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Respiratory Support for Very Low Birth Weight Infants Receiving Dexamethasone

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Abstract

Objective—To assess how neonatal intensive care units followed the American Academy of Pediatrics guidelines for use of dexamethasone in preterm infants by evaluating respiratory support at the time of dexamethasone administration.

Study design—This is an observational study of infants discharged from one of 290 neonatal intensive care units from 2003–2010. The cohort included very low birth weight (<1500 g birth weight) infants born at 32 weeks gestational age. The main outcome was respiratory support at time of exposure to dexamethasone. Significant respiratory support was defined as invasive respiratory support (conventional or high-frequency ventilation) with an $\text{FiO}_2 > 0.3$.

Results—Of 81,292 infants; 7093 (9%) received dexamethasone. At the time that dexamethasone was initiated, 4604 (65%) of infants were on significant respiratory support.

Conclusions—In accordance with the American Academy of Pediatrics recommendations, a majority of infants were on significant respiratory support when receiving dexamethasone, yet a substantial number of infants still received dexamethasone on less than significant respiratory support. Further research on reducing dexamethasone use in premature infants is required to decrease the risk of neurodevelopmental impairment.

Keywords

dexamethasone; bronchopulmonary dysplasia; chronic lung disease; very low birth weight

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Bronchopulmonary dysplasia (BPD) is the most common pulmonary morbidity among premature infants, affecting approximately 22% of all very low birth weight infants (<1500 g birth weight).(1) BPD is associated with increased risk of mortality and morbidity among survivors, including chronic pulmonary disease, pulmonary hypertension, and long-term neurodevelopmental impairment.(2) In a large number of randomized controlled trials, dexamethasone decreased the incidence of BPD,(3–5) but its use was associated with increased risk of neurodevelopmental impairment and cerebral palsy.(4, 6, 7)

Based on these findings, in 2002 the American Academy of Pediatrics (AAP) and the Canadian Paediatric Society issued a joint policy statement advising against the use of dexamethasone for the prevention or treatment of BPD, and recommended limiting the use of dexamethasone to infants on “maximal ventilatory and oxygen support.”(8) In this study, we sought to characterize the respiratory status of infants at the time of initiation of dexamethasone.

METHODS

In this observational cohort study, we identified very low birth weight (<1500 g birth weight) infants, 32 weeks gestational age, admitted from 2003–2010 from 290 neonatal intensive care units managed by the Pediatrix Medical Group. We limited the analyses to infants born from 2003–2010 to capture clinical practices after the publication of the 2002 AAP guidelines regarding the use of dexamethasone,(8) and before the new guidelines were published in 2010. The 2010 guidelines recommended against the use of high-dose dexamethasone, but reported insufficient evidence to make any conclusions regarding the use of low-dose dexamethasone.(9) We identified infants who received a course of dexamethasone beginning in the first 120 postnatal days. We excluded any infants missing data describing respiratory support at the time of dexamethasone administration.

Data were obtained from a prospective electronic medical record generated by clinicians on all infants cared for by the Pediatrix Medical Group. Data on multiple aspects of care are entered into the system to produce admission notes, daily progress notes, procedure notes, and discharge summaries.(10) Information collected included demographics, medications (without dose), respiratory support and diagnoses. This study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

A course of dexamethasone was defined as >1 consecutive day of drug. Only the first course of dexamethasone was analyzed for each infant. Death was defined as death before hospital discharge. Respiratory support and fraction of inspired oxygen (FiO₂) were defined at the time of the start of the dexamethasone course as the significant respiratory support and FiO₂ observed on either the first day of dexamethasone or the preceding day. We considered both days to describe better the significant respiratory support leading to the clinician decisions to start dexamethasone.

We grouped infants into four categories based on respiratory support: 1) no support or oxygen supplementation via hood or tent; 2) nasal cannula (NC), high-flow nasal cannula, or

nasal continuous positive airway pressure (NCPAP); 3) conventional mechanical ventilation (CMV); and 4) high-frequency ventilation (HFV). We also categorized infants by the FiO_2 required (≤ 0.3 or > 0.3). We grouped infants based on postnatal day they received dexamethasone (<14 or ≥ 14 days of life), based on AAP guidelines identifying premature infants on the ventilator beyond 2 weeks of life as having a higher risk for BPD.(9) We defined “significant respiratory support” as CMV or HFV and $\text{FiO}_2 > 0.3$.

We defined BPD as continuous respiratory support (supplemental oxygen, NC, high-flow NC, NCPAP, CMV, or HFV) between 36 0/7 to 36 6/7 weeks, postmenstrual age. Room air challenge tests were not performed uniformly. Infants who were transferred, discharged, or died before this time were evaluated on their last day of hospitalization; if such an infant was on room air, the infant was defined as not having BPD, and if the infant was on respiratory support (including supplemental oxygen), then the BPD status was defined as “missing”.

We calculated the risk of BPD or death using Neonatal Research Network (NRN) BPD risk estimator (<https://neonatal.rti.org/index.cfm?fuseaction=BPDCalculator.start>).(11) This estimator uses gestational age, birth weight, sex, race or ethnicity, postnatal day, ventilator type, and FiO_2 to determine an infant’s risk of mild, moderate, or severe BPD and death, as defined by NRN. We estimated the risk of BPD or death based on the calculator’s predictions for moderate BPD, severe BPD, or death. The estimator was only validated for infants with gestational age 23–30 weeks, birth weight 501–1249 grams, and day of life ≤ 42 , and any infants not meeting these criteria were removed from this particular analysis. The estimator assesses the risk of BPD on postnatal days 1, 3, 7, 14, 21, and 28. We rounded the day of starting dexamethasone to the nearest of these time points, until day of life 43—the day of life at which the estimator is no longer validated, so the calculated BPD risk was defined as “missing.” Using the BPD estimator, infants with $<50\%$ chance of either death or severe or moderate BPD were defined as infants in which the potential risks of steroid administration outweighed the likely benefits.(12) To assess the efficacy of the BPD risk calculator, we compared predicted incidence of BPD or death with the actual incidence of BPD and death.

Finally, to assess the practices of each site in the Pediatrix Medical Group, we determined the proportion of infants from an individual site receiving dexamethasone on significant support. For this analysis alone, we excluded sites with <10 otherwise eligible infants, as these sites were presumed to have a low patient volume, which could bias the analyses.

Statistical Analyses

We used standard summary statistics (means, percentages, 5th and 95th percentiles) to describe the study variables. Infant-level continuous and categorical variables were compared using Student *t-test* and chi-square tests, respectively. We used a univariable logistic regression to calculate the odds ratios and examine the association between admission year and proportion of infants receiving mechanical ventilation upon starting dexamethasone. Infants who received dexamethasone but did not have respiratory data were assumed to be missing at random and excluded from the analysis. All analyses were conducted using STATA 13.1 (College Station, Texas) and assumed a significance level of $\alpha=0.05$.

RESULTS

During the study period, 81,292 very low birth weight infants were identified, and 7265 (9%) received dexamethasone (Figure 1; available at www.jpeds.com). Of these, 7093 (98%) from 181 sites had respiratory status data available, representing the cohort we analyzed (Figure 1). The first course of dexamethasone began on mean day of life 38 (5th, 95th percentile; 8, 87) with a mean duration of 6 days (2, 15). The first course of dexamethasone was administered after day of life 14 in 6170 (87% of total cohort) infants. At the time of dexamethasone initiation, 4604 (65%) infants were on significant respiratory support (CMV/HFV + > 0.3 FiO₂). Of the total cohort, 6064 (85%) of infants were on the ventilator at the start of dexamethasone therapy (Table II).

Between 2003 and 2010, the proportion of infants receiving dexamethasone decreased slightly from 10% to 8%, and the percentage of infants that received significant respiratory support when treated with dexamethasone varied between 60–74%. The odds of receiving significant support decreased by 5% ($p<0.001$) for every additional year between 2003 and 2010, with the largest decrease occurring between 2003 and 2004, followed by relatively stable levels thereafter. The odds of receiving > 0.3 FiO₂ decreased 8% ($p<0.001$) for each additional year. The odds of being ventilated increased by 4% ($p=0.014$) for each additional year.

Using the Neonatal Research Network BPD risk estimator, the risk of BPD or death was calculated for 3661 (52%) of the infants (Figure 2). Within this group, the mean risk of BPD or death was 77%, and 2343 infants (69%) ultimately were diagnosed with BPD. Comparison of the actual incidence of BPD/death with predicted incidence by race, sex, respiratory support, FiO₂, and age at starting dexamethasone revealed a higher actual incidence for all subgroups, with the exception of infants receiving 0.21 FiO₂ and infants receiving dexamethasone <14 days (Table III; available at www.jpeds.com). Three thousand three hundred and seventy-five (92%) infants received dexamethasone when the risk of BPD or death was 50%. Of the 286 infants who had a risk <50%, 72 (25%) were on the ventilator, and 15 (5%) were on significant respiratory support.

Among the 180 sites with 10 infants that received dexamethasone, there was significant site variation in the level of respiratory support observed; the mean percentage of infants receiving significant support at the time of dexamethasone administration was 58% (range; 0–100%). One hundred twenty-nine (72%) of the sites had 50% of their infants on significant support at the time of dexamethasone administration, and 21 (12%) of these sites had none of their dexamethasone infants on significant support (Figure 3).

DISCUSSION

BPD is the most common pulmonary complication for premature infants and is associated with significant morbidity and mortality, including increased risk of neurodevelopmental impairment.(13–16) Dexamethasone has been shown to reduce the risk of BPD,(5, 17, 18) but is associated with neurodevelopmental impairment and cerebral palsy.(19–21) We used a large database of electronic medical records to determine the levels of respiratory support for

infants receiving dexamethasone between 2003 and 2010. We found that the majority of the time dexamethasone was used in infants on significant respiratory settings who had an increased risk of BPD, but there were still a number of infants on less than significant respiratory support at the time of dexamethasone administration.

In 2002, the AAP recommended that the use of dexamethasone be limited to infants who require significant respiratory support after the first 2 postnatal weeks of age.(8) In our study, approximately one-third of infants were not receiving significant respiratory support at the time of the first day of dexamethasone. Of all infants prescribed dexamethasone, 13% received the drug within the first 2 weeks of life. The proportion of infants receiving dexamethasone with significant respiratory support decreased from 2003–2004 and then remained relatively stable from 2004–2010. Although this overall proportion on significant respiratory support remained stable during this period, there appeared to be an increase in infants who were ventilated when starting dexamethasone and a corresponding decrease in infants who were on high levels of oxygen support. This increase in the proportion of infants who were ventilated may have partially been influenced by the DART study that was published in 2007 and recommended the use of dexamethasone in facilitating extubation (22). However, the rise we observed was gradual between 2004 and 2010 with no clear spike in 2007 (Figure 4; available at www.jpeds.com). In summary, although it appears there were some improvements in following the AAP recommendations reserving dexamethasone for infants on the ventilator, there were increases in the administration of dexamethasone in the setting of low oxygen support.

There may be some infants for whom the risk of BPD is such that the risk-benefit ratio of dexamethasone use favors the use of the drug. A meta-analysis of randomized trials of dexamethasone found that, among infants with a risk of BPD >65%, there was a statistically significant benefit for dexamethasone on the endpoint of death or cerebral palsy.(12) Infants with >50% risk of BPD were likely to benefit from dexamethasone therapy.(12, 23) Among infants for whom the BPD risk estimator could be used, 8% of infants had a BPD risk <50% when they received dexamethasone, and the majority of these were not on significant respiratory support. Comparing the predicted BPD risk to the actual risk of BPD, by race, sex, respiratory support, and start time of dexamethasone, the actual incidences of BPD/death were mostly higher than the predicted incidences. However, this analysis was limited by the fact that the risk estimator could only be used for half of the cohort (Table IV; available at www.jpeds.com). In comparison with the infants for whom the calculator could be used, the infants for whom BPD risk could not be calculated were older when they started dexamethasone, with older gestational ages and higher mean birth weights. They also had lower percentages of ventilator use (21% were non-ventilated, compared with 8%) and lower FiO₂ (34% had FiO₂ 0.3, compared with 20%) suggesting possibly lower risk of BPD at time of dexamethasone administration (Table V; available at www.jpeds.com). Furthermore, the much older age at dexamethasone administration (54 versus 24 days) suggests decreased utility in using dexamethasone to prevent BPD.

To identify whether dexamethasone administration to infants on significant support varied among sites, we examined the number of infants on significant support by neonatal intensive care unit. At a majority of the sites, over half of the infants receiving dexamethasone were

on significant support, at 28% of the sites less than half were on significant support, and at 12% of the sites none of the infants were on significant support. Thus, adherence to the published AAP guidelines was variable among the sites.

This study reports the respiratory status of infants receiving dexamethasone after the 2002 AAP guidelines. It is limited by a lack of information about the indication for dexamethasone administration. To address this, we excluded any 1-day courses of dexamethasone, because these may have been administered to assist extubation or treat upper airway obstruction. It is also possible that clinicians could have administered dexamethasone for purposes other than prevention of BPD, such as vasopressor-resistant hypotension.(24)

This study is also limited by a lack of information on dexamethasone dose. In 2010, the AAP modified the guidelines, reporting that high-dose dexamethasone should not be used, and that there was insufficient evidence to make a recommendation about the use of low-dose dexamethasone.(9) Even though the updated 2010 AAP guidelines acknowledge that some studies support the use of low-dose corticosteroids to facilitate extubation, they still advised further study of long-term risks before widespread usage of low-dose dexamethasone is recommended.(9) As revealed by the DART study (22), it is possible that administering the correct dose to high-risk infants reduces mortality and improves neurodevelopmental outcomes. Pharmacokinetic and safety studies of dexamethasone are needed to identify the optimal dose, and at this time any usage of dexamethasone for the purpose of preventing BPD, even low-dose, is not advised for infants on minimal respiratory support.

In summary, this retrospective cohort study of very low birth weight infants receiving dexamethasone demonstrates that although a large majority of infants received care in adherence to the AAP recommendations, there are still a substantial number of infants with less than significant respiratory settings or at low risk of developing BPD who received dexamethasone. Further research in optimizing the use (dose, duration, etc.) of dexamethasone is needed to reduce BPD and improve developmental outcomes.

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Appendix

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Abbreviations

AAP	American Academy of Pediatrics
BPD	Bronchopulmonary dysplasia
CPAP	Continuous peak airway pressure
CMV	Conventional mechanical ventilator
HFV	High-frequency ventilator
NC	Nasal cannula

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Figure 1.

(online): Flow diagram of the number of infants and number of sites analyzed. VLBW=very low birth weight (<1500g). GA=gestational age

Figure 2.

Predicted risk of BPD or death for infants receiving dexamethasone. Dotted line represents the 50% cut-off above which the potential risks of steroid administration outweighed the likely benefits.(12)

Figure 3. Percentage of infants receiving significant support during time of dexamethasone administration by site. Only sites with 10 or more infants receiving dexamethasone were included.

Figure 4.
(online): Percentage of infants receiving dexamethasone by site

Table 1

Demographics and clinical characteristics of infants who received dexamethasone.

Demographics and Characteristics	N=7093
Male	59%
Birth weight (g)	
<500	5%
500–749	45%
750–999	31%
1000–1499	19%
Gestational age (weeks)	
24	29%
25–27	53%
28–32	19%
Race/ethnicity	
White	46%
Black	31%
Hispanic	18%
Other	4%
Apgar score at 5 minutes	
0–3	8%
4–6	28%
7–10	64%
Died	11%
Bronchopulmonary dysplasia	73%

Table 2

Respiratory support at the initiation of dexamethasone.

	N=7093					N (%)
	FiO ₂ 0.21	FiO ₂ 0.22–0.3	FiO ₂ 0.31–0.5	FiO ₂ >0.5		
No support or oxygen via hood	63	14	10	5	92 (1)	
NC or NCPAP	101	249	346	241	937 (13)	
CMV	246	1136	1843 *	1094 *	4319 (61)	
HFV	8	70	339 *	1328 *	1745 (25)	
Total (%)	418 (6)	1469 (21)	2538 (36)	2668 (38)	7093 (100)	

* infants on significant respiratory support. NC - nasal cannula, NCPAP - nasal continuous positive airway pressure, CMV - conventional mechanical ventilator, HFV - high-frequency ventilator

Table 3**online only.** Incidence of predicted BPD and actual BPD by race, sex, respiratory support

Demographics and Characteristics	Mean Predicted BPD/Death Incidence N=3661	Actual BPD/Death Incidence N=7093	P-value
Sex			
Male (n=2180; 4171)	79%	82%	<0.001
Female (n=1481; 2919)	75%	80%	<0.001
Race/Ethnicity			
White (n=1849; 3173)	79%	82%	<0.001
Black (n=1146; 2151)	77%	80%	<0.001
Hispanic (n=666; 1268)	72%	79%	<0.001
Respiratory Support			
No support or oxygen via hood (n=11; 92)	10%	28%	<0.001
NC or NCPAP (n=295; 937)	41%	69%	<0.001
CMV (n=2097; 4319)	75%	81%	<0.001
HFV (n=1258; 1745)	90%	91%	<0.001
FiO2 Support			
0.21 (n=137; 418)	52%	39%	<0.001
0.22–0.3 (n=597; 1469)	63%	68%	<0.001
0.3–0.5 (n=1274; 2538)	74%	84%	<0.001
>0.5 (n=1653; 2668)	87%	92%	<0.001
Dexamethasone Start Day			
<14 days (n=693; 923)	77%	75%	0.009
14 days (n=2968; 6170)	77%	82%	<0.001

For each subgroup, listed above are the number of infants from the cohort for whom BPD risk could be calculated, followed by the number of infants from the total cohort.

Table 4**online only.** Reasons for inability to use BPD risk estimator

Start date of dexamethasone > 42 days	75%
Birthweight 500 g	11%
Birthweight 1250 g	11%
Gestational age >29 weeks	10%
Race/ethnicity was not white, black or Hispanic	9%
Gestational age <23 weeks	1%
Missing data	<0.1%

Table 5

online only. Comparison of infants for whom the BPD risk estimator could and could not be used.

	Able to use estimator (N=3661)	Unable to use estimator (N=3432)	P-value
Gestational Age (weeks)	25.5 (23, 28)	26.0 (23, 30)	<0.001
Birthweight (g)	785 (550, 1124)	813 (460, 1362)	<0.001
Admission Year	2006 (2003, 2010)	2006 (2003, 2010)	0.55
Postnatal age on discharge (days)	96 (25, 165)	110 (45, 193)	<0.001
Apgar	6.7 (2, 9)	6.7 (3, 9)	0.25
Postnatal age on starting dexamethasone (days)	24 (7, 40)	54 (11, 99)	<0.001
Duration of dexamethasone course (days)	6.6 (2, 16)	5.8 (2, 15)	<0.001
Ventilator use	92%	79%	<0.001
FiO ₂ >0.3	80%	66%	<0.001

Statistics above represent means (5th, 95th percentile) or percentages