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Tori Cooke	12/15/2024

Characterizing Cardiac Necrotizing Enterocolitis Within a Single Medical Center: A Retrospective Electronic Data Review

Tori N. Cooke

Nell Hodgson Woodruff School of Nursing, Emory University

NRSG 727D: DNP Scholarly Practice II

Dr. Laura Kimble

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Abstract

Neonates with certain clinical diagnoses, like congenital heart disease (CHD) are at an increased risk for developing necrotizing enterocolitis (NEC). Certain risk factors associated with congenital heart disease also contribute to a patient's risk for cardiac NEC. Cardiac necrotizing enterocolitis is diagnosed using clinical and radiological signs. The severity of and treatment for NEC is determined by Bell's Staging Criteria. The diagnosis of NEC in the CHD population can have an impact on patient outcomes. CHD patients diagnosed with NEC can have impaired neurodevelopment, increased hospital costs and length of stay, and develop other comorbidities. This retrospective electronic data review characterized cardiac NEC within a single medical center. While the initial intent was to examine risk factors associated with the development of cardiac necrotizing enterocolitis, diagnostic and treatment approaches, and patient outcomes, the data provided by the electronic data warehouse could not be used to characterize these factors. The project focused on characterizing patients with cardiac NEC and associations between diagnoses and demographic factors.

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Background

Necrotizing enterocolitis (NEC) is an acute inflammatory intestinal injury that is primarily seen in the preterm-infant population (Burge et al., 2022). However, NEC has been diagnosed in full-term infants that have certain clinical features. One of the main clinical features in which full-term infants are at risk for developing necrotizing enterocolitis is congenital heart disease (CHD) (Lau et al., 2018). Having complex congenital heart disease substantially increases a neonate's risk for developing NEC by 3.3%-11% (Lau et al., 2018). Necrotizing enterocolitis was first identified in the congenital heart disease population in 1976, and is associated with a variety of risk factors: being born prematurely (<37 weeks gestation), a low birth weight (<2500g), a high preoperative risk assessment score (RACHS-1), receiving red blood cell transfusions, having Trisomy 21, specific cardiac defects consisting of hypoplastic left heart syndrome (HLHS), atrioventricular septal defect (AVSD), tricuspid atresia (TA), aortopulmonary window (APW), truncus arteriosus, transposition of the great arteries, Tetralogy of Fallot, and an isolated aortic arch obstruction (Burge et al., 2022; Spinner et al., 2020). Congenital heart disease patients that have any of these risk factors, whether it is one or multiple, are at an increased risk of developing NEC (Burge et al., 2022).

The pathophysiology behind the increased incidence of NEC in the CHD population is not known but the prevailing theory is decreased abdominal aortic blood flow and decreased cardiac output in certain cardiac defects that leads to insufficient perfusion to the intestinal mucosa/gut (Lau et al., 2018). Bubberman et al. (2018) and Kelleher et al. (2021) examined the pathophysiology of necrotizing enterocolitis in patients with congenital heart disease in an attempt to identify the cause. Both researchers attributed the cause to be the result of circulatory changes leading to impaired mesenteric circulation and ischemia of the bowel. One reason for

decreased perfusion to the intestines is related to the "diving reflex," in which cardiac output is routed to safeguard perfusion to vital organs like the brain and heart at the cost of the other organs (Bubberman et al., 2018). Decreased perfusion can result in an injury to the gut wall which then compromises the intestinal barrier, allowing bacteria to invade causing the inflammatory cascade, which increases the risk for NEC (Kelleher et al., 2021). In addition to circulatory factors, it was found that intrinsic gut factors such as gastrointestinal dysbiosis, feedings, and changes to the actual mucosal barrier in this population can predispose infants to NEC (Kelleher et al., 2021). Bubberman et al. (2018) found NEC to be localized to the colon in patients with CHD, due to the decrease in collateral blood supply to this particular region compared to other intestinal areas. This supports the theory that CHD-NEC is a disease of ischemic/hypoxic events and requires different prevention approaches than NEC in a preterm or term infant without congenital heart disease (Bubberman et al., 2018).

Necrotizing enterocolitis occurs in 3.7% of infants with congenital heart disease, which occurs at a rate of 40-100% higher than the term infant population without a cardiac defect (Spinner et al., 2020). Spinner et al. (2020) found the overall in-hospital mortality of infants with CHD and NEC (24.4%) to be significantly higher than neonates with congenital heart disease that are not diagnosed with NEC (11.8%), with the overall mortality of NEC in CHD patients ranging from 0%-75%. Patients with NEC and CHD typically have an increase in-hospital mortality, longer stays in the ICU and step-down floors, and an increase in hospital charges, resulting in expensive hospital stays (Spinner at al., 2020). Also, patients that are diagnosed with NEC and survive typically have multiple long-term morbidities which consist of adverse neurodevelopment (Spinner et al., 2020). One of the main reasons for an increased length of stay in a patient diagnosed with NEC is feeding intolerance. The increased length of stay has major

finical implications for their families. For example, in the most recent available data, patients who developed NEC as a result of a surgical intervention incurred an average of an additional $186,200 in hospital charges due to increased length of stay (Bisquera et al., 2002). Patients who developed NEC as a result of their anatomy, not in relation to surgery incurred an average of an additional $73,700 in hospital charges due to an increased length of stay (Bisquera et al., 2002). This is a huge financial burden on families and can be very difficult for families to pay for depending on their economic resources. Consequently, reducing the rates of NEC in the congenital heart disease population can decrease hospital utilization and length of stay, and decrease the finical burden for these patient's families.

The diagnosis of NEC can definitely complicate a patient's care and chance of survival. In addition to a significant financial burden due to an increased length of stay, race and ethnicity can complicate the diagnosis even more. It is shown that Hispanic ethnicity and non-Hispanic black race are associated with higher risk of NEC compared to non-Hispanic white populations (Cuna et al., 2021). This association may be driven by two of the known risk factors for NEC in the congenital heart disease population are preterm birth and low birth weight and rates of pre-term birth and low birth weight neonates are higher among Hispanic and non-Hispanic black neonates (Cuna et al., 2021). In addition to this, breastmilk is a protective factor against NEC and breastfeeding feeding practices tend to vary among different ethnic groups. Breastfeeding rates are lower among the mothers of non-Hispanic black infants when compared to the mothers of non-Hispanic white infants. By providing access to prenatal care which can help to decrease rates of pre-term births and low-birth weight infants, as well as providing education on the benefits breastfeeding can have, could significantly impact the overall outcome for these patients and decrease their chance of developing NEC.

Significance

Necrotizing enterocolitis (NEC) is a significant life-threatening condition that affects neonates that can lead to bowel perforation and sepsis. Mortality rates for infants diagnosed with NEC can be as high as 20-30% and in most cases infants require surgical intervention to prevent mortality (Bubberman et al., 2019). Due to the increased risk of mortality in congenital heart disease patients diagnosed with NEC, it is important to identify patients that are at highest risk for developing NEC and those who are in its earliest stages. Early identification of high-risk patients can lead to reduction in morbidity and mortality rates as providers promptly engage in strategies to prevent NEC in this fragile population. However, not only is it important for providers to be able to identify the infants at risk, but it is also important to know strategies on how to best prevent and/or minimize the risk of NEC in this fragile patient population.

In particular, infants that have a single ventricular anatomy due to their heart defect are at the greatest risk of developing NEC and have up to a 97% mortality rate (Roychaudhuri et al., 2022). After the diagnosis of NEC among single ventricular anatomy patients, they are at risk for developing multiple co-morbidities such as intestinal strictures, short bowel syndrome, and neurodevelopmental delay (Roychaudhuri et al., 2022). If prevention protocols are implemented it could result in decreased rates of NEC, ultimately decreasing the patient's chance of developing co-morbidities and result in a better quality of life for the patient.

To date, there are many different protocols used to detect and treat NEC in the congenital heart disease population. However, there is not one standardized universally accepted protocol on how to treat NEC in the CHD population. Studies have been emerging that focus on ways to prevent NEC and the implementation of several strategies that could be used universally to decrease the rates of NEC. Further exploration of this topic could lead to the development of a

specific standardized practice that can be applied to all congenital heart disease neonates that are at a high risk for NEC or to those who have been diagnosed with NEC. The use of these standardized practices can be effective in decreasing the rates of CHD-NEC.

Project Aims

The original aim of this project was to characterize the risk factors, diagnostic practices, treatment approaches, and patient outcomes within the Heart Center at Shawn Jenkins Children's Hospital. It was anticipated that information extrapolated from the review of retrospective data obtained from the electronic medical record would be analyzed to determine the rates of cardiac NEC, consistency of treatment approaches, and if there is a need for a standardized protocol for treating necrotizing enterocolitis in the congenital heart disease population. However, the data provided by the data warehouse, was not really sufficient to address the original aim. Therefore, the project was changed to focus on a description of the demographic and clinical characteristics of infants with cardiac NEC within the Heart Center at Shawn Jenkins Children's Hospital.

Clinical Question

The original clinical question proposed for this project was: "What are the risk factors associated with the development of cardiac necrotizing enterocolitis (NEC), as well as the diagnostic and treatment approaches, and patient outcomes of cardiac NEC within a single medical center?" However, the electronic medical record data provided by the data warehouse required revising the clinical question to: What are the demographic and clinical characteristics of infants with cardiac NEC within a single medical center?

Review of the Literature

The focus of this project was on cardiac NEC. Although necrotizing enterocolitis mainly occurs in the preterm infant population, it has been found in full-term infants that have certain clinical features. One of the main clinical features in which full-term infants are at risk for developing necrotizing enterocolitis is congenital heart disease (CHD) (Lau et al., 2018). NEC occurs in 3-5% of patients with congenital heart disease and is associated with doubled increase in risk for mortality (Ali et al., 2023).

Necrotizing enterocolitis is a disease that results from necrosis in the intestinal mucosa or in the entire gastrointestinal layer (Choi et al., 2022). In the first few months of life, a neonate's gastrointestinal system is immature and underdeveloped, making their GI mucosal barrier is more susceptible to being penetrated by bacteria, triggering an inflammatory cascade which can ultimately result in perforation of the bowels. The pathophysiology of cardiac NEC is not known but has been theorized. One theory is due to the decrease in abdominal aortic blood flow and the decreased cardiac output that occurs in certain cardiac defects, that leads to insufficient perfusion to the intestinal mucosa/gut (Lau et al., 2018). Therefore, any cardiac defect that results in hemodynamic changes in the gut can lead to ischemia and ultimately NEC (Roychaudhuri et al., 2022).

Due to the high morbidity and mortality rates of necrotizing enterocolitis it is imperative to determine what patients are at greatest risk of developing cardiac-related NEC, as well as diagnose and treat congenital heart disease patients with NEC in a precise and timely manner to prevent significant complications. Specifically, this review will summarize the literature with a focus on clinical characteristics that put infants at risk for cardiac NEC, diagnostic studies used to diagnosis cardiac NEC, the medical treatment for cardiac NEC, and the outcomes of patients diagnosed with cardiac NEC.

Search Strategy

A literature review on these topics was completed using a variety of databases that consisted of: PubMed, Google Scholar, and CINAHL (Cumulative Index to Nursing and Allied Health Literature). Also, an electronic edition of the Journal of Pediatric Surgery was searched for information. Terms "necrotizing enterocolitis," "NEC," "risk factors," and "risk factors for NEC" were combined with "congenital heart disease" and "cardiac defects." Articles that were published within the last 5 years, 2018-2023, and available in full text were included in this review. More than 30 relevant research studies were found using the above databases and search terms. In order to be included in this review, studies had to address the occurrence of necrotizing enterocolitis in the congenital heart disease population specifically. Articles were excluded if the prevalence of NEC in preterm infants without a cardiac defect was addressed or the occurrence of NEC in infants with other morbidities not related to congenital heart disease.

In addition to the above search, the use of PubMed was used to search terms "necrotizing enterocolitis," "NEC," and "CHD NEC," were combined with "treatment protocols," "diagnosis of," and "patient outcomes," which resulted in a limited number of articles. Due to the limited number of articles that were related to diagnosis, treatment, and patient outcomes for cardiac necrotizing enterocolitis, additional searches were performed using the reference lists of pertinent articles. Articles that were published between 2010-2023, available in full-text, and in English were included.

All the articles were then sorted into categories based on the overarching themes of the article. Four primary themes that resulted from this categorization consisted of: evaluation of risk factors for necrotizing enterocolitis in the congenital heart disease population, the evaluation of diagnostic criteria for necrotizing enterocolitis in the congenital heart disease population, the

evaluation of treatment protocols for necrotizing enterocolitis in the congenital heart disease population, and patient outcomes for congenital heart disease patients that were diagnosed with cardiac NEC.

Evaluation of Risk Factors for NEC in the CHD Population

Five articles examined the risk factors for infants with CHD that developed NEC in order to determine risk factors that are related to the development of NEC (Diez et al., 2020; Gong et al., 2022; Choi et al., 2022; Van Der Heide et al., 2020; Burge et al., 2022). Burge et al. (2022), Choi et al. (2022), and Diez et al. (2020) discussed the importance of being able to identify characteristics of necrotizing enterocolitis in neonates with CHD in a timely manner in order to increase the neonate's chance of survival and decrease the rates of mortality associated with NEC.

Major risk factors that were associated with the development of NEC in all studies consisted of premature birth (<37 weeks gestation), low birth weight (<2500g), high preoperative risk adjustment for congenital heart surgery score (RACHS-1), red blood cell transfusions, Trisomy 21, being on cardiopulmonary bypass, hypoxic/ischemic hits, and specific cardiac defects such as hypoplastic left heart syndrome, atrioventricular septal defect, tricuspid atresia, aortopulmonary window, transposition of the great arteries, Tetralogy of Fallot, hypoplastic aortic arch, truncus arteriosus, and ductal-dependent (DD) lesions (Burge et al., 2022). Preoperative risk adjustment for congenital heart surgery scores (RACHS-1) are calculated according to the severity of the cardiac defect and evaluate a patient's risk for NEC (Burge et al., 2022). Factors in addition to the complexity of the cardiac defect that can increase the RACHS-1 scores are time spent on cardiopulmonary bypass or time spent hypothermic in the operating room during the cardiac intervention. Increased incidence of NEC is associated with RACHS-1

scores that are greater than 2 on a scale of 0 to 15 (Burge et al., 2022). The association between red blood cell transfusions and the increased risk of NEC is not fully understood. It has been difficult to determine if it is related to the actual administration of RBCs or the underlying anemia that is associated with NEC that requires the administration of RBCs (Burge et al., 2022). Trisomy 21 in a patient with CHD is associated with and increased incidence of NEC due to the fact that patients with Trisomy 21 have certain GI and immune abnormalities that contribute to the development of NEC. In addition, patients with Trisomy 21 are at an increased risk of being born with an atrioventricular septal defect, which results in shunted blood flow and decreased blood flow to the gastrointestinal system, increasing their risk for NEC (Burge et al., 2022).

Diez et al. (2020) and Gong et al. (2022) examined patients with ductal dependent circulation. Diez et al. (2020) studied patients with a patent ductus arteriosus (PDA) and CHD and patients without a PDA and CHD. It was found that patients with a PDA and CHD were found to have a more intense course of NEC. Diez et al. (2020) found that an early diagnosis and a timely intervention, whether surgical or medical, needs to be considered to avoid removal of a portion of the bowel or other detrimental outcomes. Gong et al. (2022) examined ductal dependent CHD patients vs. non-ductal dependent CHD patients and then evaluated the occurrence of NEC in these specific populations. Approximately 19% of the DD CHD patients that were studied developed NEC compared to the 11.1% of non-DD CHD patients. It was found that 100% of non-DD patients developed NEC after surgical intervention for their cardiac defect, and 24% of the infants in the DD group developed NEC prior to surgery for their cardiac defect (Gong et al., 2022). Patients with non-ductal dependent lesions were found to have low cardiac output which contributed to multi-organ dysfunction and organs not receiving the proper blood supply, which led to the development of NEC (Gong et al., 2022). As a result of this finding,

Gong et al. (2022) believes that improving low cardiac output and tissue perfusion in a timely manner is one way to prevent severe cases of NEC from occurring in the specific patient population.

Van der Heide et al. (2020) examined the association between increased hypoxic/ischemic events at birth and within the first 48 hours and how that contributes to the development of NEC. It was found that infants who had lower APGAR scores at birth and at 5 minutes developed NEC along with infants who needed respiratory support right at birth. It is believed that during this stressful time at birth the intestines are exposed to increased ischemic time in the first few minutes of life which increases the risk for NEC development later (Van der Heide et al., 2020). Infants that need respiratory support, like CPAP, are exposed to increased positive pressure in the intestines leading to impairment of intestinal wall perfusion which can increase the risk of NEC (Van der Heide et al., 2020). Overall, it is important to maintain sufficient abdominal blood flow and oxygen in infants with CHD to decrease the risk of developing NEC.

Evaluation of Diagnostic Criteria for NEC in the CHD Population

Cardiac necrotizing enterocolitis can present in a variety of ways in infants, making it difficult to diagnose in the earliest and least severe stages (Kashif et al., 2022). Cardiac NEC can present at any stage on the clinical spectrum, ranging from very mild and slow to very rapid and progressive necrotizing enterocolitis (Kashif et al., 2022). In the congenital heart disease population, the colon is the most commonly affected area of the bowel (Kashif et al., 2022). The presence of dilated loops of bowel, pneumatosis intestinalis, which is the finding of small amounts of air in the bowel wall, and/or portal venous gas are all radiologic signs that signify cardiac necrotizing enterocolitis (Ginglen & Butki, 2023). The use of an abdominal x-ray in the

anterior-posterior and left lateral decubitus views are used to detect the main radiologic signs of necrotizing enterocolitis (Ginglen & Butki, 2023). Portal venous gas is not always found on imaging, but when it is found, it signifies a poor prognosis (Ginglen & Butki, 2023). In addition to its use for initial diagnosis, abdominal x-rays are also used as a valued tool for tracking the advancement of the disease (Ginglen & Butki, 2023). Blood work such as electrolytes, a complete blood cell count, a blood culture, and inflammatory markers like C-reactive protein (CRP), are performed in addition to the abdominal x-ray (Neu, 2020). However, laboratory tests have a poor sensitivity and poor positive predictive value (Neu, 2020).

The diagnosis of cardiac necrotizing enterocolitis is based on clinical and radiologic signs as well as the extent of involvement as stated above. Bell's Staging Criteria, which is the standard assessment, is used to determine the severity of the NEC and determine the treatment needed (Kashif et al., 2021). Bell's Staging Criteria ranges from IA suspected NEC to IIIB advanced NEC-severely ill, and perforated bowel (Kashif et al., 2021). Stage IA is classified as suspected NEC; with clinical signs of bradycardia and lethargy; intestinal signs consisting of mild abdominal distention, emesis, and occult fecal blood; and radiologic signs indicative of a normal mild ileus (Kashif et al., 2021). Stage IB is classified as suspected NEC; with clinical signs of bradycardia and lethargy; intestinal signs consisting of rectal bleeding; and radiologic signs indicative of a normal mild ileus (Kashif et al., 2021). Stage IIA is classified as proven NEC-moderately ill; with clinical signs of bradycardia and lethargy; intestinal signs of rectal bleeding, absent bowel sounds, and tenderness; and radiologic signs indicative of intestinal dilation, an ileus, and pneumatosis intestinalis (Kashif et al., 2021). Stage IIB is classified as proven NEC-moderately ill; with clinical signs of bradycardia, lethargy, mild metabolic acidosis, and/or thrombocytopenia; intestinal signs of rectal bleeding, absent bowel signs, tenderness, and

potential abdominal cellulitis or mass; and radiologic signs indicative of IIA plus portal venous gas and ascites (Kashif et al., 2021). Stage IIIA is classified as advanced NEC-severely ill bowel intact; with clinical signs that are the same as IIB plus hypotension, and DIC; intestinal signs of rectal bleeding, absent bowel signs, generalized peritonitis, and marked distention and tenderness of the abdomen; and radiologic signs indicative of IIB plus definite ascites (Kashif et al., 2021). Stage IIIB is classified as advanced NEC-severely ill, bowel perforated; with clinical signs the same as IIIA; intestinal signs the same as IIIA; and radiologic signs indicative of the same signs of IIB plus pneumoperitoneum (Kashif et al., 2021).

Congenital heart disease patients diagnosed with necrotizing enterocolitis can present with nontypical radiologic findings, which can result in a misdiagnosis or delayed diagnosis, leading to severe progression of NEC resulting in bowel perforation (Kashif et al., 2021). It is important that providers have an increased radar for the development of necrotizing enterocolitis in the congenital heart disease population.

In addition to clinical and radiologic signs, new advancements in biomarker screening for early identification of NEC are being identified. NEC often has a subtle presentation and can be easy to miss, unless it presents in the mid to late stage. Due to the subtle presentation, researchers are working to identify biomarkers from stool and urine samples to diagnose NEC (Hu et al., 2024). The urine of patients diagnosed with NEC was found to have higher levels of intestinal fatty acid binding protein (I-FABP) (Hu et al., 2024). In addition, elevated calprotectin levels found in the stool has been associated with the diagnosis of NEC (Hu et al., 2024). The use of I-FABP and calprotectin levels can be used to diagnose NEC in the early stages and potentially improve patient outcomes due to early identification and diagnosis.

Evaluation of Treatment Protocols for NEC in the CHD Population

The treatment for cardiac NEC is a byproduct of the treatment for classical NEC, however due to the difference in pathophysiology for cardiac NEC vs. classical NEC, patients may need to be cared for using a different approach (Kashif et al., 2021). Once a patient has been diagnosed with NEC through radiologic imaging and bloodwork, treatment begins with stabilization of the patient's vital signs and overall clinical picture taking into consideration airway, breathing, and circulation (Ginglen & Butki, 2023). Once a patient is stable, if NEC is suspected, it is paramount to stop all enteral feedings and make the patient NPO (nothing per oral) to rest the bowels (Ginglen & Butki, 2023). When patients are NPO they must have parental nutrition in order to stay hydrated, which usually consists of total parental nutrition (TPN) with soybean oil, medium-chain triglycerides, olive oil, and fish oil (SMOF lipids) depending on their clinical status and anticipated length of NPO status (Aurora et al., 2023). The placement of a nasogastric tube (NG) to low suction is essential to decompress the dilated bowels (Aurora et al., 2023). There is no evidence supporting a specific bacterial organism cause for necrotizing enterocolitis, but NEC is still treated with broad spectrum antibiotics that cover both aerobic and anaerobic bacteria (Gill et al., 2022). Medical centers that have a standardized treatment protocol for necrotizing enterocolitis base their antibiotic choice according to the patient's clinical status and Bell's Staging Criteria. In general, the main antibiotic regimen consists of ampicillin, gentamicin, and either clindamycin or metronidazole (Ginglen & Butki, 2023). Interdisciplinary teamwork with pediatric surgery and pediatric infectious disease is sometimes necessary depending on the Bell's Stage, clinical concern, blood culture result, or need for longer antibiotic duration (Aurora et al., 2023). A patient may need a peripherally

inserted central catheter for intravenous access, if the need for total parental nutrition and antibiotics for greater than 48 hours is a possibility (Aurora et al., 2023).

Most articles that discussed the re-initiation of feeding post necrotizing enterocolitis focused on premature infants but this information can be extrapolated and applied to cardiac NEC. While there are no definitive guidelines that pertain to optimal timing for re-initiating enteral feeds after the diagnosis of necrotizing enterocolitis, feeds must be restarted with caution in order to prevent reoccurrence (Good et al., 2014). Patients who recover from NEC medically and therefore do not need surgery, benefit from a period of 7-10 days of NPO status (Good et al., 2014). Some studies suggest a standard re-introduction feeding regimen consisting of re-initiating feeds at a low volume of 10-20mL/kg/day and then advancing feeds by 20mL/kg/day until the goal volume is reached (Hock et al., 2018). The earlier enteral feeds are re-introduced correlates with an earlier time in which full enteral feeds are reached, which overall decreases a patient's length of stay (Hock et al., 2018).

Evaluation of Patient Outcomes Related to the Diagnosis of NEC in the CHD Population

Patient outcomes for those diagnosed with necrotizing enterocolitis who are treated medically are not well defined. However, it is known that infants diagnosed with necrotizing enterocolitis can have impaired neurodevelopment, increased hospital costs, increased length of stay, and develop other comorbidities as a result of NEC (Mowitz et al., 2018). Patients that survive NEC and their parents can have long-term complications that impact their quality of life, social life, and physical and mental health (Canvasser et al., 2023).

Infants that are diagnosed with NEC are more likely to be neurodevelopmentally impaired when compared to infants of similar age and gestation. However, patients that require surgical treatment for NEC are at greatest risk for neurodevelopmental impairments when

compared to their medically treated counterparts (Rees et al., 2007). Some of the most prevalent neurodevelopmental impairments consist of cerebral palsy, visual impairments, cognitive impairments, and psychomotor impairments (Rees et al., 2007).

In addition to impaired neurodevelopmental outcomes, patients diagnosed with NEC can encounter an increase in hospital costs and length of stay (Mowitz et al., 2018). According to Mowitz et al. (2018), infants diagnosed with NEC encountered a hospital cost that is 1.4 times higher than those without necrotizing enterocolitis. The increased hospital costs are due to the increase in length of stay, parental nutrition, and multiple diagnostic interventions (Mowitz et al., 2018). The increased length of stay in this population is mainly due to the for treatment of NEC, delayed feeding, and feeding intolerance. When patients are NPO it can lead to patients developing an oral aversion, which increases their time in the hospital, since they must learn how to feed (Mowitz et al., 2018).

Other comorbidities that patients who are diagnosed with necrotizing enterocolitis can develop consist of; feeding difficulties resulting in failure to thrive, malabsorption, short bowel syndrome, and developmental delays (Mowitz et al., 2018). In a study conducted by Canvasser et al. (2023) evaluating long-term outcomes and life impacts of NEC, discovered that the most reported, long-term complication was digestive complications. As a result of these comorbidities, infants with medical NEC encountered higher medical costs between 6 to 12 months of age when compared to their counter parts (Mowitz et al., 2018). The stage of NEC plays a vital role in patient outcomes as well as morbidity and mortality, so it is important to intervene and begin treatment as early as possible.

Appraisal of Research

The reviewed studies reported consistent findings related to risk factors, diagnosis, treatment, and outcomes for cardiac necrotizing enterocolitis. However, the information from these articles can be extrapolated and applied to congenital heart disease patients who are diagnosed with necrotizing enterocolitis. An in-depth appraisal of the research has allowed for better understanding of current findings and has established the need for further research.

This review of the literature involved reviewing information about the risk factors, diagnosis, treatment, and patient outcomes for necrotizing enterocolitis in the congenital heart disease population. One commonality among the research was the small sample sizes of multiple studies. According to Kelleher et al. (2021), the incidence of NEC in the CHD population is between 3 and 5%. The small population size makes it difficult to solely study cardiac NEC therefore information on cardiac NEC is quite minimal. This establishes the need for further research in this specific patient population in order to expand our knowledge about NEC in the cardiac population not related to the preterm population. For example, there may be improvements in diagnoses, treatment, and patient outcomes for those diagnosed with cardiac NEC if more studies are conducted.

Additionally, another study limitation is the retrospective nature of a majority of the articles. When conducting retrospective research, the researcher is dependent on appropriate charting and correct diagnostic coding of the patient's diagnosis to have reliable and valid data and also to assure that the patients are correctly classified as having NEC. In this study, the diagnosis of necrotizing enterocolitis is dependent on the correct ICD-10 code, so if a patient is coded incorrectly or not coded at all, the diagnosis of NEC would be missed and that patient would be excluded from the study.

Summary

In this review, multiple articles were reviewed to examine risk factors associated with the development of cardiac necrotizing enterocolitis, diagnostic and treatment approaches, as well as patient outcomes for cardiac NEC patients. Several studies evaluated the risk factors for necrotizing enterocolitis in the CHD population. These risk factors were determined to be related to a variety of factors such as events at birth, birth weight and gestation, the risk preoperatively and postoperatively with cardiac interventions, receiving blood products, genetic syndromes, and certain cardiac defects. Other studies examined the diagnostic criteria that is used to diagnose necrotizing enterocolitis in the cardiac population. The main diagnostic test used to diagnose NEC is an abdominal x-ray, which reveals the presence of dilated loops of bowel, pneumatosis intestinalis, which is the finding of small amounts of air in the bowel wall, and/or portal venous gas (Ginglen & Butki, 2023). Multiple studies evaluated the treatment for necrotizing enterocolitis, which consists of making the patient NPO, placing a nasogastric tube to suction, obtaining serial abdominal x-rays, starting IV antibiotics, and parental nutrition. Importantly, the literature suggests that the use of protocols for treating cardiac NEC is not necessarily a standard of practice within healthcare settings, which could lead to practice variations (Kelleher et al., 2021). Lastly, a small number of articles examined the long-term effects/outcomes of necrotizing enterocolitis. Congenital heart disease patients diagnosed with NEC are more likely to have impaired neurodevelopmental outcomes, increased hospital costs, prolonged hospital stays, and feeding difficulties resulting in failure to thrive, malabsorption, short bowel syndrome, and developmental delays (Mowitz et al., 2018).

Within the practice setting where this project was implemented, there are currently no standardized protocol for the treatment of cardiac NEC. It was anticipated that the project could

potentially inform the development of a standardized protocol and potentially address the gaps in current practice for cardiac NEC.

Methods

Design

The project involved a retrospective review of electronic medical record data obtained through the Biomedical Informatics Center (BMIC) at the Medical University of South Carolina (MUSC). The MUSC Institutional Review Board (IRB) and Emory University's IRB evaluated the project aims and determined this project to be quality improvement, therefore no further approval was needed from either IRB. All patient information extracted for this project was de-identified to protect confidentiality of the patients. There were no potential conflicts of interest in this project.

Quality Improvement Project Population

Data from patients admitted to the Pediatric Heart Center at Shawn Jenkins Children's Hospital at MUSC between January 2018 and December of 2023 who had congenital heart disease and were diagnosed with necrotizing enterocolitis were included in this project. Those whose primary hospital location was not in the heart center or those with prematurity were excluded from this project.

Data Sources

The Services, Pricing, & Application for Research Centers (SPARC) request tool was used to place a request for data to be obtained. De-identifiable data were extracted from the electronic medical record system from the Research Data Warehouse (RDW) at MUSC through the use of a data analyst and specific procedures required by MUSC. A data use agreement (DUA) was

secured between the Medical University of South Carolina Hospital Authority and the University of Emory to allow for the sharing of data between the two parties. The data extracted by the MUSC data analyst were provided in an Excel spreadsheet to the doctoral student via secure email and subsequently downloaded to a password protected OneDrive folder where only the doctoral student and her advisor had access. SPSS version 29.0.2.0. (20) was used for data wrangling and to create the final analytic dataset for the quality improvement analysis.

Data Elements and Creation of the Analytic Database for Quality Improvement

Patient data related demographic characteristics, diagnosis, surgical interventions, and length of stay data were extracted from the RDW. Demographic information consisted of age, gender, race, and ethnicity. Diagnosis information consisted of what congenital heart defect/s the patient had, what stage of NEC the patient had, and any other pertinent diagnoses. Surgical intervention data contained what surgical intervention, if any, that the patient received. Length of stay consisted of how long the patient was admitted to the hospital for. Data was extracted on the use of imaging and laboratory tests and treatments administered during their course of NEC. Data provided in different excel spreadsheets were merged such that the unit of analysis was the patient. In examining the data, there were challenges in how to analyze and interpret the extracted data. The doctoral student sought additional clarifying information from MUSC and in cases where inquires could not be answered, these data were deleted from the data set.

Results

Demographic Characteristics

A total of 46 patients with CHD who were diagnosed with NEC from January of 2018 to December of 2023 were identified. Table 1 depicts the demographical characteristics of the

sample. In this sample, the mean length of stay was about 84 days (M=84) with a SD=71 days. The majority of the sample were male, which were about 57% of the patients. The sample was evenly distributed between Black or African American patients and white or Caucasian patients. The predominate ethnicity was non-Hispanic or Latino.

Table 1 Characteristics of patients (n=46)

Characteristics	**Mean (SD)/no. (%)**
Length of Stay- mean (SD)	84.4 (71.8)
Sex, female- no. (%)	20 (43.5)
Sex, male- no. (%)	26 (56.5)
Race	
Black or African American- no. (%)	20 (43.5)
White or Caucasian- no. (%)	19 (41.3)
Other- no. (%)	7 (15.2)
Ethnicity	
Hispanic or Latino - no. (%)	3 (6.5)
Not Hispanic or Latino - no. (%)	42 (91.3)
Unknown- no. (%)	1(2.2)

Clinical Characteristics

Each patient was given an ICD-10 code for their diagnosed stage of NEC. Table 2 represents the NEC staging in this sample. In this sample the greatest percentage of patients were diagnosed with NEC stage II, which was about 44% of patients, followed by patients diagnosed with an unspecified stage of NEC in the newborn period which represented about 22% of the patients.

The number of heart defects and type of cardiac defect were also analyzed, see Tables 3 and 4. The highest number of heart defects seen per patient were seven. The majority of patients had two defects. There was a total of 25 different cardiac defects seen in this sample population, but the seven most common were listed in Table 4. Atrial septal defect was the most common

occurring defect, occurring in 61% of the sample. Patent ductus arteriosus was the next most common, occurring in 52% of patients.

Table 2 Necrotizing Enterocolitis Staging

Staging	**No. (%)**
Necrotizing Enterocolitis, unspecified- no. (%)	4 (8.7)
Necrotizing Enterocolitis in Newborn, unspecified- no. (%)	10 (21.7)
Stage I Necrotizing Enterocolitis in Newborn- no. (%)	6 (13.0)
Stage II Necrotizing Enterocolitis in Newborn- no. (%)	20 (43.5)
Stage III Necrotizing Enterocolitis in Newborn- no. (%)	6 (13.0)

Table 3 Number of Heart Defects

Defect Total	**No. (%)**
One heart defect	17 (37.0)
Two heart defects	15 (32.6)
Three heart defects	7 (15.2)
Four heart defects	4 (8.7)
Five heart defects	2 (4.3)
Six heart defects	0 (0)
Seven heart defects	1 (2.2)

Table 4 Types of Cardiac Disease

Defect	**No. (%)**
Atrial Septal Defect	28 (60.9)
Coarctation of Aorta	5 (10.9)
Double Outlet Right Ventricle	5 (10.9)
Hypoplastic Aortic Arch	4 (8.7)
Hypoplastic Left Heart Syndrome	4 (8.7)
Patent Ductus Arteriosus	24 (52.2)
Ventricular Septal Defect	9 (19.6)

Exploratory Analysis

To further understand relationships between necrotizing enterocolitis and the clinical data gathered, it was explored whether the number of heart defects or length of stay varied based on the stage of NEC. In order to address if the stage of NEC varied based on the number of heart

defects a patient had, the unspecified stages of NEC were collapsed and a One-way ANOVA test was performed. See Table 5. Statistical analyses revealed that there was no statistical difference among the stage of NEC related to the number of heart defects F= .99 (df 3,43) p= .40. However, descriptively, the patients diagnosed with an unspecified stage of NEC had the highest number of mean heart defects followed by stage II. A One-way ANOVA test was also performed, to determine if length of stay varied based on the stage of NEC. See Table 6. Statistical analysis revealed that there was no statistical significance between a patient's stage of NEC and their length of stay F= 0.64 (df 3,43) p= .59. Descriptively, patients with an unspecified stage of NEC had a longer length of stay of.

The relationships among sex and ethnicity were also evaluated in regards to stage of NEC, see Table 7 and Table 8. To meet the statistical assumptions of Chi Square, the stages of NEC were recoded as staged vs. unstaged NEC and the unknown ethnicity category was omitted. There was no statistically significant relationship between sex and stage of NEC, X^2 (1, n=46) = .49, p=.53. In addition, there was no relationship observed between ethnicity and stage of NEC, X^2 (1, n=45) =1.45, p=.54. Overall, there was not a large number of Hispanic or Latino patients included in this sample.

Table 5 Number of Heart Defects Compared to Stage of NEC

	Mean (SD)
Necrotizing enterocolitis, unspecified and necrotizing enterocolitis in newborn, unspecified	2.57 (1.2)
Stage I necrotizing enterocolitis	1.66 (.8)
Stage II necrotizing enterocolitis	2.25 (1.5)
Stage III necrotizing enterocolitis	1.66 (1.6)

Table 6 Length of Stay Compared to Stage of NEC

	Mean (SD)
Necrotizing enterocolitis, unspecified and necrotizing enterocolitis in newborn, unspecified	93.42 (67.9)
Stage I necrotizing enterocolitis	111.8 (107.9)

Stage II necrotizing enterocolitis	79.63 (59.5)
Stage III necrotizing enterocolitis	56.0 (71.8)

Table 7 Sex Compared to Stage of NEC

Sex	**% Unspecified Stage of NEC**	**% Staged NEC**
Male	64	53
Female	36	47

Table 8 Ethnicity Compared to Stage of NEC

Ethnicity	**% Unspecified Stage of NEC**	**% Staged NEC**
Non-Hispanic or Latino	100	90
Hispanic or Latino	0	10

Discussion

In examining the available data, the focus of this project shifted from the initial aim to evaluate the diagnostic practices, treatment protocols, outcomes to evaluating the characteristics of patients with CHD that developed necrotizing enterocolitis. With this particular sample population, it was found that an increase in the number of heart defects was not associated with a more complex stage of NEC. In addition, it was found that there was no relationship between patients with a more complex stage of NEC having a longer hospital stay. Surprisingly, there were more patients diagnosed with ASDs, PDAs, and VSDs than any other type of defect, and according to the literature these are not typically the cardiac defects that are associated with the development of NEC.

Demographics were also evaluated in relationship to the occurrence of NEC. According to the literature, there is a large variation in the rate of occurrence and patient outcomes associated with NEC when comparing patients by race and ethnicity. Patients of Hispanic

ethnicity and non-Hispanic Blacks were found to have a higher rate of NEC occurrence when compared to their non-Hispanic White counterparts (Cuna et al., 2021). However, in this particular patient population, it was not observed that those of Hispanic or Latino ethnicity had increased rates of NEC, but it was observed that Black or African Americans had the highest rate of NEC compared to their counterparts. Social factors and biological factors are believed to drive the racial differences in NEC. Social factors consist of access to health care, nutrition, economic stability, health insurance, education and physical environment (Cuna et al., 2021). Biological factors consist of preterm birth rates, breastfeeding rates, breastmilk consumption, neonatal survival, genetics, and epigenetics (Cuna et al., 2021). Prematurity and low birth weight are both risk factors for NEC, and rates of pre-term birth and low birth weight infants are higher in non-Hispanic Black and Hispanic infants (Cuna et al., 2021). Breastmilk is considered to be a protective factor against NEC, and breastfeeding rates are lower among non-Hispanic Black infants compared to non-Hispanic White infants, which could potentially explain the increased rate of NEC in non-Hispanic Black infants (Cuna et al., 2021). Poor access to healthcare, including prenatal care can potentially lead to a variety of complications, which can lead to pre-term delivery. By providing access to prenatal care to help decrease rates of pre-term births and low-birth weight infants, as well as providing education to mothers on the benefits that breastfeeding can have, can significantly impact the overall outcome for patients that are at an increased risk of NEC due to social and biological impacts and decrease their chance of developing NEC.

This study was limited due to its retrospective nature and the ability to only obtain certain data from the Research Data Warehouse. The data that was pulled was believed to not fully capture an accurate picture of patients diagnosed with CHD and NEC due to the small sample

size. In addition, the data obtained had to be cleaned and data was omitted that was unable to be clarified from research analyst. Moving forward it would be important for a prospective study to be completed in order to evaluate the risk factors, diagnostic practices, treatment regimens, and overall outcomes to determine if a standardized protocol would be beneficial.

In summary, this study demonstrated the demographic characteristics and certain clinical relationships among patients with congenital heart disease who were diagnosed with necrotizing enterocolitis. NEC and CHD are associated with longer hospital length of stays, hospital charges and mortality, which was not evaluated in this study. The occurrence and stage of NEC in patients with congenital heart disease differs significantly based on the patient's heart defect. Race and ethnicity also play a major role in the occurrence of and particular stage of NEC. Future studies can help to investigate risk factors, patient outcomes, and practices to prevent the occurrence of necrotizing enterocolitis in the congenital heart disease population.

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