IBS: What's Rome got to do with it?

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Introduction

IBS is a complex disorder, the pathophysiology of which is not well understood. Introduced in 1988, the Rome diagnostic criteria for Irritable Bowel Syndrome (IBS) mainly focus on the symptoms of abdominal pain, stool frequency and consistency. The Rome criteria have undergone four updates, with Rome IV being introduced in 2016. Comparative studies of Rome III and IV have shown that only a proportion of Rome III positive patients were also diagnosed as IBS under Rome IV criteria[1]. While this scheme tells a clinician whether an IBS patient is constipation-predominant (IBS-C), diarrhoea-predominant (IBS-D) or a mixed subtype (IBS-M) and has pain, how informative this tool is for proper diagnosis and treatment of patients is questionable given the heterogeneity of the disorder and the fact that sufferers can transition from one clinical subtype to another. In addition, amendments of Rome criteria result in variations in the prevalence of IBS; this has already been reported for Rome IV[1] and Enck *et al* question if *All roads lead to Rome, why does none lead out?* and why have we not progressed defining, diagnosing and treating IBS[2]. Over the last decade, research has focused on the gut microbiome and its relevance in IBS, and increasing evidence suggests that an altered gut microbiota may be a contributor and current therapies (e.g. Rifaximin) which target the gut microbiome have shown some efficacy in the treatment of IBS[3]. Here we recruited patients with IBS and healthy controls to investigate the microbiome profiles of the clinical IBS subtypes (IBS-C, IBS-D and IBS-M) and distribution of these subtypes across microbiome signatures[4] to see if this yielded a more meaningful diagnostic approach than Rome criteria to direct a personalised medicine treatment for patients.

Methods

Male and female healthy controls (n=64) and patients with IBS (n=78) aged >16 and <70 years were recruited to the study under an ICH-GCP protocol approved by the Cork Research Ethics Committee. All subjects were included if they had not used antibiotics within 6 weeks of screening, and patients with IBS were recruited under Rome IV criteria. Faecal samples were collected at baseline for all subjects and follow-up samples were obtained from 30 patients with IBS for microbiome temporal analysis. The follow-up sample collection timepoint varied for each patient and ranged from 3-11 months from the baseline sample. 16S amplicon sequencing of the V3-V4 variable region was performed using the MiSeq (2x250 bp) chemistry platform. Microbiome data analysis was performed using an in-house bioinformatics pipeline of our MicroDx® platform which included the USEARCH global alignment algorithm and UPARSE algorithm. Microbiome alpha and beta diversity of the clinical subtypes was carried out using the Shannon Index and Principal Component Analysis (PCoA) using Spearman distance (Fig. 1 and Fig. 2) respectively. The IBS population was stratified into normal-like microbiome IBS or altered microbiome IBS sub-groups whereby healthy controls and patients with IBS were optimally split to define an IBS population associated with an altered microbiota (using PCoA) based on Spearman distance (distribution summarized in Table 1). These methods were used to evaluate the temporal stability of the microbiome in a subset of patients with IBS (summary Table 2) where the baseline sample of an individual was compared to their follow-up sample.

Results

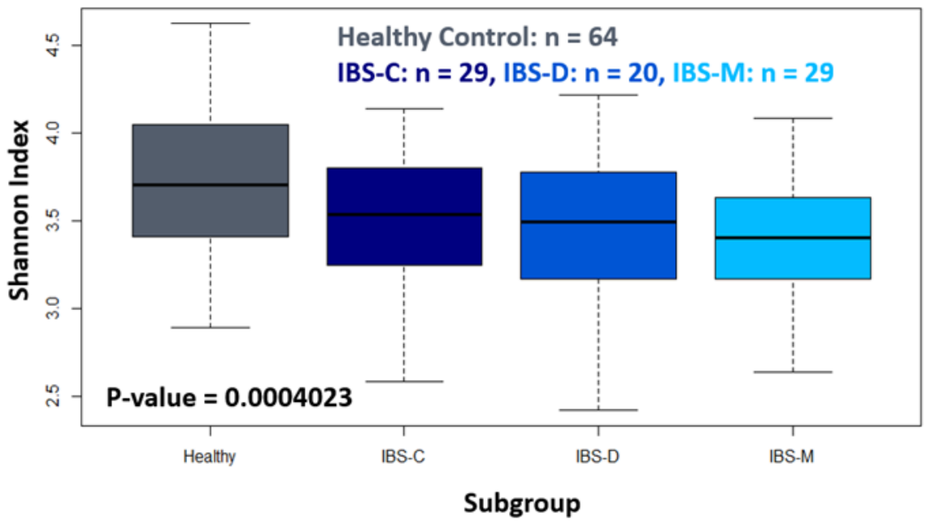

Fig. 1: Microbiota profiles are not significantly different among IBS clinical subtypes but significant from healthy controls.

	IBS-C	IBS-D	IBS-M	Total
Altered microbiota	13	12	18	43
Normal-like microbiota	16	8	11	35
			Total IBS	78

Table 1: Patients with each IBS clinical subtype were found in both the altered and normal-like microbiome IBS subgroups.

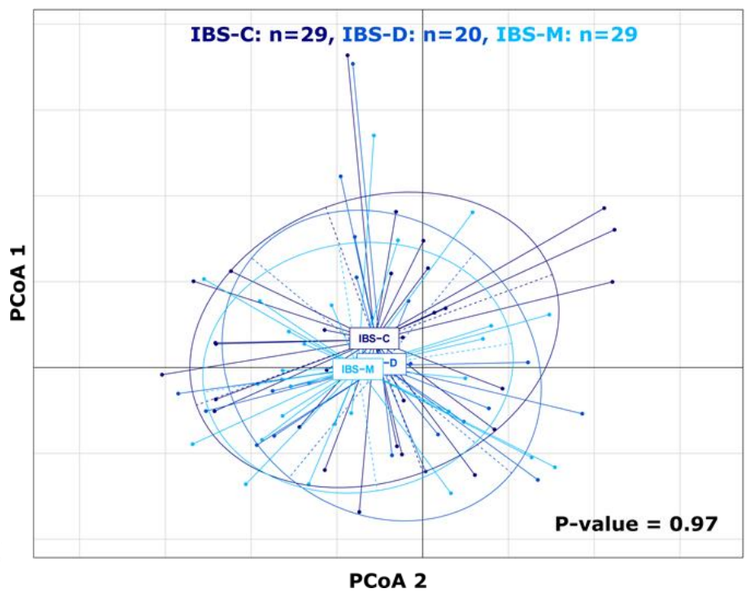

Fig. 2: Microbiota profiles are not significantly different among IBS clinical subtypes.

Change	IBS-C (n=7)	IBS-D (n=14)	IBS-M (n=9)	Total (n=30)
Altered to Normal-like	0	0	1	1
Normal-like to Altered	2	1	1	4
No change	5	13	7	25

Table 2: Temporal analysis of a subset of the IBS cohort (n=30: IBS-C (7), IBS-D (14), IBS-M (9)), showed the microbiome status in 17% of the patients changed from their baseline.

Conclusions

- The complexity of IBS is not captured by Rome diagnostic criteria.
- An objective measurement with mechanistic insight is likely to be more useful
- Microbiota compositional analyses question the so-called clinical sub-types of IBS of the Rome criteria.
- Some patients frequently shift from one clinical sub-type to another demonstrating the constant flux that is associated with the disorder.
- Since patients with IBS have microbiome signatures which can also shift over time and this supports the clinical utility of stratifying and monitoring individuals for a more informed diagnosis and prescribe more appropriate treatments.
- Rome diagnostic criteria are insufficient to adequately inform or design studies towards the development of new therapeutic strategies for IBS.

References

1. Enck P, et al. Irritable bowel syndrome – dissection of a disease. A 13-steps polemic. *Z Gastroenterologie* 2017; 55(07): 679 – 684

2. Bai T, Xia J, Jiang Y et al. Comparison of the Rome IV and Rome III criteria for IBS diagnosis: A cross-sectional survey. *J gastroenterol hepatol* 2017; 32: 1018–1025

3. Stern EK and Brenner DM. Gut Microbiota-Based Therapies for Irritable Bowel Syndrome. *Clin Transl Gastroenterol*. 2018 Feb 15;9(2)

4. Jeffery IB, et al. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. *Gut*. 2012 Jul, 61(7):997-1006