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More than a gut feeling: predicting surgical necrotising enterocolitis

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Despite recent advances in neonatal practice, necrotising enterocolitis (NEC) remains the most common and devastating gastrointestinal emergency in premature infants. In fact, as more extremely premature infants survive, the incidence appears to be increasing worldwide.¹ Severe NEC is characterised by coagulative necrosis of the distal ileum and proximal colon with clinical presentation ranging from abdominal distension, pneumatosis intestinalis, frank blood in stools, intestinal gangrene, bowel perforation, sepsis and shock. Approximately 9000 infants develop NEC in the USA each year and mortality rates range from 10%–50%.²³ The associated costs—both financial and personal—are significant; the average hospital stay for infants with surgical NEC is an additional 43.1 days at an average additional cost of US\$200 000 per child compared with extremely low birthweight infants without NEC.⁴ Treatment strategies are mainly supportive and include administration of antibiotics and fluids, blood product replacement and withholding of feedings. About 40% of NEC patients require surgery to remove necrotic bowel, which can result in short bowel syndrome, with prolonged medical expenses and chronic gastrointestinal difficulties. In particular, surgical NEC is a significant predictor of lasting neurodevelopmental morbidity independent of other factors.⁵⁶ While the outcomes for many prematurity-related illnesses have improved over the past decades, mortality and morbidity rates for NEC have remained constant.

Progress in prevention of the disease has been severely limited by our inability to predict which subset of premature infants is at highest risk for surgical NEC.⁷ Studies in this highly vulnerable population of extremely premature infants are challenged by ethical and technical limitations such as very small sample volumes and the current unfeasibility of intestinal biopsies. The paper by Sylvester *et al*⁸ describes a new non-invasive approach of combining clinical data and selected urine peptide biomarkers to develop an algorithm to predict progression of suspected medical NEC to surgical disease. For this study, the investigators analysed prospectively collected demographic, clinical and laboratory data from 550 infants in eight university-based paediatric teaching hospitals and measured peptide profiles in urine samples collected at the time of initial clinical concern for NEC from a subset of 65 patients. The study confirmed the previously observed higher risk of male infants for surgical NEC.⁷⁹

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However, application of machine learning techniques demonstrated that clinical parameters alone could not accurately predict NEC progressing to surgical disease in over 40% of patients (area under curve (AUC) of 0.817 by receiver operating characteristic analysis). The authors used a biomarker discovery and validation protocol to identify a set of three urine peptides able to differentiate surgical from medical NEC but with only slightly better predictive value (AUC of 0.858). However, an ensemble algorithm combining clinical data with urine peptide biomarkers identified all infants with surgical NEC correctly. Subsequent pathway analysis of peptide biomarkers revealed some insights into the possible pathophysiology of progressive NEC such as advancing intravascular coagulation and changes in integrin expression.¹⁰¹¹

Prevention is the key element in reducing the burden of NEC. Therefore biomarker discovery to identify patients at highest risk prior to clinical signs of the disease is of high priority. By the time NEC is diagnosed, tissue injury and inflammatory sequelae have already occurred and the patient is typically committed to 5–10 days of withholding enteral nutrition and treating with broad-spectrum antibiotics. While identifying the subgroup of diagnosed NEC patients that progress towards extensive necrosis and/or bowel perforation is helpful, accurately predicting NEC prior to clinical suspicion is likely to be of bigger impact. The study by Sylvester *et al* is an important contribution to this quest. Several challenges remain: while machine learning is a powerful tool for predictive modelling of neonatal outcomes,¹²¹³ urine peptidomics are currently limited by sample inconsistency, lack of normalisation protocols and labour-intensive technology. In addition, specific examples of how a predictive algorithm for surgical NEC can be applied to clinical practice in the neonatal intensive care unit remain open for discussion. The mean duration between time of urine sample collection and confirmed diagnosis of NEC reported by Sylvester *et al* was 31 h. What if the prediction model declares a high risk for surgical NEC? Will paediatric surgeons be willing to operate sooner? This is questionable since the optimal timing and type of surgery (eg, peritoneal drainage vs laparotomy with or without intestinal resection) remains controversial for this disease.¹⁴¹⁵ On the other hand, what would be the suggestions to the clinician in case the prediction model declares low risk for surgical NEC? Decide against transfer to a higher-level care facility, reduce the number of serial radiographs, limit duration and spectrum of antimicrobial coverage and/or earlier reinitiation of enteral feedings? These strategies could decrease cost and morbidity. However, any proposed change in management based on predicted risk would require a prospective clinical trial prior to clinical implementation.

Another important question is how the proposed algorithm can be combined with other published methods of predicting surgical NEC.^{16–18} Would a combination of computerised decision support systems with validated urine, serum and/or faecal biomarkers including recently discovered microbial signatures¹⁹ improve negative and positive predictive values for surgical NEC?

In order to prevent this devastating disease, two things need to happen: first, we need to better understand the pathophysiology of various NEC subsets and identify high-risk patients earlier;²⁰ second, neonatologists and paediatric surgeons need to agree to a more uniform practice style including implementation of proven prevention measures such as

early breast milk feeding, standardised feeding regimens and reduction of unnecessary antibiotics.²¹ One would hope that studies providing better prediction tools for NEC like the one by Sylvester *et al* would stimulate movement in this direction.

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