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## The impact of prenatal and neonatal infection on neurodevelopmental outcomes in very preterm infants

Iris Lee, BA<sup>1</sup>, Jeffrey J. Neil, MD, PhD<sup>1,2,3</sup>, Phyllis C. Huettner, MD<sup>4</sup>, Christopher D. Smyser, MD<sup>1,2</sup>, Cynthia E. Rogers, MD<sup>5</sup>, Joshua S. Shimony, MD, PhD<sup>3</sup>, Hiroyuki Kidokoro, MD<sup>1</sup>, Indira U. Mysorekar, PhD<sup>6</sup>, and Terrie E. Inder, MBChB, MD<sup>1,2,3</sup>

<sup>1</sup>Department of Pediatrics, Washington University in St. Louis, St. Louis, USA

<sup>2</sup>Department of Neurology, Washington University in St. Louis, St. Louis, USA

<sup>3</sup>Mallinckrodt Institute of Radiology, Washington University in St. Louis, St. Louis, USA

<sup>4</sup>Department of Pathology and Immunology, Washington University in St. Louis, St. Louis, USA

<sup>5</sup>Department of Psychiatry, Washington University in St. Louis, St. Louis, USA

<sup>6</sup>Department of Obstetrics and Gynecology, Washington University in St. Louis, St. Louis, USA

### Abstract

**Objective**—Determine the association of prenatal and neonatal infections with neurodevelopmental outcomes in very preterm infants.

**Study Design**—Secondary retrospective analysis of 155 very preterm infants at a single tertiary referral center. General linear or logistic regression models were used to evaluate the association with hospital factors; brain injury, growth, and development; and neurobehavioral outcome.

**Result**—Necrotizing enterocolitis with sepsis was associated with reduced transcerebellar diameter (38.3 vs 48.4 mm,  $P < 0.001$ ) and increased left ventricular diameter (12.0 vs 8.0 mm,  $P = 0.005$ ). Sepsis alone was associated with higher diffusivity in the left frontal lobe ( $1.85$  vs  $1.68 \times 10^{-3}$  mm<sup>2</sup>/s,  $P = 0.001$ ) and right cingulum bundle ( $1.52$  vs  $1.45 \times 10^{-3}$  mm<sup>2</sup>/s,  $P = 0.002$ ). Neurobehavioral outcomes were worse in children exposed to maternal genitourinary infection (Cognitive Composite:  $\beta = -8.8$ ,  $P = 0.001$ ; Receptive Language Score:  $\beta = -2.7$ ,  $P < 0.001$ ; Language Composite:  $\beta = -14.9$ ,  $P < 0.001$ ) or histological chorioamnionitis (Language Composite  $\beta = -8.6$ ,  $P = 0.006$ ), but not neonatal infection.

**Conclusion**—Neonatal infection was associated with changes in brain structure but not with neurobehavioral outcomes whereas the opposite pattern was observed for maternal genitourinary tract infection. These findings emphasize the potential importance of infections during pregnancy on the neurodevelopmental outcomes of preterm infants.

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Corresponding Author: Terrie E. Inder, MBChB, MD, Department of Pediatrics, Neurology, and Radiology, Campus Box 8116, 660 S. Euclid Ave., Washington University in St. Louis, St. Louis, MO 63110. Telephone: +1-314-4542200. Fax: +1-314-4544633.

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## Keywords

brain injury; metrics; diffusion; behavior

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## INTRODUCTION

Children born very preterm (<30 weeks' gestation) score lower on intelligence scales<sup>1</sup> and perform more poorly on tests of motor functioning,<sup>2</sup> language,<sup>3</sup> memory,<sup>4</sup> attention, and executive functioning<sup>5, 6, 7</sup> than children born full-term. The increasing survival rates of very preterm infants have thus led to greater research focus on the pathogenesis of these adverse neurobehavioral outcomes.

Neurodevelopmental outcomes in very preterm children may be influenced by many factors, two of which are prenatal and neonatal infection,<sup>8, 9, 10</sup> thought to be related to a unique sensitivity of pre-oligodendrocytes in immature white matter to inflammatory-mediated injury.<sup>15, 16</sup> For example, histological chorioamnionitis has been associated with increased rates of cerebral palsy.<sup>11</sup> Maternal urinary tract infection<sup>12</sup> and neonatal sepsis<sup>8</sup> have also been associated with poor neurobehavioral outcomes. Interestingly, while neonatal sepsis is associated with increased extent of white matter injury,<sup>13, 14</sup> an association was not observed between maternal infections ultrasonographic brain structural abnormalities.<sup>12</sup> However, these studies did not assess both prenatal and neonatal infections in the same cohort. Furthermore, despite the association between chorioamnionitis and cerebral palsy, other studies have not observed additional neurobehavioral alterations.<sup>17, 18, 19</sup> Given the high rates of prenatal<sup>17</sup> and neonatal<sup>8</sup> infections in very preterm infants, accurate identification of the risk of neurodevelopmental impairment associated with such infections may render an opportunity for targeted neuroprotection.

In this retrospective cohort study, we assessed the association between prenatal and neonatal infection and three magnetic resonance imaging (MRI) measures of brain structure: white matter injury, brain structure metrics (measures of growth), and diffusion (a measure of microstructure). We also assessed the association between infections and neurobehavioral outcome at two years of age. We hypothesized that the presence of prenatal or neonatal infection would correlate with adverse neurobehavioral outcomes and altered white matter structure.

## MATERIALS AND METHODS

### Study population

This investigation was a secondary retrospective analysis of patients recruited for a larger study prospectively investigating the factors influencing brain development in preterm infants. Patients in this cohort were recruited from the neonatal intensive care unit (NICU) at St. Louis Children's Hospital between 2007 and 2012 in studies approved by the Washington University in St. Louis Institutional Review Board. All infants were enrolled within the first 48 hours of birth. Exclusion criteria included chromosomal abnormalities or

proven congenital infections (e.g., cytomegalovirus, toxoplasma, rubella). Written, informed consent was obtained from parents.

### **Clinical methods**

Chart review provided an extensive database of prenatal and neonatal data. Maternal report was employed to define infant race, which was dichotomized as African-American or non-African American. Chart abstraction of records and laboratory results at time of delivery and emergency room visits to Barnes-Jewish Hospital during pregnancy was used to determine the presence of genitourinary infections. These included urinary tract infections, gonorrhea/chlamydia, bacterial vaginosis, vaginitis, and trichomoniasis. Infants were categorized for neonatal infection as previously defined by Stoll et al.<sup>20</sup> No analyses were conducted on meningitis because of the small number of affected infants (n=2).

### **Placental Evaluation**

An experienced placental pathologist (P.H), blinded to infant and clinical outcomes, reviewed hematoxylin-and-eosin-stained slides for histological chorioamnionitis and fetal vasculitis.<sup>21</sup> Histological chorioamnionitis included inflammation of the chorionic membrane, free membrane chorioamnionitis, subchorionitis, and chorionitis. Fetal vasculitis included vasculitis (in the umbilical cord or placenta), phlebitis, arteritis, or funisitis.

### **Imaging**

Infants received serial magnetic resonance imaging (MRI) during their NICU stay as a part of the prospective study. Magnetic resonance images were collected at term-equivalent postmenstrual age (PMA) and assessed by a single investigator (H.K) blinded to infection status. A Siemens Magnetom Trio 3-T scanner with an infant head coil was used according to previously published acquisition methods.<sup>22</sup> White matter injury was classified as periventricular leukomalacia (PVL), cerebellar hemorrhage, or intraventricular hemorrhage.<sup>23</sup> In addition, intraventricular hemorrhage was recorded from independent evaluation of all cranial ultrasounds undertaken during the infants' NICU stay, grading them on the basis of the Papile classification (grades 1–4). For brain structure metrics, six measurements were made on tissue and fluid spaces on MR images: bifrontal, biparietal, transverse cerebellar, right and left ventricular diameters, and interhemispheric distance.<sup>24</sup> Diffusion MRI analysis was performed with laboratory-written software. Regions of interest were placed in the genu and splenium of the corpus callosum, cingulum bundle, posterior and anterior limbs of the internal capsule, and optic radiations. In addition, white matter regions of interest were placed in the superior frontal lobes and centrum semiovale. The following parameters were measured with Analyze (Mayo Clinic, Rochester, MN): mean diffusivity, fractional anisotropy, axial diffusivity, and radial diffusivity.

### **Neurobehavioral testing**

At age two years, participants underwent developmental assessment with the Bayley III Scales of Infant Development and behavioral evaluation with the Infant Toddler Social and Emotional Assessment,<sup>25</sup> which assesses social-emotional problems and competencies. Four

domains are scored: social-emotional competence, externalizing, internalizing, and dysregulation.

### Statistical analysis

SPSS 19 (IBM Corporation, 1989, 2010) was used for statistical analyses. For unadjusted comparisons, statistical significance was determined by Fisher's Exact Test for dichotomous outcome variables, independent Student's t-test for continuous and normally distributed outcome variables, and Mann-Whitney U test for continuous and nonparametric outcome variables (length of stay, days of ventilation, and days of total parenteral nutrition [TPN]). Levine's test for equality of variance was used to test normality. Analysis of covariance was used to adjust the natural log of nonparametric outcomes for PMA. For continuous variables, including metrics and diffusion measures, adjusted models were analyzed with a general linear model. Missing data were eliminated listwise. Known predictors of outcomes were entered into models using forced entry. These included PMA at birth for impact on clinical factors and white matter injury; race, gender, and PMA at term-equivalent scan for brain metrics and diffusion; and social risk for two-year neurobehavioral outcomes. A social risk score, modified from another study,<sup>26</sup> was calculated from family structure; primary caregiver education level, occupation, and employment status; language spoken at home; and maternal age at birth. Race was not used to control for two-year developmental outcomes because it was associated with social risk (data not shown).

Log conversion was undertaken to assess the influence of infection on highly skewed hospital factors such as days of TPN, days of ventilation, and length of stay. Additionally, because days of TPN and ventilation were associated with sepsis, they were dichotomized by upper quartile of exposure and used to control for outcome. Because of the number of variables examined, a *P*-value cutoff of 0.01 was considered significant to reduce the risk of Type I error. For our primary outcome measure of neurobehavioral outcome, we used a two-tailed t-test with  $\alpha = 0.05$  and possessed 80% power to detect true differences between means that were 7.75 in cognitive, 9.5 in language, and 9.8 in motor scores.

## RESULTS

### Study population

The study population consisted of 155 infants—102 singletons, 42 twins, and 11 triplets—with a median gestational age at birth of 26 weeks. This represented 43% of the 360 eligible infants admitted during the study period. Lack of parental access due to maternal illness or sedation was the most common reason for failure to enroll. Race and gender of the infants enrolled did not differ from those not enrolled ( $P > 0.05$ ). We were unable to enroll one infant from each of four twin pairs and one triplet set because of very early death. Both maternal records and placental histology were available for 138 infants. Twelve records were not available because of birth at an outside hospital. An additional five placental records were missing because of obstetrical emergencies that limited placental examination. These consisted of emergent home delivery, severe maternal pre-eclampsia and bleeding, and death of the first twin.

## Infections

Histological chorioamnionitis was the most frequent prenatal infectious/inflammatory exposure, affecting 60 infants (43.5%). Fetal vasculitis was noted in 36 infants (24.7%), all of whom were exposed to histological chorioamnionitis. Additionally, 43 infants (31.2%) were exposed to a maternal genitourinary tract infection. Although 53% of infants exposed to maternal genitourinary tract infections were also exposed to histological chorioamnionitis, there was no association between infants exposed to histological chorioamnionitis or fetal vasculitis and those exposed to prenatal genitourinary tract infection. Three infants (5%) exposed to histological chorioamnionitis had early onset sepsis (sepsis within 48 hours of delivery). Fifty-eight infants (42.0%) were not exposed to any prenatal infection or inflammation.

Postnatally, four infants (2.6%) died within three days of birth, 35 (22.6%) had at least one episode of sepsis, 10 (6.5%) had necrotizing enterocolitis (NEC), seven (4.5%) had NEC with sepsis, two (1.3%) had meningitis, and 24 (15.5%) had clinically suspected infection. Forty-nine infants (31.6%) did not have any neonatal infection. Baseline characteristics between infected and control groups were not statistically different except for a higher rate of preeclampsia in the control group than in those with sepsis, histological chorioamnionitis, or fetal vasculitis (Table 1).

### Associations between infection and hospital course

Prenatal genitourinary and placental infections were not associated with length of stay or days of ventilation or TPN (data not shown). For neonatal infection, clinically suspected infection and sepsis with NEC were associated with more days of ventilation and TPN than no infection. Sepsis and NEC without sepsis were also associated with more days of TPN. Clinically suspected infection and sepsis were associated with prolonged length of stay (Table 2). All associations were controlled for PMA at birth.

### Infection, death, and white matter injury

Eighteen infants died before discharge. After controlling for PMA, NEC without sepsis was the only prenatal or neonatal infection related to death (OR 14.4, 95% CI 2.1–99.5,  $P = 0.007$ ), but not after additionally controlling for days of TPN and ventilation ( $P = 0.99$ ). Prenatal infection was not associated with death.

Clinically suspected infection was associated with cerebellar hemorrhage on univariate analysis, after controlling for PMA, and additionally after controlling for days on TPN and ventilation. Sepsis trended towards an association with intraventricular hemorrhage but did not meet our standard for statistical significance (Table 3). PVL was evaluated qualitatively and was not associated with any of the examined infections (data not shown). Representative images of PVL, cerebellar hemorrhage, and intraventricular hemorrhage are shown in Figure 1.

A combined outcome of intraventricular hemorrhage grades 3 and 4, PVL, cerebellar hemorrhage, or death before 44 weeks PMA was associated with neonatal infection (except for sepsis with NEC); this association persisted after controlling for PMA at scan (Table 3).

After controlling for days of TPN and ventilation, only sepsis and clinically suspected infection were still associated with a higher rate of white matter injury or death. Prenatal infection was not associated with death, injury, or the combined outcome (data not shown).

### Brain structure metrics at term equivalent

Univariate analysis between brain structure metrics and neonatal infection showed associations between sepsis with NEC and biparietal diameter, transcerebellar diameter, and left ventricular diameter (Table 4). These associations persisted after controlling for gender, PMA at scan, and race. Except for biparietal diameter, these associations persisted after additionally controlling for days on TPN and ventilation (Table 4). Prenatal infection was not associated with changes in brain metrics (data not shown).

### Diffusion measures

Univariate analyses revealed no significant associations between prenatal infections and measures of diffusion. After controlling for race, gender, and PMA at scan, histological chorioamnionitis was associated with higher fractional anisotropy in the body of the corpus callosum (0.52 vs. 0.46;  $P = 0.008$ ). This resulted from lower radial diffusivity (1.06 vs. 1.2;  $P = 0.006$ ). These associations remained significant after controlling for days on TPN and ventilation (0.44 vs 0.5,  $P = 0.003$  and 1.1 vs 1.3,  $P = 0.004$  respectively). Prenatal infections were not related to any other diffusion measures.

For neonatal infections, neonatal sepsis and alterations in mean diffusivity in the left frontal lobe and right cingulum. Additionally, higher values for axial and radial were observed in the left frontal lobe. For the right cingulum bundle, neonatal sepsis was not associated with increased axial or radial diffusivity (Table 4). All diffusion measures were controlled for gender, race, PMA at scan, and days of TPN and ventilation.

### Neurobehavioral outcomes

Eighty-six of 104 eligible subjects (83%) returned for follow-up at two years of age. Infants with private insurance ( $P = 0.01$ ) and who were not African American ( $p = 0.003$ ) were more likely to return for follow up. The infant's gender did not associate with return for follow-up. On univariate analysis, only maternal genitourinary infections were associated with changes in neurobehavioral outcomes (Table 5), which persisted after controlling for social risk. After controlling for social risk, histological chorioamnionitis was associated with a reduced Language Composite score ( $\beta = -8.6$ , 95% CI:  $-14.7$  to  $-2.5$ ,  $P = 0.006$ ). Infection was not associated with Infant Toddler Social and Emotional Assessment scores.

## DISCUSSION

This study complements recent literature on the adverse associations between prenatal and neonatal infection and white matter injury, brain structure metrics, and diffusion in very preterm infants. Importantly, maternal genitourinary tract infections were not associated with any of the measured neuroimaging structural domains, but were associated with adverse neurobehavioral outcomes. In contrast, neurobehavioral outcomes at two years of

age did not differ significantly between those with and without neonatal infection, but did impact perinatal outcomes.

The association between histological chorioamnionitis and neurodevelopmental outcomes of infants has varied in the literature. In our study, histological chorioamnionitis was not associated with white matter injury or brain structure metrics. However, it was associated with higher anisotropy, reflected by lower radial diffusivity, in the corpus callosum. Reductions in radial diffusivity in the immature brain are often thought to reflect increasing myelination and maturation within the fiber tracts. However, one recent study showed a relationship between histological chorioamnionitis and a decreased mental developmental index score at 18 months;<sup>18</sup> another reported an association between cerebral palsy and histological chorioamnionitis.<sup>11</sup> Others have not observed associations between histological chorioamnionitis and neurobehavioral outcomes at two years.<sup>19, 40</sup> Histological chorioamnionitis in our cohort was associated with a lower Bayley Composite Language score at two years of age. Unlike the previous studies, we uniquely controlled for social risk, which is associated with cognitive impairment at two years.<sup>40</sup> The lack of association between fetal vasculitis and neurobehavioral outcomes in our study was not consistent with a prior report showing associations between funisitis and moderate to severe disability.<sup>19</sup> However, we did not differentiate between fetal inflammation in different placental compartments.

Interestingly, the neurobehavioral consequences associated with infection were most notable in the domain of language and especially in association with maternal genitourinary tract infections during pregnancy. These associations were stronger after adjusting for sociodemographic variables that may be associated with prenatal infection. Prior studies have shown associations between maternal infection at delivery and the risk of cerebral palsy in preterm infants<sup>9</sup> as well as between urinary tract infections and the risk for mental retardation. Although we were unable to disentangle the impact of antibiotic use on neurodevelopmental outcomes<sup>27</sup> because of almost universal antibiotic use, our findings highlight the importance of maternal genitourinary tract infections as an arena that may be worthy of targeted fetal neuroprotection. Furthermore, the lack of MRI structural correlates complements prior studies examining ultrasonographic structural differences<sup>12, 28</sup> and suggests the involvement of functional dysregulation in observed neurobehavioral changes.

Neonatal infection, in contrast, was not associated with two-year neurobehavioral outcomes, but was associated with several brain structural changes. We found associations between neonatal infections and smaller trans cerebellar and left ventricular diameters, indicating that brain growth was impaired. Additionally, we observed associations between neonatal infections and increased diffusivity in the left frontal lobe, indicating that brain microstructure was abnormal. These findings are consistent with prior studies,<sup>29, 30, 31, 32, 33</sup> and support the role of infection/inflammation in perturbing white matter microstructural integrity. The fact that neonatal infections were associated with brain structural changes but not neurobehavioral outcomes may be related to the timing, extent, or other unique characteristics of these infections. However, other studies, which used different outcome measures than we used, have observed an association between neonatal infection and neurobehavioral outcomes.<sup>8</sup> It also is possible that our measurements of neurobehavioral

outcomes at age two years may not accurately predict future clinical outcomes.<sup>34, 35, 36</sup> Sophisticated testing of higher cognitive and executive skills at older ages may reveal an association between neonatal infections and neurobehavioral outcomes.

In addition to defects in brain structure metrics, neonatal infection was also associated with higher rates of white matter injury. We found an increased incidence of hemorrhagic brain injury, particularly cerebellar hemorrhage, and a combined outcome of death and injury among infants with sepsis or clinically suspected infection. Our study did not reveal an association between neonatal infection and PVL as was reported by Stoll et al<sup>20</sup>, which may be because of lower power in our study or improvements in hospital practices.<sup>37</sup> The associations between neonatal infection and increased duration of hospitalization, TPN, and ventilator support were also similar to previously noted associations between neonatal infection and increased surfactant and postnatal steroid administration,<sup>8</sup> and longer length of NICU stay.<sup>38</sup> Interestingly, ventilation time has recently been shown to contribute to the inflammatory cascade<sup>39</sup> thought to result in brain injury,<sup>8, 13, 14</sup> but many of our associations persisted after controlling for days on ventilation. Although no differences in behavioral outcomes were observed, these associations may highlight the importance of neonatal sepsis as a marker for infants at increased risk for gross brain injury in the perinatal period. Furthermore, whether as a consequence of the infection itself or from complications of infection, ventilation and TPN are not benign interventions and may simultaneously increase the risk for further complications.

The strengths of the current study include the systematic review of placental pathology by an experienced placental pathologist and the evaluation of brain structure through multimodal MR techniques. The limitations include retrospective chart review, which precludes definitive conclusions about infectious contributions to worsened neurodevelopmental outcomes. For example, mothers who had emergency room records and were subsequently diagnosed with asymptomatic urinary tract infection may have had other factors associated with adverse neurodevelopmental outcomes, despite controlling for social risk. A further limitation of this study is the small sample size, which did not allow for subgroup analyses of specific types of maternal infection or organisms. Although infant death contributed to a smaller sample size for MRI measures and two-year follow-up testing, this is unlikely to bias our data because of the lack of association between infection and death in our cohort.

Despite these limitations, our data highlight the negative influence of infection/inflammation on neonatal brain health and development. Although neonatal infection was not associated with neurobehavioral changes, later neurobehavioral changes may emerge at older ages when more sophisticated psychometric testing is feasible. In addition, the lack of brain structural changes associated with maternal genitourinary tract infection during pregnancy suggests that the mechanism behind these neurobehavioral changes may be an area worthy of future study.

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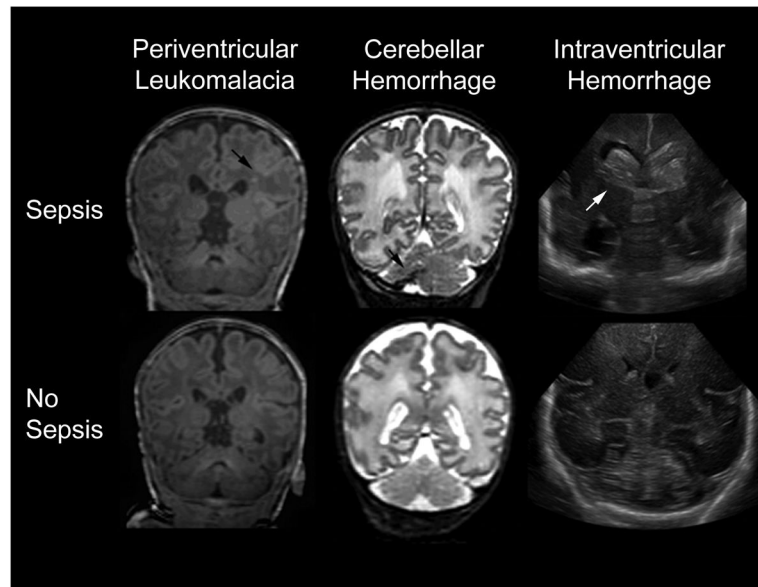
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**Figure 1.** Representative T1-weighted image of periventricular leukomalacia (left), T2-weighted MR image of cerebellar hemorrhage (middle), and coronal ultrasound images of intraventricular hemorrhage (right). Images from infants exposed to sepsis (top) have arrows indicating the relevant pathologies. The bottom images are from a very preterm infant without any infectious exposure.

Table 1

Maternal and infant characteristics in relation to prenatal and neonatal infection

	Prenatal Infection					Neonatal Infection				
	None	Maternal GU	Chorioamnionitis	Fetal vasculitis	None	Sepsis	NEC	Sepsis and NEC	Clinically suspected infection	
Number	65	31	60	34	48	35	10	7	24	
Estimated gestational age, mean in wks (SD)	26 (1)	27 (2)	26 (2)	26 (2)	26 (2)	26 (2)	26 (2)	26 (2)	26 (2)	
Birthweight, median in gms (IQR)	940 (785–1153)	730 (700–960)	765 (700–990)	765 (700–1012)	985 (840–1290)	750 (700–930)	750 (728–880)	710 (660–740)	745 (693–898)	
Male, no. (%)	31 (48)	14 (45)	32 (53)	17 (50)	15 (31)	21 (60)*	5 (50)	4 (57)	13 (54)	
African-American, no. (%)	30 (46)	22 (71)	36 (60)	20 (59)	23 (48)	21 (60)	4 (40)	5 (71)	13 (54)	
Medicaid, no. (%)	29 (64)	16 (80)	26 (68)	12 (67)	21 (55)	13 (72)	3 (75)	3 (100)	10 (71)	
Maternal high school education, no (%)	20 (53)	9 (47)	24 (67)	10 (63)	20 (56)	10 (59)	2 (40)	1 (33)	8 (67)	
Preeclampsia, no. (%)	28 (43)	7 (23)	7 (12)*	1 (2.9)*	20 (42)	5 (14)*	2 (20)	3 (43)	5 (21)	
Prenatal Steroids, no. (%)	55 (85)	24 (77)	49 (82)	26 (77)	42 (88)	27 (77)	8 (80)	5 (71)	19 (79)	

\* P &lt; 0.01 compared to no infection

Abbreviations: GU – genitourinary; IQR – interquartile range; NEC – necrotizing enterocolitis; PMA – postmenstrual age; SD – standard deviation.

**Table 2**

Impact of postnatal infection on hospital factors (controlled for PMA)

	Length of stay (95% CI)	Total days on TPN (95% CI)	Total days of ventilation (95% CI)
	<i>P</i> value*	<i>P</i> value*	<i>P</i> value*
Sepsis	16.2 (11.3, 23.4) < <b>0.001</b>	30.5 (23.9, 38.8) < <b>0.001</b>	87.7 (70.8, 108.5) 0.018
Necrotizing enterocolitis	53.1 (51.8, 74.4) 0.479	28.1 (18.1, 43.5) <b>0.003</b>	5.7 (3.1, 10.3) 0.016
Necrotizing enterocolitis with sepsis	85.4 (56.6, 128.8) 0.149	47.4 (29.0, 77.6) < <b>0.001</b>	12.9 (6.4, 26.3) < <b>0.001</b>
Clinically suspected infection	19.3 (12.3, 30.3) <b>0.001</b>	47.4 (24.7, 44.1) < <b>0.001</b>	96.8 (76.9, 122.1) <b>0.003</b>
No infection	2.5 (1.9, 3.4)	13.4 (11.0, 16.4)	62.4 (52.5–74.2)

\* Compared to no infection

TPN - Total parenteral nutrition

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**Table 3**

Impact of neonatal infection on white matter injury and death

	Unadjusted odds ratio (95% CI)	* Adjusted odds ratio (95% CI)	† Adjustment including TPN and vent (95% CI)
	<i>P</i> value	<i>P</i> value	<i>P</i> value
<b>Intraventricular hemorrhage</b>			
Sepsis	5.2 (1.3, 20.9)	5.8 (1.3, 24.8)	4.9 (0.8, 29.3)
	0.02	0.02	0.08
Necrotizing enterocolitis	6.4 (1.1–38.4)	6.2 (1.0, 37.7)	14.1 (1.4, 138.0)
	0.04	0.05	0.02
Clinically suspected infection	3.0 (0.6, 14.7)	3.1 (0.6, 15.6)	4.1 (0.6, 26.1)
	0.175	0.165	0.133
<b>Cerebellar hemorrhage</b>			
Sepsis	3.6 (1.0, 12.5)	3.5 (1.0, 12.4)	1.8 (0.4, 8.6)
	0.05	0.05	0.5
Necrotizing enterocolitis	3.8 (0.5, 26.4)	3.9 (0.5, 27.9)	N/A
	0.177	0.182	0.999
Clinically suspected infection	8.4 (2.3, 30.9)	8.5 (2.3, 30.8)	6.2 (1.5, 25.9)
	<b>0.001</b>	<b>0.001</b>	<b>0.01</b>
<b>Any injury or death</b>			
Sepsis	8.1 (2.5, 25.6)	8.5 (2.6, 27.7)	6.5 (1.6, 26.5)
	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>0.009</b>
Necrotizing enterocolitis	10.1 (1.7, 59.1)	10.1 (1.7, 59.1)	10.7 (1.6, 72.6)
	<b>0.01</b>	<b>0.01</b>	0.02
Clinically suspected infection	13.3 (3.7, 47.6)	14.0 (3.8, 51.6)	10.7 (2.5, 44.8)
	<b>&lt; 0.001</b>	<b>0.001</b>	<b>0.001</b>

\* adjustment model includes PMA

† adjustment model includes PMA, days of TPN, and days of ventilation

**Table 4**

Impact of proven neonatal sepsis on brain metrics and diffusion measures

	Unadjusted means			* Adjusted means			† Adjusted mean including TPN and vent		
	Control (SE)	Sepsis (SE)	P value	Control (SE)	Sepsis (SE)	P value	Control (SE)	Sepsis (SE)	P value
<b>Brain metrics (cm)</b>									
Bifrontal diameter	59.8 (0.9)	56.3 (2.7)	0.224	60.7 (1.1)	55.8 (3.0)	0.141	60.0 (1.8)	56.0 (3.5)	0.367
Biparietal diameter	70.4 (0.9)	63.5 (2.7)	0.02	72.2 (1.0)	62.6 (2.7)	<b>0.002</b>	71.4 (1.6)	63.3 (3.1)	0.046
Interhemispheric diameter	3.7 (0.3)	3.7 (1.0)	0.959	3.9 (0.4)	3.0 (1.1)	0.455	3.7 (0.7)	3.3 (1.3)	0.822
Transcerebellar diameter	48.4 (0.7)	38.3 (2.2)	< <b>0.001</b>	49.5 (0.8)	36.8 (2.3)	< <b>0.001</b>	49.7 (1.4)	37.0 (2.7)	<b>0.001</b>
Right ventricular diameter	8.1 (0.6)	11.9 (1.8)	0.046	7.6 (0.7)	12.5 (2.0)	0.027	8.1 (1.0)	13.6 (2.0)	0.038
Left ventricular diameter	8.0 (0.4)	12.0 (1.3)	<b>0.005</b>	8.0 (0.5)	12.3 (1.4)	<b>0.007</b>	8.5 (0.7)	13.0 (1.4)	<b>0.01</b>
<b>Diffusion (× 10<sup>-3</sup> mm<sup>2</sup>/s)</b>									
<b>Right Frontal Lobe</b>									
Mean diffusion	1.71 (0.02)	1.79 (0.04)	0.17	1.69 (0.03)	1.79 (0.05)	0.05	1.70 (0.04)	1.83 (0.05)	0.02
Axial diffusion	1.93 (0.02)	2.02 (0.05)	0.12	1.90 (0.03)	2.02 (0.05)	0.04	1.90 (0.04)	2.05 (0.05)	<b>0.01</b>
Radial diffusion	1.61 (0.02)	1.67 (0.05)	0.22	1.58 (0.03)	1.68 (0.05)	0.07	1.60 (0.04)	1.72 (0.05)	0.04
<b>Left Frontal Lobe</b>									
Mean diffusion	1.71 (0.02)	1.79 (0.04)	0.07	1.68 (0.02)	1.82 (0.04)	<b>0.004</b>	1.68 (0.03)	1.85 (0.04)	<b>0.001</b>
Axial diffusion	1.93 (0.02)	2.03 (0.04)	0.04	1.90 (0.02)	2.05 (0.04)	<b>0.003</b>	1.88 (0.03)	2.07 (0.04)	< <b>0.001</b>
Radial diffusion	1.60 (0.02)	1.67 (0.04)	0.12	1.57 (0.02)	1.70 (0.04)	<b>0.007</b>	1.58 (0.03)	1.74 (0.04)	<b>0.001</b>
<b>Right Cingulum Bundle</b>									
Mean diffusion	1.46 (0.01)	1.5 (0.02)	0.08	1.46 (0.01)	1.51 (0.02)	0.04	1.45 (0.01)	1.52 (0.02)	<b>0.002</b>
Axial diffusion	2.01 (0.02)	2.04 (0.04)	0.42	2.00 (0.02)	2.06 (0.04)	0.12	1.99 (0.03)	2.07 (0.04)	0.09
Radial diffusion	1.19 (0.01)	1.23 (0.02)	0.18	1.19 (0.02)	1.23 (0.03)	0.21	1.18 (0.02)	1.24 (0.03)	0.03

\* adjustment model includes PMA at scan, gender, and race

† adjustment model additionally includes upper quartiles of days of TPN and days of ventilation

\*\*\* Brain metrics compared infants with both sepsis and NEC



**Table 5**

Impact of maternal genitourinary tract infection on neurobehavioral outcomes

	Unadjusted beta [95% CI]	* Adjusted beta [95% CI]
	<i>P</i> value	<i>P</i> value
Cognitive Composite	-7.0 [-12, -2.1] 0.006	-8.8 [-13.9, -3.7] 0.001
Language Composite	-12.9 [-19.1, -6.6] < 0.001	-14.9 [-21.6, -8.1] < 0.001
Receptive Language	-2.3 [-3.4, -1.3] < 0.001	-2.7 [-3.8, -1.6] < 0.001

\* adjustment model includes social risk

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