

Logan, M., Ijaz, U.Z., Hansen, R., Gerasimidis, K. and Russell, R.K. (2017) Letter: reproducible evidence shows that exclusive enteral nutrition significantly reduces faecal calprotectin concentrations in children with active Crohn's Disease. *Alimentary Pharmacology and Therapeutics*, 46(11-12), pp. 1119-1120.

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Sirs,

We read with interest the recent meta-analysis by Swaminath *et al* (2017) that reviewed studies on induction of remission with exclusive enteral nutrition (EEN) in paediatric Crohn's disease (CD)<sup>1</sup>.

We feel however that the title of the article is slightly misleading as the authors only include studies that directly compare the efficacy of EEN against corticosteroids (CS), excluding other studies where EEN was used, without a direct comparator arm with CS (table 2, page 1) excluding also points of secondary analysis like faecal calprotectin (FC).

We were encouraged to note the authors describe EEN to be as efficacious as CS, as shown in the previous *AP&T* meta-analysis; with the advantage of superior outcomes in terms of mucosal healing<sup>2</sup>.

We are aware that FC associates with rates of mucosal healing<sup>3</sup>. Therefore, it seemed paradoxical to us that there was no difference in FC levels between EEN and CS, despite the significant differences in mucosal healing rates. We looked for the FC data mentioned but found no evidence of the studies from which the abstract data was generated.

We performed our own literature search specifically for studies reporting changes to FC levels during EEN, independent of the necessity including a CS arm. From an initial search using MEDLINE with the term "Exclusive enteral nutrition AND Crohn's" we identified and reviewed 181 abstracts and were left with 18 relevant studies, including five studies from overlapping patient cohorts<sup>4-10</sup>. To prevent duplication of results, only one study from the group were considered for the analysis. Using the mean or median FC as values presented from each study, we calculated the percentage decrease during the course of EEN and found that on average FC drops 48% on completion of an EEN course (figure 1 A and B).

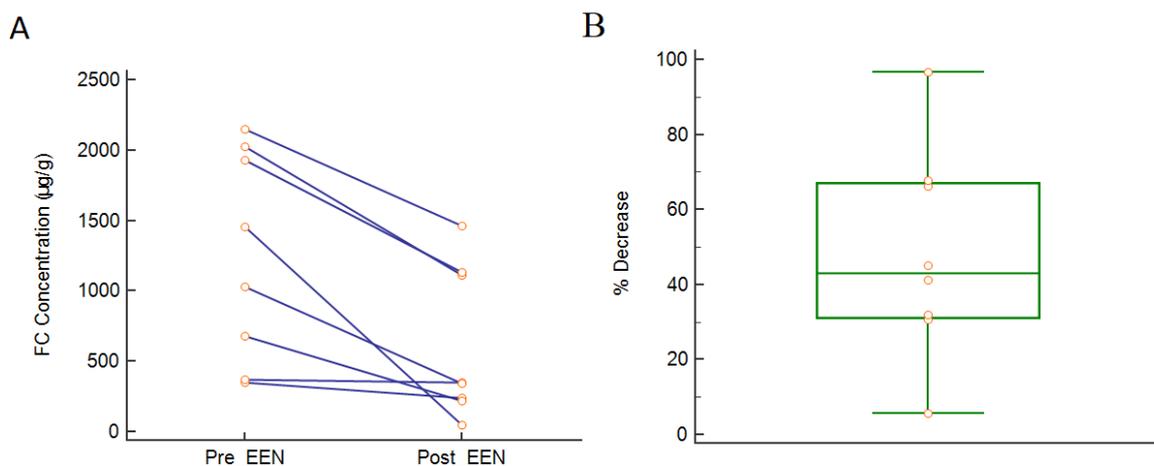


Figure 1: A) Mean/median faecal calprotectin of each study at treatment initiation and treatment end. B) The percentage decrease in faecal calprotectin from treatment initiation and end of EEN

All studies except Dunn *et al* report a significant decrease in FC concentration while on EEN. This study reports FC as binary < or > 250 µg/g. This may mask significant reductions in FC during EEN, that remains above normal reference values. We identified only one study with paired longitudinal

endoscopic mucosal healing and FC data. However, the analysis performed in this study combined patients treated with either EEN or CS. As they did not distinguish the treatment arms of the patients it was removed from our analysis <sup>11</sup>.

While the exact mechanisms by which EEN works, and drives FC reduction, remain elusive; the gut microbiota plays a pivotal role<sup>9,12</sup>.

It is well known that the composition and metabolic activity of the microbiota is altered during EEN. The study from our group, Quince *et al* (2015), collected serial faecal samples and by using stepwise regression, we identified 14 operational taxonomic units that predicted 78% of the variation to FC.

This study and others have shown that EEN substantially modulates the microbiota, by reducing bacterial diversity, altering the relative abundance of metabolic pathways while altering the local microenvironment and major bacterial metabolites. We suspect these mechanisms by extension would be important in the process of mucosal healing too although specific studies addressing this are needed.

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