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The Chronic Intestinal Pseudo-obstruction subtype has prognostic significance in patients with severe gastrointestinal dysmotility related Intestinal Failure

Dipesh H. Vasant¹⁻³, Ramya Kalaiselvan¹, Joanne Ablett¹, Ashley Bond¹, Arun Abraham¹, Antje Teubner¹, Darren Green³, Peter A. Paine^{2,3}, Simon Lal¹⁻³

¹ Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Salford, United Kingdom

² Gastroenterology department, Salford Royal NHS Foundation Trust, Salford, United Kingdom

³ Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom

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Corresponding Author:

Professor Simon Lal,
Intestinal Failure Unit,
Salford Royal Foundation Trust,
Salford, United Kingdom,
Simon.Lal@srft.nhs.uk

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Abstract:

Background and Aims: Severe gastrointestinal dysmotility (GID) is a significant cause of chronic intestinal failure (CIF) with unclear benefits of sub-classifying into Chronic Intestinal Pseudo-obstruction (CIPO) and non-CIPO sub-types. We compared outcomes between CIPO and non-CIPO sub-types in a tertiary cohort of patients with CIF resulting from severe GID.

Methods: Adults with primary GID, commenced on home parenteral nutrition (HPN) over a 16-year period at a national referral centre, were included. All patients satisfied GID clinical criteria which mandated evidence of small bowel involvement either objectively (abnormal antroduodenal manometry) or pragmatically (failure to progress on small bowel feeding). Clinical outcomes including HPN dependency and survival were compared between CIPO and non-CIPO sub-types.

Results: Patients with primary GID requiring HPN ($n=45$, age 38 ± 2 , 33 females, 23/45 (51%) CIPO, 22/45 (49%) non-CIPO) were included. Patients with CIPO had more surgical interventions ($P=0.03$), higher incidence of bacterial overgrowth ($P=0.006$), greater parenteral energy ($P=0.02$) and volume requirements ($P=0.05$). Overall, during a mean 6 years' follow-up, 36/45 (80%) patients remained HPN dependent. Multivariate analyses confirmed that the non-CIPO sub-type ($P=0.04$) and catheter related blood stream infections/1000 days ($P=0.01$) were predictive factors for time to discontinuing HPN. Overall 5-year survival on HPN was 85%, with no difference between sub-types ($P=0.83$).

Conclusions: The CIPO sub-type is associated with higher HPN dependency and should be recognized as a separate entity in severe GID. In multidisciplinary settings with continuous close monitoring of risks and benefits, our data confirm HPN is a safe, life-preserving therapy in severe GID related CIF.

Keywords: gastro-intestinal dysmotility, parenteral nutrition, intestinal failure, Chronic Intestinal Pseudo-obstruction, Enteric dysmotility

Abbreviations: ADM; antroduodenal manometry, CIF; chronic intestinal failure, CIPO; chronic intestinal pseudoobstruction, CRBSI; catheter related blood stream infection, ED; Enteric Dysmotility, FTB; Full thickness biopsies, GID; gastrointestinal

dysmotility, GINMD; gastrointestinal neuromuscular disorder, PN; Parenteral Nutrition, SIBO; small intestinal bacterial overgrowth.

Introduction

Severe gastrointestinal dysmotility (GID) represents a significant cause of chronic intestinal failure (CIF), accounting for up to 18% of adult patients requiring long-term parenteral nutrition (PN) [1]. In the absence of universally agreed guidelines, the diagnosis of severe GID is often delayed (5.8-8 years from the onset of symptoms [2-4]), contributing adversely to symptom chronicity, nutritional status, quality of life, significant morbidity and exposure to multiple surgeries. [2-3, 5-9].

Since 2002, it has been proposed that patients with severe GID should be sub-categorised into Chronic Intestinal Pseudo-obstruction (CIPO) and Enteric Dysmotility (ED) subtypes, [6, 10-14] based on findings from radiological and motility tests. CIPO, an umbrella term encompassing a range of heterogeneous conditions leading to severe, end-stage gut motor failure [8], is defined clinically and radiologically by evidence of abnormal small bowel motility and episodic or chronic signs mimicking mechanical obstruction [6, 10, 13]. Meanwhile, ED is defined by demonstrable abnormal small bowel motor activity but without any features mimicking mechanical obstruction [6, 10-13]. However, there remains considerable debate on the merits of sub-classifying severe gastrointestinal motility disorders into CIPO and ED and, as a result, these disorders are typically grouped together under the encompassing term 'chronic intestinal dysmotility' by clinicians and researchers [14-16].

In addition to the clinical sub-classification, it is recognised that patients with GID have a high incidence of gastrointestinal neuromuscular disorders (GINMD) on full-thickness histopathology biopsies (FTB) [17]. Patients with CIPO have been shown to have a higher incidence of visceral myopathy, whereas ED patients have a higher incidence of enteric neuropathy [12]. Based on these findings, international consensus guidelines for histopathological diagnosis of GINMD have been published [18], but due to concerns about the risk/benefit ratio of its invasive approach, and given the limited evidence that small bowel histology influences patient outcomes, FTB is not routinely practiced [14]. Furthermore, one of the main difficulties with differentiating ED and CIPO in clinical practice has been the requirement for

antroduodenal manometry (ADM) which has been proposed more recently as being important when confirming the diagnosis of ED. [6, 11-12]; however, there are well documented pitfalls of ADM, including invasiveness and poor tolerability of the test, its variability, poor correlation with symptoms and histopathology, its limited impact on patient management and its limited availability [8, 13, 15, 19-21].

In response to these limitations and/or pitfalls of FTB and ADM in clinical practice, a pragmatic, clinically useful and evidence-based algorithm for defining 'chronic severe gastrointestinal dysmotility' has recently been published (Table 1) [14]. In our centre, we have adopted this 'pragmatic' approach to diagnosing and managing patients with a working diagnosis of severe GID referred for consideration of long-term PN.

The objectives of this study, therefore, were to determine the influence of CIPO and pragmatic GID criteria diagnoses (non-CIPO) on patient prognoses and outcomes following commencement of long-term PN at a UK national Intestinal Failure Unit (IFU).

Materials and Methods

Patient population

Patients referred with a working diagnosis of GID for consideration of long-term PN to the Intestinal Failure Unit (IFU) at Salford Royal NHS Foundation Trust (1st April 1999 and 31st April 2015) were identified retrospectively from a prospectively maintained CIF database. Screening blood tests for secondary causes of GID were performed [14], and patients were managed by a multidisciplinary team including clinicians with specialist CIF, neurogastroenterology and surgical expertise with input from dieticians, pharmacists, GI physiologists, histopathologists, pain management and clinical psychology teams. Patients underwent cross sectional imaging and/or small bowel contrast studies to exclude mechanical obstruction, followed by selected, individualised multi-modal investigations to characterise patterns of dysmotility (including ADM, where possible) that were customised to the patient's symptom profiles using the 'pragmatic approach' described by Paine et al. (Table 1,

Figures 1 and 2) [14]. Motility investigations were performed off enterokinetic or opiate medications, wherever possible.

Antroduodenal Manometry (ADM)

Some patients underwent ADM using a water perfused catheter with 8 sensors passed per nares to 90 to 110 cms, with the flow rate controlled at 0.4 ml/min/sensor. Migrating Motor Complexes (MMC) and phase 1, 2 and 3 contractions were recorded in the fasted state (3 h), then post-prandially following a standard feed (Ensure Plus 220 ml; 1–2 h). Parameters included frequency, amplitude and propagation. ADM reports were reviewed retrospectively by investigators and manometric findings were noted using internationally agreed standard definitions of normal and abnormal small bowel motility [22].

Full thickness gastrointestinal biopsies (FTB)

FTB when available from previous intra-operative specimens were reported by specialist histopathologists with an interest in GINMD. Abnormalities described on these expert reports were noted and classified retrospectively by investigators according to international consensus definitions of gastrointestinal neuromuscular pathology [18].

Glucose-Hydrogen-Methane Breath Tests

Glucose-hydrogen-methane breath tests were used to diagnose small intestinal bacterial overgrowth (SIBO). Patients ingested 50 g dextrose monohydrate (glucose) made up to 250 ml with water. End-expiratory breath samples were taken at baseline for hydrogen (H₂) and methane (CH₄) levels and samples were obtained every 15 minutes for 2 hours after ingestion of the test drink and analysed using a Quintron breath analyser (Milwaukee, WI, USA). A rise in peak H₂ concentration of 20 ppm, or a rise peak CH₄ concentration of 12 ppm above the basal level were deemed positive for SIBO.

Long-term Parenteral Nutrition protocol

The majority of patients were managed with single-lumen tunnelled central venous catheters and PN was delivered using a stringent catheter care protocol either by the patients, their relatives or trained nursing staff, as previously described [23]. Patients were given the minimum number of nights PN to meet their nutritional needs and encouraged to have oral and/or enteral nutrition if able. Where possible, parenteral lipids were delivered once or twice per week and lipid dosing was limited to 1 g/kg/day. All patients were reviewed regularly in the clinic and the PN content and volume optimised according to on-going requirements.

Data collection and analyses

Retrospectively, two investigators reviewed case notes to identify patients with primary (idiopathic) GID. Clinical data were collected from case records, motility test reports, imaging reports, FTB when specimens were available from previous resections, breath tests for SIBO, medications (including prokinetics and opiates).

Survival outcomes and long-term follow-up data were collected until the censorship date of 31 December 2016. Intravenous support requirements were calculated using the methodology proposed in the recent ESPEN clinical classification [1]. Intravenous volume requirements were calculated as the daily mean of the total volume infused per week = volume per day of infusion x number of infusions per week/7. Energy of the intravenous supplementation was determined by calculating the daily mean of the total energy infused per week = energy per day of infusion x number of infusions per week/7/ body weight (Kg)[1].

Diagnostic Criteria

Patients fulfilling the diagnostic criteria for CIPO [10] or the pragmatic GID criteria (Table 1)[14] were included in this study. Based on the aforementioned diagnostic criteria [10, 14], primary GID patients with CIF were sub-categorised into CIPO and non-CIPO groups for analysis. For the purposes of this study we defined 'non-CIPO' as including all patients satisfying the criteria in Table 1 [14], without clinical and radiological features of CIPO.

Exclusion criteria:

Previous publications have shown that PN dependence and survival outcomes differ between primary and secondary GID due to factors independent of GID, such as the underlying systemic disease process, with poorer survival outcomes in conditions such as Systemic Sclerosis [4, 24-25]. In order to compare outcomes between CIPO and non-CIPO more effectively, without survival outcomes being confounded by the trajectory and prognosis of underlying systemic diseases, patients with all known secondary causes of GID including Systemic Sclerosis, connective tissue disorders and neurological diseases were excluded from this study.

Statistical Analysis:

Data are presented as means ($\pm$ standard error of the mean (SEM)) unless otherwise stated. Outcomes data were compared between CIPO and non-CIPO subtypes. Where appropriate, Chi-square tests (χ^2) or Fishers exact test were used, parametric data were compared using t tests or one-way analysis of variance (ANOVA), and Mann Whitney U test was used to compare non-parametric data. Univariate and multivariate analyses were performed by an independent investigator with expertise in medical statistics using Cox proportional hazard models (SPSS version 24.0, IBM) to determine predictive factors for time to coming off PN and time to mortality. P values ≤ 0.05 were considered statistically significant (only two sided P values have been displayed).

Results:

Patient population

Patients referred to the IFU at Salford Royal between 1999 and 2015 for consideration of long-term PN with an initial working diagnosis of chronic severe GID ($n=87$) were identified. Patients with secondary systemic causes of GID ($n=30$; Systemic Sclerosis $n=23$, Sarcoidosis $n=2$, Mitochondrial Cytopathy $n=2$, Myaesthesia Gravis $n=1$, undefined neurological disorder $n=1$, and probable paraneoplastic syndrome associated with advanced malignancy $n=1$) were excluded for the purposes of this study. In addition, 5 patients did not require PN after completing an IFU assessment, and were also excluded from further analysis.

Specificity of pragmatic diagnostic criteria

Of the remaining 52 patients referred to the IFU with an initial working diagnosis of primary GID, 7/52 (13%) did not meet diagnostic inclusion criteria for this study (CIPO or pragmatic GID criteria; Figure 1) [10, 14], and were also excluded. Of these 7 excluded patients, none – after evaluation on the IFU - had evidence of small bowel involvement, none had GINMD (2/7 had FTBs from surgical specimens that were normal, 5/7 were opiate dependent, 4/7 were ultimately diagnosed with other segmental functional gastrointestinal or motility disorders (gastric dumping syndrome $n=1$, oesophageal dysmotility $n=2$, functional defecation disorder $n=1$), 1/7 was diagnosed with an eating disorder following specialist gastrointestinal psychological assessment, and 1/7 had short bowel syndrome as the likely mechanism of CIF with investigations showing rapid small bowel transit.

Characteristics of patients with primary Gastrointestinal dysmotility (GID)

All patients included in this study ($n=45$) met the pragmatic GID diagnostic criteria described by Paine et al.. All patients had previously trialled and failed jejunal tube feeding and all had been referred due to weight loss. Overall, the mean age of patients included in this study was 38 ± 2 (range 17-61) years at presentation to IFU, and 33/45 (73%) patients were female. Patients were followed up for a mean 6 ± 1 (range 1-17) years post commencement of long-term PN.

Twenty three patients (51%) met the diagnostic criteria for CIPO [10], and the breakdown of the included non-CIPO patients ($n=22$) is summarised in Figure 1.

Patients with CIPO and non-CIPO GID had similar demographics, but patients with CIPO had a history of significantly more surgical interventions including loop or end stoma formation and small bowel resections (Table 2).

Motility Investigations using the 'pragmatic' approach

Figure 2 summarises the selected motility and other complimentary investigations that were performed to characterise patterns of GID in patients referred with related CIF.

Upper gastrointestinal motility testing revealed oesophageal motor abnormalities in 8/11 (73%) of patients who had oesophageal manometry, and abnormally delayed gastric emptying on gastric scintigraphy in 20/29 (69%) patients.

ADM was requested in 22/45 (49%) of patients but was not tolerated by almost a third (7/22 (31%)). Of those that completed ADM, small bowel motility was abnormal in 14/15 (93%). In CIPO, ADM was abnormal in all 7 patients tested (100%), manometric abnormalities in this group included; absence of MMC activity ($n=3$), abnormal fed motor response ($n=2$), hypercontractility (bursts/ sustained uncoordinated pressure activity) ($n=3$), and low amplitude ($<20\text{mmHg}$) small bowel contractions ($n=2$). In non-CIPO, ADM was abnormal in 7/8 patients tested (88%), where abnormalities included; absence of MMC activity ($n=1$), abnormal fed motor response ($n=1$), hypercontractility (bursts/ sustained uncoordinated pressure activity) ($n=5$), and low amplitude ($<20\text{mmHg}$) small bowel contractions ($n=2$). In addition, abnormal small bowel contractility was observed on barium contrast studies in 17/22 (77%) of GID patients with evidence of stasis, delayed transit or aperistalsis.

Colorectal motility studies revealed slow colonic transit in 7/8 (88%) patients who had x-ray colonic transit studies with radio-opaque markers and anorectal manometry was abnormal in 5/6 (83%).

Small Intestinal Bacterial Overgrowth (SIBO)

The majority of patients with GID (41/45, 91%) underwent glucose-hydrogen-methane breath testing for SIBO; this included all patients with CIPO (23/23) and 18/22 with non-CIPO. Overall, 14/41 (34%) GID patients tested positive for SIBO on breath tests, with a significantly higher prevalence of SIBO in CIPO compared to non-CIPO (12/23 (52%) vs. 2/18 (11%), $\chi^2=7.6$, $P=0.006$).

Gastrointestinal neuromuscular disorders (GINMD)

FTBs were obtained from intra-operative specimens from previous surgical interventions ($n=23/45$, 51% of patients). The yield of FTBs for GINMD from these specimens was 17/23, 74% (visceral myopathy $n=11$, enteric neuropathy $n=6$).

The proportion of abnormal FTBs did not differ between CIPO and non-CIPO patients (CIPO 11/15 (73%) vs. non-CIPO 6/8 (75%), *Fishers exact test* $P>0.99$). Whilst not statistically significant, there were trends towards higher prevalence of visceral myopathy on abnormal FTBs in CIPO (9/11 (82%) vs. non-CIPO 2/6 (33%), *Fishers exact test* $P=0.11$) and higher prevalence of enteric neuropathy in non-CIPO patients (CIPO 2/11 (18%) vs. non-CIPO 4/6 (67%), *Fishers exact test* $P=0.11$).

Psychological disorders in GID related CIF

Psychological co-morbidities were common in GID patients, and as part of the multidisciplinary approach, 26/45, 58% (CIPO $n=14$, non-CIPO $n=12$) were seen by a specialist gastrointestinal psychologist (median 8 sessions, range 1-30). The majority of those assessed by a psychologist (23/26, 88%) had a range of symptoms of psychological conditions. Specific psychological interventions included; Acceptance and Commitment Therapy (ACT) $n=17$, Cognitive Behavioural Therapy (CBT) $n=8$, Hypnotherapy $n=5$, Schema Therapy $n=4$, relaxation ($n=1$), bereavement therapy ($n=1$) and mindfulness ($n=1$).

Nutritional Outcomes in GID

Parenteral Support Requirements

Overall in GID, the mean number of PN infusions per week was 6.1 ± 0.2 (range 1-7), with mean daily volume requirement of $2,173 \pm 122$ ml and mean energy requirement of 25.5 ± 2.1 kcal/kg body weight/day as determined using the ESPEN classification formulae [1]. PN improved BMI (pre PN commencement BMI = 19.6 ± 0.6 Kg/m² vs. 22.5 ± 0.7 Kg/m² at most recent follow-up, $t=7.8$, $P<0.0001$).

CIPO patients had higher intravenous energy (median 31.3 vs. 21.8 kcal/kg body weight/day, $U=354$, $P=0.02$), and volume requirements (mean 2,406 vs. 1,928 ml, $t=2.0$, $P=0.05$) compared to non-CIPO patients.

Long-term PN dependency

Overall, only 9/45 (20%) of GID patients with CIF achieved nutritional autonomy from PN during follow-up. Patients that discontinued PN improved their mean BMI (pre. 18.5 ± 0.9 to 20.6 ± 0.9 on discharge from IFU services, t (df 1,7) =3.45, $P=0.01$). Seven of these patients were discharged on oral sip feeds and 2/9 with jejunal tube feeding.

Of the nine patients that weaned off PN, nutritional outcomes were influenced by prokinetic medications in only one patient. This particular patient with CIPO had a dramatic symptomatic response to Pyridostigmine and managed to achieve nutritional autonomy.

FTB results did not influence nutritional outcomes in any patient. Based on the FTB result, medical management was only changed in one patient, where the FTB suggested a post-inflammatory neuropathic process (enteric ganglionitis). This prompted a trial of immunosuppression with Corticosteroids and Cyclosporin, which proved to be unsuccessful with no improvement in symptoms or motility, and the patient remained PN dependent.

Predictive factors for time to coming off PN in GID

Cox proportionate Hazard models for time to coming off PN were estimated for the following variables; CIPO/non-CIPO sub-type (Hazard Ratio 3.6, 95% CI 1.3 to 10.3, $P=0.02$, Figure 3), opiate use (Hazard Ratio 0.5, 95% CI 0.1 to 1.9, $P=0.28$), previous surgical intervention (Hazard Ratio 1.4, 95% CI 0.4 to 5.3, $P=0.63$), psychological disorders requiring intervention (Hazard Ratio 3.3, 95% CI 0.7 to 16.0, $P=0.13$), SIBO (Hazard Ratio 3.4, 95% CI 0.4 to 31.5, $P=0.27$), Catheter related Blood stream Infections (CRBSI) per 1000 catheter days (Hazard Ratio 1.8, 95% CI 1.3 to 2.6, $P=0.001$) and Catheter related venous thromboses (CRVT) per 1000 catheter days (Hazard Ratio 1.7, 95% CI 0.5 to 6.6, $P=0.41$).

Multivariate analysis confirmed that the only independent predictive factors for time to coming off PN were the non-CIPO sub-type (Hazard Ratio 3.1, 95% CI 1.0 to 9.0, $P=0.04$) and higher CRBSI/1000 days (Hazard Ratio 1.6, 95% CI 1.1 to 2.3, $P=0.01$).

Intestinal Transplantation

Two patients from our series, both with primary CIPO, and both with visceral myopathy on FTB, were transplanted. One patient received a successful isolated small bowel transplant following referral with limited venous access, and poor quality of life on PN. This patient is alive four years post-transplant, and remains autonomous from PN. The second patient, referred with decompensated intestinal failure associated liver disease (IFALD), died shortly after receiving a multi-visceral transplant due to opportunistic central nervous system infection.

CIF-related Complications

Catheter related blood stream infections (CRBSI)

During follow-up, 21/45 GID patients (CIPO n=11, non-CIPO n=10) had 52 CRBSI episodes. Overall in GID, mean CRBSI rate was 1.0 ± 0.2 / 1000 catheter days. Patients were treated for CRBSI with a standardized treatment protocol involving antibiotic and urokinase central venous catheter locks and systemic antibiotic administration [26]. PN was recommenced after line salvage or CVC replacement as per the protocol [26].

There was no significant relationship between SIBO and CRBSI/1000 days ($U=151$, $P=0.19$). CRBSI/1000 catheter days ($U=227$, $P=0.53$) did not differ between CIPO and non-CIPO sub-types.

Catheter related venous thromboses (CRVT)

There were 15 episodes of catheter related venous thrombosis (CRVT) in 12/45 patients (CIPO n=5, non-CIPO n=7) during follow-up. Overall in GID, the mean CRVT rate was 0.15 ± 0.1 /1000 catheter days and did not differ between CIPO and non-CIPO sub-types ($U=213$, $P=0.26$).

Intestinal Failure Associated Liver Disease (IFALD)

Three patients with CIPO on long-term PN (mean duration 11.0 ± 2.1 years), developed IFALD. All three patients underwent liver biopsy. As detailed above, one of these patients received a multivisceral transplant in the context of decompensated

cirrhosis. The other two patients, both of whom had macrovascular steatosis but only mild periportal and perivenular fibrosis, have completed transplant assessments and remain under consideration for multivisceral transplantation.

Survival Outcomes

Eight patients died during long-term follow-up. Overall, actuarial survival in GID was 95% at 1 year, 92% at 3 years, 85% at 5 years, and 69% at 10 years. One patient died from infective complications following multi visceral transplantation (detailed above), three died from sepsis (n=1 biliary sepsis and n=2 osteomyelitis). One patient with CIPO had an expected death from GID after making an informed decision to adopt a palliative approach due to intolerance of PN, and after declining intestinal transplantation. Another patient died from complications of end-stage renal failure unrelated to underlying GID or CIF management. The cause of death was not available for two patients, one of whom was followed-up at another centre for eight years prior to death.

Predictive factors for time to mortality

Univariate and multivariate analyses using Cox proportionate Hazard models for time to death did not reveal any significant associations with the following variables; Age at IFU referral (Hazard Ratio 1.0, 95% CI 1.0 to 1.1, P=0.47), gender (Hazard Ratio 1.2, 95% CI 0.5 to 2.6, P=0.38), CIPO/non-CIPO sub-type (Hazard Ratio 0.9, 95% CI 0.5 to 1.9, P=0.83, Figure 4), opiate use (Hazard Ratio 0.5, 95% CI 0.1 to 2.0, P=0.32), previous surgical intervention (Hazard Ratio 0.6, 95% CI 0.1 to 3.0, P=0.54), psychological disorders requiring intervention (Hazard Ratio 1.4, 95% CI 0.3 to 5.7, P=0.63), SIBO (Hazard Ratio 1.1, 95% CI 0.3 to 4.8, P=0.87), Catheter related Blood stream Infections (CRBSI) per 1000 catheter days (Hazard Ratio 1.3, 95% CI 0.8 to 2.0, P=0.31) and Catheter related venous thromboses (CRVT) per 1000 catheter days (Hazard Ratio 0.2, 95% CI 0.0 to 10.3, P=0.38) and IFALD (Hazard Ratio 0.9, 95% CI 0.3 to 2.7, P=0.94).

The role of non-CIPO diagnostic criteria and small bowel motility studies in predicting outcomes in CIF patients

Sub-analysis of non-CIPO data did not reveal any significant benefits of a manometric diagnosis of ED. In the non-CIPO group, Cox proportional hazards model comparing those with an 'objective' abnormal ADM diagnosis did not reveal any difference in the time to coming off PN (Hazard Ratio 1.2, 95% CI 0.3 to 5.1, P=0.80) compared to those who did not have an ADM. Moreover, there were no differences in the demographics, symptom profiles, patient characteristics, GINMD yield on FTB, number of deaths, SIBO prevalence, and catheter related complication rates between non-CIPO patients, regardless of whether they were diagnosed based upon ADM, abnormal small bowel contractility on barium contrast studies or pragmatically diagnosed based upon intolerance of small bowel feeding alone (Table 3).

Discussion:

In the context of one of the largest primary GID cohorts with CIF to date, we have demonstrated important differences in patient characteristics including prior surgical interventions, bacterial overgrowth and outcomes including parenteral nutrition requirements and dependency in patients with primary GID related CIF. These findings have important clinical implications for the diagnosis and management of severe GID.

Since introduction of the Wingate-Bangkok classification [10], it is recognised that non-CIPO patients can develop CIF [6-7]. A single-centre study of GID patients in Sweden has previously shown that patients with CIPO have a poorer prognosis, are more likely to develop CIF (49% vs. 14%), and have poorer health related quality-of-life, when compared to non-CIPO patients with manometrically defined small bowel dysmotility (ED) [6, 11]. Findings from our study strongly support making the distinction between CIPO and non-CIPO patients for several reasons. Firstly, our data demonstrate for the first time that patients with CIPO have higher parenteral energy and volume requirements. These novel findings may be representative of differences in propulsive function and hence ability to tolerate oral or enteral calories, and/ or better absorptive capacity in patients with non-CIPO, a group who had a

significantly lower prevalence of SIBO and fewer surgical resections. Secondly, whilst up to a third of patients in our series with non-CIPO could be weaned off PN within the first three years of follow-up, patients with CIPO remained PN dependent long-term. Thirdly, based on supportive evidence in the literature [27-31], our finding of higher incidence of SIBO in our CIPO cohort may also imply worse intestinal motor function and related stasis of enteric contents in this group. Finally, the majority of patients with CIPO underwent surgery, and had significantly more operations compared to the non-CIPO cohort. Whilst previous studies have shown that the majority of patients with CIPO undergo multiple non-contributory and potentially harmful operations [19, 32], ours is the first to confirm a difference in the number and type of surgeries between CIPO and non-CIPO subtypes.

It is notable that adoption of the ED diagnostic category to differentiate non-CIPO patients from CIPO patients has been hampered by the reliance on ADM [8, 13, 15, 19-21]. In our study, a third of patients could not tolerate ADM, and in those able to complete the test, 93% had an abnormal result which did not alter management in any patient. Similar experiences with low diagnostic specificity [3, 8, 19-21], complexity [19], lack of availability [13], poor correlation with FTB findings [21], and the lack of effects on patient management [8], are widely recognised. Whilst there are emerging technologies for small bowel motility including wireless motility capsule [27, 33-36] and cine-MRI [19, 37-38], these are not currently widely available. Our observations using a broader definition of non-CIPO GID [14] than the previously described manometrically-defined ED criteria [6, 10-12] are interesting and merit further discussion. In terms of specificity, we found the pragmatic criteria could differentiate, and exclude, seven patients who had other severe functional digestive syndromes, but who did not have sufficient evidence of small bowel dysmotility. The pragmatic criteria also proved to be sensitive; all patients that would have met the Wingate-Bangkok or manometric definitions of ED [6, 10] satisfied pragmatic criteria. Furthermore, the pragmatic criteria permitted the inclusion of an additional patient with GINMD in the absence of ADM. Finally, in non-CIPO patients, we found that - regardless of whether GID diagnosis was made using ADM or pragmatic GID criteria [14] - HPN outcomes did not differ. These findings suggest that broadening the present measurement-based definitions of ED, to the evidence-based pragmatic

definitions may be clinically helpful, particularly in reducing the need for invasive, poorly tolerated and infrequently available manometric tests, which, may in turn, help reduce delays in diagnosis.

Whilst small bowel motility assessments have a supportive role, an advantage of the pragmatic approach is that diagnosis does not rely on one particular investigation but takes into account a broader clinical picture incorporating other important investigations including FTB (where available). The diagnostic yield of FTBs for GINMD in patients who underwent previous resections in our cohort (74%) is comparable to previous studies [17]; however, FTBs did not affect clinical outcomes in any patients in our series. For this reason we do not routinely perform FTBs in our centre due to concerns about the risk/benefit ratio [14], but when specimens are available from previous or planned surgeries, these results may be helpful in establishing a GID diagnosis.

Our survival data in primary GID patients (85% at 5-years), confirm that long-term PN is safe in this setting and should be considered as a life-preserving therapy in severe GID related CIF. These data compare favourably with survival data from our own centre from all aetiologies of CIF (5 year survival 71% [23]) and are similar to GID 5-year survival data reported by other CIF centres [4] [25]. There were, however, no differences in survival outcomes and catheter complication rates between patients with CIPO and non-CIPO. That said, it is notable that the CRBSI rate in patients with severe GID in this study was notably higher than that found in our entire cohort of CIF patients over the same time period [23, 39]. Patients that sustained CRBSIs were treated according to a standardized protocol with published catheter salvage rates of up to 91% [26, 39-40]. Catheters were salvaged where possible according to this protocol [26]. Whilst CRBSI rates were not predictive of mortality in our study, they were an independent predictor of discontinuing PN. This finding likely reflects our clinical practice in managing PN safely in this population by constantly re-assessing the risk and benefit ratio of PN in a multi-disciplinary IFU environment on an individualised basis, with input from specialist IFU clinicians, dieticians, neurogastroenterologists, pain management team, psychologists and microbiology. Moreover, patients in our cohort that discontinued PN, were able to

sustain this whilst being observed following re-introduction of oral or enteral nutrition with multidisciplinary care. This approach to the care of patients with GID is likely to be an important factor in the encouraging survival data presented in this study. Given the high success rates using our standardized catheter salvage protocol for CRBSIs [26, 39-40], our policy to confirm eradication on repeat cultures before recommencing PN, and removal of the catheter in cases of unsuccessful salvage/ recurrent infection [26], it is very unlikely that attempts to salvage catheters have influenced these findings.

The main limitation of our study is that it is a retrospective, single-centre study. To the best of the authors' knowledge there are no prospective HPN series in primary GID in the literature. This likely reflects the rarity of severe GID related CIF - only 45 cases during 16 years at a national centre - making a prospective study with long-term outcome data difficult. Whilst not possible in our pragmatic, retrospective study, due to patients having had different diagnostic tests, future collaborative prospective studies could evaluate the sensitivity and specificity of different diagnostic criteria and investigations. Another limitation is that whilst all patients received written instructions to discontinue medications which can influence enterokinetic function prior to motility studies, it is possible that despite this, a minority of patients on maintenance treatment with these drugs (e.g. opiates) may have declined discontinuation. It was not possible to capture these data in a retrospective study spanning 16 years; however, we noted that only two patients with non-CIPO who underwent ADM had been opiate users (Table 3), confirming that the majority of our data in this group would not have been affected by this issue.

In conclusion, our data highlight the importance of recognising CIPO as a separate entity in patients with GID and related CIF. We have demonstrated some advantages of broadening the definition of non-CIPO disorders beyond manometrically defined ED, using a pragmatic diagnostic algorithm which takes into account a broader clinical picture, and have shown that invasive tests such as ADM and FTB may not be mandated to diagnose or classify severe GID in this context.

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Tables:

**Table 1: The pragmatic evidence-based algorithm for non-CIPO severe GID
(adapted from Paine et. al. [14])**

- Exclusion of mechanical obstruction and inflammation
- Need to fulfil A, B and C to meet criteria for severe gastrointestinal dysmotility
- A. Clinical morbidity - severe symptoms, malnutrition, refractory to treatment)
- B. At least one of:-
- Abnormal manometry >1 region
 - Abnormal transit/scintigraphy >1 region
 - Abnormal Full Thickness Biopsy
- C. Small bowel involvement at least one of: -
- Abnormal small bowel motility or transit studies
 - Intolerance of small bowel feeding

719 **Table 2: Summary of patient characteristics and demographics**

Baseline factor	CIPO (n=23)	Non-CIPO (n=22)	P-value
Age (years)	37 ± 3	38 ± 3	P=0.71
Gender (no. females, %)	16/23, 70%	17/22, 77%	P=0.56
BMI (Kg/m²) at referral to IFU	19.7 ± 1.0	19.4 ± 0.9	P=0.81
Time interval from onset of symptoms to IFU referral (years)	5.9 ± 1.4	9.5 ± 2.0	P=0.16
Opiate usage at time of referral to IFU	10/23, 43%	13/22, 59%	P=0.29
Number of patients undergoing surgical interventions	17/23, 74%	9/22, 41%	P=0.03
Mean number of operations per patient	1.6 ± 0.1	0.9 ± 0.1	P=0.02
Type of surgical interventions:			
Loop/end stoma formation	10/23, 43%	1/22, 5%	P=0.002
Subtotal Colectomy	7/23, 30%	3/22, 14%	P=0.18
Small Bowel resection	7/23, 30%	1/22, 5%	P=0.02
Upper GI resections	3/23, 9%	4/22, 18%	P=0.63
Adhesiolysis/exploratory laparotomy	5/23, 22%	2/22, 9%	P=0.24
Subtotal enterectomy	2/23, 9%	0/22, 0%	P=0.49
Miscellaneous procedures	6/23, 26%	10/22, 45%	P=0.17
Number with Short Bowel Syndrome (%)	4/23, 17%	0/22, 0%	P=0.06
Psychological symptoms requiring intervention	12/23, 52%	10/22, 45%	P=0.88

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725 **Table 3: Clinical characteristics and outcomes of patients with non-CIPO GID**

Baseline characteristics and symptoms (%)	Enteric Dysmotility on antroduodenal manometry (ADM) (N=7)	Abnormal Small Bowel motility on Barium contrast study (N=8)	Intolerance of small bowel feeding only(pragmatic criteria) (n=7)	P Value
Age (years)	41 ± 5	40 ± 6	34 ± 5	P=0.59
Gender (no females,%)	5/7, 71%	5/8, 63%	7/7, 100%	P=0.20
BMI at referral to IFU (Kg/m ²)	18.8 ± 1.0	19.8 ± 1.6	19.5 ± 2.2	P=0.91
Opiate usage at the time of referral to IFU	2/7, 29%	6/8, 75%	5/7, 71%	P=0.14
Abdominal pain	4/7, 57%	5/8, 63%	5/7, 71%	P=0.85
Distension	0	0	1/7, 14%	P=0.33
Nausea and Vomiting	3/7, 43%	7/8, 88%	5/7, 71%	P=0.18
Diarrhoea	1/7, 14%	0	1/7, 14%	P=0.53
Constipation	5/7, 71%	4/8, 50%	4/7, 57%	P=0.70
Bloating	2/7, 29%	0	1/7, 14%	P=0.27
Previous Surgery	3/7, 43%	3/8, 38%	3/7, 43%	P=0.93
Unable to tolerate ADM	0	0	3/7, 43%	P=0.02*
GINMD on Full thickness biopsy	3/3, 100%	2/3, 66%	1/2, 50%	P=0.41
SIBO on Breath tests	0/6, 0%	2/6, 33%	0/6, 0%	P=0.11
CRBSI/1000 days	1.7 ± 1.1	1.6 ± 0.9	1.1 ± 0.6	P=0.90
CRVT/1000 days	0.5 ± 0.3	0.1 ± 0.1	0.2 ± 0.1	P=0.33
No. weaned off PN	3/7, 43%	2/8, 25%	3/7, 43%	P=0.70
No. deaths observed	0	2	1	P=0.37
Psychological symptoms requiring intervention	4/7, 57%	3/8, 38%	5/7, 71%	P=0.41

726 ADM: antroduodenal manometry, CRBSI: Catheter related blood stream infections,
727 CRVT: Catheter related venous thromboses, GINMD: Gastrointestinal
728 Neuromuscular Disorder, SIBO: small intestinal bacterial overgrowth

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731 **Figure Legends:**

732 Figure 1: Flowchart summarising inclusion of patients with primary gastrointestinal
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734 dysmotility related Intestinal Failure at a U.K. national Intestinal Failure Unit
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Figure 2: Summary of selected motility and other complimentary investigations performed in patients with intestinal failure secondary to chronic severe gastrointestinal dysmotility using pragmatic diagnostic criteria.

Figure 3 - Kaplan Meir curve showing the proportion of GID patients that came off PN over time - patients with the non-CIPO sub-type were significantly more likely to come off PN (P=0.02).

Figure 4 - Long-term survival outcomes after commencing PN did not differ between CIPO and non-CIPO patients with Intestinal Failure ($P=0.83$).

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ALL authors approved the final version of the article, including the authorship list.