Methodological Challenges in Conducting Case-Control Studies in Necrotizing Enterocolitis

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Necrotizing Enterocolitis (NEC) is a multifactorial disease of the gastrointestinal tract that is of greatest concern among premature infants. The overall hospitalization rate for NEC in the U.S. is about 110/100,000 live births. [1] Prematurity and low birth weight are the strongest risk factors for NEC such that the hospitalization rate among infants born at 1500–2499 g is 420/100,000 live births and among those weighing <1500 g, it is 4323/100,000 live births. [1] Many case-control studies have been conducted to identify risk factors for NEC, but results have been inconsistent. Although NEC etiology has traditionally been described as having three etiologic pathways (i.e., the ischemic, infectious, and enteral feeding pathways), the relationship between these pathways and the risk factors contributing to disease has not been well-delineated. That is, investigators typically classify NEC as a single outcome, rather than differentiating the outcome according to its probable etiologic pathway. At the time we started our case-control study to investigate risk factors associated with NEC stratified by etiologic pathway, we were unaware of other researchers taking this approach. Recently, however, Neu and Walker [2] have also proposed investigating NEC disease according to its etiologic pathway.

We are currently conducting a retrospective case-control study of NEC in a Neonatal Intensive Care Unit (NICU). While conducting this study, we encountered methodological challenges pertaining to case definition and control selection. We searched the peer-reviewed literature for solutions to these challenges, and although there are multiple published case-control studies, they did not have enough detail in the methods sections to explicate how these challenges were addressed. The purpose of this editorial is to 1) identify the challenges specific to conducting case-control studies in NEC, and 2) propose solutions to these challenges, and thus, allow other researchers to comment on the appropriateness of these solutions.

First, one challenge in conducting a case-control study of NEC is differentiating NEC cases by etiologic pathway. In the absence of a NEC outbreak with a known pathogen, it may not be clear whether the necrotic tissue was initiated by ischemic or infectious events. We approached classifying NEC cases by their etiologic pathway as follows. First, we consider the enteral feeding pathway as a subset of the ischemic pathway; unless there is evidence the feeding products were contaminated and led to an infection, which would then place the enteral feeding pathway as a subset under the infectious route. Next, we tried to find evidence of infection by collecting data on cultures (blood, stool, viral, etc.), microbiologic tests, white blood cell counts, C-reactive protein tests, or any other indicators of infection in the nursing or medical notes. If there was sufficient evidence of infection, the case was classified as such; otherwise, it was classified as an ischemic case of NEC.

Second, identifying the ideal at-risk period for controls presents another set of challenges in control selection. Although we feel certain we should match controls to cases on gestational age, we are less certain of how close that match should be. We propose using caliper matching by ± 1 week gestational age. Although a closer match may be ideal, the younger the case infant, the more difficult it is to find eligible infants who live long enough to serve as matched controls (particularly for cases who are <30 weeks gestational age).

Third, defining the time period for data collection has been difficult and therefore impacts the identification of the at-risk period for controls. Following the logic that gestational age is a strong risk factor for NEC and we control for this factor by matching, we do not feel it is appropriate to collect data on each control from admission to discharge. Consider an example where a case infant of 27 weeks gestational age develops NEC within the first week of life. If the control infant born at 27 weeks of life stays in the NICU for two months, any data collected after one month (31 weeks gestational age) effectively breaks the matching already implemented. When examining cases of NEC, it appears that factors contributing to disease have a rather rapid onset, often two days or less. Thus, we propose defining the at-risk period for cases as two days prior to NEC onset through the resolution date. To establish a proxy “onset date” in controls, we used the number of days from admission to two days prior to NEC onset in the matched case. The end of the at-risk period for controls was defined as seven days after the proxy onset date.

Finally, there is uncertainty related to the inclusion of NEC stage I cases. Although we initially planned to exclude all NEC stage I cases from both cases and controls, we found it difficult to justify excluding an infant as an eligible control if their at-risk period of interest preceded their time period of being a NEC stage I case. Thus, we propose that if an infant was diagnosed with NEC stage I before their at-risk period was over, they are ineligible to be controls. However, if they go on to become a NEC stage I case after their at-risk period, they are eligible to serve as a control.

In conclusion, there is much interest in identifying the risk factors leading to NEC in premature infants. However, until the methods used to investigate NEC are more closely evaluated and ultimately standardized, it will be difficult to determine if the reported risk factors are attributable to the disease or to inconsistent methods.

References

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