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## Treatment for hypotension in the first 24 postnatal hours and the risk of hearing loss among extremely low birth weight infants

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### Abstract

**Objective:** To evaluate whether treated hypotension in the first 24 postnatal hours is associated with hearing loss in extremely low birth weight (ELBW) infants.

**Study Design:** In a cohort of 735 ELBW infants, we identified 25 with sensorineural hearing loss at 12–24 months adjusted age. For each case we selected 3 controls with normal hearing. Logistic regression models were used to adjust for confounding variables.

**Results:** 60% of cases and 25% of controls were treated for hypotension. After adjusting for confounding variables (gestational age, antenatal glucocorticoids, 5 minute Apgar < 6, insertion of an umbilical catheter, treatment with high frequency ventilation, and major cranial ultrasound abnormality), treated hypotension was associated with an increased risk of sensorineural hearing loss (adjusted odds ratio: 3.6; 95% confidence interval: 1.3–9.7).

**Conclusions:** Treated hypotension in ELBW infants in the first 24 hours of life is associated with an increased risk of sensorineural hearing loss.

### Introduction

Advanced technology and improvements in obstetric and neonatal care have increased the survival of ELBW infants, however neurodevelopmental disability still occurs frequently among this population. Improving the long term outcomes associated with prematurity in this population remains a major challenge. Sensorineural hearing loss (SNHL) is a neurodevelopmental disability that is associated with an increased risk of adverse language and cognitive outcomes. (1) SNHL occurs ten times more often among ELBW infants than among normal birth weight infants (1, 2), and in a majority of cases no etiology is identified. (2)

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There is no agreement on diagnostic criteria for hypotension and the benefits and risks of treatment of hypotension among ELBW infants. In a cohort study of extremely low gestational age newborns, 14 centers varied considerably in the proportion of infants treated for hypotension, even after adjusting for maternal and neonatal risk factors (3) This variance in practice suggests a lack of clarity about the impact of hypotension on important outcomes and thus the potential benefit of treatment (3, 4). The duration (5) and the severity (6) of hypotension have been associated with neurodevelopmental impairment, but no study has found that treating low blood pressure improves neurologic outcome. It is possible that treatment itself increases risk for adverse outcomes (4). For example, in a small sample of ELBW infants, treated hypotension was associated with an increased risk of hearing impairment (7, 8). The current study is an attempt to replicate the findings from that study. We hypothesized that treated hypotension is associated with an increased risk of hearing loss among ELBW infants.

## Methods

### Subjects:

This is a case-control study (Figure 1). Cases and controls were identified in an electronic database of babies admitted to two tertiary level neonatal intensive care units (NICU) in Winston-Salem, North Carolina. These are the only NICUs that care for extremely low birth weight (ELBW) infants in a 13-county region in northwest North Carolina. Over the interval between 11/01/1997 and 5/31/2006, 1161 ELBW infants without a major congenital anomaly were admitted to the two NICUs; 214 died in the NICU, 17 died after discharge from the NICU, and 930 survived to 24 months adjusted age and were eligible for follow up. The follow up hearing assessment for babies who were born before January 1, 2001, was performed at 12 months adjusted age; for those born after that date, the hearing assessment was performed at 18–24 months adjusted age. Follow up hearing screen was available for 735 (79%) babies; 25 (3.4%) were diagnosed with sensorineural hearing impairment (as defined below). For each case, we identified as controls the 3 ELBW infants without hearing impairment who were born closest in time to the respective case.

### Hearing assessment:

Initial auditory brainstem-evoked response testing was performed with either ALGO 2e or ALGO 3 portable devices (Natus Medical Incorporated, San Carlos, CA). All of the infants who failed the first screening had a repeat screening test. Infants who failed the repeat screening were referred for a diagnostic auditory brain stem-evoked response audiometry and an examination by an otolaryngologist. Infants who failed the ABR had visual reinforcement audiometry for hearing at the time of follow-up at 12–24 months corrected age. Hearing impairment was defined as unilateral or bilateral sensorineural hearing loss of > 35 dB. Any patient who was diagnosed with another cause of hearing loss other than the sensorineural hearing loss was excluded.

### Data sources and definitions:

Demographic and clinical data were obtained from medical records. Gestational age was based on the first trimester ultrasound when available, otherwise it was based on maternal

last menstrual period or clinical examination of the baby. Data about the receipt of antenatal steroids was obtained from medical records and was recorded as none, a partial course (less than two doses of betamethasone), or a complete course (two doses of betamethasone). Major cranial ultrasound abnormalities were identified on ultrasound scans performed, by protocol, at 7–10 days of life (“early scan”) and at 36 weeks’ postmenstrual age (“late scan”). No effort was made to standardize ultrasound interpretations. Major abnormalities were defined as moderate or severe ventricular dilatation on the late scan, cerebral white matter echolucency, or post-hemorrhagic hydrocephalus (14;15). Early-onset neonatal sepsis was defined as sepsis that manifests within the first 72 hours of life (9, 10).

### **Ascertainment of treated hypotension:**

Umbilical arterial catheters were inserted in 84 infants (87%) for blood pressure and blood gas monitoring. In these infants, blood pressures were measured continuously with a disposable pressure transducer connected to a single lumen umbilical arterial catheter, positioned between T6 and T10 in the aorta. The system was calibrated with zero reference at mid-chest level. The blood pressure of infants without an umbilical arterial catheter was estimated by the oscillometric technique with Classic-cuff Neonatal 3 (GE Healthcare) blood pressure cuffs in either the arms or legs. Blood pressure was typically measured at least every four hours during the first day of life.

By protocol during the interval covered by this study, patients were treated for hypotension if their mean arterial pressure was less than their gestational age. Initial treatment was a 10 ml/kg infusion of normal saline. If the mean arterial blood pressure did not increase to at least equal the gestational age, a dopamine infusion was initiated and was increased to 20 micrograms/kilogram/minute until the mean arterial blood pressure increased to at least the gestational age. If the mean arterial blood pressure did not increase to equal the gestational age, treatment was initiated, in sequence, with dobutamine, followed by hydrocortisone, and then with epinephrine infusion as long as the mean arterial blood pressure remained below the gestational age. For the present study, we prospectively defined treated hypotension as receipt of any of these treatments.

### **Data analysis:**

Descriptive statistics were obtained for groups of infants with and without hearing impairment and groups with and without treated hypotension. Groups were compared using chi square tests for categorical variables and Wilcoxon rank sum test for continuous variables. Variables that were associated at the  $p < 0.2$  level with either hypotension or hearing impairment were entered in multivariate logistic regression models. By stepwise backwards elimination of the variable with the highest  $p$  value, we arrived at a model in which all variables were significant at  $p < 0.1$ . We used a chi square test for trend to analyze the relationship between the risk of sensorineural hearing loss and the level of support provided for treatment for hypotension in the first 24 postnatal hours, categorized as follows: 1-no volume expansion, vasopressors, or hydrocortisone; 2-volume expansion without vasopressors or hydrocortisone; 3-vasopressor without volume or hydrocortisone; 4- volume expansion plus vasopressor without hydrocortisone; and 5-volume expansion plus vasopressor plus hydrocortisone. All analyses were performed by using SAS Version 9.0.

### Sample size considerations:

Based on a multi-center study, in which Wake Forest participated [18], we estimated that 50% of infants would have experienced hypotension. Based on this estimate, our sample of 25 cases and 75 controls provided 80% power to detect odds ratios of 4 or higher with  $\alpha=0.05$ .

The Wake Forest University and Forsyth Medical Center institutional review boards approved this study and the waiver of consent.

## Results

### Characteristics of infants with and without hearing impairment (Table 1)

In the cohort of 735 extremely low birth weight infants, 25 (3.4%) were found to have hearing impairment. The median gestational age, but not the median birth weight, of infants with hearing impairment was significantly lower than that of infants without hearing impairment. Infants with hearing impairment were more likely to have been born to a mother who did not receive antenatal steroids, to have had a five minute Apgar score less than 6, to have been treated with high frequency ventilation on the first day of life, to have had an umbilical artery catheter placed, and to have had a major cranial ultrasound abnormality on the initial cranial ultrasound evaluation.

### Indicators of hypotension among infants with and without hearing impairment (Table 2)

The median lowest mean arterial blood pressure in the first 24 hours was lower among infants with hearing impairment than infants without hearing impairment ( $p < 0.002$ ). A greater proportion of infants with hearing impairment received treatment to increase blood pressure (15/25 versus 19/75; odds ratio: 4.4; 95% confidence limits: 1.7, 11.5). The most frequently received treatment for hypotension was an infusion of volume followed by a dopamine infusion, which was used in 79% of infants who were treated for hypotension and 23% of control infants. Less than 10% of infants treated for hypotension received two vasopressors or hydrocortisone.

### Characteristics of infants with and without treated hypotension (Table 3)

The median gestational age, but not the birth weight of infants with hearing impairment was significantly lower than that of infants without hearing impairment, and infants with hearing impairment were more likely to have had a five minute Apgar score less than 6, to have been treated with high frequency ventilation on the first day of life, to have had an umbilical artery catheter placed, and to have had a major cranial ultrasound abnormality on the initial cranial ultrasound evaluation.

### Multivariate analysis of the association of hypotension and hearing impairment

The factors that were associated with either hearing impairment and treated hypotension at a significance level of less than 0.2 (i.e., antenatal steroids, gestational age, five minute Apgar  $< 6$ , treatment with high frequency ventilation, umbilical artery catheter placement, and major cranial ultrasound abnormality) were entered in a logistic regression model in which the outcome was hearing impairment at 12–24 months corrected age, and treated

hypotension was entered as an independent variable. After stepwise elimination of variables not significant at the  $p < 0.1$  level, two variables remained. Treated hypotension was associated with 3.6 times increase ( $p=0.01$ ) in the odds of hearing impairment with 95% CI: (1.3– 9.7) when adjusted for gestational age and maternal treatment with antenatal steroids. As can be seen in Table 2, hearing loss was associated with an increasing level of support for blood pressure (test for trend  $p < 0.01$ ).

## Discussion

The primary finding from this study is that treated hypotension in ELBWs was associated with subsequent sensorineural hearing impairment measured at 12–24 months corrected age. In the current context, treated hypotension refers primarily to treatment with volume infusion, followed by dopamine, initiated during the first 24 hours of life for those infants with mean arterial blood pressure less than their estimated gestational age. Using this criterion to define hypotension, we can estimate, based on data from the controls in the current study, that treatment for hypotension in the first 24 hours occurs in 25% of extremely low birth weight infants admitted to our neonatal intensive care units.

The frequency of hearing impairment that we observed in a sample of extremely low birth weight infants was 3.4% which is similar to the prevalence of hearing aid use among extremely low birth weight infant in the NICHD Neonatal Research Network study (3%) (11). Bilateral hearing impairment requiring amplification in recent reports ranged from 1% to 9% of ELBW infants. In NICHD Phototherapy Trial, rates of bilateral hearing impairment with amplification were 1% in the aggressive phototherapy arm and 3% in the conservative phototherapy arm (12). In a Canadian study of preterm infants  $< 800$  g, the overall rate of bilateral permanent HL was 9% (50/586 infants) (13) and rates of permanent bilateral hearing loss were higher at lower gestational age (14). Based on these estimates of prevalence, hearing impairment would be the third most prevalent major developmental impairment identifiable during infancy among extremely low birth weight infants after cognitive impairment and cerebral palsy (15). Despite this substantial frequency, few etiologic studies have been completed of hearing impairment among extremely low birth weight infants.

Multiple neonatal risk factors associated with sensorineural and/or conductive hearing loss were described by Joint Commission on Infant Hearing in 1994. In 2000, Vohr et al. found that the most common of these factors were ototoxic medications (44.4%). (16). Unfortunately, we did not collect data on ototoxic drug exposure and are not able to address this potential risk factor. However, in 2003 De Hoog et al. studied 625 neonates over 2 years and found that exposure to vancomycin alone or in combination with tobramycin or furosemide was not associated with a significant rise in hearing screening failure rates. (17) Similarly, in a retrospective study of more than 7000 infants, Gopel et al found no association between aminoglycosides and hearing loss (18). Wang et al also found there was no statistically significant difference in abnormal hearing screening in 1020 premature babies who were exposed to prolonged furosemide (19). Despite historical concerns, a large body of evidence now supports the favorable safety profile of vancomycin, aminoglycosides

and furosemide, mainly because of conservative dosing regimens in neonates and dose modification of drugs based on serum levels (20, 21).

Multiple studies have shown that there is enormous variation in diagnosis, management and clinical practice of hypotension in extremely low gestational age infants. (3, 4, 14, 15). Laughon et al showed that the proportion of infants treated for hypotension ranged from 29% to 98% in extremely low gestational age newborns, involving fourteen medical centers (3). The lower proportion treated for hypotension in the current study (25% of controls) can be explained because only surviving infants, who would be expected to be treated less often, were the subjects of this study. Nonetheless, the very large variation in the frequency of treatment indicates how limited the evidence is upon which treatment of hypotension practices are based, and the importance and need of clinical trials related to such practices.

The association reported here has been previously reported by Fanaroff et al (7), although in that study, perhaps because of the small number of infants with hearing impairment, the association was not statistically significant in multivariate analysis. In that study, 33% of a sample of extremely low birth weight survivors were treated for hypotension, defined as receipt of a fluid bolus, vasopressor, or glucocorticoids to increase blood pressure in the first 72 hours, and initiated at the discretion of the treating clinicians. In the current study, using a mean arterial blood pressure less than estimated gestational age as the criterion for treatment, the frequency of treatment for hypotension was slightly over 25% based on the frequency among control subjects. Fanaroff et al defined hearing impairment as sensorineural, conductive, or mixed hearing loss. We focused on sensorineural hearing loss (7,8) because we are not able to posit a biological mechanism by which hypotension could result in conductive hearing loss. Our observational study does not allow us to draw a conclusion as to whether hypotension, treatment for hypotension, or neither of these is causally related to hearing impairment. Randomized trials are needed to evaluate the influence of treatment (22).

In healthy infants, children, and adults, changes in peripheral blood pressure tend not to result in appreciable changes in cerebral blood flow. However, there is evidence suggesting that the ability to maintain sufficient cerebral blood flow despite decreased systemic blood pressure might be impaired in extremely low birth weight infants. If so, hypotension might reduce cerebral blood to a point at which brain damage could occur. In some studies(23–26), but not in others (5, 27–30), lower blood pressure was associated with a higher risk of IVH or cerebral white matter damage, as detected with ultrasound. Fewer studies have analyzed the relationship of hypotension and developmental outcomes in extremely low birth weight infants. A mean blood pressure < 30 mm Hg on two or more occasions was associated with an increased risk of cerebral palsy (31), and hypotension (defined as a systolic blood pressure < 35 mmHg for infants with birth weight < 750, and < 40 mmHg for infants with birth weight 750–1500 grams) was associated with lower scores on the Bayley Scales of Infant Development at 24 months adjusted age (32). Low superior vena cava blood flow during the first 24 hours of life, a marker of low systemic blood flow, has been associated with an increased risk of adverse neurodevelopmental outcome at 3 years of age (33).



Hypotension has been identified as a possible causative factor of acute sensorineural hearing loss in adults(34). Several reports have supported the hypothesis that hemodynamic imbalance plays a role in the genesis of (35)cochlear damage. Experiments in animals indicate that inner ear blood flow is reduced after a hemorrhagic hypotension (23), suggesting a mechanism by which systemic hypotension might result in sensorineural hearing loss.

Limitations of the current study include the relatively small sample of infants drawn from admissions to only two hospitals which might limit the degree to which the conclusions can be generalized. In addition, data about hypotension were not collected prospectively, so that more severely ill infants might have had more frequent measurement of blood pressure, biasing the ascertainment of hypotension. Furthermore, the relationship of sensorineural hearing loss and the existence of non-syndromic hearing loss genes were not studied because no bio specimens were stored for exploring genome. On the other hand, the sample used in the current study provided greater statistical power than the only previous study of early hypotension and hearing impairment, and the outcome of interest was more homogenous.

Our finding that treated hypotension on the first day of life has implications for researchers interested in the identification of strategies for reducing the prevalence of developmental impairments among the most vulnerable newborns. If this finding is replicated in larger multi-site studies, randomized trials of treatments to increase blood pressure in extremely low birth weight and extremely low gestational age newborns should include careful assessment of hearing at follow up.

## Conclusion:

Our analysis suggests that hearing impairment is associated with treated hypotension in the first day of life in extremely low birth weight infants. Randomized trials of treatment for hypotension are needed to evaluate whether the association of hearing loss is causal and is related to hypotension or treatments of hypotension. Awaiting the results of such trials, clinicians should be aware of that treatment for hypotension or hypotension itself might be a risk factor for subsequent hearing impairment among ELBW infants and these infants should be closely monitored for hearing impairment especially during the first two years of life.

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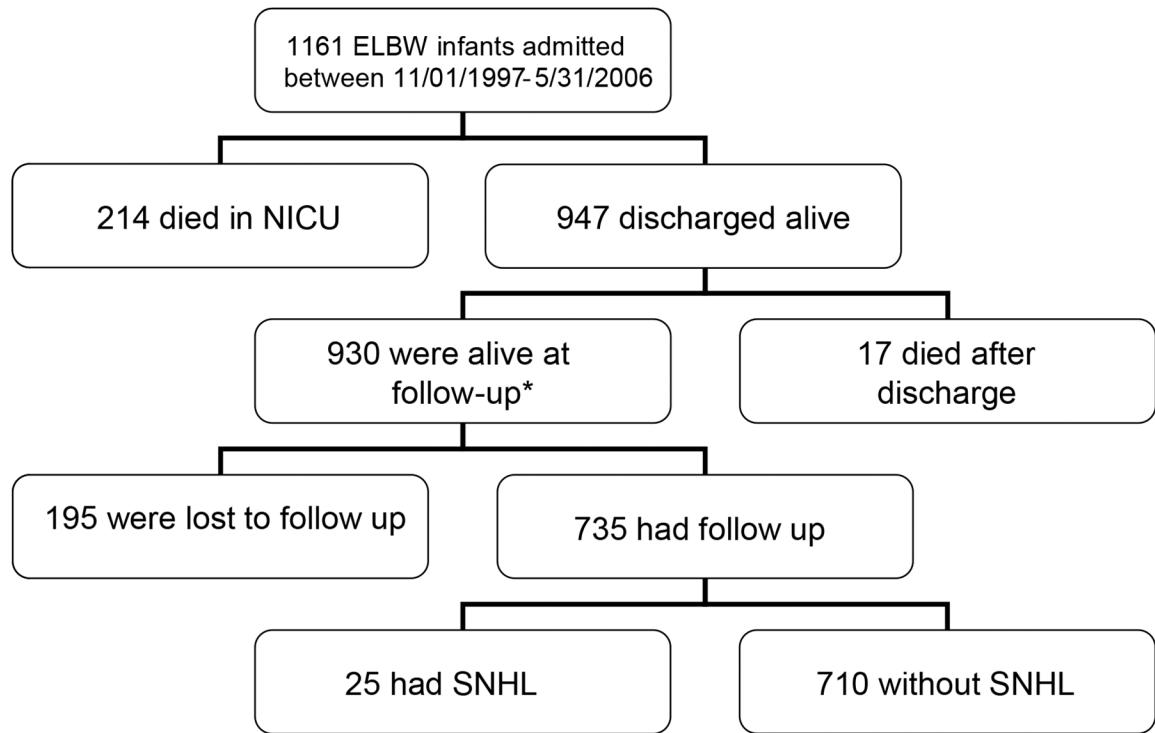
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**Figure 1.**  
Flow diagram for study subjects

**Table 1**

Characteristics of infants with and without hearing impairment. Data are group medians (5<sup>th</sup> and 95<sup>th</sup> percentiles) or percentages.

Variable	Hearing Impairment n = 25	No Hearing Impairment n= 75	p
Birth weight, grams	750 (555–932)	833 (579–969)	0.1
Birth weight in lowest quartile (%)	32	21	0.3
Gestational age, weeks	25 (23–28)	26 (23–30)	0.004
Gestational age in lowest quartile (%)	48	17	0.002
Male %	56	61	0.6
Race			0.8
White, non-Hispanic (%)	52	60	
Black (%)	36	29	
Hispanic (%)	12	11	
Antenatal steroids – complete course (%)	44	63	0.1
Antenatal steroids – partial course (%)	20	20	
No antenatal steroids (%)	36	17	
5 minute Apgar < 6 (%)	32	17	0.1
High frequency ventilation (%)	76	93	0.02
Umbilical artery catheter (%)	100	87	0.06
Major cranial ultrasound abnormality (%)	32	13	0.04
Early sepsis (%)	4	1	0.4

**Table 2**

Treated Hypotension<sup>a</sup> among infants with and without hearing impairment. Data are group medians (5<sup>th</sup> and 95<sup>th</sup> percentiles in parentheses) or percentages (number of infants in parentheses)

Variable	Hearing Impairment n=25	No Hearing Impairment n=75	P value
Lowest mean arterial blood pressure (mm Hg)	21 (12–28)	26 (19–38)	0.002
Treatments given to increase blood pressure			0.008 <sup>a</sup>
None	40 (10)	75 (56)	
Volume infusion less than 15 ml/kg	12 (3)	1 (1)	
Volume infusion greater than 15 ml/kg	4 (1)	0	
Vasopressor	12 (3)	9 (7)	
Volume + Vasopressor	28 (7)	15 (11)	
Volume + Vasopressor + Hydrocortisone	4 (1)	0	

<sup>a</sup> p value for test for trend; no treatment/volume only/vasopressor only/volume and vasopressor/volume, vasopressor, and hydrocortisone

**Table 3**

Characteristics of infants with and without hypotension. Data are group medians (5<sup>th</sup> and 95<sup>th</sup> percentiles) or N (percent).

Variable	Treated for Hypotension <sup>a</sup> n=34	Not treated for Hypotension n=66	p
Birth weight, grams	780 (512–955)	844 (635–969)	0.08
Birth weight in lowest quartile (%)	29	21	0.4
Gestational age, weeks	25 (23–28)	26 (23–30)	0.05
Gestational age in lowest quartile (%)	26	24	0.8
Male (%)	56	62	0.6
Race			0.8
White, non-Hispanic (%)	53	60	
Black (%)	37	29	
Hispanic (%)	10	11	
Antenatal steroids – complete course (%)	53	61	0.4
Antenatal steroids – partial course(%)	18	21	
No antenatal steroids (%)	29	18	
5 minute Apgar < 6 (%)	33	16	0.05
High frequency ventilation (%)	20	7	0.03
Umbilical artery catheter (%)	100	85	0.01
Major cranial ultrasound abnormality (%)	27	14	0.1

<sup>a</sup>hypotension refers to receipt of a bolus of saline, dopamine, dobutamine, or hydrocortisone