Original Investigation

Postnatal Cytomegalovirus Infection and the Risk for Bronchopulmonary Dysplasia

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IMPORTANCE Postnatally acquired cytomegalovirus (CMV) is typically benign in term infants but in very low-birth-weight (VLBW) infants can cause pneumonitis and sepsis-like illness. Whether postnatal CMV infection results in long-term pulmonary sequelae in these infants is unknown.

OBJECTIVE To investigate the association between postnatal CMV infection and bronchopulmonary dysplasia (BPD) and mortality in a large multicenter cohort of VLBW infants.

DESIGN, SETTING, AND PARTICIPANTS Conducted between October 2014 and June 2015, this propensity-matched retrospective cohort study involved 101,111 hospitalized VLBW (<1500 g) infants at 348 neonatal intensive care units in the United States from 1997 to 2012. We matched infants with postnatal CMV infection 1:1 to comparison infants using propensity scores, and we used Poisson regression to examine the effect of postnatal CMV on the combined risk for death or BPD at 36 weeks' postmenstrual age. To describe features of postnatal CMV infection, we extracted clinical and laboratory data from 7 days before until 7 days after infants met criteria for postnatal CMV.

EXPOSURES Postnatal CMV infection was defined as a diagnosis of CMV or detection of CMV from blood, urine, cerebrospinal fluid, or respiratory secretions on or after day of life 21. Infants with a CMV diagnosis or virologic detection of CMV prior to day of life 21 were not considered to have postnatal infection.

MAIN OUTCOMES AND MEASURES The primary outcome was death or BPD at 36 weeks' postmenstrual age.

RESULTS Of 101,111 infants, 328 (0.3%) had postnatal CMV infection. We matched a comparison infant to 303 CMV-infected infants (92%) for a final cohort of 606 infants. The median gestational age and birth weight of this cohort were 25 weeks and 730 g, respectively. Postnatal CMV infection was associated with an increased risk for death or BPD at 36 weeks' postmenstrual age (risk ratio, 1.21; 95% CI, 1.10-1.32) and BPD (risk ratio, 1.33; 95% CI, 1.19-1.50). Changes in cardiorespiratory status associated with postnatal CMV infection included a new requirement for vasopressor medications (9%; n = 29), intubation for mechanical ventilation (15%; n = 49), a new oxygen requirement (28%; n = 91), and death (1.2%; n = 4).

CONCLUSIONS AND RELEVANCE In VLBW infants, postnatal CMV infection was associated with increased risk for BPD. Further studies are needed to determine the role of preventive measures against CMV in this population.
Cytomegalovirus (CMV) is the most common perinatal viral infection worldwide.\(^1\) Cytomegalovirus may be acquired in utero (congenital CMV infection), at delivery (postnatal CMV infection), or later in life. Postnatal infection among infants most frequently results from exposure to virus shed in breast milk and—prior to widespread use of CMV-negative and leukoreduced blood products in premature infants—through blood transfusion.\(^2\)\(^-\)\(^6\) Postnatal infection is not typically associated with clinical signs in term infants, likely as a result of the relative maturity of the term infant immune system and maternal antibody acquired during the third trimester.\(^7\)\(^,\)\(^8\) In contrast, very low-birth-weight (VLBW; birth weight <1500 g) infants with postnatal CMV infection can manifest sepsislike illness, pneumonitis, hepatitis, or hematological abnormalities.\(^2\)\(^-\)\(^6\)\(^,\)\(^9\) Although many VLBW infants with clinically apparent postnatal CMV experience a deterioration in respiratory status coinciding with infection, it is unclear whether this results in long-term pulmonary sequelae such as bronchopulmonary dysplasia (BPD).

In this study, we investigated the relationship between postnatal CMV infection and BPD and mortality in a large multicenter cohort of VLBW infants. As a secondary objective, we described the clinical and laboratory characteristics associated with postnatal CMV infection in this cohort to inform diagnostic testing in VLBW infants.

Methods

Study Setting

From October 2014 to June 2015, we identified VLBW infants hospitalized on day of life (DOL) 21 in neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group from 1997-2012. Data were obtained from an electronic medical record that prospectively captures information from daily progress notes generated by clinicians using a computer-assisted tool. The method of data extraction was previously described in detail.\(^10\) During the study, the Pediatrix Medical Group included 348 NICUs in the United States. Data on multiple aspects of patient care are available, including demographics, medications, laboratory and culture results, and diagnoses. This study was approved by the Duke University institutional review board; patient consent was waived because this was a retrospective study with no identifiable information collected.

Postnatal CMV Infection

We defined postnatal CMV infection as a diagnosis of CMV infection, acquired CMV infection, or congenital CMV infection or detection of CMV by culture or polymerase chain reaction of blood, urine, cerebrospinal fluid, or respiratory secretions on or after DOL 21. To limit identification of infants who were infected congenitally, infants were not considered to have postnatal CMV if they had a diagnosis of intracranial calcifications or any of the following prior to DOL 21: (1) detection of CMV by culture or polymerase chain reaction from any source; (2) a diagnosis of CMV infection, acquired CMV infection, or congenital CMV infection; (3) a diagnosis of microcephaly; (4) treatment with ganciclovir, valganciclovir, cidofovir, or foscarin; or (5) a transaminitis, defined as aspartate transaminase level greater than 150 U/L (to convert to microkatal per liter, multiply by 0.0167) and alanine aminotransferase level greater than 90 U/L (to convert to microkatal per liter, multiply by 0.0167). For the purposes of this analysis, only postnatal CMV infections occurring at less than 36 weeks’ postmenstrual age were included.

Outcomes

The primary outcome was death or BPD at 36 weeks’ postmenstrual age. Secondary outcomes were BPD and death prior to hospital discharge, considered separately. Infants were classified as having BPD if they received respiratory support (nasal cannula oxygen or continuous positive airway pressure, conventional mechanical ventilation, or high-frequency ventilation) continuously from a postmenstrual age of 36 0/7 to 36 6/7 weeks.\(^11\) Infants taking room air without any respiratory support for at least 1 day between 36 0/7 and 36 6/7 weeks’ postmenstrual age were classified as not having BPD. Infants discharged prior to 36 6/7 weeks’ postmenstrual age who did not receive respiratory support on the day of discharge were classified as not having BPD. The outcome of BPD was considered missing for infants who died before 36 6/7 weeks’ postmenstrual age or were discharged prior to 36 6/7 weeks’ postmenstrual age and received respiratory support on the day of discharge.

Other Definitions

We defined small for gestational age as a birth weight below the tenth percentile for gestational age (GA), based on Olsen growth curves.\(^12\) Sepsis was defined as isolation of 1 or more bacterial or fungal pathogens from blood. We excluded likely bacterial contaminants, including nonspeciated streptococci, Bacillus species, Corynebacterium species, and Micrococcus species. We divided coagulase-negative Staphylococcus infections into 3 categories: definite, probable, and possible, as previously described.\(^13\) Only definite and probable infections were included in this analysis. We considered the following medications to be vasopressors: amrinone, dobutamine, dopamine, epinephrine, milrinone, and norepinephrine. We defined neutropenia as an absolute neutrophil count less than 1500/µL (to convert to ×10⁹ per liter, multiply by 0.001), thrombocytopenia as a platelet count of less than 100 ×10⁹/µL.
(to convert to $10^9$ per liter, multiply by 1), and direct hyperbilirubinemia as a serum direct bilirubin level greater than 1.0 mg/dL (to convert to micromoles per liter, multiply by 17.104).

**Statistical Analyses**

We compared outcomes among VLBW infants with postnatal CMV infection with infants without postnatal CMV. Infants without postnatal CMV infection were selected from all VLBW infants hospitalized on DOL 21 who did not meet criteria for postnatal CMV, including infants who were not tested for CMV and infants who tested negative for CMV. Because postnatal CMV infection is more likely to be associated with clinical signs among the subset of VLBW infants with extreme prematurity and significant comorbidities, we used propensity score matching to obtain similar populations for comparison. Co-morbid conditions and surrogates for severity of illness were assessed in relation to DOL 21, the day on which infants were first at risk for postnatal CMV infection. We included the following variables, including previously reported risk factors for BPD, in a logistic regression model to generate propensity scores: GA; birth weight; small-for-gestational-age status; sex; race/ethnicity; discharge year; NICU site; days of breast milk exposure between DOL 15 and 21; number of days on which surfactant was received; necrotizing enterocolitis, grade III or IV intraventricular hemorrhage, patent ductus arteriosus, and sepsis episode occurring on or before DOL 21; and number of vasopressor medications, type of respiratory support, and fraction of inspired oxygen assessed on DOL 21. We included discharge year as a categorical variable in the model to adjust for changes in clinical practice and outcomes over time. We matched 1:1 on the propensity score using nearest-neighbor matching, provided that the difference in the propensity scores matched comparison infants was less than 0.01. We examined the distributions of propensity scores across groups using histograms and kernel density plots. We assessed covariate balance across groups within both the unmatched and propensity score–matched cohorts using $\chi^2$ tests.

We used Poisson regression with a sandwich variance estimator conditioning on the matched pair to determine the effect of postnatal CMV infection on outcomes in the propensity score–matched cohort. This modeling approach, as opposed to logistic regression, was appropriate because the odds ratio obtained using logistic regression is an upwardly biased estimate of the risk ratio (RR) when the outcome is not rare (>10%), as was the case for our primary outcome and secondary outcome of BPD.

We conducted sensitivity analyses to assess whether our findings would have differed had alternative assumptions been made. First, we examined the effect of postnatal CMV infection on outcomes when infants meeting criteria for postnatal CMV based only on diagnostic coding (and not virologic data) were excluded (n = 106). In originally defining postnatal CMV infection, we included infants with a diagnosis of congenital CMV infection on or after DOL 21 because we felt that the distinction between congenital and postnatal CMV infection may not be accurately assessed. Thus, our second sensitivity analysis excluded infants with a diagnosis of congenital CMV infection on or after DOL 21 (n = 135). Finally, to assess whether the observed association of postnatal CMV with BPD might be related to a transient respiratory deterioration associated with acute CMV infection, we repeated analyses excluding postnatal CMV infections occurring at 34 weeks’ postmenstrual age or later (n = 94). In conducting each of these sensitivity analyses, we first excluded children who met the specified condition and then repeated the procedures for generating propensity scores and matching comparison infants to infants with postnatal CMV by propensity scores.

To describe the features of postnatal CMV infection, we extracted clinical and laboratory data from 7 days before until 7 days after infants met criteria for postnatal CMV. For each variable, we calculated the maximum (or minimum) value recorded during the period. We also determined the proportion of infants who died during this period or required initiation of vasopressor medications, increased level of respiratory support or intubation, and increased fraction of inspired oxygen.

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**Figure. Participant Flow Diagram**

[Diagram showing participant flow with labeled steps and exclusions.]

Inclusion criteria were cytomegalovirus (CMV) diagnosis on day of life (DOL) 21 or later or positive CMV culture/polymerase chain reaction (PCR) on DOL 21 or later. Exclusion criteria were intracranial calcifications, positive CMV culture/PCR before DOL 21, CMV diagnosis before DOL 21, microcephaly before DOL 21, anti-CMV treatment before DOL 21, and transaminitis before DOL 21. VLBW indicates very low birth weight.
or initiation of supplemental oxygen on 1 or more days. All statistical analyses were conducted using Stata version 13.1 (StataCorp).

Results

Patient Characteristics

We identified 101,111 VLBW infants, and 328 infants (0.3%) met study criteria for postnatal CMV infection (Figure). Of these infants, 144 (44%) met criteria for postnatal CMV based on diagnosis and virologic testing, 106 (32%) based on diagnosis only, and 78 (24%) based on virologic testing only. The sources of specimens for the 222 infants with virologic testing were urine (72%), trachea (12%), blood (8%), and nasopharynx (8%). We matched a comparison infant to 303 of 328 infants (92%) with postnatal CMV infection. For the remaining 25 infants with postnatal CMV, data were missing for 1 or more variables included in the model to generate propensity scores. The 606 infants in the final propensity score–matched cohort were from 70 NICUs sites. Propensity score matching resulted in a population that was closely matched on baseline characteristics, with no statistically significant differences in covariates observed across the 2 groups (Table 1). Median (25th percentile–

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unmatched Cohort (n = 101 111)*</th>
<th></th>
<th>Propensity Score–Matched Cohort (n = 606)*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Standardized Mean Difference</td>
<td>P Value</td>
<td>No. (%)</td>
</tr>
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<td>Postnatal CMV (n = 328)</td>
<td>No Postnatal CMV (n = 100 783)</td>
<td></td>
<td>Postnatal CMV (n = 303)</td>
<td>No Postnatal CMV (n = 303)</td>
</tr>
<tr>
<td>No. (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postnatal CMV</td>
<td>144 (44%)</td>
<td>0.73</td>
<td>&lt;.001</td>
<td>105 (35)</td>
</tr>
<tr>
<td>No Postnatal CMV</td>
<td>106 (32%)</td>
<td>0.35</td>
<td></td>
<td>176 (58)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>24 (7%)</td>
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<td></td>
<td>22 (7)</td>
</tr>
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<td>White</td>
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<td>.02</td>
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<td>African American</td>
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<td>Hispanic</td>
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<td>0.13</td>
<td></td>
<td>74 (24)</td>
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<tr>
<td>Other</td>
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<td>0.08</td>
<td></td>
<td>23 (8)</td>
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<td>Breast milk exposure on DOL 14–21, d</td>
<td>100 (31)</td>
<td>-0.29</td>
<td>&lt;.001</td>
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<td>Nortoculating enterocolitis</td>
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<td>.04</td>
<td>10 (3)</td>
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<tr>
<td>Patent ductus arteriosus</td>
<td>239 (73)</td>
<td>0.65</td>
<td>&lt;.001</td>
<td>223 (74)</td>
</tr>
<tr>
<td>Grade 3 or 4 intraventricular hemorrhage</td>
<td>36 (11)</td>
<td>0.20</td>
<td>&lt;.001</td>
<td>34 (11)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>60 (18)</td>
<td>0.32</td>
<td>&lt;.001</td>
<td>56 (18)</td>
</tr>
</tbody>
</table>

(continued)
Outcomes

In the propensity score–matched cohort, infants with postnatal CMV infection were discharged (or died) at a median of 40.6 weeks’ postmenstrual age. Infants without postnatal CMV infection were discharged (or died) at a median of 38.6 weeks’ postmenstrual age. Primary and secondary outcomes by postnatal CMV infection status in this cohort are shown in Table 2. Overall, 69% of the cohort of matched infants died or met criteria for BPD at 36 weeks’ postmenstrual age, including 76% of infants with postnatal CMV infection and 63% of infants without postnatal CMV. Postnatal CMV infection was associated with an increased risk for death or BPD at 36 weeks’ postmenstrual age (RR, 1.21; 95% CI, 1.10-1.32) and BPD (RR, 1.33; 95% CI 1.19-1.50). There was no significant association between postnatal CMV and death prior to hospital discharge (RR, 0.71; 95% CI, 0.43-1.16). The effect of postnatal CMV infection on primary and secondary outcomes was substantively unchanged in sensitivity analyses (eTable in the Supplement).

Clinical and Laboratory Characteristics of Postnatal CMV Infection

The median (25th percentile–75th percentile) GA and birth weight of infants with postnatal CMV infection were 25 weeks (24-27) and 730 g (611-915 g), respectively. GA and birth weight of infants in the propensity score–matched cohort were 25 weeks (24-27) and 730 g (611-915 g), respectively.

The median (25th percentile–75th percentile) GA and birth weight of infants in the propensity score–matched cohort were 25 weeks (24-27) and 730 g (611-915 g), respectively.
centile–75th percentile) postnatal age at CMV diagnosis was 49 days (38–60 days) (Table 3). We observed 1 or more changes in cardiorespiratory status or laboratory abnormalities in 293 infants (89%) within 7 days before or after CMV diagnosis. Changes in cardiorespiratory status included a new requirement for vasopressor medications (9%; n = 29), intubation for mechanical ventilation (15%; n = 49), a new oxygen requirement (28%; n = 91), and death (1.2%; n = 4). Among infants with available data, thrombocytopenia (66%; 188 of 283), direct hyperbilirubinemia (66%; 119 of 180), and neutropenia (34%; 88 of 261) were the most frequent laboratory abnormalities.

### Discussion

We present findings from, to our knowledge, the largest reported cohort of VLBW infants with postnatal CMV infection to date. Our results indicate that postnatal CMV infection at less than 36 weeks’ postmenstrual age was associated with an increased risk for BPD. Postnatal CMV was not associated with death before hospital discharge.

There are several plausible mechanisms by which postnatal CMV infection might increase the risk for BPD. Damage to lung tissue may occur as a direct result of viral infection or indirectly through the immune response to the virus. Infection of the lung by CMV is characterized by a mononuclear inflammatory process, deposition of fibrin, hemorrhage, and sloughing of lung epithelial cells. Cytomegalovirus might also increase BPD risk by causing a deterioration in respiratory status that leads to increased exposure to other known risk factors, such as prolonged mechanical ventilation.

A potential association between postnatal CMV and BPD was first observed in the 1970s. Whitley et al described 2 infants who developed a protracted pneumonitis with histopathology suggesting a causative role for CMV. Approximately 10 years later, investigators reported radiographic findings consistent with BPD in 24 of 32 infants (75%) diagnosed as having postnatal CMV infection compared with 12 of 32 control infants (38%) in a single-center study. Other case reports have since attributed multicystic lung disease, interstitial fibrosis, and pulmonary hypertension to postnatal CMV infection.

However, postnatal CMV infection was not associated with BPD in several previous prospective studies. In contrast to earlier studies, these cohorts identified incident CMV infections through serial virologic monitoring, and most of the identified infections were not clinically apparent. Neuberger et al monitored the premature infants of CMV-seropositive mothers with biweekly CMV culture and polymerase chain reaction of urine, comparing the clinical course of 40 infants with postnatal CMV infection with matched control infants. They found no association between postnatal CMV and BPD, although the overall incidence of BPD was low (16%). Nijman et al prospectively screened 315 infants born at less than 32 weeks’ GA, identifying 39 infants with postnatal CMV infection. Bronchopulmonary dysplasia, defined in this study as the requirement for fraction of inspired oxygen of 30% or greater or positive pressure ventilation at 36 weeks’ postmenstrual age, was diagnosed in none of the infants with postnatal CMV infection and 2% of infants without postnatal CMV.

Eighty-five percent of infants in this cohort did not have clinical signs or laboratory abnormalities that could be attributed to CMV infection. Finally, Prösch et al collected urine samples and tracheal or pharyngeal aspirates from 66 VLBW infants during the first month of life. Bronchopulmonary dys-
Postnatal CMV and Bronchopulmonary Dysplasia Risk

Original Investigation Research

plasia developed in 12% of non-CMV-infected infants and 29% of infants with CMV infection, including 3 of 4 infants (75%) with postnatal infection.27 There were no significant differences in the prevalence of BPD by CMV infection status, although the small number of postnatally infected infants precluded specific comparisons with this group.27

The incidence of postnatal CMV infection in our cohort was lower than was reported in most prior studies. In a meta-analysis of 17 studies, the risk for postnatal CMV infection among VLBW infants in the United States was estimated to be 6.5%, with 1.4% of infants developing a sepsislike syndrome.28 Only 0.3% of VLBW infants in our cohort met criteria for postnatal CMV infection at less than 36 weeks’ postmenstrual age. This comparatively low incidence likely reflects nonrecognition of postnatal CMV infections associated with no or few clinical signs. Specifically, we identified infants with postnatal CMV infection based on physician diagnoses or virologic testing in a nonresearch setting. Although CMV screening practices at our NICU were unavailable, few NICUs in the United States were routinely screening for postnatal CMV infection during the study period. Thus, most CMV-infected infants identified in our cohort had clinical signs or laboratory abnormalities consistent with postnatal infection. Moreover, establishing a diagnosis of postnatal CMV in practice is challenging, even in the presence of clinical signs, given substantial overlap with the presentation of bacterial or fungal sepsis. Hence, many of the postnatal CMV infections in our cohort may further represent the minority of infections that result in severe or protracted symptoms. While our identification of infants with postnatal CMV reflects standard practice in most NICUs during the study, our findings may not be generalizable to settings that routinely screen VLBW infants for CMV. Large prospective studies are needed to determine whether CMV acquisition without clinical signs is associated with BPD.

The clinical signs and laboratory abnormalities associated with postnatal CMV infection in our cohort were generally similar to those previously reported in smaller studies.26,29 Notably, however, direct hyperbilirubinemia and thrombocytopenia were substantially more common in our cohort than in prior studies. While these results may accurately reflect the true prevalence of these findings in clinically apparent postnatal CMV infections, it is also possible that these laboratory abnormalities prompt clinicians to consider CMV infection in VLBW infants.

Breast milk has established nutritive and immunological benefits and reduces the incidence of late-onset sepsis and necrotizing enterocolitis in premature infants.30,31 However, with the practice of transfusion of CMV-seronegative or leukoreduced blood, breastfeeding is also the primary route of CMV acquisition among infants in the United States.3 Up to half of pregnant mothers are CMV seropositive, and more than 80% of these mothers shed CMV in their breast milk.32-34 Pasteurization of breast milk eliminates infectious virus but diminishes the beneficial properties of the milk, while freezing reduces but does not eliminate CMV transmission.34-36 Our study suggests that alternative strategies are needed to prevent CMV transmission to VLBW infants while preserving the beneficial properties of breast milk.

Our study had a number of limitations, most of which relate to the retrospective observational design. First, criteria for postnatal CMV infection were based on virologic testing and physician diagnoses in a nonresearch setting. As a result, most infants in our cohort had signs of CMV infection, which generally represents only 10% to 33% of infections among VLBW infants.26,28,29 Second, given that most congenital CMV infections are not associated with clinical signs and that prolonged urinary shedding and viremia are common, some infants in our cohort may have had congenital infections.37 To minimize this possibility, we excluded infants with CMV-related diagnoses, characteristic laboratory abnormalities, or treatment with antivirals with activity against CMV prior to DOL 21. Moreover, pneumonitis is infrequent among infants with congenital infection, so misclassification would tend to bias our results toward the null.18 We did not consider BPD and death in a single model as competing risk events, choosing instead to examine the effect of postnatal CMV on a composite outcome variable. Finally, we could not exclude the possibility of unmeasured confounding variables. However, infants with CMV were closely matched to comparison infants on other known risk factors for BPD, including all variables that predicted the risk for BPD in a prior multicenter study.38

Conclusions

Among VLBW infants, postnatal CMV infection was associated with an increased risk for BPD. Further research is needed to define the long-term sequelae of postnatal CMV on pulmonary and neurological outcomes and develop novel CMV prevention measures to permit safe breast milk feeding in VLBW infants.

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Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kelly, Daniel K. Benjamin, Laughon. Obtained funding: Daniel K. Benjamin Jr. Administrative, technical, or material support: Laughon, Clark, Smith. Study supervision: Laughon, Clark, Smith, Permar.

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REFERENCES