Does Ribavirin Impact on the Hospital Course of Children With Respiratory Syncytial Virus (RSV) Infection? An Analysis Using the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV Database

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ABSTRACT. *Objectives.* **To determine the relationship between receipt of aerosolized ribavirin and the hospital course of high-risk infants and children with respiratory syncytial virus (RSV) lower respiratory infection (LRI).**

Methods. **The 1993–1994 Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV database consists of prospectively enrolled children with acute RSV LRI, admitted to nine Canadian pediatric tertiary care centers. After excluding cases with compromised immunity and/or nosocomial infection, subsets with any congenital heart disease (CHD), chronic lung disease (CLD), age 6 weeks (INFANT), gestation 36 weeks (PREM), or severe disease within 48 hours of admission as shown by an oxygen saturation 90% or an FiO_2 requirement of >.35 (EARLY HYPOXIA) were studied in two ways. First, each risk group subset was analyzed separately to assess the association between ribavirin receipt and measures of disease severity including duration of intensive care, mechanical ventilation, hypoxia and RSV-attributable hospital stay. Secondly, ribavirin was added as an independent variable to a previously described multiple regression model for RSV-attributable length of hospital stay and two mutually exclusive subsets were analyzed: 1) previously healthy patients with 1 of: INFANT, PREM, or EARLY HYPOXIA; 2) patients with CHD and/or CLD.**

Results. **Between January 1993 and June 1994, 1425 community-acquired hospitalized cases of RSV LRI were entered into the RSV database. Among these 750 (52.6%) fit into one or more of the defined subsets including 97 CHD, 134 CLD, 213 INFANT, 211 PREM, and 463 EARLY HYPOXIA. The proportion ventilated in each group was 20.6%, 20.9%, 15.5%, 15.2%, and 13.3%, respectively. Across the subsets ribavirin use ranged from 36% to 57% of ventilated patients and 6% to 39% of nonventilated patients. For nonventilated patients in each subset the median RSV-attributable hospital length of stay (RSV-LOS) was 2 to 3 days longer for ribavirin recipients and the duration of hypoxia was significantly increased. Duration of intensive care unit (ICU) stay was also increased for all ribavirin-treated subgroups except those with CHD. In contrast, for ventilated patients, ribavirin therapy was not significantly associated with any of the outcome measures regardless of risk group. In the multiple regression model, ribavirin was significantly associated with a prolonged RSV-LOS both for children with CHD and/or CLD as well as for those whose only risk factors included INFANT, PREM, and/or EARLY HYPOXIA.**

Conclusions. **These data raise further doubts about the clinical effectiveness of ribavirin in infants and children with risk factors for severe disease. Selection bias, with ribavirin used for sicker children, may have influenced outcome. Nevertheless the long durations of hospitalization, ICU, ventilation, and oxygen supplementation in nonventilated ribavirin recipients stress the need for further randomized trials to assess its efficacy.** *Pediatrics* **1997;99(3). URL: http://www.pediatrics.org/cgi/content/full/99/3/e7; *ribavirin, respiratory syncytial virus, pneumonia, bronchiolitis.***

ABBREVIATIONS. RSV, respiratory syncytial virus; LRI, lower respiratory infection; ICU, intensive care unit; CHD, congenital heart disease; CLD, chronic lung disease; PREM, gestation ≤36 weeks; INFANT, postnatal age ≤6 weeks; EARLY HYPOXIA, oxygen saturation ≤90%.

Respiratory syncytial virus (RSV) is the major cause of lower respiratory infection (LRI) and hospitalization among infants and toddlers in North America.[1] Nearly all children are infected by age 2 years and 1% to 2% of those infected require hospitalization.[2] Among those admitted to hospital with no apparent risk factors for severe disease, 4% to 15% are admitted to the intensive care unit (ICU), 1% to 5% require assisted ventilation, and <1% die.[3–7] In contrast, among children with underlying heart/lung disease, prematurity (gestation ≤36 weeks) and young age (≤6 weeks) the corresponding figures for ICU, ventilation, and mortality range from 10% to 40%, 8% to 27%, and up to 10%, respectively.[3–7]

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Ribavirin, first approved in the United States in 1986, is the only licensed antiviral therapy for RSV infection. In 1993 the American Academy of Pediatrics (AAP) recommended that ribavirin should be given to selected infants and children at risk for or already manifesting severe disease as well as for all ventilated patients.[8] Although several randomized trials suggested that ribavirin was efficacious among nonventilated patients,[9–14] the use of the drug remained controversial, due to the small numbers studied, and concern over the validity, generalizability, and clinical relevance of the outcome measures used. For ventilated patients, controversy existed as well, with one trial supporting a beneficial effect for ribavirin[15] while another failed to show a difference.[16] Large increases in the cost of ribavirin since 1993 raised further questions about its relative cost-benefit. In Canada over 90% of RSV-related hospital costs are due to daily bed charges.[17] With the daily cost of ribavirin at approximately $1500 (Canadian funds), therapy would have to lead to a substantial reduction in the duration of hospital stay to justify the costs of ribavirin. Accordingly, the AAP recommendations for patients who should receive ribavirin were used to select cases enrolled in a prospective study of children hospitalized for RSV LRI and outcomes were examined to determine the relationship between ribavirin therapy and length of hospitalization.

METHODS

The Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV Database includes prospectively collected data on demographic factors, disease severity, and daily management in hospital of 1516 infants and children with acute RSV LRI, admitted to nine Canadian pediatric tertiary care hospitals between January 1993 and June 1994. Details of study design and methodology have been reported previously.[18] After enrollment each child was followed daily by a study nurse to assess respiratory status and oxygen saturation and to record management regimens including the use of supplemental oxygen, ribavirin, bronchodilators, steroids, and antibiotics. The durations of mechanical ventilation, receipt of intensive care, and hospitalization were recorded. For all analyses, hypoxia was defined as an oxygen saturation of ≤90% on room air or a fraction of inspired oxygen (FiO_2) requirement of ≥.35. Hypoxia occurring within 48 hours of hospital admission was used as an indicator of moderate or severe disease.

From the database, cases were selected if at least one of the AAP recommended indications for ribavirin use was present, including: any underlying CHD or CLD, PREM, INFANT, and EARLY HYPOXIA. Excluded from analysis were nosocomially acquired RSV LRI, defined as onset of symptoms 3 or more days after admission to hospital, and patients with known congenital or acquired abnormalities of the immune system.

The association between ribavirin use and hospital outcomes was examined separately in ventilated and nonventilated patients in each of the CHD, CLD, PREM, INFANT, and EARLY HYPOXIA subsets. The groups were not mutually exclusive and some children were included in two or more analyses. However, before analysis the subsets were separated according to the presence or absence of cardiopulmonary disease, such that the CHD/CLD group could include cases that fit the PREM, INFANT, or EARLY HYPOXIA criteria, but none of the latter three subsets included patients with CHD or CLD. The outcomes were duration-measured in days of: hypoxia, mechanical ventilation, management in the ICU, and RSV-attributable hospitalization. For children on oxygen supplementation before the onset of RSV infection, the duration of hypoxia was defined as the number of days until return to pre-illness baseline. RSV-attributable hospital days were defined as days required for specific or supportive therapy or observation relative to the RSV illness. Additional days spent in hospital for investigation of other problems, elective surgery, or delayed discharge due to social or transportation problems were not counted. Because the data were not normally distributed, the Wilcoxon test was used throughout to compare outcome duration. χ^2 or Fisher's exact tests of proportion were used to compare distribution of demographic factors, coexisting risk factors, and indicators of disease severity among the ribavirin and no-ribavirin therapy groups.

Receipt of ribavirin was also added as an independent variable to a previously developed multiple regression model for predicting RSV-attributable length of hospitalization.[18] Separate analyses were performed for the CHD/CLD subsets and the INFANT/PREM/EARLY HYPOXIA subsets. The other independent variables included in the model for both analyses were INFANT, PREM, EARLY HYPOXIA, aboriginal racial background, history of apnea or respiratory arrest before or at the time of admission to hospital, consolidation on the admitting chest radiograph, and hospital center. For analysis of children with prior heart or lung disease CHD and CLD were included as independent variables.

RESULTS

Study Groups

Between January 1, 1993 and June 6 1994, 2116 children were hospitalized with acute RSV LRI at the participating PICNIC study centers. Of these 1516 (72%) were enrolled in the prospective RSV study. Excluded from this analysis were 91 cases of hospital-acquired RSV infection. Among the remaining 1425 community-acquired cases of RSV LRI, previously recognized chronic disease affected 220 (15%). From these, the 173 cases with underlying cardiopulmonary disease and no known immunodeficiency were chosen for analysis, including 97 CHD and 134 CLD. Among the CHD group, 49 (50%) had a left to right shunt and 20 (21%) had pulmonary hypertension. Among the CLD group 88 (66%) had a history of current or past home oxygen supplementation. The other 1205 patients with community-acquired RSV LRI had no known underlying disease. From this group 577 (48%) fit one or more of the recommended guidelines for use of ribavirin, including 213 INFANT, 211 PREM, and 463 with EARLY HYPOXIA. The proportion of the PREM group with a gestational age range of ≤28 weeks, 29 to ≤32 weeks, and 33 to ≤36 weeks was 8%, 21%, and 71%, respectively. The proportion ventilated in each subset was CHD (20.6%), CLD (20.9%), INFANT (15.5%), PREM (15.2%), and EARLY HYPOXIA (13.3%). Within the ventilated and nonventilated strata of each risk group category, the respective proportions treated with ribavirin were: CHD (45% and 39%), CLD (57% and 32%), INFANT (36% and 12%), PREM (44% and 10%), and EARLY HYPOXIA (39% and 6%).

The cumulative proportion of ribavirin-treated patients whose therapy was initiated by hospital day 2 and 3 was 66% and 81%, respectively for children with cardiopulmonary disease, and 76% and 95%, respectively, for previously healthy children.

Specific Risk Group Analysis for Effect of Ribavirin

The use of ribavirin was determined by the attending physician and study personnel were not involved in the decision. Consistent with previous reports, there was marked variation in the use of ribavirin among the nine participating centers.[7,18] Among ventilated patients the individual centers varied in the

use of ribavirin from 0% to 100% for CHD, CLD, and INFANT, and from 25% to 85% for PREM. Among nonventilated cases ribavirin use varied from 0% to 43% for CHD, 12% to 62% for CLD, 0% to 43% for INFANT, and 2% to 33% for PREM.

The variation in duration of hospitalization, hypoxia, and ICU management stratified by receipt of ventilation and ribavirin are presented in Table 1. There were no significant differences in any of the four outcomes for ventilated cases regardless of risk group. For nonventilated patients ribavirin was associated with a prolongation of hypoxia and hospital days for each of the five risk subgroups and of ICU days for all but the CHD subgroup.

Table 2 shows the distribution of factors previously shown in a multiple regression model to predict the duration of RSV-attributable hospital days (CHD, CLD, PREM, INFANT) or to be evidence of early severe RSV disease (apnea as a presenting problem, infiltrate on an admitting chest radiograph, EARLY HYPOXIA) for patients who did or did not receive ribavirin within the ventilated and nonventilated strata of each risk subgroup. Significant differences (all by Fisher's exact test) between ribavirin treated versus those not given ribavirin, respectively, were: *ventilated cases*–a) CHD subgroup: coexisting CLD in 67% vs 0% ($P = .002$); b) CLD subgroup: coexisting CHD in 38% vs 0% and apnea as a presenting problem for 12% vs 50% ($P < .05$); and c) PREM subgroup: infiltrate on an admitting radiograph in 36% vs 78% ($P < .05$); *nonventilated cases*–a) CHD subgroup: infiltrate on an admitting radiograph in 77% vs 34% ($P < .001$) and EARLY HY-POXIA in 80% vs 53% ($P = .03$); b) PREM subgroup: EARLY HYPOXIA in 72% vs 43% ($P = .03$) and apnea as a presenting problem in 33% vs 11% ($P = .02$); c) EARLY HYPOXIA subgroup: INFANT in 54% vs 20% and PREM in 54% vs 18% ($P < .001$) and apnea as a presenting problem in 29% vs 8% ($P = .002$). There were no differences in the distribution of left to right shunt or pulmonary hypertension between treatment groups for the ventilated and nonventilated CHD subgroups. For the ventilated CLD group, a current or past requirement for home oxygen was less common in ribavirin recipients versus those not treated (38% vs 83%; $P = .04$). For nonventilated CLD patients 68% of each of the ribavirin-treated and untreated groups had a prior home oxygen requirement.

TABLE 1. Impact of Ribavirin on Total Hospital Days Attributable to Respiratory Syncytial Virus, as Well as Days of Hypoxia, Intensive Care Stay, and Mechanical Ventilation, Among Children With Community-acquired Respiratory Syncytial Virus Lower Respiratory Infection

Ribavirin	Ventilated		Not Ventilated	
	Yes	No	Yes	No
A. Heart Disease	N = 9	N = 11	N = 30	N = 47
Hospitalization	14 (6–52)	12 (6–47)	10 (6–21)*	7 (3–23)
Hypoxia	9 (2–36)	8 (1–47)	7 (0–19)*	1 (0–14)
Intensive Care	14 (5–22)	7 (2–38)	0 (0–13)	0 (0–8)
Ventilation	9 (4–19)	6 (1–26)	· · ·	· · ·
Mortality No. (%)	1 (11%)	0 (0%)	0 (0%)	1 (1.7%)
B. Lung Disease	N = 16	N = 12	N = 34	N = 72
Hospitalization	15 (7–52)	15.5 (1–22)	11 (4–20)*	7.5 (2–17)
Hypoxia	12 (2–36)	10.5 (1–21)	5.5 (0–20)†	2 (0–16)
Intensive Care	12.5 (3–22)	8 (2–21)	0 (0–12)†	0 (0–7)
Ventilation	11 (3–33)	7 (1–21)	· · ·	· · ·
Mortality No. (%)	2 (12%)	1 (8.3%)	0 (0%)	1 (1.4%)
C. Age <6 wk	N = 12	N = 21	N = 21	N = 159
Hospitalization	9.5 (7–46)	12 (3–18)	7 (4–14)*	5 (2–15)
Hypoxia	5 (0–27)	7 (1–15)	2 (0–6)‡	1 (0–11)
Intensive Care	5 (3–27)	7 (3–14)	2 (0–6)*	0 (0–6)
Ventilation	4 (1–24)	5 (2–10)	· · ·	· · ·
Mortality No. (%)	0 (0%)	1 (4.8%)	0 (0%)	0 (0%)
D. Premature	N = 14	N = 18	N = 18	N = 161
Hospitalization	11.5 (7–46)	11.5 (5–32)	7 (5–18)*	5 (1–22)
Hypoxia	5.5 (0–27)	7.5 (0–30)	3 (0–10)*	1 (0–14)
Intensive Care	6 (2–27)	7 (4–13)	0 (0–4)*	0 (0–6)
Ventilation	5 (1–24)	6 (2–12)	· · ·	· · ·
Mortality No. (%)	0 (0%)	2 (11%)	0 (0%)	0 (0%)
E. Early Hypoxia	N = 24	N = 38	N = 24	N = 377
Hospitalization	11 (6–46)	11.5 (3–32)	7 (5–18)*	5 (2–22)
Hypoxia	7 (3–27)	8 (1–30)	3 (0–10)†	2 (0–17)
Intensive Care	7 (3–27)	7 (1–14)	0 (0–4)*	0 (0–7)
Ventilation	7 (3–27)	5 (1–13)	· · ·	· · ·
Mortality No. (%)	0 (0%)	2 (5.3%)	0 (0%)	0 (0%)

Data are stratified by the need for mechanical ventilation and host risk factor. All results are expressed as median (range) days unless otherwise indicated.
Univariate analysis for ribavirin versus no ribavirin: * $P \leq .001$; † $P \leq .01$; ‡ $P < .05$.

TABLE 2. Distribution of Factors Associated With Duration of RSV-Attributable Hospital Stay[18] Among Specified Risk Groups According to Whether or Not They Received Ribavirin

Risk Group	CHD		CLD		INFANT		PREM		HYPOXIA	
Ribavirin	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Ventilated (N)	(9)	(11)	(16)	(12)	(12)	(21)	(14)	(18)	(24)	(38)
% With:										
CHD	100	100	**38***	**0**	0	0	0	0	0	0
CLD	**67†**	**0**	100	100	0	0	0	0	0	0
INFANT	0	9	0	8	100	100	43	33	42	47
PREM	22	9	50	58	50	28	100	100	38	39
HYPOXIA	89	100	94	83	83	86	64	83	100	100
APNEA	22	18	**12***	**50**	67	57	71	67	46	53
INFILTRATE	56	64	75	67	50	62	**36***	**78**	54	68
Not Ventilated (N)	(30)	(47)	(34)	(72)	(21)	(159)	(18)	(161)	(24)	(377)
% With:										
CHD	100	100	21	12	0	0	0	0	0	0
CLD	23	19	100	100	0	0	0	0	0	0
INFANT	7	6	0	1	100	100	28	12	**54†**	**20**
PREM	23	13	62	64	24	12	100	100	**54†**	**18**
HYPOXIA	**80***	**53**	68	62	62	48	**72***	**43**	100	100
APNEA	3	6	3	3	24	11	**33***	**11**	**29†**	**8**
INFILTRATE	**77†**	**34**	59	51	33	30	50	37	46	44

Significant differences are indicated by boldface type. * $P < .05$; † $P \leq .002$; Two-tailed Fisher's exact test.

Effect of Ribavirin in a Multiple Regression Model for Duration of RSV-Attributable Hospitalization

After adjustment for other prognostic factors children receiving ribavirin had longer hospitalization: +1.44 days (95% CI, 1.18–1.70; $P = .0001$) for children with underlying cardiopulmonary disease and +1.40 days (95% CI 1.26–1.63; $P < .0001$) for previously healthy children.

Mortality

There were a total of six deaths among the 577 cases included in the analysis. The case fatality rates for each of the subgroups are shown in Table 1. None of the rates were significantly different but the numbers were small. For the groups used in the multivariate analysis the mortality was: CHD/CLD group–3.3% (2/61) of those treated with ribavirin and 2.0% (2/99) of those not given ribavirin; previously healthy INFANT/PREM/EARLY HYPOXIA group–0% (0/61) of ribavirin treated and .4% (2/453) of those not given ribavirin. These differences were not significant.

DISCUSSION

The randomized placebo-controlled trials used to support ribavirin as an efficacious therapy for RSV LRI used outcomes based on respiratory status scores, duration of viral shedding, and hypoxemia.[9–14] The studies on healthy children differed in terms of eligibility criteria such that some included premature infants[9,13] whereas others did not[10,12] and none stratified by age group making it difficult to extrapolate the results to specific populations such as those mentioned in the AAP guidelines. Furthermore the clinical significance of improvement in respiratory score as well as the effect on viral shedding and hypoxemia are not clear. A high mortality rate among children with cardiopulmonary disease has been cited as a reason for ribavirin therapy,[3] but ribavirin has not been shown to reduce the RSV case fatality rate. More recent series have reported mortality as much as 10-fold lower than previously reported rates.[6,7,18,19] One retrospective study did not find any difference in pulmonary function tests between ribavirin recipients and nonrecipients, but the recipients appear to have been sicker.[20]

Given the absence of evidence that ribavirin therapy reduces mortality in the short-term, or improves pulmonary function in the long-term, to be cost-effective ribavirin therapy must reduce associated morbidity such as the need for intensive care management and/or mechanical ventilation, or shorten hospital stay. When outcomes in the CHD, CLD, INFANT, PREM, and EARLY HYPOXIA subgroups were examined using our database, the benefit of ribavirin could not be demonstrated. Recently, Moler et al[21] showed that ribavirin therapy was not associated with reductions in duration of hospitalization, days in ICU, or days on mechanical ventilation for previously healthy term and premature infants who required ventilation during the course of community-acquired RSV LRI. Despite methodological differences between that study and the currently reported PICNIC study, the data were quite similar with respect to the median days spent in hospital, in ICU, and on a ventilator for the ribavirin and no-ribavirin treatment groups. The lack of significant difference observed for the ventilated subgroups in our cohort could reflect a lack of power to detect a difference given the small number of cases.

The major limitation of this analysis is that the administration of ribavirin was not randomized. Thus, selection of the sickest patients for ribavirin may have accounted for the greater morbidity. Yet when the ribavirin-treated and untreated subgroups were compared in terms of coexisting risk factors for prolonged RSV-attributable hospitalization, only a few significant differences were found. In general, as shown in Table 2, ribavirin was more likely to be given to patients with more than one of the criteria for ribavirin use as recommended by the AAP. However, this observation was not consistent for all risk

groups. Furthermore, the association between ribavirin therapy and longer hospital stay was also shown using multivariate analysis, which controlled for many of the factors known to increase the risk of severe disease as well as some indicators of disease severity. Nevertheless, other factors not included in the model may have affected disease severity.

A second weakness of the analysis is that ribavirin therapy was not started at a uniform time during the hospital course, and in a few instances was delayed until the fourth to seventh hospital day. In such cases the increased number of days in hospital attributable to RSV may have been an artifact of the late introduction of therapy and subsequent requirement for extra days of hospitalization. This was unlikely to have a pronounced effect, however, because the majority of treated children were started on ribavirin within 2 to 3 days of hospital admission.

The only randomized placebo-controlled trial in which treatment was started within 72 hours of symptom onset, involving cases with significant cardiopulmonary disease, showed that none of 20 ribavirin-treated and none of 27 placebo-treated children required intensive care management.[14] The only other randomized controlled trials that have used intensive care, ventilator, and total hospital days as outcome measures focused exclusively on ventilated patients.[15,16] When the control group received inhaled water, ribavirin-treated patients had significant reductions in the ventilator and total hospital days.[15] In contrast, with inhaled normal saline as the placebo, these reductions were not observed.[16] These two studies differed significantly in the type of patient studied in that the water placebo study focused on young infants of whom 75% had no known preexisting disease whereas the saline placebo study included older children, 54% of whom had known cardiopulmonary or other abnormalities. Neither study included cases ventilated because of apnea.

The prospective enrollment of cases at nine centers across Canada with specific recording of RSV-attributable days for total hospital stay increases the generalizability of the study. The data strengthen and extend similar observations made by Wheeler et al[22] who found that the duration of hospitalization for RSV LRI was similar between a center that used ribavirin according to the AAP criteria and a center which used no ribavirin. It is possible that there are fewer restrictions to hospital admission in Canada, such that children are not as severely ill. Yet data summarizing the hospital course of RSV-infected children admitted to large centers in the United States suggest that the proportion of previously healthy children,[3–7] as well as those with underlying cardiac,[6,19] pulmonary,[6,23] or immunodeficiency[3] disease, admitted to the ICU or ventilated mechanically are similar to what we have observed among the centers participating in the PICNIC RSV studies.[7,18]

Recently, the recommendations of the AAP regarding ribavirin use among high-risk infants and children were revised to read "may be considered" instead of "should be used."[24] For physicians who may be reluctant to be more restrictive in their approach to the use of ribavirin, these data should provide some assurance. Additional data from large randomized controlled trials are needed to determine if ribavirin is cost-effective in a clinically relevant sense.

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REFERENCES

1. Parrott RH, Kim HW, Arrobio JO, et al. Epidemiology of respiratory syncytial virus infection in Washington, DC. II. Infection and disease with respect to age, immunologic status, race and sex. *Am J Epidemiol.* 1973;98:289–300
2. Kim HW, Arrobio JO, Brandt CD, et al. Epidemiology of respiratory syncytial virus in Washington, DC. I. Importance of the virus in different respiratory tract diseases syndromes and temporal distribution of infection. *Am J Epidemiol.* 1973;98:216–25
3. Hall CB, Powell KR, MacDonald NE, et al. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med.* 1986;315:77–81
4. Green M, Brayer AF, Schenkman KA, Wald ER. Duration of hospitalization in previously well infants with respiratory syncytial virus infection. *Pediatr Infect Dis J.* 1989;8:601–605
5. Pohl C, Green M, Wald ER, Ledesma-Medina J. Respiratory syncytial virus infections in pediatric liver transplant recipients. *J Infect Dis.* 1992;165:166–169
6. Meert K, Heidemann S, Lieh-Lai M, Sarnaik A. Clinical characteristics of respiratory syncytial virus infections in healthy versus previously compromised hosts. *Pediatr Pulmonol.* 1989;7:167–170
7. Navas L, Wang E, Carvalho V, et al. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. *J Pediatr.* 1992;121:348–354
8. Committee on Infectious Diseases, American Academy of Pediatrics. *1994 Red Book. Report of the Committee on Infectious Diseases.* 23rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 1994:570–574
9. Hall CB, McBride JT, Walsh EE, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med.* 1983; 308:1443–1447
10. Taber LH, Knight V, Gilbert BE, et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics.* 1983;72:613–618
11. Hall CB, McBride JT, Gala CL, Hildreth SW and Schnabel KC. Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. *JAMA.* 1985;254:3047–3051
12. Barry W, Cockburn F, Cornall R, Price JF, Sutherland G, Bardag A. Ribavirin aerosol for acute bronchiolitis. *Arch Dis Child.* 1986;61:593–597
13. Rodriguez WJ, Kim HW, Brandt CD, et al. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. *Pediatr Infect Dis J.* 1987;6:159–163
14. Groothuis JR, Woodin KA, Katz R, et al. Early ribavirin treatment of respiratory syncytial viral infection in high-risk children. *J Pediatr.* 1990; 117:792–798
15. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med.* 1991;325:24–29
16. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med.* 1994;22:566–572
17. Langley JM and members of PICNIC. Economic evaluation of hospitalized Canadian children with respiratory syncytial virus (RSV) infection. Poster. Annual meeting of the Royal College of Physicians and Surgeons, Toronto, Ontario, September 1994
18. Wang EEL, Law BJ, Stephens D, et al. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr.* 1995;126: 212–219

19. Moler FW, Khan AS, Meliones JN, Custer JR, Palmisano J, Shope TC. Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: a recent experience. *Crit Care Med.* 1992; 20:1406–13
20. Krilov LR, Mandel FS, Fagin JC, and the Bronchiolitis Study Group. Follow-up of children with respiratory syncytial virus bronchiolitis in 1986–1987: Potential effect of ribavirin on long-term pulmonary function. *Pediatr Res.* 1995;37:180A. Abstract #1068
21. Moler FW, Steinhart CM, Ohmit SE, et al. Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. *J Pediatr.* 1996;128:422–428
22. Wheeler JG, Wofford J, and Turner RB. Historical cohort evaluation of ribavirin efficacy in respiratory syncytial virus infection. *Pediatr Infect Dis J.* 1993;12:209–213
23. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. *Pediatrics.* 1988; 82:199–203
24. Committee on Infectious Diseases, American Academy of Pediatrics. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. *Pediatrics.* 1996;97:137–140

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