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# Exploring growth failure in neonates with enterostomy

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**ABSTRACT**

**Aim of the Study:** Neonatal enterostomy is a known risk for growth failure. We hypothesized that episodes of inflammation may drive a catabolic state, exploring this by assessing serum biochemistry alongside growth trajectory in enterostomy patients.

**Methods:** A **r**etrospective analysis of infants with histologically confirmed NEC from 01/2012–07/2021 in a tertiary neonatal surgical centre was performed. Change in weight-for-age Z-score ($\Delta Z$) between stoma formation and closure was calculated. Serum CRP (C-reactive protein), urea, and creatinine levels were recorded and duration of elevated levels calculated as Area Under Curve (AUC). We examined for trends of serum levels rising together using intersecting moving averages. Spearman's correlation analysis was performed, while multivariable linear regression examined factors associated with $\Delta Z$.

**Results:** 79 neonates were included. At stoma formation, median Z-score was -1.42 [range -4.73, +1.3]. Sixty-two patients (78%) had a fall in Z-score during their time with a stoma, 16 (20%) had a $\Delta Z$ less than -2. Urea AUC was significantly univariably correlated with $\Delta Z$ and remained statistically significant in a multivariable model (Exp(B) x 100= -0.57[-1,-0.09]; p=0.022). The number of biomarker peaks correlated significantly with ΔZ for urea (r=-0.25;p=0.025) and CRP (r=-0.35;p=0.0017) but not Creatinine (r=-0.21;p=0.066). Analysing the number of peaks of any combination of variables coinciding was consistently significantly correlated negatively with ΔZ (r=-0.29 to -0.27; p≤0.016 for all).

**Conclusion:** Our data shows that infants who were more severely affected by growth failure had more frequent and severe uremia while they had a stoma (suggesting a catabolic state). Disturbances in urea were commonly associated with CRP, suggesting that inflammation is a significant factor in growth failure in these infants. These findings promote aggressive management of sepsis in these infants, as well as suggesting an earlier closure of stoma to minimise their "at-risk"' period.

**Keywords:** Necrotizing enterocolitis; Stoma; Growth failure

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**Introduction**

Enterostomy formation is often carried out as part of emergency surgery in neonates undergoing laparotomy for necrotising enterocolitis (NEC)[1,2]. Recent reports have demonstrated that growth failure is common in neonates living with an enterostomy [3,4]. Although there may be an element of "catch up" growth following enterostomy closure [4], the disruption to growth occurs during a key developmental period, particularly for the preterm neonatal brain and the long-term effects of this are only recently coming to light[5–7]. The underlying reasons for faltering growth while living with an enterostomy are unclear but are likely multifactorial.

Episodes of presumed or confirmed sepsis present a challenge to growth in the neonate. Firstly, inflammation itself is a catabolic process characterised by the breakdown of complex molecules to release energy rather than laying them down for growth. In addition to this catabolic response, nutritional support (both enteral and parenteral) is frequently paused during periods of inflammation and presumed sepsis, limiting caloric intake. Both these processes would contribute to growth failure.

C-reactive protein (CRP) is well recognised to rise during periods of acute inflammation, and has validity in premature neonates although its use is better validated as a serial measurement[8]. Raised serum urea may indicate an increase in protein catabolism, as has been observed in neonates with persistent inflammatory catabolic syndrome [9], although serum urea can also be raised due to concomitant renal failure. Conversely, a low serum urea may indicate inadequate feeding[10].

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We used serum levels of CRP and urea as surrogate markers of inflammation and catabolism respectively and explored their association with growth in a cohort of infants with enterostomy following surgical treatment of NEC at a tertiary neonatal surgical centre.

**Methods**

The study was registered locally as a review of clinical practice (reference number N12363). Infants who underwent stoma formation as part of surgical management for histologically confirmed NEC within a 9-year period (January 2012 – June 2021) were identified from the electronic clinical record (Badgernet, Clevermed UK). Infants who died prior to stoma closure or had their stoma for fewer than fourteen days were excluded. Exclusions were also applied to neonates with either underlying renal disease and/or a diagnosed syndrome as these were predicted to be significant confounding factors. For all included babies, data were extracted including: gender, date of stoma formation, weight at stoma formation, date of stoma closure, weight at stoma closure, all measures of serum CRP, urea and creatinine.

Weight-for-age Z-scores [11] were calculated at the time of stoma formation and stoma closure, with the difference referred to as a change in Z ($\Delta Z$). World Health Organisation (WHO) definitions of weight Z score <-2 as underweight and <-3 as severely underweight were adopted. Throughout the manuscript, a negative $\Delta Z$ is referred to as faltering growth – as these infants would be losing weight relative to their age-corrected centile. Z score at the time of stoma formation and closure were compared using a paired T-test with Mean Difference after confirming a normal distribution.

Serum measurements of CRP, urea and creatinine were plotted against time spent with enterostomy. The resulting graphs were used to calculate the area under the curve (AUC) for each variable using two different baselines: low (median value of the normal range) and high (upper limit of the normal range or clear elevation above baseline for CRP)(Fig. 1). These baselines were taken from local chemical pathology reference data and corresponded to CRP values of 5 and 20 mg/dL; Urea values of 5 and 8.3 mmol/L; and Creatinine values of 33 and 48 μmol/L. The AUC essentially describes the burden of a particular marker experienced by a neonate, corrected for the time spent with an enterostomy. By excluding lower values that are within the "normal" range and only including values above a certain threshold, much of the potential noise is removed, giving a more reliable picture of persistently elevated levels of a given marker. Association between AUC and $\Delta Z$ for each marker and each baseline were assessed in univariate analyses (Spearman's correlation) and the stronger predictor of the two threshold baseline values was taken forward into a multivariate analysis to identify independent factors associated with changes in *Z*-score.

It was necessary to establish the temporal relationship between biochemical parameters in order to clarify that episodes of inflammation were correlated with a catabolic state (i.e. raised CRP and urea without raised creatinine – otherwise indicative of renal impairment). This was approached using a trend-deviation model: intersection of a 2-day moving average line through an 8-day moving average. A link was accepted if parameters showed a rise above this threshold within 72 hours of each other. In order to minimise noise in this model, thresholds were set at the same values identified for calculating AUC. Analysis was performed with Pearson's R to examine correlation between $\Delta Z$ and both the number of peaks of each biochemical marker alone and in combination with one another.

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Statistical significance was accepted at $p<0.05$. Analyses were performed in Prism 9.0 (GraphPad, La Jolla, California), SPSS 26.0 (IBM™) and R version 4.2.2 (2022-10-31). Data are presented as median [range] unless otherwise stated.

**Results**

A total of 79 neonates met the inclusion criteria, with a median gestational age at birth of $27^{+3}$ [$22^{+6}$ – $39^{+4}$] weeks and birthweight of 880 [450 - 3150] grams. These infants underwent stoma formation (22 jejunostomy / 57 ileostomy) at laparotomy on day 25 [1 - 81] of life (Corrected Post Conceptual Age: $31^{+5}$ [$24^{+3}$ - 46] weeks). At stoma formation, 72/79 (91%) of infants had a Z-score below zero (median -1.42 [+1.3 to -4.73]), with 17/79 (22%) being underweight ($Z \leq -2$) and 6 (8%) severely underweight ($Z \leq -3$). The median duration lived with enterostomy was 63 [27-148] days. A decline in Z-score occurred in 78% (62/79) of infants during this period (mean $\Delta Z$ [+/- 95%CI]: -0.87 [-1.14 to -0.61]; Paired T-test: $p<0.0001$; Figure 2). Severe growth faltering ($\Delta Z < -2$) was observed in 16/79 (20%) of infants.

Univariate analysis (Spearman's correlation) did not demonstrate a significant correlation between faltering growth ($\Delta Z$) and Days with Stoma ($r= -0.17$; $p=0.13$); however infants with severely faltering growth ($\Delta Z$ greater than -2) had a significantly longer time with stoma (median [+ interquartile range] = 81[62-94] vs 61[46-79]; $p=0.012$) suggesting that growth failure would be more pronounced with a longer period with enterostomy. Faltering growth also significantly correlated with Urea AUC using either baseline (threshold 5: $r=-0.31$; $p=0.006$; threshold 8.3: $r=-0.30$; $p=0.007$) but not with CRP AUC (Threshold 5: $r=-0.13$; $p=0.25$; Threshold 20: $r=-0.19$; $p=0.09$) or Creatinine AUC (Threshold 33: $r=-0.22$; $p=0.057$; Threshold

48: r=-0.15; p=0.201). Mann Witney U test of the distributions of these values against those with severely faltering growth showed significant differences in each (p≤0.038 for all). The strongest correlations for each biochemical parameter were included in a multivariate linear model: Urea AUC (Threshold 5), CRP AUC (Threshold 20), and Creatinine AUC (Threshold 33). Pre-selected variables (Birthweight, Days with Stoma, and Gender) were also included in the model. A significant association remained between Urea AUC and faltering growth (p=0.022).

To investigate the temporal relationship between biochemical parameters, elevations in serum measurements were analysed using a trend analysis. Across the 79 patients, there were 145 peaks in serum Urea >5mM, 135 in serum CRP >20 mg/dl, and 86 in Creatinine >33 µmol/l. More severe faltering growth was correlated with a greater number of peaks for both Urea (r=-0.25; p=0.025) and CRP (r=-0.35; p=0.0017), but not Creatinine (r=-0.21; p=0.066). However, when one measurement coincided with one or both of the others (i.e. CRP with Urea, or Creatinine with CRP and Urea) this consistently demonstrated a significant negative correlation with $\Delta Z$ (r=-0.29 to -0.27; p≤0.016 for all).

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**Discussion**

We have shown faltering growth in the majority of infants in a cohort living with enterostomy following surgery for NEC. In addition, our data show that infants with more frequent and severe disturbances in their serum biochemistry during the time spent with a stoma are more affected by growth failure. Significant correlations between faltering growth and the burden of Urea and CRP are observed. Creatinine did not show the same correlations. Our findings suggest that inflammatory burden is a significant factor in growth failure in neonates with enterostomy, plausibly due to an associated catabolic state.

Others have described faltering growth in infants living with an enterostomy[4] and a persistent inflammatory catabolic state in infants [9]. In our cohort we have shown that these states (enterostomy and acute inflammation) co-exist and contribute to worsen growth failure. Urea was more strongly associated with growth failure than CRP in a multivariate model. Although this might be due to a direct causative role of catabolism in growth failure, urea and CRP are also somewhat co-linear (when the number and timing of peaks in biochemical markers is analysed, over 40% of CRP and Urea peak measurements coincide with one another).

The key strength of our study is its size and completeness, we have examined a reasonable size cohort of babies living with an enterostomy and have complete data for all three biomarkers studied. This allows us reasonable confidence we have demonstrated a biologically plausible association between inflammation, protein catabolism and growth failure. It is, however, a retrospective cohort and there are likely to have been unmeasured confounders. For example, we did not show an association of poor growth with extreme

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prematurity or high enterostomy (jejunostomy) as might have been anticipated. One weakness of the study is the lack of information about nutritional delivery, both parenteral and enteral, during this period. Examination of urinary sodium levels was outside the limits of this study but will form part of our prospective data collection on neonatal enterostomies.

There are likely to be many factors affecting growth of infants with a stoma, for example a child with a higher stoma is more likely to suffer from high output, and be kept on parenteral nutrition, which may prompt an earlier plan for closure. However, we feel the association of inflammatory burden with urea levels, and the association of each factor with growth failure, is interesting and potentially mechanistically important. Timing of enterostomy closure is a topic with little evidence in neonatal surgery, and we await the results of the national observational ToSCIN (Timing of Stoma Closure in Neonates) study to contribute to the evidence base[12]. Clearly if the time spent with a stoma is an 'at-risk' period, it would seem logical to reduce this exposure. There is strong evidence that nutrition in premature neonates plays a significant role in early brain development[13,14], and may significantly impact long-term cognitive function [15]. We plan to assess neurodevelopmental outcomes in these infants prospectively to further establish evidence for this. Future research into prophylactic measures to reduce neonatal sepsis in these patients (i.e. probiotics or non-absorbed oral antibiotic agents).

The prevailing message of our findings would strongly supports the close involvement of nutrition and dietetic specialists in the care of neonates with a stoma, as well as aggressive management of sepsis to minimise the inflammatory burden on these particularly vulnerable infants.

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**Figure Legends**

**Figure 1.** Example of Area Under Curve of CRP. Graphs represent the same data (CRP vs. Time) from a single patient with different thresholds drawn. A: With no threshold (i.e. all values more than 0 are counted) the AUC can be calculated at 3450. B: Threshold of >5 (AUC = 2962) and C: Threshold of >20 (AUC = 2013).

**Figure 2.** Change in Weight for Age Z-score between stoma formation and stoma closure. Mean difference shown in purple. Paired T-Test Stoma Formation vs. Stoma Closure; $p<0.0001$.

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TABLE 1

| Number of peaks vs ΔZ | Spearman's R [95% CI] | p-value |
|---|---|---|
| Total Urea | -0.07 [-0.29 to +0.16] | 0.56 |
| Total Creatinine | **-0.23 [-0.43 to +0.002]** | **0.05** |
| Total CRP | **-0.26 [-0.46 to -0.04]** | **0.02** |
| Urea *and* CRP | -0.15 [-0.37 to +0.079] | 0.18 |
| Urea *and* Creatinine | **-0.30 [-0.49 to -0.08]** | **0.007** |
| CRP *and* Creatinine | **-0.26 [-0.46 to -0.03]** | **0.02** |
| Urea *and* CRP *and* Creatinine | **-0.30 [-0.49 to -0.08]** | **0.007** |

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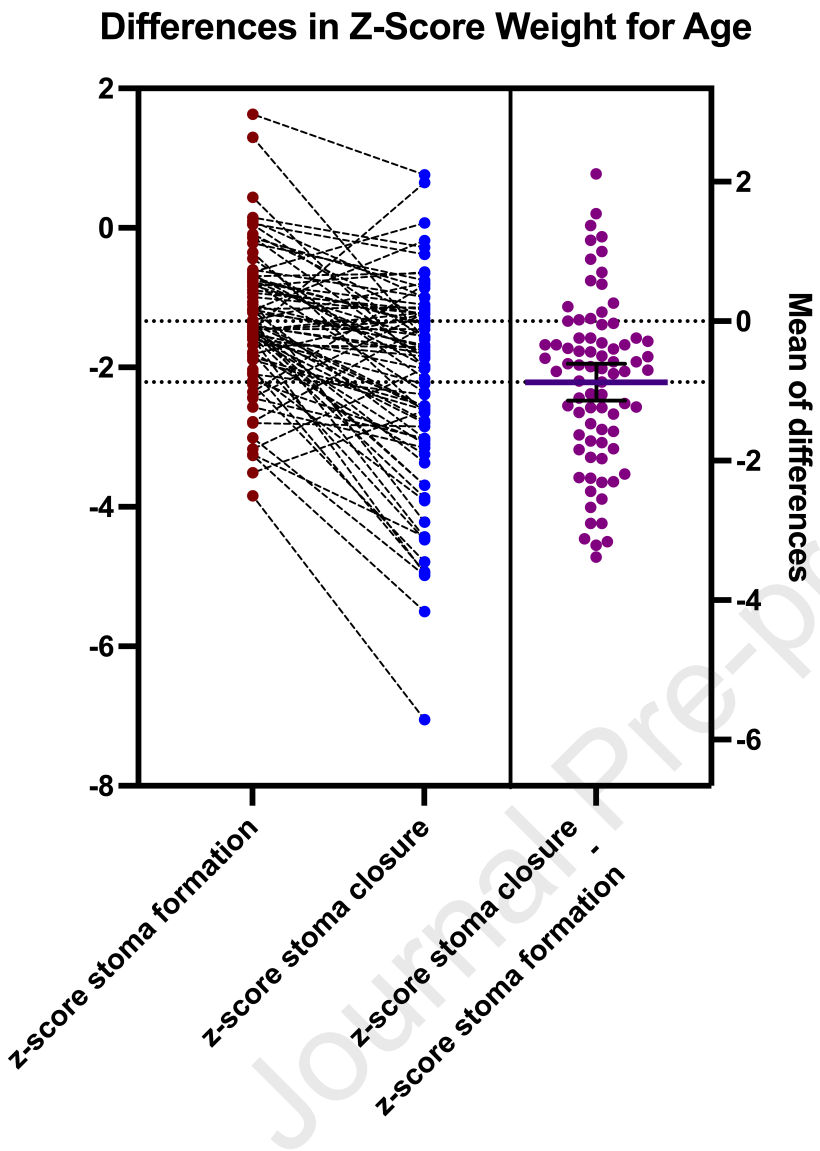


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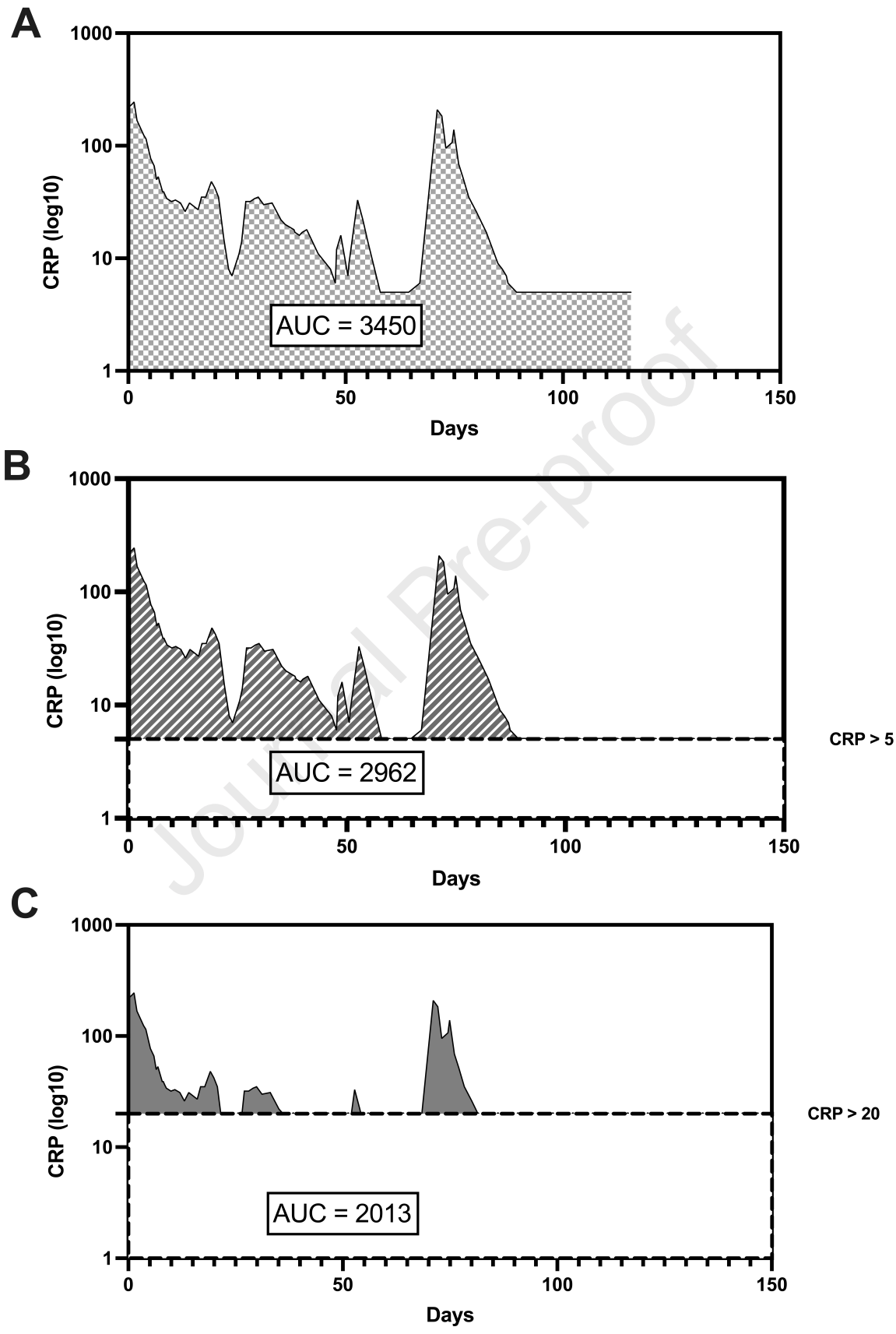


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**Highlights**

- Growth failure is common in infants with an enterostomy, factors associated with this have not been explored.
- Serum biochemical markers (urea and CRP) were shown to associate with growth failure.
- Raised urea suggests a catabolic state, while raised CRP suggests periods of sepsis or inflammation may drive this faltering growth.
- Reducing time with a stoma and aggressive sepsis management may improve outcomes in a future prospective cohort study.

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