical criteria. In our series, the clinical criteria proposed by McConnochie³ were used. Several studies^{4,5} have been published on the presence of wheezing during the years after an AIVB event. However, to our knowledge, there is not any study that analyzes the long-term consequences of this disease in adulthood. Therefore, we sought to evaluate the long-term respiratory repercussions of AIVB.

MATERIALS AND METHODS

The study population consisted of 2 groups of young men and women aged 19 to 24 years. The first group was taken from the cohort studied by our group⁶ when they were 9 to 14 years

old. The group comprised 71 individuals with a history of AIVB according to the criteria proposed by McConnochie³ who were younger than 1 year at the time of diagnosis and required hospital admission for AIVB between 1973 and 1978. For the present evaluation, the study subjects and their parents were contacted by telephone. Of the 97 patients studied in the first evaluation, 71 (73%) agreed to take part in this second stage of the study, 9 refused to undergo the tests, and 17 were not located. The mean age of the study population was 21.1 years (range, 19–24 years); 36 (51%) were men and 35 (49%) were women.

The control group was composed of 32 young adults with similar demographic features. The only criterion they had to meet was no hospital admission for respiratory causes before 1 year of age. They were medical students who voluntarily agreed to take part in the study. The mean age of the control group was 21.4 years (range, 20–24 years); 13 (41%) were men and 19 (59%) were women.

All of the participants underwent the following tests: medical history, forced spirometry, methacholine challenge, and skin prick testing (SPT) to common aeroallergens in Spain. When discussing the results, we refer to data obtained from the study performed during the subjects' infancy as the "first evaluation." Data obtained in this second evaluation performed in adulthood are referred to as "present data." All of the interviews and diagnostic tests were performed simultaneously in both groups between 4 and 8 PM during the first half of the year (January to June).

Study approval was obtained from the ethics committee of Hospital Clínico, Zaragoza, Spain. All of the study participants were given written and oral information about the possible risks of the test, after which they signed an informed consent form.

* Servicios de Neumología y Alergia, Hospital Clínico de Zaragoza, Zaragoza, Spain.

† Hospital Miguel Servet de Zaragoza, Zaragoza, Spain.

Received for publication December 11, 2003.

Accepted for publication in revised form June 11, 2004.

Cases and controls were interviewed after arranging an appointment by telephone. A smoker was considered to be anyone who regularly consumed any tobacco product. To detect the presence of respiratory symptoms, participants were questioned about the presence of wheezing or any other common respiratory symptom during the past 10 years. A background of allergy or asthma was based on previous diagnoses made by specialists obtained from medical reports or histories. In the absence of a previous diagnosis, asthma was defined as the presence of bronchial hyperresponsiveness (BHR) plus wheezing events in the past 12 months.

The functional values were obtained by using forced spirometry (Hans E. Ruth Pony graphic spirometer; Cosmed, Rome, Italy). All of the procedures were performed following the recommendations of the American Thoracic Society.⁷ The reference values used were those obtained by Roca⁸ for a Mediterranean population.

The nonspecific methacholine challenges were performed using a Cockcroft method, with a starting concentration of 0.012 mg/mL, which was successively doubled to 8 mg/mL. When a forced expiratory volume in 1 second (FEV₁) of less than 80% was obtained, a bronchodilation test was performed instead. The challenge was considered to be positive if the FEV₁ declined by more than 20%.

Skin prick tests were performed to determine immediate hypersensitivity to the aeroallergens most commonly identified as causing allergic conditions in Spain. The allergens used were *Phleum*, *Cynodon*, *Phragmites*, olive, plantago, *Chenopodium*, *Alternaria*, *Cladosporium*, *Aspergillus*, *Dermatophagoides pteronyssinus*, dog epithelium, and cat epithelium. The test reaction was considered positive if the papule caused by any allergen was equal to or greater than that caused by histamine at 10 mg/mL.

Statistical analysis was performed using a statistical software package (SPSS version 6.1; SPSS Inc, Chicago, IL). Group comparison tests were performed using the *t* test for normally distributed values and the Mann-Whitney *U* test for nonnormally distributed values. The χ^2 test was also used. The level of significance required in the comparison of hypotheses was $P < .05$ in all cases.

RESULTS

The study population includes 2 groups of young men and women aged 19 to 24 years. The demographic features of the 2 groups are given in Table 1. There were no statistically significant differences regarding age, sex, and smoking habit. We found a higher prevalence of asthma, wheezing episodes, and respiratory symptoms during the past 10 years in the group with a history of AIVB (Fig 1).

On analyzing this group, asthma was seen to be more prevalent among women and individuals with impaired respiratory function during childhood (values obtained from the tests performed 10 years earlier), the difference being statistically significant. There was also a trend, although without attaining statistical significance, for participants whose mothers smoked during their childhood to have a higher prevalence of asthma (odds ratio [OR] for asthma among the

Table 1. Characteristics of the Study Population

Characteristics	Bronchiolitis group (n = 71)	Control group (n = 32)
Sex, No. (%)		
M	36 (51)	13 (41)
F	35 (49)	19 (59)
Smokers, No. (%)		
Yes	40 (56)	12 (38)
No	31 (44)	20 (62)
Students, No. (%)*		
Yes	29 (41)	31 (97)
No	42 (59)	1 (3)
Age, mean (SD), y	21.1 (1.4)	21.4 (0.9)
Weight, mean (SD), kg*	69.3 (13.4)	61 (9.5)
Height, mean (SD), cm	170.7 (8.3)	168.7 (6.6)

* $P < .05$.

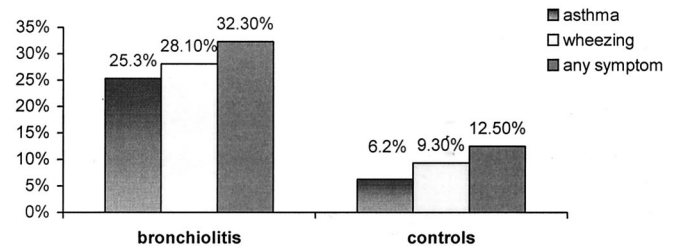


Figure 1. Current presence of respiratory symptoms in the 2 groups. Asthmatic patients are included in all groups. The odds ratio for asthma is 5.09 (95% confidence interval, 1.1–23.47; $P < .05$).

offspring of mothers who smoked, 3.28) and for those individuals who had BHR in the first evaluation (OR for asthma among hyperresponsive patients in the first evaluation, 3.77). We have not found any association between the development of asthma and the presence of positive SPT reactions in either the present evaluation or the first evaluation. Neither has any relationship been found with total serum IgE values in the first evaluation.

Regarding the evaluation of respiratory function, when comparing cases with controls, we found similar values in all the parameters except the absolute value of the peak expiratory flow rate (PEFR), which was significantly lower in cases than in controls ($P = .02$), and the PEFR as a percentage of the theoretical value, which was also greater in controls, although without attaining statistical significance ($P = .09$) (Table 2). These differences lessen when individuals who have been asymptomatic since the bronchiolitis event are compared with controls (PEFR, 7,451 vs 7,935 mL/s).

The challenge test with methacholine was performed in 59 cases and 31 controls. It was not performed in 9 cases with FEV₁ less than 80%; 3 cases and 1 control refused to undergo the test. Five cases with an obstructive spirometry and a positive bronchodilation test result were considered to show BHR. We found a significantly higher prevalence of BHR in

Table 2. Current Values for Respiratory Function and History of Bronchiolitis*

Value	Bronchiolitis group (n = 71)	Control group (n = 32)
FVC, %	93.2 (9.7)	92.6 (8.7)
FEV ₁ , %	94.9 (12.6)	95.7 (7.7)
FEV ₁ /FVC, %	83.8 (7.4)	84.1 (4.4)
MMEF, %	93.6 (25.8)	94.6 (17.0)
PEFR, mL/s†	7,004 (2,317)	7,946 (1,484)
PEF, %	90.7 (16.7)	95.6 (11.3)

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; MMEF, maximal midexpiratory flow; PEF, peak expiratory flow; PEFR, peak expiratory flow rate.

* Data are given as mean (SD).

† $P < .05$.

the bronchiolitis group (OR, 3.81; 95% confidence interval, 1.51–9.60; $P = .003$) (Fig 2). These differences were maintained when only the members of the bronchiolitis group who had remained asymptomatic to the present were included (Fig 3).

Forty-three participants (34 in the bronchiolitis group and 9 controls) showed a provocation concentration that caused a decrease in FEV₁ of 20% of less than 8 mg/mL. The mean value was 3.4 mg/mL in the bronchiolitis group and 4.9 mg/mL in controls ($P = .1$).

When analyzing BHR in nonsmokers we found a higher prevalence in the bronchiolitis group (57%) compared with controls (15%). This difference was statistically significant (OR, 7.5; $P = .003$). We did not find any differences between the bronchiolitis group and the control group in the prevalence of positive SPT reactions (47.7% vs 43.3%).

DISCUSSION

Our findings show that acute bronchiolitis in childhood provokes respiratory repercussions in adulthood. We found a higher prevalence of asthma, wheezing episodes, and respiratory symptoms during the past 10 years in the group with a history of AIVB. Except for PEFR, pulmonary function test

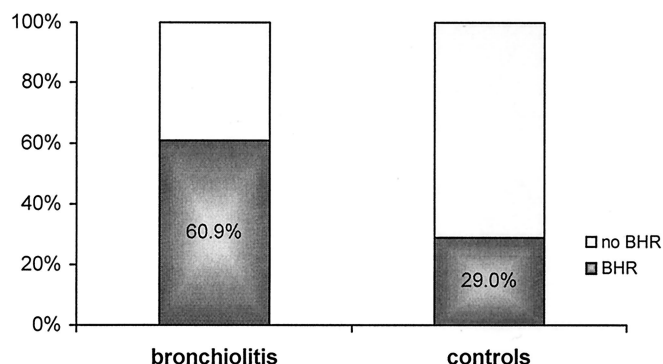


Figure 2. Current presence of bronchial hyperresponsiveness (BHR) in the 2 groups ($P < .01$).

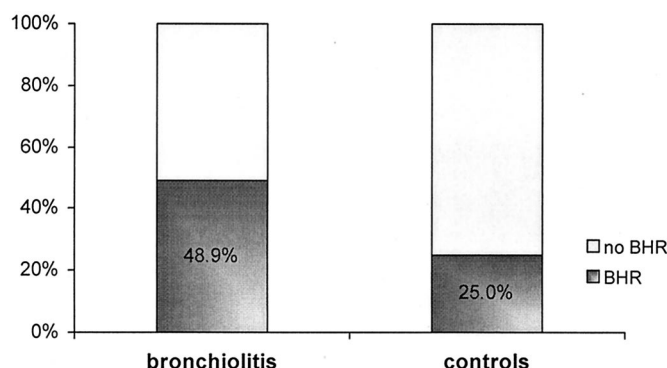


Figure 3. Current presence of bronchial hyperresponsiveness (BHR) in individuals who have been asymptomatic since the bronchiolitis event and in the control group ($P < .05$).

results were similar in both groups. The prevalence of BHR in the bronchiolitis group was statistically significantly higher. We have not found any association between the development of asthma and the presence of positive SPT reactions in our patients.

The present study consists of the second evaluation of a cohort initially composed of 97 children aged 9 to 14 years⁶ that has now reached an age of 19 to 24 years. This age was chosen because it marks the beginning of adult life and is the time of life when a person has the highest lung function values. In our study, we included 71 of the original 97 participants in the second evaluation, which gives a success rate for the follow-up of 73%. We consider that this high follow-up rate allows us to generalize the results to the original group, although, among the cases lost, we are particularly concerned about the 9% who refused to undergo the second evaluation, whereas the 18% who could not be located is less important to us.

The control group in this study consisted of 32 individuals with an age and sex distribution similar to the bronchiolitis group. The prevalence of smoking was higher in the study group, but the difference was not statistically significant.

Many studies^{4,5,9–11} have found an increase in respiratory symptoms during the first years of life in individuals who have experienced a respiratory tract infection (RTI) during infancy. The general impression obtained from these studies is the high prevalence of wheezing, asthma, and respiratory symptoms during the years after a lower RTI (LRTI) experienced during early childhood. Our results support this idea and go even further by confirming that the high prevalence of respiratory symptoms continues even in adult life. Hence, the particular interest of our study is that it shows the long-term impact on people's health of RTIs experienced during infancy, a particularly vulnerable period. The prevalence of respiratory symptoms in the studies mentioned previously herein was higher than ours. We consider that this is because of the longer follow-up time in our series. Thus, as the child develops, the proportion of symptomatic individuals decreases. The possible role played by atopy in the presence or

not of clinical symptoms during the years after an LRTI in infancy is highly controversial. Our results agree with those of Mok and Simpson^{9,12} in suggesting the nonexistence of such an association.

Regarding the development of asthma in our series of cases with a history of bronchiolitis, we find particularly interesting the predictive power of decreased respiratory function values during adolescence. Thus, our results agree with those of Jenkins et al¹³ regarding the existence of decreased forced midexpiratory flow (values that are 14% lower in the first evaluation in our series) in individuals who subsequently develop asthma. Thus, we could suggest that individuals who have had a severe LRTI during childhood and decreased forced midexpiratory flow in adolescence should be monitored closely in an attempt to diagnose as early as possible the asthma cases that will undoubtedly appear with time in this group. Again in agreement with Jenkins et al,¹³ we found that the risk of developing asthma in this group is increased in women.

There is evidence of an association between experiencing an RTI during childhood and lung function impairments in later years. Several explanations can be given for this association.¹⁴ Studies designed to address this issue could be based on studying a cohort after the RTI to analyze their respiratory function, as in our case. Thus, Duiverman et al¹⁵ studied children with a history of bronchiolitis and found decreased respiratory function in the symptomatic group only. The results of this study concur with our results regarding the absence of functional differences between cases and controls in the asymptomatic group. Two studies by Mok and Simpson¹⁶ and Sims et al¹⁷ agree with us in finding statistically significantly lower values for PEFR in children with a history of RTI caused by respiratory syncytial virus in infancy compared with their controls.

The respiratory function of the general population can also be studied by analyzing for a history of RTI by survey. Following this method, some researchers^{18,19} found that individuals with a history of LRTI in childhood had statistically significantly lower respiratory function values in adulthood.

Finally, another approach has been proposed that consists of studying respiratory function beginning at birth with a view to monitoring subsequent RTIs and the development of the lung function. Martínez et al^{20,21} concluded that impaired respiratory function after birth was a predisposing factor to experiencing wheezing disease during childhood. Young et al²² also reported impaired baseline respiratory function with respiratory diseases during childhood.

We did not find statistically significant differences in pulmonary function test results between groups except for PEFR. Considering the fact that this parameter is effort dependent, this finding may not be noteworthy.

There are several methods for determining bronchial responsiveness, and they may have varying degrees of sensitivity in showing the presence of BHR.²³ However, most of the studies mentioned previously herein, like ours, used methacholine for studying BHR. It has been found that chil-

dren with a history of bronchiolitis and other LRTIs experienced during early childhood have a higher bronchial response compared with children without such a history.^{5,12,24,25} We found that the trend, described in the studies mentioned previously herein, toward high levels of BHR in childhood after an LRTI is maintained in adulthood, even in individuals who remained asymptomatic after the bronchiolitis event. It is well known that a smoking habit enhances bronchial responsiveness. To avoid this confounding factor, we analyzed the prevalence of BHR in nonsmokers. We found that BHR remained higher in the bronchiolitis group.

The results obtained by several researchers,^{26,27} which show an increase in IgE levels during infectious diseases of the lower airways (including bronchiolitis), suggest the existence of a link between an atopic constitution and a greater risk of experiencing such diseases during early childhood. However, the role that would be played by atopy in later repercussions of such infections is much more debatable. In our study, we discarded the effect of subjective assessments, determining the presence of an atopic constitution by means of SPT using aeroallergens common in Spain.

In the present study, we found a prevalence of 43% for a positive SPT reaction in the control group. We consider that the performance of epidemiologic studies on supposedly healthy individuals who voluntarily agree to undergo tests that evaluate certain disease states could allow the inclusion of excessively high quantities of individuals who suspect that they have a related condition. Our findings agree with those of a study performed in southern Spain in 365 students with a mean age of 18 years by Garcia-Gonzalez et al.²⁸ They found a positive SPT reaction in 46% of subjects; neither this study nor ours is free of the risk of overestimating the prevalence of atopy.

In the studies performed with a design similar to ours, we find differing results on the role of atopy in the years after a lower airway infection. Some studies^{29,30} find a role for atopy in the individual's subsequent course. On the other hand, other studies^{5,31} reject a role for atopy in the individual's subsequent course. In our cohort, a significantly greater prevalence of atopic constitutions was found in the first evaluation in the children with a history of bronchiolitis compared with their controls.⁶ These results suggest that the occurrence of bronchiolitis could have been facilitated by the existence of an atopic constitution in the individual, which would confirm the relationship between atopy and bronchiolitis mentioned by several researchers. In this second evaluation of our cohort, performed at the beginning of adult life, we did not find any differences in the percentage of positive findings in SPT between individuals with a history of bronchiolitis and their controls.

We conclude that a history of bronchiolitis before 1 year of age determines an increased prevalence of asthma and respiratory symptoms in adult life. Previous bronchiolitis is associated with decreased PEFR values in adulthood. This impairment disappears when only the participants who have been asymptomatic since the bronchiolitis event are analyzed.

Bronchiolitis in infancy alone is an important risk factor for BHR independent of atopy by the time the individuals reach adulthood.

REFERENCES

1. Hubble D, Osborn GR. Acute bronchiolitis in children. *BMJ*. 1941;1:107–110.
2. Panitch HB, Callahan CW, Schidlow DV. Bronchiolitis in children. *Clin Chest Med*. 1993;14:715–731.
3. McConnochie KM. Bronchiolitis: what's in the name? *Am J Dis Child*. 1983;137:11–13.
4. Henry RL, Hodges IG, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child*. 1983;58:713–716.
5. Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *BMJ*. 1982;284:1665–1669.
6. Arribas J, Colás C, Sebastián A, et al. Atopy and pulmonary function abnormalities in children with a history of acute bronchiolitis. *J Asthma*. 2000;37:73–80.
7. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144:1202–1218.
8. Roca J. *Reference Values for Forced Spirometry in a Mediterranean Population* [doctoral thesis]. Barcelona, Spain: University of Barcelona; 1982.
9. Mok JY, Simpson H. Outcome for acute bronchitis, bronchiolitis and pneumonia in infancy. *Arch Dis Child*. 1984;59:306–309.
10. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354:541–545.
11. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellmann B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000;161:1501–1507.
12. Mok JY, Simpson H. Symptoms, atopy and bronchial reactivity after lower respiratory infection in infancy. *Arch Dis Child*. 1984;59:299–305.
13. Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. *BMJ*. 1994;309:90–93.
14. Britton J, Martínez FD. The relationship of childhood respiratory infection to growth and decline in lung function. *Am J Respir Crit Care Med*. 1996;154:240–245.
15. Duiverman EJ, Neijens HJ, Van Strik R, Affourtit MJ, Kerrebijn KF. Lung function and bronchial responsiveness in children who had infantile bronchiolitis. *Pediatr Pulmonol*. 1987;3:38–44.
16. Mok JY, Simpson H. Outcome of acute lower respiratory tract infection in infants: preliminary report of seven-year follow-up study. *BMJ*. 1982;285:333–337.
17. Sims DG, Downham MA, Gardner PS, Webb JK, Weightman D. Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *BMJ*. 1978;1:11–14.
18. Shaheen SO, Barker DJ, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in adult life. *Am J Respir Crit Care Med*. 1994;149:616–619.
19. Britten N, Davies JM, Colley JR. Early respiratory experience and subsequent cough and peak expiratory flow rate in 36-year-old men and women. *BMJ*. 1987;294:1317–1320.
20. Martínez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med*. 1988;319:1112–1117.
21. Martínez FD, Morgan WJ, Wright AL, Holberg C, Taussig LM. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. *Am Rev Respir Dis*. 1991;143:312–316.
22. Young S, O'Keefe PT, Arnott J, Landau LI. Lung function, airway responsiveness, and respiratory symptoms before and after bronchiolitis. *Arch Dis Child*. 1995;72:16–24.
23. Mellis CM, Kattan M, Keens TG, Levison H. Comparative study of histamine and exercise challenges in asthmatic children. *Am Rev Respir Dis*. 1978;117:911–915.
24. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*. 1996;312:1195–1199.
25. Tepper R, Rosenbreg D, Eigen H. Airway responsiveness in infants following bronchiolitis. *Pediatr Pulmonol*. 1992;13:6–10.
26. Sieber OF Jr, Riggan R, Ryckman D, Fulginiti VA. Elevation of serum immunoglobulin E (IgE) levels in infants with lower respiratory tract infections (LRTI) caused by parainfluenza viruses (PV) [abstract]. *Am Rev Respir Dis*. 1976;113(Suppl):39.
27. Stempel DA, Clyde WA Jr, Henderson FW, Collier AM. Serum IgE levels and the clinical expression of respiratory illnesses. *J Pediatr*. 1980;97:185–190.
28. Garcia-Gonzalez JJ, Vega-Chicote JM, Rico P, et al. Prevalence of atopy in students from Malaga, Spain. *Ann Allergy Asthma Immunol*. 1998;80:237–244.
29. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Borksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics*. 1995;95:500–505.
30. Zweiman B, Schoenwetter WF, Pappano JE, Tempest B, Hildreth EA. Patterns of allergic respiratory disease in children with a past history of bronchiolitis. *J Allergy Clin Immunol*. 1971;48:283–289.
31. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren: relative importance of associated factors. *Clin Allergy*. 1987;17:283–290.

Requests for reprints should be addressed to:

Roberto Gómez, MD, PhD

Vía de la Hispanidad 31, bloque 1, esc 1, 1° A

Zaragoza 50012, España

E-mail: algc-colas@hcu-lblesa.es