Is it necrotising enterocolitis? Is it focal intestinal perforation? Or is it something else? And does it matter?

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Making an accurate distinction between necrotizing enterocolitis (NEC) and focal intestinal perforation (FIP) in a preterm infant presenting with obvious abdominal pathology has challenged neonatologists and neonatal surgeons for some time. With significant overlap between the epidemiology, presenting symptoms, clinical signs, radiology, surgical findings, histopathology and even post-mortem findings, it is unsurprising that making an accurate distinction between these disease entities is fraught with difficulty. Indeed according to some published definitions there is significant overlap and using some of these may result in inability to differentiate at all.[1 2] Yet there are reasons why making this distinction is important in our quest to improve both understanding and outcomes.

The recent report by Berrington and Embleton illustrates some of the difficulties nicely.[3] They reviewed a large series of pre-term infants born less than 32 weeks gestation treated over a 10-year period in a tertiary neonatal unit in Newcastle, UK. Through detailed clinical review by two senior clinicians they assigned each infant presenting with abdominal pathology to a final diagnosis of either NEC or FIP. Although we are not told precisely how a final diagnosis was arrived at, they used a host of clinical, laboratory, radiological and surgical information combined with their extensive clinical experience. The review of all these data must have been time consuming and challenging. Through this work they note that there were only a very few features that were statistically different between infants with NEC or FIP. They also evaluated of a number of previously reported tools for making this distinction and found them inaccurate. For example, over 85% of infants with FIP fulfilled the criteria for Bell's stage 2 NEC or the Centre for Disease Classification NEC criteria. Using the system used by the Vermont Oxford Network or the 'two-out-of-three rule' (thrombocytopenia, pneumatosis and age at presentation 'in keeping with NEC') misclassified 70% and 43% of FIP as NEC respectively.

For the clinical neonatologist faced with a deteriorating preterm baby and abdominal distention, making an accurate distinction at first presentation is perhaps not the immediate priority. The initial clinical management of such an infant is likely to be the same regardless of underlying aetiology. Resuscitation, intravenous broad spectrum antibiotics, full supportive therapy, gut rest and gastric decompression are the mainstay of the initial management of these infants. Understanding indications for surgical assessment is clearly important but again with significant overlap between indications for surgery across both NEC and FIP, is further distinction necessary? Assigning a label of NEC in this context may be 'easy' since it allows the wider team to understand that there is an abdominal problem and an intention to treat in a certain way.

Let's consider this from a number of viewpoints. Firstly for clinical practice. Once we move beyond initial management and consider the role of surgery for these two diseases, two possible interventions are typically available - laparotomy or peritoneal drainage.

Recently the results of the NEST trial have been published.[4] This multicenter randomized controlled trial randomized preterm infants < 1000g deemed to require surgical intervention for either NEC of FIP to either peritoneal drainage or laparotomy. Of note, two previous randomized controlled trials have attempted to answer this clinical conundrum with inconclusive results.[5 6] There are two important novel aspects to the NEST trial. First is the inclusion for the first time in a neonatal surgical trial of neurodevelopmental assessment as part of the primary outcome. Secondly is the use of a preplanned Bayesian approach to the analysis (Spiegelhalter et al. provide an overview of Bayesian of approaches in RCT's[7] for those interested). The results of this trial for the first time demonstrate that there may be a different effect from each intervention - peritoneal drainage or laparotomy - based on the pre-procedural diagnosis. This interaction is revealed through the Bayesian analysis and reveals that in infants with a pre-procedural diagnosis of NEC laparotomy is 97% likely to confer a benefit. For peritoneal drainage the strength of the interaction is not as strong yet there remains an 82% probability that peritoneal drainage will be beneficial in this group. These data for the first time suggest that a personalized surgical approach may provide the best outcome for these tiny babies. Only by distinguishing between NEC and FIP early in the disease process can we have any hope of delivering this.

A further argument for accurate distinction of NEC from other pathologies within clinical practice may be made based on a desire to identify children as highest risk of poor longer term outcomes. NEC is widely recognized as having a negative impact on neurodevelopment over and above prematurity alone. Being able to accurately identify them is therefore important.

The success of clinical research to improve outcomes is conditional on high quality, accurate data. Several trials in recent years have used a diagnosis of NEC as a primary outcome – trials of probiotic administration, different feeding practices amongst others. It is obvious that being able to accurately identify NEC and distinguish it from FIP is of upmost importance in this context. Similarly in research involving treatments for NEC, distinguishing NEC from FIP would be important to identify eligible infants correctly. Failure to accurately make the distinction between NEC and FIP may result in the inclusion of infants with a diagnosis other than NEC in a therapeutic intervention trial and may mis-classify an infant felt to have met criteria for a primary outcome of NEC. Either of these scenarios may jeopardise the security of trial findings. Thus there are potentially significant consequences for research of failure to accurately distinguish between NEC, FIP and indeed other causes of abdominal pathology in preterm infants.

Just a word on those other pathologies. Whilst NEC and FIP are the most commonly encountered causes of abdominal pathology that may require surgery in the preterm infant, they are not the only ones. Meconium ileus of prematurity, milk curd obstruction and volvulus without malrotation may all require surgical intervention in ELBW infants.[8] The aforementioned NEST trial found a diagnosis other than NEC or FIP in 7.3% of recruited infants.[4] Although Embleton and Berrington did not include these pathologies in their report,[3] it would be interesting to know which other pathologies they encountered and whether they were able to distinguish between these and either NEC or FIP. Clinicians and researchers should keep an open mind and consider these other diagnoses in clinical practice, routine data collection and research.

Advances in technology now permit the capture of routine data on a scale that was previously unimaginable. Recording such data has become integral to neonatal care in many settings including in the UK. Such data have the potential to be extremely powerful for purposes such as national audit, quality improvement and research. The automatic feed of routinely collected data into the National Neonatal Research Database (NNRD) in the UK provides an excellent example of how these data may be made available for research. It goes without saying that for these data to have

maximum impact and patient benefit they need to be accurate. It is therefore something of a concern that Berrington and Embleton found that a final diagnosis was inaccurate in the data source that feeds into this routinely collected dataset for 15% of NEC and 70% of FIP cases respectively.[3] I applaud them for this honesty and for bringing this to our attention. Whilst we cannot be certain how representative this finding is of the wider NNRD dataset it highlights once again the importance of making an accurate distinction between NEC, FIP and other pathologies. As these data become increasingly relied upon for the range of purposes already mentioned we must ensure that those data are fit for purpose. It is therefore essential that the importance of accurate data recording permeates all those involved in neonatal care: nursing staff, clinicians, data managers and others alike. Routine data collection is not just a box ticking exercise; failure to do it accurately may have significant consequences and may be worse that not doing it at all.

So in my view Berrington and Embleton have brought an important consideration to our attention. The data suggest an 'over diagnosis' of NEC. Perhaps 'NEC' is a relatively easy label to assign to a preterm baby with significant abdominal concern. Yet 'easy' is almost certainly not 'best' and not all that looks like NEC, is in fact NEC. We should all strive to improve our diagnostic accuracy when treating these infants.

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