Chyme reinfusion in patients with intestinal failure due to temporary double enterostomy: a 15-year prospective cohort in a referral centre

Denis Picot, Sabrina Layec, Laurence Dussaulx, Florence Trivin, Ronan Thibault

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Denis Picot,[a] Sabrina Layec,[a] Laurence Dussaulx,[a] Florence Trivin,[a] Ronan Thibault[b]

[a] Department of Nutritional and Digestive Rehabilitation, Clinique Saint Yves, Rennes, F-35044, France

[b] Nutrition unit, Department of Endocrinology, Diabetology and Nutrition, Home parenteral nutrition centre, CHU Rennes, Université de Rennes 1, INSERM U991, Rennes, F-35000, France

Short title: chyme reinfusion and intestinal failure

Corresponding authors:
Dr Denis Picot, MD
Nutrition Clinique
Clinique Saint Yves
4 rue Adolphe Leray
CS 54435
35044 Rennes Cedex
France
phone +33 2 99 26 26 17 – Fax +33 2 99 26 25 84
E-mail picot@clinique-styves.fr

Prof. Ronan Thibault, MD, PhD

Unité de Nutrition

Service d'Endocrinologie-Diabétologie-Nutrition

CHU Rennes

2, rue Henri Le Guilloux

35000 Rennes

France

Phone +33 2 99 28 96 46

Fax +33 2 99 28 96 47

E-mail ronan.thibault@chu-rennes.fr

Abstract (292 words)

Background and aims: Patients with double temporary enterostomy may suffer from intestinal failure (IF). Parenteral nutrition (PN) is the gold standard treatment until surgical reestablishment of intestinal continuity. Chyme reinfusion (CR) is a technique consisting in an extracorporeal circulation of the chyme. The aims were to determine: i) whether CR could restore intestinal absorption, decrease PN needs, improve nutritional status and plasma liver tests; ii) the feasibility of home CR.

Methods: From the 232 patients IF consecutively referred for CR from 2000 to 2014, the 212 patients with IF, technical feasibility of CR, and effectively treated by CR, were included. Were collected prospectively before and during CR: daily stomal and fecal outputs, coefficients of nitrogen (CNDA) and fat (CFDA) digestive absorption, weight loss, body mass index (BMI), Nutritional Risk Index (NRI), plasma albumin, citrulline, and liver tests.

Results: 183 patients had temporary double enterostomy and 29 exposed enterocutaneous fistulas. CR reduced the intestinal output (2444 ± 933 vs 370 ± 457 ml/day, P<0.001), improved CNDA (46 ± 16 vs 80 ± 14%, P<0.001) and CFDA (48 ± 25 vs 86 ± 11%, P<0.001), and normalized plasma citrulline concentration (17.6 ± 8.4 vs 30.3 ± 11.8 µmol/l, P<0.001). PN was stopped in 126/139 (91%) patients within 2 ± 8 d. Nutritional status improved (P<0.001): weight (+4.6 ± 8.6%), BMI (+3.8 ± 7.7%), plasma albumin (+6.2 ± 6.1 g/l), and NRI (+10.9 ± 9.5). The proportion of patients with plasma liver tests abnormalities decreased (88 vs 51%, P<0.01). Home CR was feasible without any serious complications in selected patients.

Conclusions: CR corrected the intestinal failure by restoring intestinal absorption, allowing PN weaning in 91% of patients. CR contributes to improve nutritional status and to reduce plasma liver tests abnormalities, and is feasible at home.

61 **Keywords**: malnutrition; succus entericus reinfusion; fistuloclysis; parenteral nutrition;

62 ileostomy; enterocutaneous fistula.

63

1. Introduction

In the course of an intestinal surgery procedure, several clinical situations (small bowel resection, peritonitis, fistulae, anastomosis protection...) lead the surgeon to undertake a double temporary enterostomy. The surgical reestablishment of intestinal continuity (SRIC) is usually scheduled at least three months later. In England, the annual incidence of temporary double enterostomy requiring parenteral nutrition (PN) for more than 14 days would be of 18 patients per million [1]. Enterostomy may lead to serious complications, such as acute or chronic dehydration, reported in 18 to 29% of patients [2,3] and responsible for 40 to 50% of hospital readmissions [4,5], renal failure [6], electrolyte disturbances, micronutrients and mineral deficiencies, and malnutrition. These complications are responsible for hospital readmissions, increased healthcare-related costs [7] and affect patients' quality of life [8]. Patients with high enterostomy outputs are exposed to intestinal failure (IF) due to type 1 short bowel syndrome (small bowel ended by a terminal stoma without colon in circuit). A small bowel length lower than 100 cm between the duodeno-jejunal flexure and the stoma mostly leads to intestinal deficiency or IF [9]. ESPEN recommends to define IF as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth" [10]. In the setting of temporary double enterostomy, the IF is type 2 according to the ESPEN endorsed recommendations, and defines as a prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months [10]. Thus, IF patients with temporary double enterostomy require PN, including home PN, the gold standard therapy until the SIRC. However, PN has its own morbidity and, in the absence of expertise, the risks of infectious, hepatic dysfunction, mechanical and metabolic complications are increased. Chyme reinfusion (CR) is a kind of enteral nutrition technique which reestablishes the small bowel continuity by reinfusing the chyme collected from the afferent, i.e. upstream, small

bowel, in the efferent, i.e. downstream, small bowel through an extracorporeal circulation of the chyme [11]. Small series in adults [12-15] and pediatric patients [16-18] strongly suggest that CR could restore intestinal absorption. This could allow PN interruption only after few days and the improvement of frequent observed liver tests abnormalities [15]. However, the efficacy of CR in patients with temporary double enterostomy waiting for SIRC has never been assessed in larger prospective cohorts including a systematic assessment of intestinal function, PN needs, nutritional status, and plasma liver tests. Moreover the feasibility of home CR has never been assessed. Therefore, the aims of this prospective study were to determine: i) whether CR could restore intestinal absorption, decrease PN needs, improve nutritional status and plasma liver tests; ii) the feasibility of home CR.

2. Materials and methods

2.1. Study design

This is a prospective observational cohort of the consecutive patients with IF secondary to temporary double enterostomy or entero-cutaneous fistula (ECF) exposed to the abdominal wall, specifically referred for CR to the department of nutritional and digestive rehabilitation at Clinique Saint Yves, Rennes France, from January 2000 to December 2014.

2.2. Centre description

Our 50-bed department is a referral rehabilitation centre for gastrointestinal diseases, including IF, and is staffed with specially trained nurses and nutritionist gastroenterologist physicians. Most patients were referred by the departments of visceral surgery and intensive care of Brittany and West of France. During the five last years, were admitted 120 patients with enterostomy per year, including 20 to 25% with high stoma outputs who were treated by CR.

2.3. Inclusion criteria

The inclusion criteria were: IF defined as a theoretical indication to PN, plus a stoma output nihil per mouth of at least 1200 ml/24h; existence of a double enterostomy or at least two orifices of ECF visible on the abdominal wall; theoretical temporary nature of the stoma or ECF in the expectancy of SIRC; presence of efferent small bowel between the stoma and the colon, or a terminal ileostomy; absence of obstruction of digestive fistula between the mouth and the afferent stoma, and in the efferent intestinal tract; ability to catheterize the efferent stoma with a feeding tube on more than 15 cm; absence of progressive peritoneal carcinosis; age >17 years; full agreement of the patient to carry out CR and accept the food constraints (the ingested meals must have the consistency of a smooth puree).

2.4. Data collection

The clinical and biological data were collected prospectively and recorded in a specific Access (Microsoft) database registered, as required by the French law, at the French Committee for computing and freedom CNIL (N° 1452427). Height was measured at admission and weight twice a week. The enterostomy or fistula output was quantified daily. The biological tests were carried out by the same laboratory. These data were collected for all patients at their admission, before CR was initiated, and repeatedly during CR. Body mass index (BMI) (weight (kg)/height (m)²), weight loss at admission as compared to usual weight (100*(usual weight - actual weight) / usual weight) and Nutritional Risk Index (NRI=1.519*Alb+41.77* weight/usual weight) where Alb is plasma albumin concentration, were calculated. Severe malnutrition risk was defined as NRI<83.5, moderate malnutrition risk as 83.5≤NRI≤97.5, and absence of malnutrition risk as NRI>97.5. Plasma values of liver tests, i.e. alanine amino-transferase (ALAT), aspartate amino-transferase (ASAT), alkaline phosphatase (AP), γ-glutamyl-transpeptidase (γGT), and total bilirubin, higher than two times the normal values (i.e. for total bilirubin ≥30 μmol/l), were considered as increased. Proximal stoma or fecal outputs were daily measured in all patients before and after the initiation of CR, respectively. During CR, anal stools were not daily weighed when their number was ≤2/day. Intestinal nitrogen and fat outputs were measured over three consecutive days, before the initiation of CR, and at least three weeks after CR initiation. Nitrogen and fat fecal concentrations were measured according to the Kjeldahl's [19] and the Van de Kamer's [20] methods, respectively. Nitrogen and fat fecal outputs were expressed as the mean daily nitrogen or fat fecal output in g/day. Simultaneously, oral protein and fat intakes were determined using a daily dietary record. Total protein and fat dietary intakes were evaluated by dieticians from: (1) the proportion of food proposed that was consumed (25%, 33%, 50%, 66%, 75%, 100%); and (2) food composition tables coupled with the software allowing patient's meal choice (Nutriciel_ SCJ Informatique, Mont Saint Aignan, France). Nutritional

food intakes (oral, enteral and parenteral) were expressed as kcal/kg actual body weight/day and g/kg actual body weight/day for energy and protein, respectively. PN formulas consisted of tricompartimental bags delivering 0.62–1.14 kcal/ml of energy (15-20% proteins, 29% lipids (80% olive oil, 20% soy oil), and 51% carbohydrates). PN formulas came from Baxter, USA. The coefficients of nitrogen (CNDA) and fat (CFDA) digestive absorption, expressed in percentage of ingested protein and fat, represent the proportion of oral nitrogen or fat not recovered in stomial or fecal wet weight, and was calculated as: CNDA = (1-(intestinal nitrogen (g/day)/ protein intake (g/day)/6.25)*100 and CFDA = (1-(steatorrhea (g/day)/ fat intake (g/day))*100 [21]. Values higher than 85% were considered as physiological.

Fasting plasma citrulline concentration was determined simultaneously with the CNDA and CFDA within the three days before and after CR initiation. Simultaneously, creatinine clearance was calculated with the Cockcroft's formula for 1.73 m² because alteration of renal function prevents from interpreting plasma citrulline. Plasma citrulline concentration was determined using reverse-phase high performance liquid chromatography (HPLC). As Crenn et al. [22] showed that a plasma citrulline below 20 µmol/l was predictive of IF, we chose this threshold to define a low plasma citrulline.

2.5. Measurement of small bowel length

The length of the post-duodenal remnant small bowel from the duodeno-jejunal flexure to the proximal stoma was determined by the surgeon during surgery (97%) or estimated from X-ray documents obtained by digestive opacification using hydrosoluble contrast (3%). The downstream small bowel length was measured from the distal stoma to the end of the terminal part of the remnant downstream small bowel, i.e. the ileo-caecal valvula, an ileo-colic anastomosis or a terminal ileostomy (by surgeon 61%, by X-ray opacification 39%). The total remnant post-duodenal small bowel length used for the CR was defined as the sum of the upstream and the downstream small bowel lengths.

2.6. Chyme reinfusion (CR)

CR consisted in a closed system of extra-corporal circulation of chyme. Continuous CR was performed using the Entéromate™ II system (Labodial, Les Clayes Sous Bois, France), marketed since 1998 (**Figure 1**). Entéromate™ II auto-regulates continuous CR without any adjustment or nurse's intervention, and no uncomfortable odor. The dead space volume of the extra-corporeal circuit is lower than 50 ml and does not cause any volemic deprivation. The tubulures are closed and prevent from outside infectious contamination. The automaton has two peristaltic pumps. One pump works permanently and aspirates the jejunal effluent toward a 30 mL disposable plastic container, so that the upper stoma pouch is always empty. The weight of the container is continuously and electronically monitored. When the minimal volume of approximately 10 ml is exceeded, the second pump starts and the contents are infused into the diverted downstream small bowel until the return to minimal volume.

The downstream small bowel was intubated through the efferent enterostomy with a simple lumen polyurethane naso-gastric tube ch 14-16, Levine-typed, without balloon, into the first 15-20 centimeters of the small bowel. A radiologic opacification with water-soluble contrast agents checked the tube position and controlled the anatomy and the length of the downstream small bowel until the colon. During the two days before CR initiation, enteroclysis was initiating by instilling one liter of oral rehydration solution, together with laxatives in case of fecal residues or fecaloma in the colon. At the same time, anti-motility drugs, e.g. loperamide, were stopped to prevent ileus. Antispasmodic agents could be useful in case of abdominal pain, and cholestyramine was given by enteroclysis in the event of diarrhea during the first days. In case of persisting diarrhea, loperamide was used. Antisecretory drugs were used in all patients before and during CR. Octreotide was never used. Once the patient has been adequately trained and is capable of correctly adjusting the rate of reinfusion, portable non-autoregulated Enteromate Mobile™ (marketed since 2010 by Labodial, Les Clayes Sous Bois,

France) pump was used secondly to give autonomy to the patient during the hospitalization and at home. This pump is autonomous thanks to batteries. During CR, patients were mandatorily orally fed ad libitum with puree meals. If the oral intakes seemed insufficient, enteral nutrition was delivered by naso-gastric feeding tube, by gastrostomy, by jejunostomy or by "en Y" enteroclysis in the reinfusion tube in the downstream small bowel. In the cases where oral hydration was insufficient, enteroclysis of additional hydration solutions was used.

2.7. Definitions

PN intake was defined as parenteral infusions including administration of nitrogen; otherwise, parenteral infusion was defined as intravenous hydration. The presumed cumulative number of days with saved PN was defined as the number of days between the PN weaning day and the SRIC day, assuming that PN needs would remain stable and PN administered daily until the SRIC day, and was expressed as patients-days and patients-years. The median ± IQ duration of home CR was defined as the number of days between the CR initiation day and the day before the SRIC day, i.e. the day of CR stop.

2.8. Statistical analysis

Statistical analyses were performed with XLSTAT 2014 (Addinsoft-SARL). The normality of data distribution was analyzed by the Smirnoff–Kolmogorov test. Categorical variables were compared using the Fisher exact test. According to their normal or non-normal distributions, continuous variables were reported either as mean ± standard deviation (SD), median ± interquartile (IQ), and compared between groups using Student's paired t-test or Wilcoxon matched-pairs signed rank test as appropriate. P values equal or less than 0.05 were considered as statistically significant.

3. Results

3.1. Patients recruitment and characteristics

According to the inclusion criteria, 232 consecutive patients were eligible for CR. Eight (3%) patients were excluded because CR had to be stopped early because of complications, and 12 patients did not match the inclusion criteria. The remaining 212 patients were included (**Figure 2**). Demographics and aetiology of small bowel resection are summarized in **Table 1**. Twenty nine (14%) had entero-parietal fistulae exposed to the abdominal wall, mainly due to peritonitis (44%) and cancer (34%). Patients' characteristics did not differ between patients with ECF or enterostomy (data not shown).

3.2. Surgical procedure and subsequent small bowel anatomy

Surgical procedure and subsequent small bowel anatomy is shown in **Table 2**. In addition, an additional susmesocolic organ resection (oesophagectomy, gastrectomy, Roux-en-Y gastric bypass, cephalic pancreatectomy) was performed in 15 patients (7%).

3.3. Intestinal absorption (**Figure 3**)

CR was associated with a dramatic improvement of intestinal function. CR reduces from 52 to 3% ($P<0.0001$) the proportion of patients with a remnant length of small bowel below 100 cm. The intestinal losses were reduced by 85% ($P<0.001$) and the number of patients with output higher than 1200 ml/24h decreased from 155 to 9 ($P<0.0001$). CNDA and CFDA were measured before and after CR initiation in 56 and 36 patients, respectively. CNDA, CFDA, and plasma citrulline were measured with a median ± IQ follow-up of 27 ± 35 days (range 10–186 days) after CR initiation. CNDA and CFDA strongly improved with CR (**Figure 3**). Whereas they were largely below physiological levels before CR, attesting intestinal malabsorption, CNDA and CFDA went back to physiological levels in 47% and 67% of patients, respectively ($P<0.0005$). The number of patients with plasma citrulline <20 µmol/l decreased from 47 (65%) to 8 (11%) ($P<0.0005$) ($n=72$). In eight patients with a creatinine

clearance <60 ml/mn/1.73 m², plasma citrulline was <20 µmol/l before CR, and plasma citrulline increased after CR in seven patients despite the improvement of renal function.

3.4. Parenteral nutrition needs

At admission, within a median (±IQ) time of 33 ± 25 days after initial surgery, 139 (65%) patients received PN (n=111) or IV hydration (n=28). Despite all patients displayed characteristics of IF and would have to be treated with PN, PN was not initiated in the surgical departments referring the patients. Nevertheless patients with PN at admission had shorter upstream small bowel length, worse intestinal function and lower plasma citrulline than patients who did not receive PN (data not shown). Mean (± SD) energy and protein PN intakes were 24 ± 9 kcal/kg/day and 0.9 ± 0.3 g/kg/day respectively, in a mean volume of 2110 ± 974 ml/day. During CR, mean energy and protein oral intakes were 31 ± 14 kcal/kg/day and 1.4 ± 0.7 g/kg/day, respectively. An additional enteral nutrition was needed in 72 (34%) patients ("en Y" enteroclysis, n=46; nasogastric tube, n=17; gastrostomy, n=7; jejunostomy, n=2). The total mean amounts of energy and protein oral and enteral intakes were 36 ± 14 kcal/kg/day and 1.6 ± 0.7 g/kg/day. As a result, PN and/or IV hydration could be stopped in 126 of 139 patients (91%), within a median ± IQ of 2 ± 9 days after CR initiation. PN was carried on in 17 patients with a maximum of 186 days. Therefore the median (± IQ) time with saved PN was 59 ± 57 days per patient. The presumed cumulative median (± IQ) number of days with saved PN was 9723 patients-days (or 26.6 patients-years).

3.5. Nutritional status

At admission, a majority of patients had one or several criteria of malnutrition (**Table 3**). CR was associated with the improvement of nutritional status and NRI: mean (± SD) weight gain of 4.6 ± 8.6%, BMI increase of 3.8 ± 7.7%, plasma albumin of 6.2 ± 6.1 g/L, and NRI increase of 10.9 ± 9.5 (P<0.001 for all).

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284 3.6. Plasma liver tests

285 At admission, 177 (84%) patients had one or several abnormal plasma liver tests: ALAT
286 (n=57, 27%), ASAT (n=16, 8%), AP (n=96, 45%), γGT (n=170, 81%), and total bilirubin
287 (n=11, 6%).

288 Plasma liver tests (ALAT, ASAT, AP, γGT) were performed before and during CR in 155
289 patients, and total bilirubin in 91 patients. With CR, the number of patients who had one or
290 several plasma liver tests abnormalities decreased from 87 to 51% (P<0.001) (**Figure 4**). In
291 addition, only 4% of patients had liver cholestasis-related jaundice, defined as total bilirubin
292 ≥60 µmol/l [23], at admission. In all these patients, CR allowed the normalization of total
293 bilirubin. The prevalence of plasma liver tests abnormalities at admission were compared
294 between the 139 patients who received PN and the 73 who did not. Plasma liver tests values
295 were not significantly different between the two groups (patients with PN vs. without PN,
296 median ± IQ; ALAT, 44 ± 65 vs. 34 ± 59 UI/l; ASAT, 32 ± 35 vs. 27± 29 UI/l; γGT, 175 ±
297 121 vs. 226 ± 231 UI/l; AP, 251 ± 184 vs. 289 ± 258 UI/l; total bilirubin, 11 ± 8 vs. 10 ± 8
298 µmol/l), and the percentage of patients with at least one abnormal value (79 vs. 86%) as well.
299 These findings suggest that PN is not the direct cause of plasma liver tests abnormalities in IF
300 patients with temporary double enterostomy.

301

302 3.7. Feasibility of home chyme reinfusion

303 In 59 (28%) patients (37 males), CR was feasible at home in selected patients after specific
304 training and education. At admission, these patients were significantly younger (53 ± 15 vs
305 64 ± 14 years, P<0.001), with lower BMI (21 ± 4 vs. 23 ± 5, P<0.002), upper plasma albumin
306 (30.4 ± 6.2 vs. 27.6 ± 6.4 g/l, P<0.01), but without any difference in the proportion of patients
307 with nutritional risk assessed by NRI. The upstream small bowel length was longer (138 ± 67
308 vs. 110 ± 71 cm, P=0.05) and the proportion of patients with an upper small bowel length

<100 cm was lower (32 vs. 56%, P=0.025). The median (±IQ) follow up of CR from its initiation to the SRIC was 63 ± 51 days. The median (± IQ) duration of hospital stay after CR initiation was 22 ± 14 days with a median duration of home CR of 36 ± 40 days, accumulating 2697 patients-days or 7.4 patients-years. Fifteen patients (25%) received home CR for more than two months (maximum 170 days). Nine hospital readmissions of eight patients for minor problems were reported, lasting six to ten days. No patient had to stop CR.

4. Discussion

To our knowledge, is reported here the largest cohort of CR performed in IF patients with temporary double enterostomy or ECF and waiting for SRIC. Our study clearly shows that CR corrected the IF by restoring intestinal absorption, allowing quick PN weaning in 91% of patients. CR contributes to improve nutritional status and to reduce plasma liver tests abnormalities. In addition, the study reports for the first time the feasibility of home CR. Our results confirm those of small series in adults [12-15]. The interruption of the small intestine by a double enterostomy or an ECF separates the small bowel into an upstream afferent segment, with impaired digestive and absorptive function, and a downstream efferent segment, totally deprived of digestive secretions, bowel flow and succus entericus. This leads to IF since the upstream segment insufficiently absorbs macronutrients, micronutrients, minerals, water, electrolytes, and biliary salts, the latter resulting in enterohepatic cycles disruption. CR artificially re-establishes the digestive function by an extra-corporeal circuit. The chyme collected from the upstream small bowel segment is permanently reinfused via the enterostomy into the diverted distal small bowel segment. One supposed mechanism of CR-induced improvement of intestinal function is the restoration of the ileal brake [24,25]. CR differs from fistuloclysis in which enteral nutrition is instilled in the downstream intestine without any reinfusion of the upstream stoma outputs [26]. In our experience, in case of

insufficient food intake during CR, enteral nutrition could be administered classically through a nasogastric tube, or in some cases, by fistuloclysis.

Although first described in 1977 by Etienne Levy, and recently suggested as an alternative therapy in IF patients [10], CR is rarely used, under recognized, and not endorsed, as in France, by most health insurances. At this time, PN remains the gold standard therapy for IF patients with temporary double enterostomy, until the patients underwent the SRIC, i.e. within a minimal duration of three months. The PN and catheter-related complications are well known [27] and their frequency is more important when the patient is not managed by an expertise centre, which is the most frequent situation. PN costs are much higher than those of enteral nutrition and increase with complications [28]. In this study, the presumed cumulative number of days with saved PN could reach of maximal value of almost 10'000 patients-days, i.e. 27 patients-years. In UK, Saunders [7] evaluated the minimal median costs of 25 type 2 IF patients' therapies as: 56'400€ of initial costs, 4'522€ of hospital readmissions costs, 25'892 € of SRIC costs, i.e. 520, 551 and 855€/patient/day, respectively. For this author, a great part of the costs resulted from PN-related complications. Therefore, by allowing the PN weaning within a short period, CR could be associated with substantial cost-savings. The prospective randomized controlled trial FRY, supported by the French National Clinical Research Program, will determine the impact of CR compared to PN on the incidence of complications, healthcare costs and quality of life in IF patients with temporary high-output double enterostomy.

One considerable advantage of CR is, by using the whole remnant small bowel, to prefigure the post-SRIC intestinal function. Indeed some symptoms occurring during CR, such as pain, fecal incontinence, diarrhea, would have occurred after SRIC. Thus CR should allow anticipating and even preventing situations that would have occurred after the SRIC with potentially more serious consequences. In the presented study, eight patients were excluded because of CR early complications, including one lethal. In the other cases, CR allows

tailoring the surgical strategy or initiating preoperative specific therapy, such as anal biofeedback for fecal incontinence. Besides these advantages, CR has some inconveniences. The main inconvenience of CR is the permanent obligation for the patients to eat a smooth texture food to avoid tubes obstruction. This could affect quality of life. Also CR is not adapted to most university or general hospitals which are dedicated to acute diseases and where the hospital length of stay must be as short as possible. Indeed CR should be integrated in a global approach of intestinal rehabilitation. Patients require complex management of opened abdominal wounds, high intestinal outputs and need a multi-disciplinary nutrition team during the minimal three months period before the SRIC. Our centre is dedicated to intestinal rehabilitation. We strongly believe that such centres should be developed worldwide to improve the management of IF patients.

This study shows for the first time that CR is feasible at home. For this purpose, dedicated portable pumps were developed. Unfortunately, home CR is not yet recognized by French health insurances as a nutrition support technique, needing us selecting only the most specifically trained and educated patients (28% of the cohort), who have thus acquired total autonomy for CR and basic stoma care. For home CR, a dedicated clinical pathway was elaborated including a thesaurus of solutions facing well defined technical problems. As a result, none of the patients were discouraged to return home, only a few were readmitted for minor problems, and none had to go back to PN. More studies are needed including a greater number of patients and centres to demonstrate that home CR is definitively safe and beneficial for IF patients with temporary double enterostomy awaiting for SRIC.

Plasma liver tests abnormalities, mostly cholestatic liver disease, have been reported with a prevalence of 28 to 65% of PN-treated IF patients [29]. At admission, plasma liver tests abnormalities were not significantly more prevalent in patients with PN compared to those without, suggesting that PN does not explain alone plasma liver tests abnormalities. Small bowel bacterial overgrowth is one cause of liver damage. In the diverted downstream small

bowel, in the absence of intestinal motility and nutrients, increased intestinal permeability, adherence of bacteria to the intestinal epithelium and release of bacterial toxins can promote bacterial translocation to the liver [30]. In the upstream small bowel, bacterial overgrowth is facilitated by the profusion of unabsorbed nutrients, and the use of antimotility drugs and proton pump inhibitors. The endoluminal production of alcohol and acetaldehyde in the intestinal lumen and in the hepatocytes could also explain in part the plasma liver tests abnormalities [31,32]. Another presumed mechanism is the disruption of entero-hepatic cycles, especially bile salts malabsorption. When entero-hepatic cycles are restored by the SRIC or CR reestablishment of intestinal continuity, plasma liver tests normalized in adults [13] and children [18]. Their improvement seems greater in patients treated by fistuloclysis coupled with succus entericus reinfusion than by fistuloclysis alone [25]. Bile salts are potent signaling molecules, and at physiological state, activate an intracellular bile salt receptor FXR during transcellular passage of the small intestinal and hepatic epithelium [33]. Bile salts-induced FXR activation is in part mediated by endocrine-acting fibroblast growth factor (FGF) 19, a bile salt-induced enterokine. The release of the FGF19 subsequently inhibits bile salt synthesis from cholesterol. In case of IF-induced enterohepatic cycle disruption, bile salts synthesis is not inhibited, resulting in overproduction and liver accumulation that could have a direct toxicity on hepatocytes. CR could act by restoring bile salts enterohepatic cycle and bile salts signalling, decreasing liver inflammation and plasma liver tests. A study is ongoing to demonstrate this hypothesis. Our study has some limitations. The prevalence of CR-related technical problems (e.g. tube disinsertions, chyme leaks, stoma care problems,…) and gastrointestinal side effects were not collected. Their management requires dedicated healthcare staff education. The patients' quality of life was not assessed whereas the permanent obligation of smooth texture food could have affected it. The data collection was prospective but not performed at predefined endpoints after CR initiation. However it has unlikely affected the main findings since data were collected in the three weeks before SRIC,

412 at a time when CR did not further improve intestinal function or plasma liver tests values.
413 Finally, as we could not identify the patients who could have received PN during their stay in
414 the surgical departments (where was performed the initial surgery) in whom PN could have
415 been stopped within the few days before admission at Clinique St Yves, our study could not
416 exclude beneficial effects of PN in the early phase.
417

418 **5. Conclusions**

419 In case of IF secondary to high output temporary enterostomy, CR is an efficient and reliable
420 technique of enteral nutrition which corrects IF by restoring intestinal absorption, allowing
421 PN weaning in 91% of patients. CR contributes to improve nutritional status and to reduce
422 plasma liver tests abnormalities, and is feasible at home in well selected patients. Our study
423 should improve the awareness of intensivists, digestive surgeons and gastroenterologists
424 involved in IF management to spread the use of CR.

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Statement of authorship

DP designed the study, carried out the collection of data, performed the statistical analyses, and drafted the manuscript. SL carried out the collection of data, and drafted the manuscript. LG carried out the collection of data. FT carried out the collection of data. RT designed the study, performed the statistical analyses, and drafted the manuscript.

Conflict of interest statement

DP declares advisory activities without any financial retribution with Labodial. SL, LD, FT and RT declare no conflict of interest regarding this study.

References

[1] Strategic Framework for Intestinal Failure and Home Parenteral Nutrition Services for Adults in England. Implementation Plan 2009 http://www.webarchive.org.uk/wayback/archive/20130328001800/http://www.specialisedservices.nhs.uk/library/28/Strategic_Framework_for_Intestinal_Failure_and_Home_Parenteral_Nutrition_Services_for_Adults_in_England.pdf

[2] Paquette IM, Solan P, Rafferty JF, Ferguson MA, Davis BR. Readmission for dehydration or renal failure after ileostomy creation. Dis Colon Rectum 2013;56:974-979

[3] Åkesson O, Syk I, Lindmark G, Buchwald P. Morbidity related to defunctioning loop ileostomy in low anterior resection. Int J Colorectal Dis 2012;27:1619-1623

[4] Messaris E, Sehgal R, Deiling S, Koltun WA, Stewart D, McKenna K et al. Dehydration Is the Most Common Indication for Readmission After Diverting Ileostomy Creation. Dis Colon Rectum 2012;55:175-180

[5] Hayden DM, Pinzon MC, Francescatti AB, Edquist SC, Malczewski MR, Jolley JM et al. Hospital readmission for fluid and electrolyte abnormalities following ileostomy construction: preventable or unpredictable? J Gastrointest Surg 2013;17:298-303

[6] Jafari MD, Halabi WJ, Jafari F, Nguyen VQ, Stamos MJ, Carmichael JC et al. Morbidity of diverting ileostomy for rectal cancer: analysis of the american college of surgeons national surgical quality improvement program. Am Surg 2013;79:1034-1039

[7] Saunders J, Parsons C, King A, Stroud M, Smith T. The financial cost of managing patients with type 2 intestinal failure; experience from a regional centre. e-SPEN Journal 2013;8:e80-e85

[8] Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther 2013;37:587-603

[9] Tappenden KA. Pathophysiology of short bowel syndrome: considerations of resected and residual anatomy. JPEN 2014;38:14S-22S

[10] Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C et al. The Home Artificial Nutrition & Chronic Intestinal Failure and the Acute Intestinal Failure Special Interest Groups of ESPEN. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015;34:171-180

[11] Levy E, Frileux P, Cugnenc PH, Honiger J, Ollivier JM, Parc R. High-output external fistulae of the small bowel: management with continuous enteral nutrition. Br J Surg 1989;76:676-679

[12] Calicis B, Parc Y, Caplin S, Frileux P, DehniI N, Ollivier JM et al. Treatment of postoperative peritonitis of small-bowel origin with continuous enteral nutrition and succus entericus reinfusion. Arch Surg 2002;137:296-300

[13] Rinsema W, Gouma DJ, von Meyenfeldt MF, Soeters PB. Reinfusion of secretions from high-output proximal stomas or fistulas. Surg Gynecol Obstet 1988;167:372-376

[14] Pflug AM, Utiyama EM, Fontes B, Faro M, Rassian S. Continuous reinfusion of succus entericus associated with fistuloclysis in the management of a complex jejunal fistula on the abdominal wall. Int J Case Rep 2013;4:716-718

[15] Picot D, Garin L, Trivin F, Kossovsky MP, Darmaun D, Thibault R. Plasma citrulline is a marker of absorptive small bowel length in patients with transient enterostomy and acute intestinal failure. Clin Nutr 2010;29:235-242

[16] Drenckpohl D, Vegunta R, Knaub L, Holterman M, Wang H, Macwan K et al. Reinfusion of Succus Entericus Into the Mucous Fistula Decreases Dependence on Parenteral Nutrition in Neonates. ICAN: Infant, Child, & Adolescent Nutrition 2012;4:168-174

[17] Richardson L, Banerjee S, Rabe H. What Is the Evidence on the Practice of Mucous Fistula Refeeding in Neonates With Short Bowel Syndrome? J Pediatr Gastr Nutr 2006;43:267-270

[18] Schäfer K, Schledt A, Schiedtl A, Linderkamp O, Gfrörer S, Roth H. Decrease of cholestasis under continuous extracorporeal stool transport (CEST) in prematures and neonates with stomas. Eur J Pediatr Surg 2000;10:224-227

[19] Kjeldhal J. A new method for the determination of nitrogen in organic substances. Zeitschrist für Analystische. Chemie 1883;22:366

[20] Van de Kamer JH, Ten Bokkel Huinink H, Weyers HA. Rapid method for the determination of fat in feces. J Biol Chem 1949;177:347-55

[21] Layec S, Beyer L, Corcos O, Alves A, Dray X, Amiot A, et al. Increased intestinal absorption by segmental reversal of the small bowel in adult patients with short-bowel syndrome: a case-control study. Am J Clin Nutr 2013;97:100–108

[22] Crenn P, C. Coudray-Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology 2000;119:1496-1505

[23] Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525-32

[24] Lévy E, Palmer DL, Frileux P, Parc R, Huguet C, Loygue J. Inhibition of upper reinfusion of succus entericus into the distal small bowel: a clinical study of 30 patients with peritonitis and temporary enterostomy. Ann Surg 1983;198:596-600

[25] Wu Y, Ren J, Wang G, Zhou B, Ding C, Gu G et al. Fistuloclysis improves liver function and nutritional status inpatients with high-output upper enteric fistula. Gastroenterol Res Pract 2014;2014:941514

[26] Teubner A,K. Morrison K, Ravishankar HR, Anderson ID, Scott NA, Carlson GL. Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. Br J Surg 2004;91:625–631

[27] Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pourcq L et al. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: a systematic review. Clin Nutr 2013;32:16-26

[28] Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. JPEN 2014;38(Suppl 1):32S-37S

[29] Shaffer JL. Hepatic complications of parenteral nutrition. Clin Nutr 1995;14 (Suppl 1):59-64

[30] Kumpf VJ. Pharmacologic management of diarrhea in patients with short bowel syndrome. JPEN 2014;38(1 Suppl):38S-44S

[31] Picot D, Lauvin R, Hellegouarc'h R. Intra-digestive fermentation in intestinal malabsorption syndromes: relations with elevated serum activity of gammaglutamyl-transpeptidase. Gastroenterol Clin Biol 1997;21:562–566

[32] Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology 2013;57:601–609

[33] Schaap FG, Trauner M, Jansen PL. Bile acid receptors as targets for drug development. Nat Rev Gastroenterol Hepatol 2014;11:55-67

538 **Table 1- Patients' demographics and aetiology of small bowel resection (n=212).**

Male / female - n	125/87
Age - mean ± SD (range)	61.4 ± 14.8 (17–90)
Aetiology of small bowel resection – n (%)	
Cancer	63 (30)
Radiation enteritis	9 (4)
Mechanical occlusion	43 (20)
Ischaemia	40 (19)
Peritonitis	36 (17)
Inflammatory bowel diseases	14 (7)
Trauma	7 (3)

539 SD, standard deviation.

Table 2- Surgical procedure and subsequent small bowel anatomy at admission.

Fistulae – n (%)	29 (14)
Jejuno-parietal	22
Ileo-parietal	7
Enterostomy – n (%)	183 (86)
Loop stomy	45 (24)
Double end-loop stomy	113 (62)
Separated double end stomy	25 (14)
SB resection ≥30cm – n (%)	147 (69)
Resection SB length (cm) (n=147)[§]	62 ± 62
Afferent SB length (cm) (n=159)[§]	100 ± 90
Afferent SB length <100 cm – n (%)	83 (52)
Efferent SB length (cm) (n=161)[§]	100 ± 100
Total SB length (cm) (n=125)[§]	220 ± 95
Total SB length <100 cm – n (%)	4 (3)
Downstream SB anatomy – n (%)	
Ileo-colon	161 (76)
Terminal ileostomy	24 (12)
Ileo-rectal anastomosis	5 (2)
Terminal colostomy	22 (10)

[§]median ± interquartiles. SB, small bowel

Table 3- Evolution of nutritional status between admission (before CR initiation) and discharge (after CR) (n=166).

Parameters	Before CR	After CR	P value
Weight loss (%)[#]	13.3 ± 9.8 (9–47)	9.7 ± 9.1 (20–42)	<0.001
Body mass index[#]	23.0 ± 5.2 (13.6–47.9)	23.8 ± 4.5 (14.9–44.9)	<0.001
Plasma albumin (g/l)[#]	27.7 ± 6.6 (11.4–46.1)	33.9 ± 5.1 (18.3–44.8)	<0.001
Plasma albumin <30 g/l	108 (65)	41 (25)	<0.001
NRI[#]	78.3 ± 10.9 (47-108)	89.2 ± 8.9 (60-113)	<0.001
NRI <83.5	115 (69)	37 (22)	
83.5≤NRI≤97.5	44 (27)	103 (62)	<0.001
NRI >97.5	7 (4)	26 (16)	

Results are expressed as n (%), except[#] mean ± standard deviation (range). Nutritional risk index (NRI) is calculated as: 1.519*plasma Albumin + 41.77* weight/usual weight. Malnutrition risk could be categorised as severe (NRI<83.5), moderate 83.5≤NRI≤97.5 and low (NRI>97.5).

Figure legends

Figure 1- Chyme reinfusion technique with the automated pump Enteromate II® (Labodial, Clayes-sous-Bois, France). The left pump works permanently and aspirates the jejunal effluent from the afferent stoma toward a 30 ml disposable plastic container, which is hung on an electronic steelyard. The upper stoma pouch is always empty. The weight of the container is continuously and electronically monitored. When the minimal volume of approximately 10 ml is exceeded, the second pump starts and the contents are infused into the diverted downstream small bowel until the return to minimal volume.

Figure 2- Study flow chart.

Figure 3- Effects of chyme reinfusion (CR) on intestinal absorption measured before CR initiation (left boxes) and at discharge (right boxes). Stomal (before CR) and fecal outputs (during CR) are expressed as dl/24h. Coefficients of nitrogen digestive absorption (CNDA) = (1-(intestinal nitrogen/ nitrogen intake))*100. Coefficient of fat digestive absorption (CFDA) = (1-(intestinal lipids/lipid intake))*100. Values are presented as mean (square points), SD (vertical solid bars), quartile 2 and 3 (shaded squares), median (horizontal bar in the shaded squares), extremes (vertical dashed bars). n, number of patients measured twice: before CR and at discharge. ***P<0.001.

Figure 4- Evolution of the percentage of patients with plasma liver tests abnormalities defined as higher than two times the normal values between admission (before CR initiation) and discharge (after CR initiation) (n=155 for ALAT, ASAT, γGT, AP; n=91 for total bilirubin). ALAT, alanine amino-transferase; AP, alkaline phosphatase; ASAT,

578 aspartate amino-transferase; γGT, gamma-glutamyl-transpeptidase; TB, total bilirubin.

579 $^{***}P<0.001$.

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581 **Figure 1**

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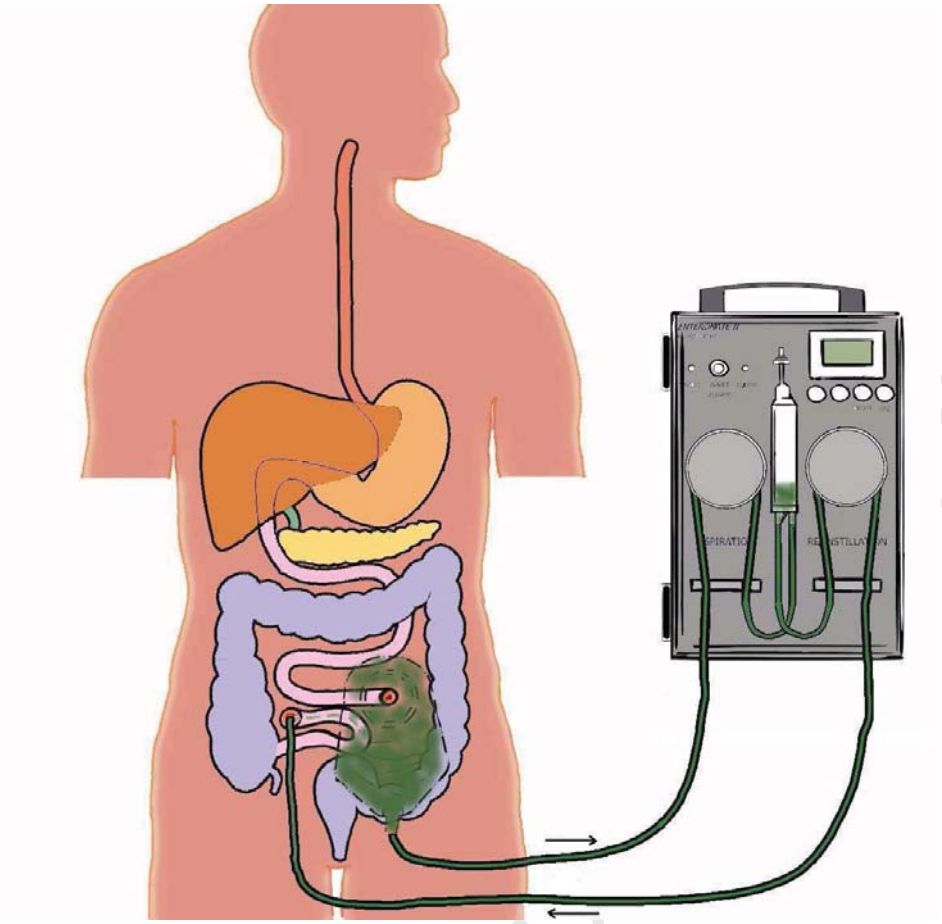

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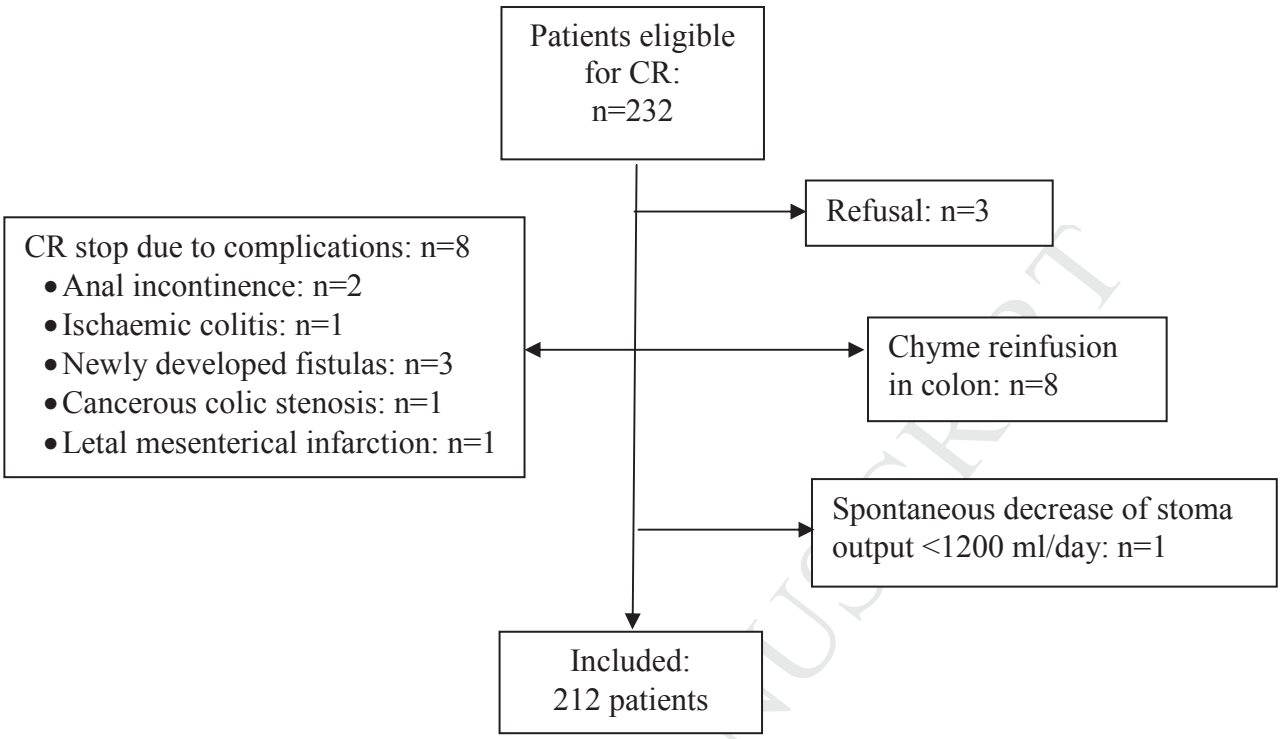
Figure 2



607 **Figure 3**

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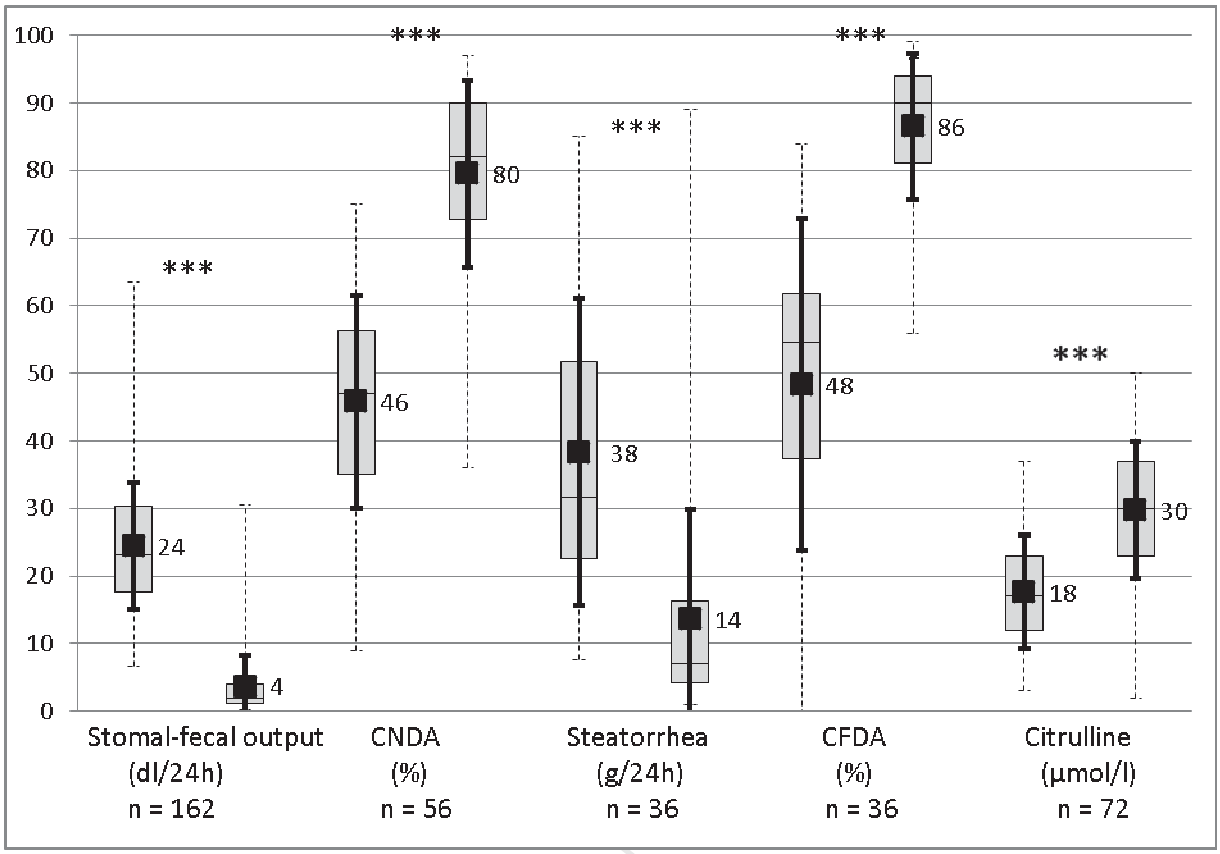

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611 **Figure 4**

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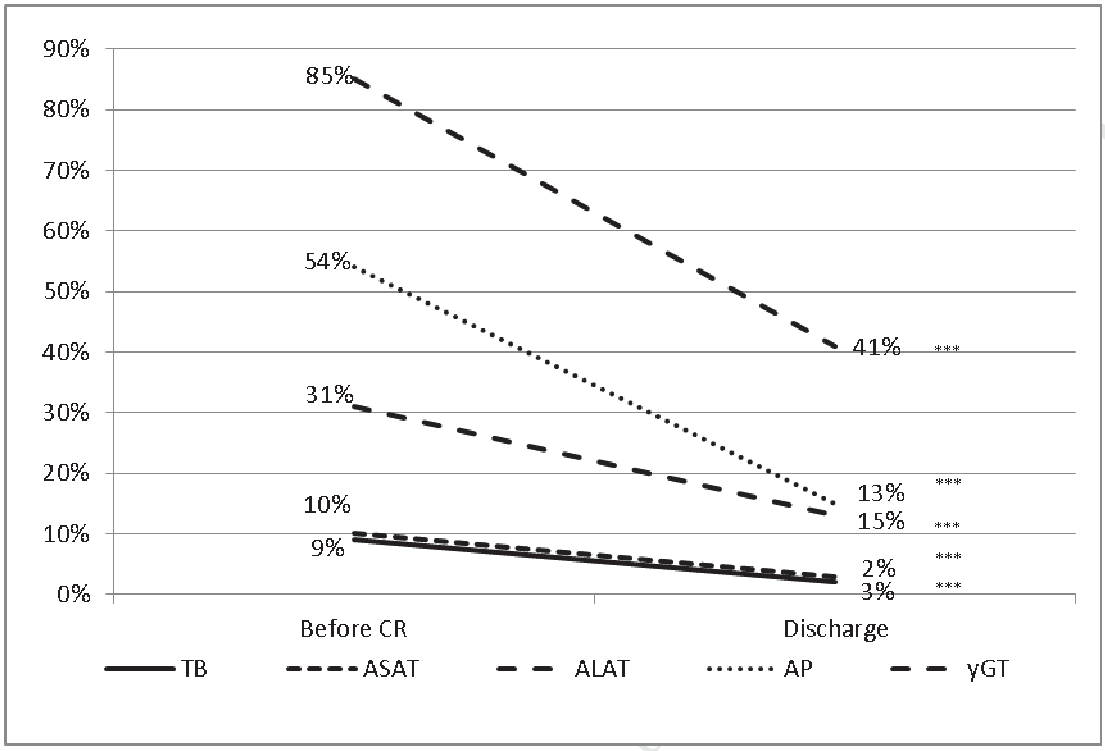

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