Serious Congenital Heart Disease and Necrotizing Enterocolitis in Very Low Birth Weight Neonates

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BACKGROUND: Infants with serious congenital heart disease (CHD) appear to be at increased risk for necrotizing enterocolitis (NEC). This study aimed to quantify the incidence and mortality of NEC among very low birth weight (VLBW) neonates with serious CHD, and identify specific CHD diagnoses at the highest risk for developing NEC.

STUDY DESIGN: Data were prospectively collected on 257,794 VLBW (401 to 1,500 g) neonates born from 2006 to 2011 and admitted to 674 Vermont Oxford Network US centers. Entries were coded for specific CHD diagnoses and reviewed for completeness and consistency. Survival was defined as alive in-hospital at 1 year or discharge.

RESULTS: Of eligible neonates, 1,931 had serious CHD. Of these, 253 (13%) developed NEC (vs 9% in infants without CHD, adjusted odds ratio [AOR] 1.80, $p < 0.0001$). Mortality for neonates with CHD and no NEC was 34%, vs 55% for those with CHD and NEC ($p < 0.0001$). Both groups of CHD patients had higher mortality than infants with NEC without CHD (28%, $p < 0.0001$). Although NEC mortality overall decreases with higher birth weight, mortality for NEC and CHD together does not.

CONCLUSIONS: The incidence of NEC is significantly higher in VLBW neonates when CHD is present. The mortality of CHD and NEC together is substantially higher than that with each disease alone. Infants with atrioventricular canal appear to have higher risk for developing NEC than other CHD diagnoses. In addition to providing benchmark incidence and mortality data, these findings may have utility in the further study of the pathophysiology of NEC. (J Am Coll Surg 2015;220:1018−1026. © 2015 by the American College of Surgeons)

Necrotizing enterocolitis (NEC) is the most common abdominal surgical emergency in neonates[1] and its incidence is inversely related to birth weight.[2] Though elements of the pathophysiology of this disease have been elucidated, the process that leads to life-threatening bowel necrosis is not fully understood. Necrotizing enterocolitis is thought to arise in the setting of an immature gastrointestinal tract with a vulnerable mucosal barrier that is breached by bacteria after some initial insult, prompting an inflammatory cascade that results in self-perpetuating tissue damage.[3,4] Perturbations in splanchnic blood flow that result in poor perfusion and tissue hypoxemia likely contribute to the initial insult.[5,6] Premature infants with abnormal cardiovascular physiology may therefore be at especially high risk for developing NEC.

A number of small studies have documented an increased incidence of NEC in infants with congenital heart disease (CHD), both in premature[7-9] and term neonates.[8,10-14] Though the incidence of serious CHD also appears to be higher in VLBW neonates[15] and despite the increased incidence of NEC in this population, premature

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Abbreviations and Acronyms

AOR = adjusted odds ratio
AV = atrioventricular
CHD = congenital heart disease
DORV = double outlet right ventricle
HLHS = hypoplastic left heart syndrome
NEC = necrotizing enterocolitis
VLBW = very low birth weight
VON = Vermont Oxford Network

infants who have both diseases are still rarely encountered, making it difficult for individual centers to study such patients. The effect of the combination of NEC and CHD on outcomes remains unclear; some studies have found higher mortality[11]; others demonstrate lower mortality with the 2 in combination vs either alone.[16]

Congenital heart disease represents a broad heading under which fall a number of structural lesions that have distinct physiologic implications. Therefore, some cardiac defects may result in alterations in blood flow that place certain neonates with CHD at higher risk of developing NEC than others. For example, hypoplastic left heart syndrome appears to result in poor superior mesenteric arterial flow[17] and may be associated with an increased risk of NEC.[8,18] Nonetheless, such interactions have not been evaluated in large cohorts of VLBW neonates with serious CHD and NEC.

Given these gaps in our understanding of the interaction between CHD and NEC, this study aimed to use a national dataset to quantify the incidence of NEC in VLBW neonates with CHD; compare the mortality of VLBW neonates with CHD and NEC to that of either disease alone; and identify which specific CHD diagnoses are at highest risk of acquiring NEC in this population.

METHODS

The Vermont Oxford Network (VON)[19] is a nonprofit voluntary collaboration that prospectively collects data on infants of birth weight 401 to 1,500 g, who are born at participating institutions or who are transferred to such an institution within 28 days of birth. Data are collected until neonates are discharged from the hospital, die, or reach 1 year of age in the hospital. Data are collected by local staff using uniform definitions and then submitted to the VON central office. Records are subjected to automated checks and returned for correction if needed. This study was performed as part of an ongoing collaboration between VON and a group of pediatric surgeons at Boston Children's Hospital. Research using the VON database is approved by the University of Vermont Institutional Review Board (#04-370) and exempted from review at Boston Children's Hospital.

For this cohort study, data were prospectively collected in the VON database from US centers, between January 2006 and December 2011, on newborns weighing between 401 and 1,500 g. Neonates with a length of stay of 3 or fewer days were excluded to remove those with diagnoses not compatible with life. Per the VON Manual of Operations definition,[20] NEC was diagnosed either by direct observation of intestine at operation or pathologic exam, or by using a set of strict clinical criteria. A clinical diagnosis of NEC was made based on at least 1 physical finding (bilious gastric aspirate or emesis, abdominal distention, or occult/gross blood in the stool in the absence of anal fissures) and at least 1 radiographic finding (pneumatosis intestinalis, hepato-biliary gas, or pneumoperitoneum). Severity of NEC was not specifically coded in the dataset and the diagnosis of NEC can only be coded once.

Congenital heart disease diagnoses were systematically coded using the VON Manual of Operations.[20] Only life-threatening cardiac defects were included, which VON defines as the primary cause of death or if treated before discharge with "specific surgical or medical therapy to correct a major anatomic defect or a life-threatening physiologic dysfunction."[20] Multiple birth defects (including cardiac anomalies) may be reported for the same infant. Each patient was reviewed by pediatric cardiologists (JA, SY) to ensure appropriate coding. These diagnoses were then sorted into 1 of 3 groups according to their dominant effect on cardiovascular physiology. Each of these classes of physiologic defects has been previously implicated in the development of NEC.[5,6,12,21,22] Category A included defects that primarily compromised systemic output (critical aortic stenosis, coarctation of the aorta, hypoplastic left heart syndrome, and interrupted aortic arch). Category B was composed of defects that create significant and sustained cyanosis (transposition of the great vessels, tetralogy of Fallot, critical pulmonic stenosis, pulmonary atresia, tricuspid atresia, and total anomalous pulmonary venous return). Category C diagnoses were those that resulted in manifestations of congestive heart failure with pulmonary over-circulation (complete atrioventricular canal, double outlet right ventricle, truncus arteriosus, and other single ventricle physiology).

Patients with multiple diagnoses were placed into 1 category based on the following schema. When present, interrupted aortic arch or surgically corrected coarctation of the aorta were considered primary diagnoses and were placed in category A. Pulmonary atresia of any form was characterized as category B. Tetralogy of Fallot was considered the primary diagnosis when associated with double outlet right ventricle (DORV) or complete