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ORIGINAL ARTICLE

Incidence of Respiratory Disease During the First Two Years of Life in Children with Hemodynamically Significant Congenital Heart Disease in Italy: A Retrospective Study

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Abstract Children affected by hemodynamically significant congenital heart disease (HSCHD) experience severe respiratory complications that can increase the frequency of hospitalizations. The aim of the SINERGY study was to describe the incidence of respiratory diseases and to collect information on active and passive immunoprophylaxis in the first 2 years of life. In this retrospective, multicenter, and epidemiologic study, children with HSCHD were enrolled across 11 Italian sites. Children born between December 31, 2007, and December 31, 2012, were observed during their first 2 years of life. Data were collected through hospital database searches and parent interviews. Four hundred twenty children were enrolled: 51.7 % were female, 79.5 % were born full-term (≥37 weeks), and 77.6 % weighed >2500 g at birth. The most frequent heart defects were ventricular septal defect (23.1 %) and coarctation of the aorta (14.3 %). The incidence of respiratory diseases was 63.1 %. Frequent respiratory diseases not requiring hospitalization were upper respiratory tract infections (76.4 %), acute bronchitis (43.3 %), and influenza (22.1 %), while those requiring hospitalization were bronchitis and bronchiolitis (8.3 % each one). While active immunoprophylaxis was applied with wide compliance (diphtheria/pertussis/tetanus, 99.5 %; *Haemophilus influenzae* type b, 72.5 %; pneumococcus, 79.9 %; meningococcus, 77.4 %), only 54 % of children received respiratory syncytial virus (RSV) passive prophylaxis (palivizumab). Of the 35 hospitalizations due to bronchiolitis, 27 (77.1 %) did not receive prophylaxis against RSV, compared with 8 (22.9 %) who received prophylaxis ($P < 0.0001$). Children with HSCHD are at major risk of respiratory diseases. Passive immunoprophylaxis can help to prevent hospitalizations for bronchiolitis.

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Introduction

Congenital heart diseases (CHDs) are a group of anatomical heart malformations caused by incomplete or improper growth of the heart during fetal development [1]. The prevalence of CHDs in Western countries is approximately 1% [2–6]. Respiratory complications are frequent in children presenting with congenital heart abnormalities [7, 8]; these patients are also at greater risk of viral or bacterial pulmonary infections and have a greater incidence of asthma in adulthood [9]. Furthermore, the disease burden from acute respiratory infections (ARIs) is greater than that of any other disease [10], resulting in a high frequency of hospitalizations and specialist consultations [11–14].

Numerous etiologic agents may be involved, which can cause reinfection during the same winter season: *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia trachomatis* are the most common bacteria responsible for ARI [15–17]. However, viruses, in particular, rhinovirus, influenza virus, and the respiratory syncytial virus [RSV], are the most frequent cause of ARIs [18].

RSV bronchiolitis is a major cause of hospitalizations for infants and children younger than 2 years of age [19]. Children with CHDs face a greater risk of severe RSV infections; these children have a two- to sixfold increased risk of mortality compared with children without any further risk factors [20–22].

Several European and American epidemiologic studies have subsequently been undertaken to evaluate the "real-world" impact of RSV comorbidity and mortality [23–30]; however, the emphasis has mainly been on preterm infants without HSCHD.

Due to geographical differences in the incidence of respiratory infections, to the variations in both active and passive prophylaxis compliance and to disparities in patient baseline characteristics, extending findings from different countries is difficult and limited. Moreover, in Italy, little information is available on comorbidities and risk factors associated with ARIs in children with HSCHD.

Therefore, the aim of the SINERGY study was to evaluate the incidence of the most frequently occurring respiratory disease and to collect and describe information on specialist medical visits, hospital admissions, emergency department admissions, admissions to the intensive care unit (ICU; with or without oxygen support), and pharmacologic respiratory therapies during the first 2 years of life in children ≥2 years of age presenting with HSCHD.

Methods

Study Population

SINERGY was a retrospective study performed in Italy to examine the incidence of respiratory diseases during the first 2 years of life in children with HSCHD defined according to the Italian Society for Pediatric Cardiology (Società Italiana di Cardiologia Pediatrica; SICP) [31].

According to SICP recommendations, a cardiopathy can be defined hemodynamically significant if there is one or more of these conditions: significant pulmonary hyperflow cardiomegaly and/or polypnea and/or Rx with pulmonary congestion and/or poor growth and/or treatment (except anti-platelet, antiarrhythmic, heparin, and/or recurrent infections of the lower respiratory tract); preoperative surgical or post palliative cyanotic heart disease; primary or secondary pulmonary hypertension (>50 % of systemic pressure); pulmonary venous congestion; dilated cardiomyopathy in medical therapy anticongestive; postsurgical or interventional procedures; heart diseases until the suspension of anticongestive medical therapy; and status of post-heart transplant [31]. Ethics committee approval from all participating centers and written informed consent for the handling of personal data were obtained from the parent for every child in the study in accordance with Italian law (DL 196/2003). This study complies with the ethical standards laid down in the 1975 Declaration of Helsinki. In cases where children's clinical charts did not contain the necessary data to capture clinical history for the first 2 years, the child's parents were asked to provide these data. Inclusion criteria were to be a child (male and female) with HSCHD aged 2 years or older and born between December 31, 2007, and December 31, 2012 (for whom data for the retrospective analysis covering the child's first 2 years of life were available) and presence of informed consent. Exclusion criteria were HIV+ and presence of neoplasia.

Study Design and Objectives

This retrospective study was conducted at 11 Italian pediatric centers selected on the basis of the following criteria: (1) regional reference pediatric outpatient clinics or wards that follow children diagnosed with HSCHD for at least the first 2 years of life; (2) the availability of an Internet connection; and (3) the availability of a hard copy or electronic clinical charts or a database at each site that contains data concerning the child from the age of 0–2 years; if data were missing, the child's parents were asked to provide them. Furthermore, these 11 national reference centers were selected as they have a large reserve

of patients, and patient distribution (range of pathologies) in these centers is representative of the Italian peninsula.

The primary objective of this study was to describe the number and type of respiratory diseases during the first 2 years of life in children ≥2 years of age presenting with HSCHD by reviewing all hospitalizations (ward or emergency department or ICU) and specialist outpatient visits (without the need for hospital admission). The secondary objective was to describe the therapeutic, active, or passive immunoprophylactic interventions performed for respiratory diseases in clinical practice in children with HSCHD being treated at pediatric cardiology wards.

Statistical Analysis

Assuming that there are 4000 Italian newborns with CHD per year [32], a sample of 400 patients allows for the estimation of a confidence interval of 95 % for the frequency of the outcomes expected from the study in the most restrictive condition (50 %) with ±4.65 % precision. Analysis of the data was mainly descriptive. The results are presented as mean, standard deviation (SD), median, quartiles (for quantitative variables), and frequency (for qualitative variables). Where applicable, a χ^2 test was used and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SAS version 8.2 for Windows (Cary, NC) and STATA version 8.0 (College Station, TX) software.

Results

Patient Characteristics

The clinical characteristics of patients who participated in this study are presented in Table 1. Four hundred and twenty children were enrolled; 51.7 % of the patients were female and 77.6 % were >2500 g at birth. Most births (79.5 %) were full-term (≥37 weeks); only 2.9 % of the patients ($n = 12$) were born <32 weeks. The median gestational age was 38 weeks. Patients were distributed equally across Italy (33.6 % in Northern Italy, 32.6 % in Central Italy, and 33.1 % in Southern Italy).

Table 1 Patient clinical and demographic characteristics

Characteristics	$N = 420$ (%)
Female sex	217 (51.7)
Birth weight g[a]	2907 ± 641.5
<1000	2 (0.5)
1000–1500	14 (3.3)
1500–2500	78 (18.6)
>2500	326 (77.6)
Twin siblings in same delivery	28 (6.7)
Gestational age (wks)[a]	37.9 ± 2.4
<37	86 (20.5)
≥37	334 (79.5)
Geographical distribution	
North	141 (33.6)
Central	137 (32.6)
South	139 (33.1)
Outside Italy	3 (0.7)
Most common cardiopathies[b]	
Ventricular septum defect	97 (23.1)
Coarctation of the aorta	60 (14.3)
Atrial-ventricular canal	59 (14.1)
Atrial septal defect	55 (13.1)
Transposition of great arteries	42 (10.0)
Surgery	
Palliative	54 (12.9)
Corrective	192 (45.7)
Catheterization	31 (7.4)
No correction	76 (18.1)

[a] Mean ± SD

[b] See Fig. 1 for other cardiopathies

Characteristics of CHD

The majority of patients (77.4 %; $n = 325$) had 1 cardiopathy, 17.1 % of patients ($n = 72$) presented with 2 cardiopathies, and approximately 5 % of patients ($n = 23$) presented with 3 or more cardiopathies. Only 14.3 % of patients ($n = 60$) had genetic/chromosomal defects, and 20 different cardiopathies were diagnosed among the entire study population. The majority of patients presented with ventricular septal defects (23.1 %), alone or in combination with other cardiopathies (Fig. 1). Approximately 14 % of patients presented with defects, atrioventricular canal defects, and coarctation of the aorta (13.1, 14.1, and 14.3 %, respectively). In 5.7 and 3.8 % of patients, atrial septal defects and atrioventricular canal defects were found in combination with other cardiopathies; coarctation of the aorta was more often associated with other cardiopathies (9.3 %). All atrial septal defects not associated with other cardiopathies ($n = 31$) were confirmed by investigators to be hemodynamically significant according to the SICP recommendations for RSV prophylaxis [31].

Surgical Interventions for CHD

In their first 2 years of life, 81.9 % of patients ($n = 344$) had a surgical intervention. The majority of patients had complete corrective surgery (45.7 %; $n = 192$), whereas 12.9 % of patients ($n = 54$) had palliative correction and

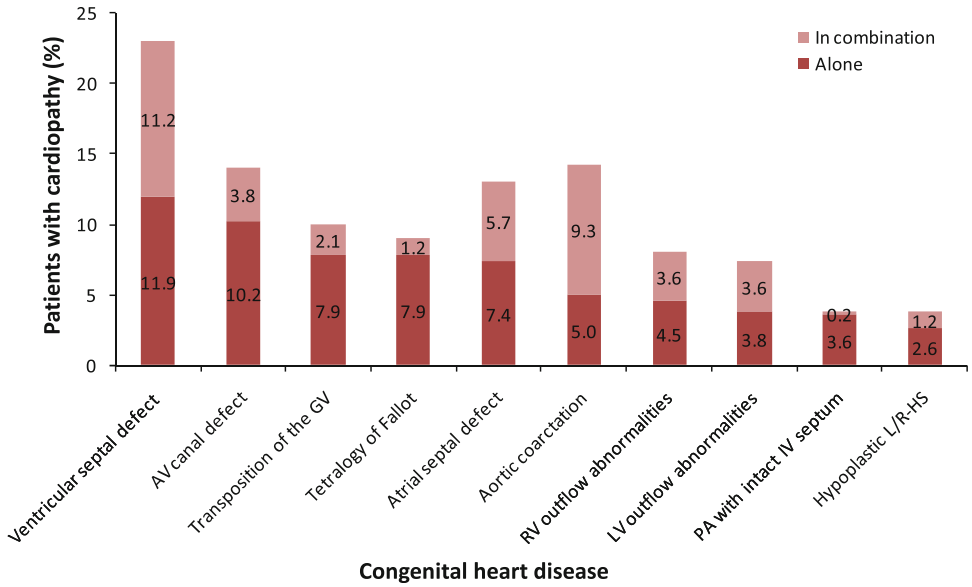

Fig. 1 Congenital heart diseases occurring alone or in combination. *AV* Atrioventricular, *GV* great vessel; *IV* ventricular septal defects, *L/R-HS* left/right heart syndrome, *LV* left ventricle, *PA* pulmonary atresia, *RV* right ventricle

Table 2 Risk factors for respiratory disease

Risk factor	($N = 420$) *N* (%)
Discharged after birth during the winter season	225 (53.6)
Presence of older siblings in family	185 (44.0)
Absence of breastfeeding	173 (41.2)
Familial predisposition to atopy	161 (38.3)
Attended nursery/preschool	136 (32.4)
Exposed to passive smoking	97 (23.1)
Birth weight ≤2500 g	94 (22.4)
Exposed to high levels of air pollution	42 (10.0)
Born as a part of a multiple birth	28 (6.7)
Prematurity (<32 weeks)	12 (2.9)

7.4 % of patients ($n = 31$) underwent cardiac catheterization; remaining patients had different combinations of surgery (i.e., complete and palliative). The median number of days since birth until first surgical intervention was 49 days: 13 days for palliative surgery, 92 days for complete corrective surgery, and 23 days for cardiac catheterization. Thirty-eight cases (11 %) of respiratory complications were recorded after surgery, including 20 cases of pneumonia (bacterial, $n = 9$; unspecified, $n = 11$) and 2 cases of bronchiolitis (1 patient had a positive test for RSV).

Of the 38 cases of respiratory complications (occurring in 37 patients), 24 patients required treatment in the ICU. All patients were treated with antibiotics in addition to corticosteroids ($n = 2$) and antiasthmatics ($n = 1$). RSV passive prophylaxis was provided following surgery in 20.6 % of the 495 surgical interventions. The proportion of RSV prophylaxis doses was similar in palliative correction and complete correction surgeries (25 and 21.2 %, respectively), whereas it was reduced in cases of cardiac catheterization (10.9 %). Variation in the proportion of patients receiving RSV prophylaxis was observed among various subtypes of CHD. Although the percentage of patients receiving prophylaxis ranged from 30.9 % in patients with atrial septal defect to 87.5 % prophylaxis in patients with hypoplastic left/right heart syndrome, the majority of subtypes received prophylaxis ranging from 60 to 87 % (Electronic Supplementary Material; ESM Table 1).

Respiratory Disease Risk Factors

Ten different risk factors for respiratory diseases (19–22) were examined (Table 2). Of the risk factors examined, 26.9 % of patients had 2 risk factors ($n = 113$), 24.3 % ($n = 102$) had 3 risk factors, and 32.9 % ($n = 138$) had ≥4 risk factors. The most frequent risk factors reported were hospital discharge after birth during the winter period (53.6 %; $n = 225$), presence of older siblings in the family (44 %; $n = 185$), children that were not breastfed (41.2 %; $n = 173$), and familial predisposition for atopy (38.3 %; $n = 161$). Supplemental data showing sub-analysis of the frequency and type of risk factors occurring among different types of respiratory diseases are presented in ESM Table 2 and ESM Table 3. Most frequently diagnosed respiratory diseases were acute bronchitis, acute rhinopharyngitis, and influenza occurring in 125, 66, and 66 patients, respectively) (ESM Table 2). Patients had on average 2–3 risk factors among the different respiratory diseases, as low as 1 risk factor for patients diagnosed with chronic adenoiditis, croup, or viral pneumonia to a maximum of 5 risk factors in patients diagnosed with

pneumonia (RSV) or acute sinusitis (ESM Table 2). Examining individual risk factors revealed a similar distribution in the frequency of different risk factors with higher frequencies observed for acute rhinopharyngitis, acute bronchitis, bronchiolitis, and influenza (ESM Table 3).

Vaccinations and RSV Prophylaxis

Active immunoprophylaxis was applied with wide compliance: 99.5 % ($n = 401/420$) of patients received the diphtheria/tetanus/pertussis (DTP) vaccine, 72.5 % ($n = 292/420$) received the *Haemophilus influenzae* type b vaccine, 79.9 % ($n = 322/420$) received the pneumococcus vaccine, and 77.4 % ($n = 312/420$) received the meningococcus vaccine. RSV passive prophylaxis was provided to 54.5 % of patients ($n = 229$); the median number of doses given was 9. Twenty-four percent ($n = 55$) of patients received between 6 and 9 doses, 14.4 % ($n = 33$) received 10 doses, and 30.6 % ($n = 70$) received >10 doses of palivizumab over 2 years of observation.

Outpatient Specialist Visits

Approximately half of the patients went to a specialist and received a diagnosis of respiratory disease (56.4 %; $n = 237$); 90.9 % of visits were with their family pediatrician, followed by a pneumologist (4 %). The most frequent respiratory diseases leading to specialist visits were upper respiratory tract infections (321; 76.4 %), followed by lower respiratory tract infections (218; 51.9 %). Few specialist visits were due to bronchiolitis (13; 3.1 %; Fig. 2a).

Hospitalizations

A total of 110 patients (26.2 %) underwent hospitalization in the first 2 years of life for respiratory diseases, for a total

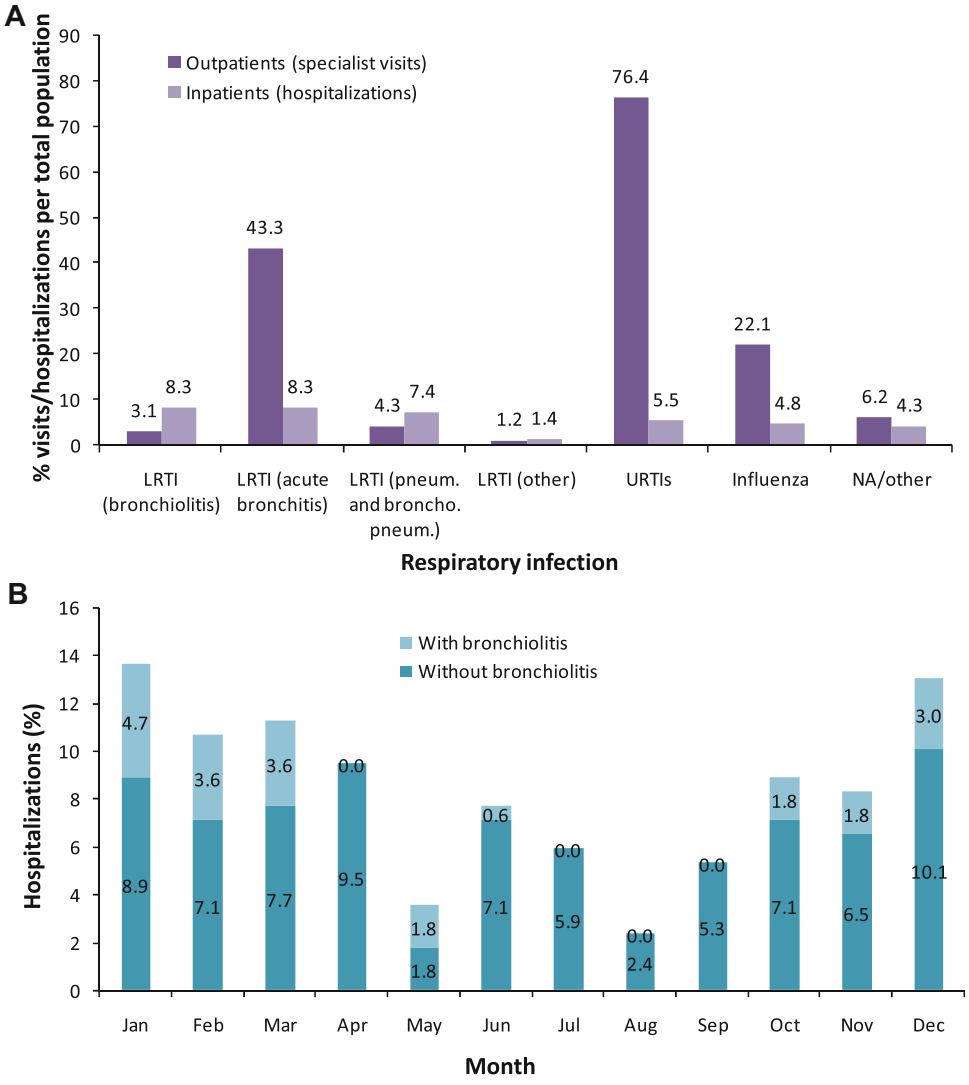

Fig. 2 Outpatient specialist visits and hospitalization frequency. **a** Proportion of specialist visits or hospitalizations associated with different types of respiratory infections. **b** Seasonal variation in hospitalization frequency in patients with and without bronchiolitis. *LRTI* Lower respiratory tract infection; *pneum and bronchopneum*, pneumonia and bronchopneumonia, *URTI* upper respiratory tract infection, *NA* not available

of 169 hospital admissions; 89/110 patients (52.7 %) were treated in the emergency unit and were then transferred to the relevant ward. The majority of cases were treated in a pediatric unit ($n = 85$; 50.3%). The median length of hospital stay was 7 days, and the median age of the patients hospitalized was <1 year old (335 days).

In contrast to respiratory infections associated with specialist visits, the most frequent respiratory diseases associated with hospitalizations were lower respiratory tract infections (107; 25.5 %), in particular bronchiolitis and acute bronchitis. Bronchiolitis (RSV or not RSV-related) and acute bronchitis occurred in 8.3 % of diagnoses (Fig. 2a). The majority of hospitalizations occurred between October and March, with approximately one-third of these patients receiving a diagnosis of bronchiolitis (Fig. 2b). The etiology of hospitalized respiratory infections was confirmed by appropriate tests in only 5.5 % of patients ($n = 23$).

In the SINERGY study, of the 35 hospitalizations for RSV bronchiolitis (8.3 %), 8 hospitalizations occurred in children who received prophylaxis with palivizumab (1.9 %) compared with 27 hospitalizations that occurred in children who did not receive prophylaxis or who did not receive prophylaxis correctly (6.4 %; $P < 0.0001$).

The frequency of hospitalizations was also stratified for birth weight, gestational age, and genetic/chromosomal defects. Although the average number of hospitalizations was similar for birth weight (underweight, 1.56; normal birth weight, 1.53) and gestational age (<37 weeks, 1.52; ≥37 weeks, 1.54), the proportion of patients with 2 hospitalizations in both stratified subsets was markedly different (Fig. 3a, b). No difference was observed in the frequency of hospitalizations for patients with or without genetic/chromosomal defects (data not shown).

Of the 35 hospitalizations for bronchiolitis, 8 (22.9 %) occurred in 7 children who received prophylaxis with palivizumab compared with 27 hospitalizations (77.1 %) in children who did not receive prophylaxis with palivizumab or did not receive correct prophylaxis (with the correct number of doses) ($P < 0.0001$; Fig. 3c). Six of the 7 children that received prophylaxis with palivizumab and were hospitalized had additional risk factors (3 were born at <37 weeks, 4 were underweight, 2 had chromosomal defects, and 3 had >1 cardiopathy). Furthermore, the

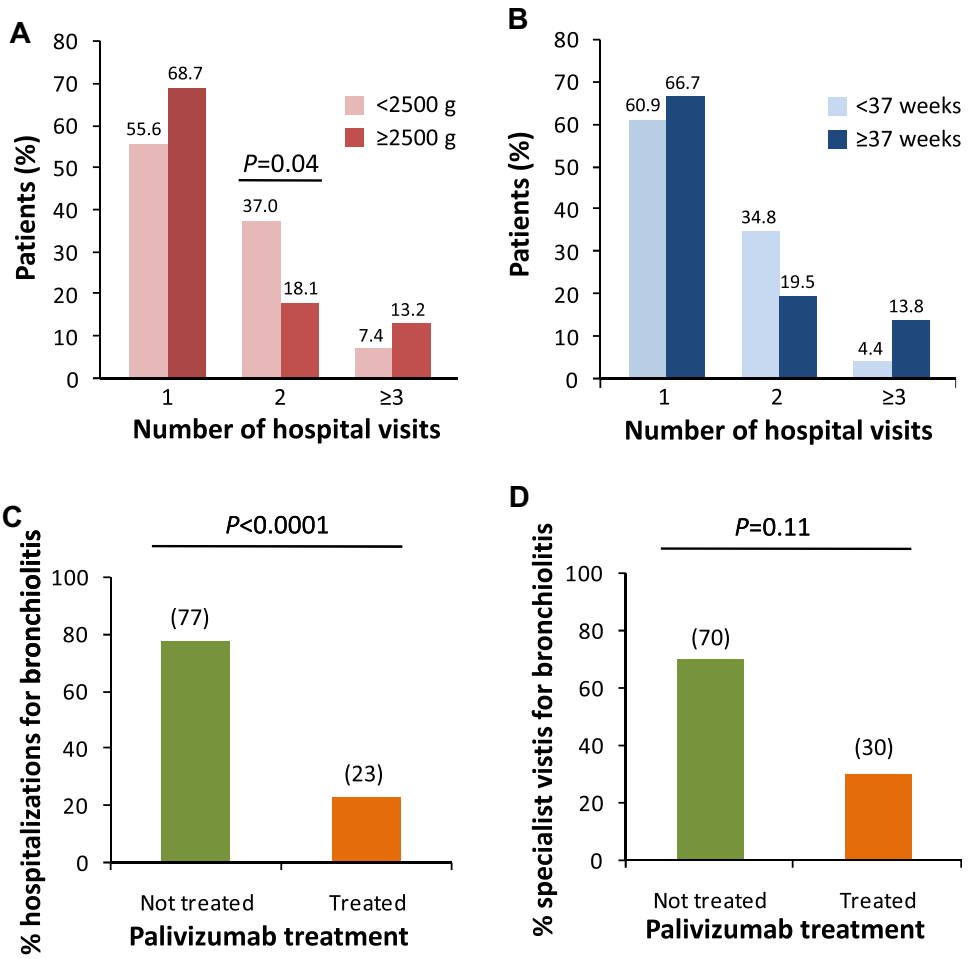

Fig. 3 Number of hospitalizations stratified for birth weight and gestational age and visits in patients receiving palivizumab prophylaxis diagnosed with bronchiolitis. **a** Number of hospitalizations in patients weighing < 2500 and ≥ 2500 g. **b** Number of hospitalizations in children born at < 37 and ≥ 37 weeks. **c** Number of hospitalizations in patients treated with palivizumab compared with those who were not treated. **d** Number of specialist visits in patients treated with palivizumab compared with those who were not treated

majority of outpatient specialist visits were in children diagnosed with bronchiolitis (70 %; $n = 7$) who did not receive prophylaxis for the prevention of RSV compared with those who did receive prophylaxis (30 %, $n = 3$; Fig. 3d).

Discussion

This retrospective multicenter study, conducted across 11 geographical sites, provides important insights on the incidence of respiratory disease in 420 patients with HSCHD in the first 2 years of life in a real-world setting in Italy.

The main finding from this retrospective study is that children with HSCHD are at major risk for hospitalization due to respiratory diseases, in particular, acute bronchitis and bronchiolitis (RSV and not RSV-related). A prospective observational study performed in Argentina examining hospitalizations due to RSV infection in patients younger than 2 years with HSCHD reported a similar proportion of hospitalized patients due to ARIs (31 vs. 26.2 % in SINERGY).

Compromised cardiorespiratory status at baseline, altered pulmonary mechanics, potential cyanosis, pulmonary hypertension, and ventilation–perfusion mismatch could exacerbate the effects of respiratory diseases [21]. Furthermore, patients with these conditions are at increased risk of RSV lower respiratory tract infection, making RSV prevention in patients with HSCHD an important goal [30]. In fact, children affected by HSCHD have a higher risk of acquiring ARIs before surgery, with or without pulmonary hypertension, due to hemodynamic compromise [30].

According to the "National Plan on Vaccination 2012–2014," released by Italian Health Ministry, it is necessary to reduce or eradicate infectious diseases through the identification of effective vaccination strategies throughout the country [33]. The objective of the national plan is to reach and maintain ≥95 % treatment coverage of different infectious diseases such as DTP, Hib, pneumococcus, and meningococcus. According to our results, there were varying levels of compliance with active immunoprophylaxis (DTP, 98 %; Hib, 72.5 %; pneumococcus, 80 %; meningococcus, 77 %); rates for DTP were likely higher because only the DTP vaccine is mandatory in Italy, whereas other vaccines are provided at the parents' discretion [33].

During the SINERGY study, the number of vaccines, palivizumab doses, and the number of hospitalizations were recorded. According to Italian guidelines, prophylaxis for RSV infections is recommended in children <2 years of age with HSCHD [31, 34]. Approximately half of patients with HSCHD received passive immunoprophylaxis with palivizumab, with some variation observed among CHD subtypes. Interestingly, although 54 % of patients with HSCHD received passive immunoprophylaxis with palivizumab (which is in line with other studies in this setting) [35], there was considerable variability in the number of administrations provided over the RSV season.

The median number of doses of palivizumab for the entire study population was 9, and about 44 % of patients received 10 or more doses. It is necessary to consider potential heterogeneity due to the severity of baseline cardiopathy, surgical outcome (palliative or complete correction), the birth month (at the beginning or at the end of the epidemic season), and economic issues.

We have divided patients who received prophylaxis into 2 groups: Correctly prophylaxed patients were those who received palivizumab with no gaps (>35 days) between doses in the epidemic season, before the complete correction of the cardiopathy; patients who did not receive correct prophylaxis were those who did not receive palivizumab or received palivizumab with gaps (>35 days) between doses in the epidemic season before the complete correction of cardiopathy.

In the SINERGY study, of the 35 hospitalizations for RSV bronchiolitis (8.3 %), 8 occurred in children who received prophylaxis with palivizumab (1.9 %) compared with 27 that occurred in children who did not receive prophylaxis or who did not receive prophylaxis correctly (6.4 %; $P < 0.0001$). This result is in agreement with a retrospective study performed in Turkey to investigate the effect of palivizumab ($n = 91$) versus no treatment ($n = 96$) among infants with HSCHD in the first 2 years of life [36]. Findings from this study demonstrated that in patients without prophylaxis, the rate of overall lower respiratory tract infections ($P < 0.001$), complicated lower respiratory tract infections ($P = 0.006$), lower respiratory tract infection-related hospitalizations ($P < 0.001$), and ICU admissions ($P = 0.008$) were significantly higher than in patients who received prophylaxis [36]. Furthermore, a recent meta-analysis examining RSV-related hospitalization rates from 5 randomized placebo-controlled trials yielded an overall odds ratio of 0.41 (95 % confidence interval, 0.31–0.55; $P < 0.00001$) in favor of treatment with palivizumab [37].

In contrast, there is also evidence indicating that omitting or delaying palivizumab prophylaxis is linked to increased rates of rehospitalization [24–26], thus highlighting the importance of adherence to a strict prophylactic program [25, 27]. However, no information is available from studies examining physician compliance with national guidelines for prophylaxis of RSV infection, which could also affect the risk of hospitalization. Similar to our findings, in an Australian study of 117 infants with symptomatic cardiac disease who received palivizumab,

only 2 patients (1.7 %) required hospital admission for RSV bronchiolitis [29].

It is worth noting that while bronchiolitis and acute bronchitis were found to be the most frequent reasons for hospital admission (8.3 % for both ARIs), the most frequently diagnosed ARIs following a specialist visit were URTIs and acute bronchitis (76.4 and 43.3 %, respectively). Bronchiolitis was only diagnosed in 3.1 % of patients following an outpatient specialist visit. Unexpectedly, when patients were stratified for birth weight, gestational age, and the presence of genetic/chromosomal defects, the mean frequency of outpatient specialist visits for infants at risk (premature, underweight, or presence of genetic/chromosomal defects) was always lower compared with patients without these risk factors. This may be explained by the fact that many of these patients would have been admitted directly to the hospital instead of visiting their family pediatrician. In Italy, little information has been available from previous studies on ARI or RSV-related infections in infants with HSCHD [22, 23]. Findings from SINERGY corroborate other international studies and provide important clinical information in this setting in Italy.

Study Limitations

Although findings from the SINERGY study provide important clinical information on the real-world therapeutic management of high-risk pediatric patients, some weaknesses need to be addressed. First, when data were not available from individual patient medical records, physicians collected information through interviews with the parents of the children; this may have resulted in missing information (i.e., hospitalization or type of respiratory disease). Second, only a small proportion of children received specific testing for the identification of respiratory infections, therefore leading to the potential underestimation of the incidence of some infections.

Regardless of these limitations, several strengths of the study are worth highlighting. This is the first study to provide extensive clinical information on the real-world therapeutic management of patients with HSCHD during the first 2 years of life, yielding fundamental insights on risk factors for ARI infection, surgical intervention, and hospital admissions in these high-risk patients. Encompassing 11 different centers across Italy, findings from this retrospective study can be considered to be representative of the Italian peninsula, not limited to a specific region.

Conclusion

In summary, findings from this retrospective multicenter study provide important clinical insights on ARIs in patients with HSCHD in Italy. Although this study was limited by the rather small sample size, the majority of patients were hospitalized for bronchitis or bronchiolitis; notably, the number of patients admitted to the hospital for bronchiolitis was twofold less in patients who received palivizumab prophylaxis compared with those who did not receive palivizumab prophylaxis.

A detailed identification of risk factors associated with ARIs, together with real-world data on specialist visits, hospital admissions, and diagnoses, could facilitate the prevention of respiratory complications in pediatric patients with HSCHD by specialists and pediatricians.

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Author contributions ULP and AMC participated in the design of the study and interpretation of data. AP and GG participated in interpretation of data and writing of the manuscript. GP, MB, AR, GA, MPC, MP, RT, PS, PF, MGR, and OM were involved in the acquisition of data from the different clinical centers. All authors were involved in drafting the manuscript and read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest AbbVie was responsible for the design, conduct, analysis, and funding of the study. AbbVie participated in the interpretation of data, writing, review, and approval of this publication. Umberto di Luzio Paparatti, Anna Maria Costanzo, and Giuliana Gualberti are employees of AbbVie and may own AbbVie stock options. Alessandro Possidoni was an employee of AbbVie. Giacomo Pongiglione and Ornella Milanesi are consultants for Abbvie. Marco Bonvicini, Maria Pia Calabrò, Alessandro Rimini, Patrizia Salice, Maria Giovanna Russo, Marco Pozzi, Roberto Tumbarello, Patrizio Fiorini, and Gabriella Agnoletti declared no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants, or their parents/legal guardians, included in the study.

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