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High faecal pH and low total microbial load associate with normalisation of faecal calprotectin in children with Crohn's disease treated with exclusive enteral nutrition; results from iPENS, a multicentre, prospective study

K. Gkikas[1], M. Lima[1], S. McKirdy[1], B. Nichols[1], C. Kerbiriou[1], L. Gervais[2], G. Smith[3], L. Armstrong[4], T. Jordan[3], I. Chalmers[5,6], H. Barlow[7], G. Al Hourani[8], R. Muhammed[9], D. Wands[2], P. Narula[10], M. Patel[11], U.Z. Ijaz[12], S. Milling[13], M. Gasparetto[14], P. Henderson[15], D.C. Wilson[15], R. Hansen[2,16], R.K. Russell[15], K. Gerasimidis[1]

[1]University of Glasgow, School of Medicine- Dentistry and Nursing, Glasgow, United Kingdom [2]Royal Hospital for Children, Department of Paediatric Gastroenterology- Hepatology and Nutrition, Glasgow, United Kingdom [3]University Hospital Wishaw, Department of Paediatrics, Wishaw, United Kingdom [4]University Crosshouse Hospital, Department of Paediatrics, Crosshouse, United Kingdom [5]Aberdeen Children's Hospital, Department of Paediatric Gastroenterology, Aberdeen, United Kingdom [6]Tayside Children's Hospital, Department of Paediatric Gastroenterology, Dundee, United Kingdom [7]Royal Manchester Children's Hospital, Department of Paediatrics, Manchester, United Kingdom [8]Forth Valley Royal Hospital, Department of Paediatrics, Larbert, United Kingdom [9]Birmingham Women's and Children's Hospital, Department of Paediatric Gastroenterology, Birmingham, United Kingdom [10]Sheffield Children's Hospital, Department of Paediatric Gastroenterology, Sheffield, United Kingdom [11]Royal London Children's Hospital, Department of Paediatric Gastroenterology, London, United Kingdom [12]University of Glasgow, James Watt School of Engineering, Glasgow, United Kingdom [13]University of Glasgow, School of Infection and Immunity, Glasgow, United Kingdom [14]Norfolk and Norwich University Hospitals, Department of Paediatric Gastroenterology, Norwich, United Kingdom [15]Royal Hospital for Children and Young People, Department of Paediatric Gastroenterology- Hepatology and Nutrition, Edinburgh, United Kingdom [16]University of Dundee, Department of Child health- Division of Clinical and Molecular Medicine- School of Medicine, Dundee, United Kingdom

Background: Exclusive enteral nutrition (EEN) is a main therapy for active Crohn's disease (CD) in children, but normalisation of faecal calprotectin (FCAL) varies among patients, even in those who enter clinical remission. To better understand disease characteristics related to EEN efficacy and its mechanism of action, we compared clinical and microbial parameters between patients whose FCAL normalised against those who did not at EEN completion.

Methods: Children with CD, clinically responding to EEN, were recruited from 11 UK hospitals (January 2020- May 2023, NCT04225689) and provided a single faecal sample before EEN completion. Patients were divided in two groups according to levels of FCAL at EEN completion (FCAL<250 and FCAL>250 mg/kg). Levels of faecal short chain fatty acids (SCFA), faecal sample characteristics (pH, water content (%), bristol stool score) and total microbial load (qPCR) were compared between the two groups. Anthropometric and clinical parameters (blood inflammatory markers, use of immunosuppressants, disease duration, disease location) were also compared. Machine learning using feature elimination with data imputation for missing data was performed to identify associations between clinical, anthropometry, microbial parameters and FCAL normalisation.

Results: At EEN completion, 84 children (female, 35%) were recruited [age, median (IQR): 13.2 (11.8, 14.9 years)] with a median (Q1, Q3) FCAL of 643 (146, 2033) mg/kg. Out of 84 patients, 35 (42%) had an FCAL<250 mg/kg. Total microbial load and SCFA were measured in a subset of patients (n=44). Patients with FCAL<250mg/kg had a higher faecal pH and lower microbial load compared to those with FCAL>250mg/kg [faecal pH; FCAL<250 mg/kg: 8.3 (8.1, 8.6) vs FCAL>250 mg/kg; 7.95 (7.6, 8.3), p=0.001; microbial load (log10 16S rRNA gene copies/g): FCAL<250mg/kg: 10.7 (10.4, 10.9) vs FCAL>250mg/kg: 11.0 (10.5, 11.2), p=0.02]. Median BMI z-score was also non-significantly (p=0.052) higher in patients with FCAL<250mg/kg. The use of immunosuppressants at EEN completion, disease duration, disease location and other faecal parameters were not different between the two groups. A multicomponent random forest model (clinical, blood inflammatory markers, anthropometry, faecal parameters) predicted normalisation of FCAL with 71% accuracy (sensitivity: 69%, specificity: 71%, p=<0.001, Figure 1). Higher faecal pH, BMI z-scores and lower total microbial load were the most influential parameters relating to FCAL<250mg/kg.

Conclusion: We showed that the efficacy of EEN in reducing gut inflammation might be, at least in part, mediated via reducing gut bacterial biomass and modulating luminal pH and the downstream effects this may have on inflammatory members of the microbial community.

Figure(s)/Table(s): see next page

Figure 1A: Random forest (RF) classification between FCAL responders and non–responders using clinical, anthropometry and microbial data.
1B: Area under the curve of the best RF model. 1C: Barplots of categorical variables included in RF model.