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Evaluation of the Safety of Palivizumab in the Second Season of Exposure in Young Children at Risk for Severe Respiratory Syncytial Virus Infection

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Abstract

Background: Palivizumab reduces respiratory syncytial virus (RSV) hospitalisations in high-risk infants. Those with severe bronchopulmonary dysplasia may require two seasons of prophylaxis. There is concern that this humanised antibody might cause an adverse immune response in a second season of use.

Objective: To evaluate and compare the occurrence of anti-palivizumab antibodies and clinical adverse events in subjects receiving monthly palivizumab injections for a first and second season, and to assess frequency and severity of RSV disease in the two groups.

Design and Patients: Subjects aged ≤2 years at severe risk for RSV disease were designated as first season (no previous palivizumab exposure) or second season subjects (received palivizumab in previous RSV season). Palivizumab injections (15 mg/kg) were administered monthly for up to 5 months. Anti-palivizumab antibody titres and serum palivizumab concentrations were measured; adverse events were recorded.

Results: No first (n = 71) or second (n = 63) season subjects experienced a significant anti-palivizumab antibody response (titre ≥1 : 80). Serum palivizumab concentrations were similar for the two groups. Nine (12.7%) first season and 8 (12.7%) second season subjects experienced one or more serious

adverse events; most were respiratory and all were considered to be not or probably not related to palivizumab. No deaths occurred during the study.
Conclusions: Monthly palivizumab injections were not associated with adverse immune responses or adverse events in young children receiving palivizumab for one or two seasons. Children receiving palivizumab for a second season did not experience more severe adverse events than those receiving it for the first time.

Background

Respiratory syncytial virus (RSV) infection represents a large public health burden worldwide, with seasonal outbreaks occurring from winter through early spring in temperate climates and during the rainy season in tropical climates.[1] RSV illness is estimated to result in more than 125 000 hospitalisations annually in the US alone.[2] RSV is estimated to cause up to 90% of all childhood bronchiolitis and up to 40% of all paediatric pneumonias.[3] Severe RSV illness commonly occurs among infants during their primary infection in the first year of life. However, certain high-risk populations experience serious RSV lower respiratory tract infection in a second season also.[4-6] Infants and children born prematurely and those with bronchopulmonary dysplasia (BPD), also known as chronic lung disease, and congenital heart disease are at particularly high risk for serious RSV infection and reinfection.[4-8]

In view of the lack of success in developing an RSV vaccine,[9] passive immunoprophylaxis was pursued. An anti-RSV humanised monoclonal antibody, palivizumab (Synagis®,[1] MedImmune, Gaithersburg, MD, USA), has recently been developed, which neutralises the RSV and prevents fusion with respiratory epithelial cell membranes, thus inhibiting viral replication and spread. This antibody was created using genetic engineering, in which the complementarity determining regions (CDRs) of a mouse antibody gene were inserted into a human IgG_1 gene framework.[10] The antibody molecule produced by the recombinant gene has only 5% homology with the mouse antibody. Nevertheless there is a theoretical, although unlikely, possibility that upon repeated exposure to this antibody, a human would mount an immune response to the mouse components. Presence of anti-palivizumab antibody could potentially cause clinical symptoms (e.g. allergic reaction, anaphylaxis), or reduce the plasma palivizumab concentration to levels that are no longer protective, which could result in increased incidence or severity of RSV disease. Preclinical studies suggested that a serum concentration of 40 μg/mL was the minimum to be protective.

In a large phase III study, palivizumab, administered intramuscularly every 30 days for 5 months reduced RSV hospitalisations in high-risk infants by 55%.[11] There were no significant differences in type or incidence of adverse events between the control and treatment groups. However, this study was conducted over only one RSV season.

Guidelines have been issued providing palivizumab usage recommendations for the prevention of severe RSV lower respiratory tract disease in certain high-risk populations.[12,13] They recommend that children with BPD requiring medical intervention (bronchodilators, corticosteroids, supplemental oxygen, diuretics) at the onset of the RSV season receive prophylaxis up to the age of 24 months. Hence, some children with severe BPD will receive palivizumab prophylaxis for more than one RSV season. We undertook this study to evaluate and compare the occurrence of anti-palivizumab antibodies and clinical adverse events in subjects receiving monthly palivizumab injections for a first and second season, and to assess frequency and severity of RSV disease in the two groups.

1 Use of tradenames is for product identification only and does not imply endorsement.

Patients and Methods

This multicentre, open-label study was conducted at 14 sites in Europe and Canada during the 1999–2000 RSV. The Institutional Review Board at each site approved the protocol and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice.[14] Each child's parent or legal guardian provided informed consent prior to enrolling the child in the study.

Children were eligible for study enrolment if they were aged ≤2 years, born at ≤35 weeks' gestation and had BPD requiring medical intervention or management within the 6 months prior to the start of the RSV season (beginning of the study) or were judged by the investigator to be at risk for serious RSV infection. There is general acceptance that children with these characteristics are appropriate candidates for RSV prophylaxis. Subjects were assigned to the first season group if they were receiving palivizumab for the first time. Subjects were assigned to the second season group if they had received two or more injections of palivizumab in the previous season (1998–1999 RSV season) through either a palivizumab expanded access programme or a named patient programme. Efforts were made within each study site to match subjects between the two groups for gestational age and sex. Subjects were excluded if they were hospitalised, required mechanical ventilation, or had an active illness or infection (including RSV infection) at the time of enrolment. Additional exclusion criteria included known renal impairment, hepatic dysfunction, chronic seizure disorder, congenital heart disease, immunodeficiency, allergy to palivizumab, treatment with respiratory syncytial virus immune globulin intravenous (RSV-IGIV) within 3 months prior to enrolment, or previous treatment with monoclonal antibodies other than palivizumab. Although representing a sizeable population of infants at continued risk for RSV lower respiratory tract infection, children with congenital heart disease were also excluded since the benefit of palivizumab in this population had not been evaluated at the time of this study.

Subjects received up to five palivizumab injections at 25- to 30-day intervals. At each study visit, an updated medical history was obtained, adverse events, concomitant medications, and supplemental oxygen use were recorded, and a physical examination was performed. Prior to palivizumab administration at the first (i.e. baseline), second, and fifth visits, blood was collected for trough palivizumab concentrations and anti-palivizumab antibody titres. Palivizumab (15 mg/kg) was administered at each visit by intramuscular injection and subjects were observed for 30 minutes following the injection. Patients were followed for a maximum of approximately 150 days, continuing through 30 days after the final injection. Subjects who were hospitalised for respiratory infection were maintained on the same injection and evaluation schedule unless medically contraindicated.

Criteria for hospitalisation were at the individual discretion of the responsible physician. Subjects hospitalised for respiratory illness had nasopharyngeal samples (aspirates, washes, or swabs) collected using standard procedures.[15-17] These samples were tested for RSV antigen using the Abbott TESTPAK® RSV kit (Abbott Laboratories, Abbott Park, IL, USA) or the facility's standard rapid antigen method. When a negative result was obtained, retesting was repeated at the physician's discretion. Details of the subject's hospitalisation, including length of stay, time in intensive care, respiratory symptoms, mechanical ventilation record, and supplemental oxygen use were recorded and blood samples were collected for serum palivizumab measurements.

Serum anti-palivizumab antibody levels were measured using an ELISA as described previously.[18] Briefly, microtitre plates were coated with palivizumab as the capture antigen and blocked with phosphate-buffered saline-Tween-0.5% BSA. Patient samples, diluted 1 : 10, were added. Bound material was probed with horseradish peroxidase-conjugated palivizumab and developed with the chromogenic substrate 3,3′,5,5′-

tetramethylbenzidine. Samples with a positive response at the 1 : 10 dilution were serially diluted and reassayed to determine the endpoint titre. Results were reported as corrected values (i.e. with the baseline subtracted). A significant titre was defined as ≥1 : 80 occurring at any timepoint in the study, based on previous experience evaluating anti-palivizumab antibody formation in adults and children.[19,20]

The primary objective of the study was to determine whether patients receiving palivizumab prophylaxis for the first or second season developed significant levels (defined as titre ≥1 : 80) of anti-palivizumab antibodies. The secondary objective was to evaluate the relationship, if any, of plasma palivizumab concentrations and/or anti-palivizumab titres to serious adverse events. Indicators of disease severity (total days of RSV hospitalisation, frequency and total days of intensive care unit stay, need for supplemental oxygen, and/or mechanical ventilation) were collected for assessment of secondary efficacy endpoints.

Adverse events were mapped to the WHO adverse event directory by preferred term and body system. Adverse events and serious adverse events were summarised by study group, severity, and relationship to study drug. A serious adverse event was one that resulted in death, was life-threatening, resulted in hospitalisation or prolonged hospitalisation, caused persistent or significant disability/incapacity, or other medically important events. The severity of an adverse event was to be rated as mild, moderate, or severe, based on the investigator's clinical judgment. A mild event was transient and easily tolerated by the patient. A moderate event caused discomfort and interrupted the patient's usual activities. A severe event caused considerable interference with the patient's usual activities and may have been incapacitating or life-threatening (in which case it was also considered serious). Severity and causality was based on the investigators' clinical judgment.

Statistical Methods

Comparisons between groups were conducted using a Chi-square or Fisher's Exact Test for proportions and a t-test or Kruskal-Wallis test for central values. Sample size was based on previous palivizumab clinical trials with design similar to this study.

Results

A total of 134 subjects were enrolled in the study, 71 as first season subjects and 63 as second season subjects. Ninety-nine percent of the first season and 94% of the second season subjects completed the study. Subjects withdrew from the study due to either loss to follow-up (one first season subject) or personal reasons (four second season subjects). All enrolled subjects were included in the safety evaluations.

Table I illustrates subject demographics and treatment. Significant differences were observed for age and weight at enrolment, gestational age and birth weight between first and second season subjects. Sex and race were similar between the two groups. The majority of subjects in both groups received five injections of palivizumab during the study (see table I).

Mean serum palivizumab concentrations measured at scheduled study visits were similar for the two groups (table II). No significant anti-palivizumab immune responses (antibody titre ≥1 : 80) were observed for any subject in either group at any timepoint. Only four patients had at least one sample with a positive titre of 1 : 10 or greater. Two patients had initial antibody titres of 1 : 40 and 1 : 80, respectively, which subsequently fell to <1 : 10 while receiving palivizumab prophylaxis. The third patient had an initial titre of <1 : 10, with a subsequent result of 1 : 10. The fourth patient had an initial titre 1 : 10, with a value of 1 : 20 upon subsequent testing. The first, second and third patient were each from the second season group. The fourth patient was from the first season group. No serious adverse events or immune re-

Table I. Subject demographics and treatment

	First season palivizumab (n = 71)	Second season palivizumab (n = 63)
Mean (SEM) [range] age at enrolment (mo)[a]	7.7 (0.53) [1.0–18.0]	15.9 (0.42) [11.0–33.0]
Mean (SEM) [range] weight at enrolment (kg)[a]	5.7 (0.26) [2.2–10.5]	8.6 (0.15) [6.1–12.0]
Mean (SEM) [range] gestational age (wk)[b]	29.3 (0.36) [24.0–37.0]	27.9 (0.34) [23.0–36.0]
Mean (SEM) [range] birth weight (kg)[c]	1.3 (0.07) [0.5–3.0]	1.1 (0.05) [1.0–2.5]
Sex		
No. (%) of males	40 (56.3)	35 (55.6)
No. (%) of females	31 (43.7)	28 (44.4)
Race		
No. (%) of White subjects	59 (83.1)	54 (85.7)
No. (%) of Black subjects	6 (8.5)	5 (7.9)
No. (%) of Asian subjects	3 (4.2)	1 (1.6)
No. (%) of other race subjects	3 (4.2)	3 (4.8)
Number of palivizumab injections		
No. (%) subjects receiving 2 injections	0 (0.0)	4 (6.3)
No. (%) subjects receiving 3 injections	8 (11.3)	1 (1.6)
No. (%) subjects receiving 4 injections	21 (29.6)	14 (22.2)
No. (%) subjects receiving 5 injections	42 (59.2)	44 (69.8)

a $p = 0$ 0.0001 Student's t test.
b $p < 0.005$ Student's t test.
c $p < 0.05$ Student's t test.

actions were temporally related to these low-level titres.

There were 19 hospitalisations in 12 subjects for respiratory illness (six from the first season group and six from the second season group). Three subjects from the first season group and one from the second season group were hospitalised more than once for respiratory illness. Initially, for 13 of the hospitalisations, patients tested negative for RSV antigen; of these, there were six retests and one was positive. A total of five tested positive for RSV antigen, 12 were RSV negative, and results were unavailable in two cases. There were no significant differences between first season and second season subjects for the incidence of hospitalisation for RSV antigen-positive respiratory illness (1 [1.4%] first season vs 4 [6.3%] second season, $p = 0.187$, Fisher's Exact Test), or for the length of hospitalisation for respiratory illnesses (5.0 days first season vs 3.8 days second season, $p = 0.468$, Kruskal-Wallace).

A total of 23 subjects (32.4%) in the first season group and 33 subjects (52.4%) in the second season group experienced one or more adverse events during the study. The majority of adverse events were mild or moderate in severity (90%) and considered to be unrelated to the administration of palivizumab (92%). The most common adverse events (reported by ≥5% of subjects) are listed in table III.

Nine first season subjects (12.7%) and eight second season subjects (12.7%) experienced one or more serious adverse events during the study

Table II. Mean (SEM) serum palivizumab concentrations (μg/mL) measured at scheduled study visits prior to administration of next dose

	First season palivizumab	Second season palivizumab
Day 0	0.0 (0.00) [n = 32]	0.0 (0.00) [n = 44]
Day 25–30	51.8 (2.54) [n = 48]	55.0 (2.98) [n = 49]
Day 100–120	104.5 (6.90) [n = 40]	89.9 (5.83) [n = 43]

Table III. Adverse events reported by ≥5% of subjects in either study group

	Number (%) of subjects	
	first season palivizumab (n = 71)	second season palivizumab (n = 63)
Body as a whole		
Fever	0	6 (9.5)
Infection	3 (4.2)	6 (9.5)
Respiratory system		
Asthma	1 (1.4)	4 (6.3)
Bronchiolitis	5 (7.0)	4 (6.3)
Bronchitis	8 (11.3)	12 (19.0)
Cough increased	3 (4.2)	6 (9.5)
Pharyngitis	3 (4.2)	5 (7.9)
Respiratory disorder	2 (2.8)	4 (6.3)
Rhinitis	4 (5.6)	10 (15.9)
Special senses		
Otitis media	7 (9.9)	6 (9.5)

(table IV). All events were related to the need for hospitalisation. The majority of the events were related to the respiratory system, were mild or moderate in severity, and all were considered to be not or probably not related to palivizumab. No deaths occurred during the study. All serious adverse events were resolved and no subject discontinued the study due to an adverse event. All subjects who were hospitalised for respiratory infection had their illness recorded as a serious adverse event. One subject from the first season group required admission to an intensive care unit for a severe case of bronchiolitis and required supplemental oxygen and mechanical ventilation that was considered to be life threatening. The causative agents were presumed to be adenovirus (primary) and a secondary nosocomially-acquired *Staphylococcus aureus* infection. This event was not related to study drug and was successfully treated with medication and mechanical ventilation.

The adverse events that were considered by the clinical investigator to be probably or possibly related to palivizumab are summarised in table V. Events not assigned causality were classified as related. All related adverse events were mild or moderate in severity. No serious adverse events

Table IV. Serious adverse events

Subject number	Age (mo)	Event
First season palivizumab		
1	9	Lower respiratory tract infection, asthma attack
2	11	Bronchiolitis, BPD aggravation (2 events), respiratory impairment
3	10	Bronchiolitis, nosocomial infection, circulatory failure, arterial pulmonary hypertension BPD aggravation, nosocomial infection, oesophagitis
4	16	Bilateral otitis media
5	10	Gastroenteritis
6	13	Bronchitis
7	3	Diarrhoea, vomiting, decreased appetite, lethargy
8	2	Bronchiolitis
9	2	Bronchiolitis, barking cough, stridor, vomiting, change in eating habits
Second season palivizumab		
1	16	Lower respiratory tract infection
2	17	Fever, diarrhoea
3	15	Bronchiolitis
4	15	Bronchiolitis
5	16	BPD aggravation, influenza
6	15	Rotavirus gastroenteritis
7	14	RSV bronchiolitis, rhinitis, pneumonia
8	15	Bronchiolitis
		Fever, bronchiolitis

BPD = bronchopulmonary dysplasia; **RSV** = respiratory syncytial virus.

Table V. Adverse events considered related to treatment[a]

	Number of subjects	
	first season palivizumab (n = 71)	second season palivizumab (n = 63)
Body as a whole	**2**	**2**
Fever	0	2
Infection	1	0
Injection site reaction	1	0
Digestive system	**1**	**1**
Diarrhoea	1	0
Anorexia	0	1
Respiratory system	**0**	**1**
Epistaxis	0	1
Nervous system	**0**	**1**
Ataxia	0	1

a All adverse events considered by the clinical investigator to have probable, possible relationship. Events not assigned causality were classified as related.

were judged by the investigator to be related to palivizumab.

Discussion

This multicentre, open-label study was undertaken to evaluate and compare the occurrence of anti-palivizumab antibodies and immunologic reactions in high-risk children receiving palivizumab during a first and second RSV season. All children in this study were at serious risk for RSV infection, primarily because of BPD. The differences observed in age and weight at enrolment were anticipated, because the second season children were receiving prophylaxis in their second year of life, whereas the first season subjects were in their first year of life. Although attempts were made to match subjects between the two groups for gestational age, the mean gestational age in the second season group was significantly lower than that of the first season group (27.9 vs 29.3 weeks, $p < 0.005$). Birth weight was also different (1.1kg second season vs 1.3kg first season, $p < 0.05$). This observation is not surprising, as the infants who have severe BPD persisting into the second year of life are more likely to have been born extremely premature and low birth weight.[4] Many of the children in the first season group may overcome their BPD by their second year.

No significant anti-palivizumab antibodies were observed between the first and final doses of palivizumab in either season, nor was antibody titre boosting observed. Further, no evidence of antibody interference with serum palivizumab concentrations was observed. Trough serum palivizumab concentrations were adequate (>40 μg/mL)[10] and comparable between the two groups. These findings suggest that the murine component of the humanised monoclonal antibody palivizumab is not immunogenic. This observation is expected, if one considers that all human IgG_1 antibodies differ only in the CDR region and that in palivizumab, it is only the CDRs that are of murine origin: >95% of the antibody is human sequences.

No evidence of clinically significant immunological reactions was observed in this study. The incidence and type of adverse events was as expected for this type of population. The most common events were those related to the respiratory system, which is to be expected, given the high prevalence of prematurity and BPD in the study population.[21,22] The majority of reported adverse events were mild or moderate in severity and most were considered to be unrelated to the administration of palivizumab. With one exception (ataxia), all events that were considered to be possibly related to palivizumab were similar to those most frequently observed in the IMpact-RSV trial.[11] Seventeen subjects (nine first season and eight second season) had serious adverse events requiring hospitalisation. Children receiving palivizumab for a second season did not experience more serious adverse events than those children receiving it for the first time. The majority of the serious adverse events involved the respiratory system, and all were considered to be not or probably not related to palivizumab.

The incidence of BPD continues to increase as a result of improved survival of very low birth weight infants.[23] Law et al. showed that lower gestational age, young postnatal age and presence

of BPD contribute independently to RSV disease severity.[24] The observation in this study that four children with BPD were hospitalised with RSV illness in a second season underscores their persistent vulnerability and that their risk for serious RSV disease extends beyond the first year of life.[4]

This study appears to confirm that palivizumab prophylaxis is safe when administered to children over two consecutive seasons. Palivizumab did not stimulate an immune response and did not appear to be associated with any allergic reaction. Serum palivizumab concentrations were similar and adequate for both groups. Children receiving palivizumab for a second season did not experience more severe adverse events than those receiving it for the first time. RSV illness occurs frequently in the highest risk subjects – those with BPD. This observation supports recommendations set forth in established usage guidelines for palivizumab.[12,13]

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References

1. Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD, editors. Textbook of pediatric infectious diseases. Philadelphia (PA): Saunders, 1998: 2084-111
2. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999 Oct 20; 282 (15): 1440-6
3. Hall CB, McCarthy CA. Respiratory syncytial virus. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 4th ed. New York (NY): Churchill Livingstone, 1995: 1501-19
4. Groothuis JR, Salbenblatt CK, Lauer BA. Severe respiratory syncytial virus infection in older children. Am J Dis Child 1990 Mar; 144 (3): 346-8
5. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988 Aug; 82 (2): 199-203
6. Boyce TG, Mellen BG, Mitchel EF, et al. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. J Pediatr 2000 Dec; 137 (6): 865-70
7. Hall CB, Powell KR, Schnabel KC, et al. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial virus infection. J Pediatr 1988 Aug; 113 (2): 266-71
8. MacDonald NE, Hall CB, Suffin SC, et al. Respiratory syncytial virus infection in infants with congenital heart disease. N Engl J Med 1982 Aug; 307 (7): 397-400
9. Piedra PA. Respiratory syncytial virus vaccines: recent developments. Pediatr Infect Dis J 2000 Aug; 19 (8): 805-8
10. Johnson S, Oliver C, Prince GA, et al. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 1997 Nov; 176 (5): 1215-24
11. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998 Sep; 102 (3 Pt 1): 531-7
12. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of respiratory syncytial virus infections: indications for the use of palivizumab and update on the use of RSV-IGIV. Pediatrics 1998 Nov; 102 (5): 1211-6
13. Carbonell-Estraney X, Giuffré L, Kimpen JLL, et al. Guidelines for the use of Synagis® (palivizumab), a humanized monoclonal antibody, for the prevention of respiratory syncytial virus (RSV) disease in high-risk infants: a consensus opinion. Infect Med 1999 Dec; 16 Suppl. G: 29-33
14. ICH Harmonized Tripartite Guideline for Good Clinical Practice (E6). International Conference on Harmonization Website. Available from URL: http://www.ifpma.org/ich5e.html#GCP [Accessed 1999 Sep 10]
15. Gardner PS, McQuillin J. Rapid virus diagnosis. 2nd ed. London: Butterworth and Co Ltd, 1980
16. Hall CB, Douglass Jr RG. Clinically useful method for the isolation of respiratory syncytial virus. J Infect Dis 1975 Jan; 131 (1): 1-5
17. Mcintosh K, Hendry RM, Fahnestock ML, et al. Enzyme-linked immunosorbent assay for detection of respiratory syncytial

virus infection: application to clinical samples. J Clin Microbiol 1982 Aug; 16 (2): 329-33
18. Subramanian KNS, Weisman LE, Rhodes T, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. Pediatr Infect Dis J 1998; 17 (2): 110-5
19. Null DM, Connor EM. Evaluation of immunogenicity and safety in children receiving palivizumab for a second RSV season [abstract]. Pediatr Res 1999; 45 (Pt 2 of 2): 170A
20. Gross R. Analytical report, evaluation of MEDI-493. Immunogenicity in children (a phase II/IV multicenter study, W99-310). MedImmune Jun 2001. (Data on file)
21. Abman SH, Groothuis JR. Pathophysiology and treatment of bronchopulmonary dysplasia: current issues. Pediatr Clin North Am 1994 Apr; 41 (2): 277-315
22. Cavalier S, Escobar GJ, Fernbach SA, et al. Postdischarge utilization of medical services by high-risk infants: experience in a large managed care organization. Pediatarics 1996 May; 97 (5): 693-9
23. Parker RA, Lindstrom DP, Cotton RB. Improved survival accounts for most, but not all, of the increase in bronchopulmonary dysplasia. Pediatrics 1992 Nov; 90 (5): 663-8
24. Law BJ, MacDonald N, Langley J, et al. Severe respiratory syncytial virus infection among otherwise healthy prematurely born infants: what are we trying to prevent? J Paediatr Child Health 1998 Nov/Dec; 3 (6): 402-4

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