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Original Article

Respiratory infection in congenital cardiac disease. Hospitalizations in young children in Spain during 2004 and 2005: the CIVIC Epidemiologic Study

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Abstract *Objectives:* To evaluate the rate of hospitalization for acute respiratory tract infection in children less than 24 months with haemodynamically significant congenital cardiac disease, and to describe associated risk factors, preventive measures, aetiology, and clinical course. *Materials and methods:* We followed 760 subjects from October 2004 through April 2005 in an epidemiological, multicentric, observational, follow-up, prospective study involving 53 Spanish hospitals. *Results:* Of our cohort, 79 patients (10.4%, 95% CI: 8.2%–12.6%) required a total of 105 admissions to hospital related to respiratory infections. The incidence rate was 21.4 new admissions per 1000 patients-months. Significant associated risk factors for hospitalization included, with odds ratios and 95% confidence intervals shown in parentheses: 22q11 deletion (8.2, 2.5–26.3), weight below the 10th centile (5.2, 1.6–17.4), previous respiratory disease (4.5, 2.3–8.6), incomplete immunoprophylaxis against respiratory syncytial virus (2.2, 1.2–3.9), trisomy 21 (2.1, 1.1–4.2), cardiopulmonary bypass (2.0, 1.1–3.4), and siblings aged less than 11 years old (1.7, 1.1–2.9). Bronchiolitis (51.4%), upper respiratory tract infections (25.7%), and pneumonia (20%) were the main diagnoses. An infectious agent was found in 37 cases (35.2%): respiratory syncytial virus in 25, *Streptococcus pneumoniae* in 5, and Haemophilus influenzae in 4. The odds ratio for hospitalization due to infection by the respiratory syncytial virus increases by 3.05 (95% CI: 2.14 to 4.35) in patients with incomplete prophylaxis. The median length of hospitalization was 7 days. In 18 patients (17.1%), the clinical course of respiratory infection was complicated and 2 died. *Conclusions:* Hospital admissions for respiratory infection in young children with haemodynamically significant congenital cardiac disease are mainly associated with non-cardiac conditions, which may be genetic, malnutrition, or respiratory, and to cardiopulmonary bypass. Respiratory syncytial virus was the most commonly identified infectious agent. Incomplete immunoprophylaxis against the virus increased the risk of hospitalization.

Keywords: Infant; congenitally malformed hearts; haemodynamically significant; respiratory syncytial virus; Trisomy 21

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Introduction

Respiratory tract infections, such as bronchiolitis or pneumonia, are the most common causes in developed countries of admission to hospital of infants and young children.[1,2] Infections by the respiratory syncytial virus have been particularly well studied,[3–6] and, in groups at risk, are known to be associated with increased morbidity and mortality.[7–10] In children with congenital malformed hearts, such infection increases the length of stay in hospital, admissions for intensive care, mortality,[11,12] and is associated with delays in elective cardiac surgery.[13,14]

Previous information about risk factors for these infections was generally attributed to the congenital cardiac disease itself. Other patients, particularly premature infants, have been studied in more detail, according to gestational age, social and family conditions. Patients with congenitally malformed hearts vary according to the effects of their lesion, producing cyanotic or acyanotic conditions, its haemodynamic significance, the need for surgical intervention or medications, while a subset of these children have other concomitant conditions, such as malnutrition, chromosomal, or genetic abnormalities that are associated with an increased susceptibility to infection of the respiratory tract.[15]

Over the past decade, strategies to decrease the impact of these infections were focussed on improving general management of the patient.[16,17] Specific prophylactic measures, such as vaccinations and immunoprophylaxis, are now available to prevent many of the common infections of the respiratory tract.[18] The cost of prophylaxis has limited its use, specifically prophylaxis against the respiratory syncytial virus with palivizumab. In a pivotal third phase trial, palivizumab reduced hospitalization by 45% in children aged less than 24 months with haemodynamically significant congenital cardiac disease.[19] As a result, guidelines for prophylaxis in North America,[20] and Europe,[21] including the United Kingdom,[22] and Spain,[23] have been established. All previous approaches, and recent controversies, about respiratory infection in young children with congenital cardiac disease were based on different methodological strategies, such as theoretical models, clinical trials, retrospective studies, hospital registries, and expert recommendations,[24] but thus far, to the best of our knowledge, there have been no specific, large, prospective, epidemiological studies. The primary objective of our study, therefore, was to assess the incidence of infection of the respiratory tract requiring hospitalization in children under 24 months of age with haemodynamically significant congenital cardiac disease in Spain, and to describe its associated risk factors. Secondary objectives were to assess compliance with preventive measures used in this population, and to describe the source and clinical course of the respiratory events.

Materials and methods

Ours was an epidemiological, multicentric, prospective, observational study in children with haemodynamically significant congenital cardiac disease. The population studies included all patients less than 24 months of age at the time of inclusion during the season from October 2004 to April 2005 who had been followed up for at least one month. The study was sponsored by the Spanish Society of Pediatric Cardiology and Congenital Heart Diseases, and was conducted at 53 Spanish hospitals. These included 16 tertiary public centres, where paediatric cardiac surgery was available, and 37 collaborative hospitals involved in follow-up of the patients (see Appendix 1 for details). The protocol was reviewed and approved by a local ethics committee (Hospital Vall d'Hebrón, Barcelona), and written informed consent was obtained from parents or guardians before enrollment.

Patients meeting the criterions of eligibility were enrolled either at the outpatient clinic or the hospital ward, depending on where the initial contact occurred. Recommendations for prophylaxis against the respiratory syncytial virus,[23] were followed for the participating children, who were regularly seen at the outpatient clinic once monthly. The main endpoint was the number of patients requiring hospitalization for acute respiratory infection at any time during the period if study. Acute respiratory infection was defined on the basis of the following grouped codes of the International Statistical Classification of Disease and Related Health Problems (ICD-10).[25] Acute upper respiratory infections (J00–J06) and influenza (J10–J11); Pneumonia (J12–J18); Brochiolitis (J20–J21); and other acute lower respiratory infections (J22). All episodes of infection requiring hospitalization occurring before the follow-up visit were recorded based on review of the medical records. Follow-up ended at the date of completion of the study, the date of death, or the date of the last visit before withdrawal of the patient.

Episodes of respiratory infection occurring during hospitalization for other reasons, such as after surgery because of nosocomial infections were excluded. Children with known infection by the human immunodeficiency virus, and current or past participation in other investigational protocols of drugs or biological agents, were not eligible.

Variables

Information collected included social and demographic data, such as gender, date of birth, gestational age, current weight, child care attendance, breastfeeding, number of children in the house under 11 years of age, and exposure to tobacco smoke, clinical data such as age at diagnosis of the cardiac disease, whether the lesion was classified as cyanotic or acyanotic using similar criterions as in previous studies,[19] surgical procedures and their risk,[26 [adapted in Spanish, 27]] or catheterization, concomitant comorbidities, including chromosomal diseases, chronic respiratory diseases, and immunodeficiencies, and information about general and specific immunoprophylaxis against influenza, pneumococcus, chickenpox vaccines and respiratory syncytial virus using palivizumab according to the recommendations of the Spanish Paediatric Association for childhood immunization,[23] provided by the parents or guardians at the time of entry and monthly thereafter when a change occurred. Information regarding hospital course and discharge were obtained by review of the medical records, and included length of stay in hospital, diagnosis at discharge, and severity, defined as death due to respiratory infection or the need for admission to an intensive care unit or mechanical ventilation or extracorporeal membrane oxygenation or occurrence of either pulmonary hypertensive crisis, pleural effusion, acute respiratory distress syndrome, or any other renal, neurological or gastrointestinal sequel. Microbiological data recorded included type of microorganism, such as bacteria, virus, or fungus, and the type of sampling and diagnostic tests used, such as spontaneous secretions, bronchial aspirate, or blood cultures, antigenemia, immunofluorescence, and serology, based on the standard practice at each hospital. Additional follow-up conditions were defined based on previously recorded data. These included borderline nutritional state when the weight was below the 10th centile (according to Spanish growth tables[28]) at any time during follow-up, new cardiac surgery or catheterization and its risk, complete vaccination, or complete immunoprophylaxis against the respiratory syncytial virus. A numeric definition is given in Appendix 2.

Analysis of data

Rate of hospitalization because of respiratory infection: Incidence was calculated by dividing the number of hospitalizations by the child-months of follow-up during the study period. Rates of hospitalization, with 95% confidence intervals, were calculated as the number of hospitalizations per 1000 patients with congenitally malformed hearts.

We used the Chi-square test or Student's t test to assess differences between patients requiring hospital admission for respiratory infection and those not hospitalized for categorical or continuous variables, respectively. A logistic regression was used to identify independent risk factors for admission to hospital because of respiratory infection. Any risk factor that was statistically significant, with a p value less than 0.05 in the bivariate analysis, was considered for entry into the multivariate model. A forward stepwise approach was used. Results are expressed as odds ratios with 95% confidence intervals.

Results

Population

Enrollment: From October 2004 to April 2005, we found 791 patients with congenitally malformed hearts who were eligible for the study. Of these, 31 patients with less than one month follow-up were withdrawn. Reasons for withdrawal included the decision of the guardian in 2 instances, the decision of the investigator in 2 further cases, was unknown in 17 patients, and was due to death in 10 patients. Hence, a total of 760 patients participated in the study with a period of follow-up longer than one month.

Most patients were enrolled in October and November, 2004, and the highest number of patients was recruited in February. Mean time of follow-up, with standard deviation shown in parentheses, was 5 (1.6) months, and mean number of visits per patient was 4.5 (1.5). A total of 453 (57.3%) patients completed at least 5 follow-up visits. No differences were found when baseline characteristics were compared between patients lost to follow-up and those who completed the study.

During the study, 25 patients died, with respiratory infection being the main cause of death in 2 patients (one of them with trisomy 21), while 14 children died after cardiac surgery. Death was attributed to 'other causes' in 9 additional cases. The overall rate of death per 1,000 patients was 9.4 (95% confidence intervals from 6.3 to 12.5), and rate of mortality due to respiratory infection was 0.8 (0.1 to 1.7).

Demographics, assessment of clinical and risk factors

Among the 760 patients recruited, 57.4% were male, and 77.5% were under 12 months of age, Their mean age, with standard deviation, was 7.3 [6.1] months. Only 6% of children had attended

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child care, 47% had been breastfed, 45.2% lived with another child under 11 years of age at home, and 48% had a smoker in the house. Cardiac disease was most often diagnosed at birth (69.7%), and acyanotic disease was most common (55.8%). Of enrolled children, 71% had some risk factor for respiratory infection, including weight below the 3rd centile (53.7%, 408 patients), chromosomal diseases (13.8%, 105 patients), respiratory conditions (10.7%, 81 patients), or immunodeficiencies (1.1%, 8 patients).

Rates of hospitalization

Figure 1 shows the monthly admission to hospital, and rates of participation during the study period. We found that 79% of patients (10.4%, 95% confidence intervals from 8.2% to 12.6%) required admission for respiratory infections. The incidence in the 3,731 child-months of follow-up was 21.4 hospital admissions per 1,000 patients-month (95% CI: 16.7–26.1) during the season. Consecutive admissions were recorded in 19 patients, with 2 and 3 admissions were reported in 12 and 7 patients, respectively, accounting for a total of 105 admissions. No statistically significant differences in social and demographic characteristics and risk factors were found in patients with consecutive admissions.

Figure 2 shows the hospitalization incidence rate by age group. Rates were higher among infants under 6 months of age, 26.7 per 1,000 infants-month (95% CI 19.1, 34.2) and less in older ages groups: 18.7 (95% CI 10.6, 26,8) and 14.5 (95% CI 6.6, 22.4) per 1,000 patients-month among 6 to 12 and 12 to 24 month children, although differences were not statistically significant.

Risk factors for hospitalization

Table 1 shows the characteristics at baseline and follow-up, stratified by hospitalization due to

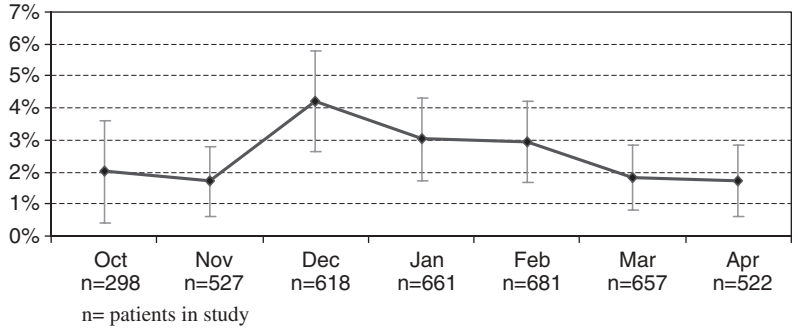

Figure 1.
Distribution of hospitalizations for acute respiratory infections by natural month for patients with congenitally malformed hearts aged less than 24 months in Spain from October 2004 to April 2005. n = *number of patients in study.*

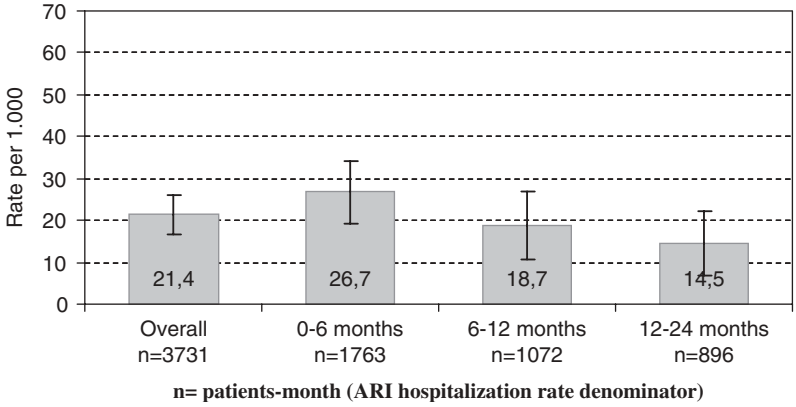

Figure 2.
Incidence of hospitalization for acute respiratory infections per 1000 patients-months per age group in patients with congenitally malformed hearts aged less than 24 months. n = *number patients-month (Acute respiratory infection hospitalization rate denominator).*

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Table 1. Baseline characteristics in children less than 24 months with haemodynamically significant congenital cardiac disease in Spain by state of hospitalization.

Characteristics	Hospitalization n = 79	No hospitalization n = 681	p
Baseline			
Gender: Males, number (%)	48 (60.8)	388 (57.0)	ns
Age in months, mean (Standard Deviation)	6.4 (5.9)	7.4 (6.2)	ns
Gestational time in weeks, mean (Standard Deviation)	37.6 (2.5)	38.1 (3.6)	ns
Weight under 3rd centile, n (%)	55 (69.6)	353 (51.9)	0.01
Child care, number (%)	4 (5.1)	42 (6.2)	ns
Breastfeeding, number (%)	37 (46.8)	365 (53.3)	ns
Brothers or sisters under 11 years old, number (%)	44 (55.7)	296 (43.9)	0.04
Exposure to tobacco smoke, number (%)	41 (51.9)	323 (47.4)	ns
Age at diagnosis of cardiac disease, number (%)			ns
Prenatal	12 (15.5)	120 (17.6)	
Neonatal	60 (75.9)	470 (69.0)	
Infants and children	7 (8.9)	91 (13.4)	
Type of cardiac disease, number (%)			ns
Cyanotic	36 (45.6)	287 (42.1)	
Acyanotic	43 (54.5)	381 (55.9)	
Other*	–	13 (1.9)	
Syndromes or chromosomal disorders, number (%)	21 (26.6)	84 (12.3)	0.01
Trisomy 21	14 (17.7)	59 (8.7)	
Deletion 22q11	5 (6.3)	10 (1.5)	
Other	2 (2.5)	15 (2.2)	
Respiratory pathologies, number (%)	19 (24.1)	62 (9.1)	0.01
Sibilance's	11 (13.8)	40 (5.8)	
Anatomic anomalies	5 (6.3)	11 (1.6)	
Other respiratory pathologies	6 (7.5)	21 (3.0)	
Immunodeficiency, number (%)	3 (3.8)	5 (0.7)	0.01
Follow-up			
Weight under 10th centile, number (%)	76 (96.2)	543 (79.7)	0.01
Cardiac intervention, number (%)	32 (40.5)	173 (25.4)	0.01
Cardiopulmonary Bypass, number (%)	26 (32.9)	123 (18.1)	0.01

*Cardiac transplantation, primary pulmonary arterial hypertension.

respiratory infection. In the bivariate analysis, the proportions of patients with weight below the 3rd centile at study baseline (69.6% versus 51.9%), siblings under 11 years (55.7% versus 43.9%), and risk factors for respiratory infection such as chromosomal diseases (26.6% versus 12.3%), respiratory disorders (24.1% versus 9.1%) and immunodeficiency (3.8% versus 0.7%) were significantly higher among patients requiring admission. Among follow-up variables, weight below the 10th centile, surgery or catheterization and/or surgery with cardiopulmonary bypass at any time during the study were significantly more common in hospitalized patients, 96.2% versus 79.7%, 40.5% versus 25.4% and 32.9% versus 18.1% respectively. No statistically significant differences were found for all other factors. We broke down congenital cardiac disease into cyanotic and acyanotic types, including 323 (42.5%) patients as cyanotic, and 424 (55.8%) as acyanotic, most of the latter with left-to-right shunt. We did not classify 13 (1.9%). Of the patients hospitalized, 36 (45.6%) were cyanotic as opposed to 43 (54.5%) who were acyanotic, this difference not being significant ($p = 0.658$). In the group of 19 patients that required multiple hospitalizations, 10 (52.6%) were cyanotic and 9 (47.4%) acyanotic. We found an augmentation in the proportion of associated conditions, that is risk factors, albeit without significant differences, in 6 (31.6%) having chromosomal or genetic disorder, 3 cases with deletion 22q11, 2 cases with trisomy 21, and 1 with another condition, in 6 (31.6%) with a chronic respiratory illness, and in 2 (10.5%) with immunodeficiency.

Main diagnosis

The median length of hospital admissions for respiratory infection was 7 days, with a mean of 9.7 and a range from 1 to 56 days. Hospital stay was shorter than 3 days in one-fifth of cases, but 18 admissions (17.1%) were defined as severe. The

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Table 2. Main cause of hospitalization for children aged less than 24 months with congenital cardiac disease according to severity.

Main cause of hospitalization	Severe RI* n = 18	Non severe RI n = 87	p
Upper respiratory infections (ICD-10 J00-11), n (%)	–	24 (27.6)	0.02
Pneumonia (ICD-10 J12-18), n (%)	7 (38.9)	13 (14.9)	
Bronchiolitis (ICD-10 J20-21), n (%)	10 (55.6)	42 (48.3)	
Other causes (ICD-10 J22), n (%)	1 (5.6)	8 (9.2)	

*Severe respiratory infection (RI), definition is in Materials and methods.

Table 3. Pathogens identified in 105 hospitalizations due to respiratory infection in children aged less than 24 months with congenitally malformed hearts.

Pathogens	Single	Multiple**	Total n = 105 (%)
Total	31	6**	37 (35.2)
Respiratory syncytial virus	21	4	25 (23.8)
Streptococcus pneumoniae	4	1	5 (4.8)
Haemophilus influenzae	1	3	4 (3.8)
Other*	5	4	9 (8.6)

*Other pathogens include staphylococcus (1), pseudomonas (1), other bacteria (4), and other viruses (3).
**The categories of multiple pathogen infection are not mutually exclusive.

main reason for hospital admission according to severity is shown in Table 2. Overall, bronchiolitis was the most common main diagnosis, accounting for 49.5% of hospitalizations. The proportions of admissions for bronchiolitis and pneumonia were significantly higher among those with severe illness, 55.6 versus 48.3, and 38.9% versus 14.9%, respectively. Infection of the upper respiratory tract was significantly higher among the hospitalizations for less severe disease (0 versus 27.6% – p 0.02).

Microbiology results are given in Table 3. Principal diagnostic tests were performed on spontaneous secretions (48.6%), bronchial aspirate (6.7%), or blood cultures (41.9%). Other specific antigen (32.4%), immunofluorescence (11.4%), and serological (9.5%) tests were used. Respiratory syncytial virus was investigated in 93% of patients using a rapid test (75%), direct fluorescent antigen test (10%), shell vial (8%), and culture (6%). A total of 37 pathogens were identified, with single infection being found in 31 patients and multiple infections in 6 patients. The most frequently identified pathogen was respiratory syncytial virus, in 25 patients (23.8%).

Table 4 shows the state of vaccination and immunoprophylaxis according to the need for hospitalization. Influenza, pneumococcus, and chickenpox vaccines had been received by 24.5% (54% adjusted in more than 6 months), 73.8%, and 5.4% of patients respectively. In addition, 85.1% of patients had received complete immunoprophylaxis for respiratory syncytial virus with palivizumab. A significantly higher rate of hospitalization for respiratory infection was seen among children with incomplete as opposed to complete immunization against the respiratory syncytial virus, 24.1% and 13.8%, respectively.

Patients with incomplete immunoprophylaxis accounted for 7.08% of hospitalizations proving to be due to respiratory syncytial virus, while the rate of hospitalizations was 2.32% among patients with complete immunoprophylaxis. This yields a 3.05 (95% CI: 2.14–4.35) relative risk of hospitalization in patients with incomplete immunoprophylaxis, and consequently a 67.2% reduction in the risk of hospitalization in those children with complete immunoprophylaxis. No statistically significant differences were found regarding the requirement of hospitalization and the state of vaccination against other pathogens.

Table 5 shows the independent risk factors associated with admission to hospital. Children with 22q11 deletion, weight below the 10th centile, previous respiratory disease, incomplete immunoprophylaxis, trisomy 21, cardiopulmonary bypass at any time during the study, and siblings less than 11 years old were more likely to require admission for respiratory infection, although estimates are not so precise.

Discussion

Our study has quantified the incidence of acute respiratory infection requiring admission to hospital of Spanish patients with congenitally malformed hearts at 10.4%, or a monthly incidence of 21.4 hospital admissions per 1,000 patients-months of follow-up. Such data are possibly influenced by the design of our study, which excluded infections in other hospitalizations, the high rate of respiratory syncytial virus immunization, which, as shown, is a protective factor both in our patients and in

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Table 4. State of vaccination and immunoprophylaxis children aged less than 24 months in Spain with congenitally malformed hearts.

	Hospitalization n = 79	No hospitalization n = 681	p
Adequate vaccination			
Influenza, number (%)*	11 (33.3)	154 (45.7)	Ns
Streptococcus Pneumoniae, number (%)	60 (75.9)	501 (73.6)	Ns
Varicella, number (%)	1 (1.3)	40 (5.9)	Ns
Complete** immunoprophylaxis			
Respiratory syncitial virus, number (%)	60 (75.9)	587 (86.2)	0.02

*Denominator for vaccination against influenza includes hospitalized and non hospitalized children below 6 months only, 33 and 337 respectively.
**Complete and incomplete respiratory syncitial virus immunoprophylaxis is defined in Appendix 2.

Table 5. Risk factors for hospitalization due to respiratory infection in children aged less than 24 months with congenital cardiac malformations.

	OR	95% CI	p
Deletion 22q11	8.13	2.51–26.31	0.03
Weight under 10th centile	5.24	1.57–17.43	0.01
Respiratory diseases	4.49	2.34–8.61	0.01
Incomplete immunoprophylaxis against respiratory syncytial virus	2.17	1.18–3.85	0.03
Trisomy 21	2.12	1.07–4.18	0.01
Cardiopulmonary bypass	1.97	1.13–3.41	0.02
Brothers less than 11 years	1.73	1.05–2.86	0.01

premature infants in our setting,[29] and the general measures for protection that were explained to all parents to prevent respiratory infections.

Seasonality, with a peak in the months of December–January, coincides with peaks of viral infections in the Northern hemisphere, specifically with infections by the respiratory syncytial virus in the southern regions of the United States in that same period.[30] A progressive decrement in incidence of hospitalization by age (Fig. 2) confirm previous data from infections due to bronchiolitis and respiratory syncytial virus,[4,8] with a maximum in patients less than 6 months, and a minimum in those older than 1 year. The fact that there is no significance in this difference probably is associated with the small number of children included in the range from 12 to 24 months.

Factors which increased susceptibility to respiratory infection and hospital admissions included 22q11 deletion, malnutrition, trisomy 21, and prior disease of the respiratory tract. Two-thirds of hospitalized patients were malnourished, being below the 3rd centile, while over nine-tenths showed a borderline nutritional state, being lower than the 10th centile at both baseline and follow-up. Malnutrition is multifactorial in children with congenitally malformed hearts.[31] The predisposition of malnourished patients to respiratory infection in general has been widely reported.[32] In cases of trisomy 21 or 22q11 deletion there are various degrees of immunosuppression or immune disorders, bronchial reactivity, abnormalities in cilia and the anatomy of the upper respiratory airways, neuromuscular disorders with hypotonicity, swallowing disorders, gastroesophageal reflux with potential microaspiration that may predispose to respiratory infection.[33,34] A study,[35] estimated a rate of hospitalization for bronchiolitis due to the respiratory syncytial virus of 153.8 per 1,000 patients in children aged less than 2 years with various risk factors, specifically trisomy 21 with and without congenital cardiac disease. This is a similar rate to that found in our study of 200 per 1,000. As in our study, one of the patients reported previously,[35] who died because of respiratory infection, had trisomy 21.

Among the general risk factors associated with severe infection by the respiratory syncytial virus reported in prior literature reviews,[36] or in premature infants in Spain,[37] only the presence of siblings less than 11 years are supported by our study. Age under 6 months, absence of breastfeeding, exposure to tobacco smoke, family history of asthma, or low educational level of parents were not found to be significant. The low number of patients in our study attending nurseries does not allow for their comparative analysis.

The only clear cardiological risk factor is surgery with cardiopulmonary bypass during the period of study, possibly because of impaired immunity to these infections, antibodies being avoided, or because it is associated with a longer stay in hospital that increases the risk of infection. No differences were seen between cyanotic and non-cyanotic patients.

Despite the high number of microbiological tests, no pathogen was found in two-thirds of our

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patients. As regards the type of specific pathogen, bronchiolitis and infections due to the respiratory syncytial virus were expected to predominate because of the type of our study, having excluded infections while the patient was admitted for other reasons or nosocomial infection, and the season. The second leading pathogen was Streptococcus pneumoniae, the main germ reported in community-acquired pneumonia.[38] Concurrent infections represented one-sixth of cases in which a pathogen was identified, and were particularly common for infection by Haemophilus influenzae, this accounting for three-quarters of cases. The low number of other viruses detected may possibly be due to the low number of specific tests for such viruses.

Compliance with schemes of vaccination or immunoprophylaxis against pathogens responsible for infections of the respiratory tract, such as influenza, pneumococcus, or haemophilus influenzae type b, and chickenpox vaccines, or immunoprophylaxis for respiratory syncytial virus, was usually high, except for vaccination against influenza, recommended for infants older than 6 months, which had a compliance of only just over one-half. There was, however, no admission with a microbiological diagnosis of influenza virus, which does not agree with other data reported patients at risk,[39,40] or as a cause of pneumonia.[38] By contrast, compliance with pneumococcal vaccination was very good, and both were administered free of charge by paediatricians at health centres on recommendation by the paediatric cardiologist. No significant differences were found between hospitalized and non-hospitalized children as regard these vaccinations.

Immunoprophylaxis with palivizumab is administered at hospital centres, and is theoretically recommended in all patients included in this study. Incomplete compliance with the recommendations 23 was found in only 113 patients (14.9%), suggesting a good compliance as compared to other reports.[41] An analysis of this subgroup with incomplete prophylaxis as compared to the group receiving complete prophylaxis confirmed a marked decrease in both the overall risk for admission for respiratory tract infection, and the specific risk for admission due to documented infection. The rate of admission for respiratory syncytial virus in the group of patients with incomplete immunoprophylaxis, at 7%, is somewhat lower than reported for the placebo group in the study of the Cardiac Synagys Group,[19] or for premature infants not given prophylaxis in Spain,[29] in which rates of 9.7% and 13.25% were found respectively, possibly due to administration of any dose could confer some degree of protection and due to methodological differences. Our study does not support other reports published in Switzerland,[42] and Sweden,[43] giving very low rates of hospitalization, ranging from 1.3% and 6.4%, in patients with congenital cardiac disease receiving no prophylaxis. Such divergence is due to methodological, rather than epidemiological, differences, because those studies were conducted in a single hospital center during the whole year, thus obviating seasonality, were based on retrospective review of hospital records, and did not use a clearly defined reference population. On the other hand, the rate of admission, at 2.32%, in the group with complete prophylaxis is lower than the rate of 5.3% seen in the group receiving palivizumab in the study performed by Feltes and colleagues,[19] and closer to data found in premature infants who received palivizumab in Spain,[29] and the United States,[44] in whom a rate of 3.95% was reported.

The mean stay of 9.5 days is similar to the 10.7 days reported elsewhere for patients infected by the respiratory syncytial virus.[45] In one-fifth of cases, hospital stay is short, and the condition was not serious. This suggests that such admissions are for the purposes of observation, and are caused by a special concern for these patients when they experience infections that, while they may be initially mild, could potentially become serious or impair the underlying cardiac condition. There were few admissions for more severe conditions. Just over one-sixth of patients were admitted to a paediatric intensive care unit, just over one-twentieth required mechanical ventilation, and mortality was low, at 0.8% overall, and 2.8% among admitted patients. Other series,[14] limited to infection by the respiratory syncytial virus reported one-third needing admission to intensive care, almost one-fifth needing mechanical ventilation, and mortality ranging from 2.5% to 3.4%, with mortality as high as one-third in historical series[11]. High protection against the virus may have possibly not only decreased the overall rate of admission, but also the severity and sequels. Readmissions occurred in one-quarter of patients, with no remarkable differences as regards risk factors.

Limitations

While the reference population is not exactly known, we think our study includes a wide sample representative of virtually all centers and potential patients aged less than 24 months with haemodynamically significant congenital cardiac disease in Spain. No information is available about eligible patients at screening not willing to participate in the study. In children withdrawn from the study, we did not find differences between patients in baseline variables, but the proportion lost to follow-up

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may therefore underestimate or overestimate the rate of hospitalization in children with congenital cardiac disease. There may be an information bias because details on the respiratory infection, microbiologic data, its cause, and its course were taken retrospectively from the discharge report and standard clinical practice. While the results are significant, some data include a low number of patients, and the ranges of risk estimators are very wide. Finally, the study is limited to a single season, and changes in the annual incidence and virulence of viral respiratory infections suggest the need for multiple years of study.

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Appendix 2: Numeric definition of immunoprophylaxis against respiratory syncytial virus with palivizumab

Complete:

- 5 or more doses
- Same number of doses as visits
- If a patient enrolled in November 2004 has received 4 or more doses
- If a patient enrolled in December 2004 has received 3 or more doses
- If a patient enrolled in January 2005 has received 2 or more doses
- If a patient enrolled in February 2005 has received 1 or more doses
- If a patient enrolled in March 2005 has received 0 or more doses

Non-complete:

- If the above criteria for complete immunoprophylaxis are not met.

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