

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

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36 **Abstract (292 words)**

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

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

48 *Results:* 183 patients had temporary double enterostomy and 29 exposed enterocutaneous
49 fistulas. CR reduced the intestinal output (2444 ± 933 vs 370 ± 457 ml/day, $P < 0.001$),
50 improved CNDA (46 ± 16 vs $80 \pm 14\%$, $P < 0.001$) and CFDA (48 ± 25 vs $86 \pm 11\%$,
51 $P < 0.001$), and normalized plasma citrulline concentration (17.6 ± 8.4 vs 30.3 ± 11.8 $\mu\text{mol/l}$,
52 $P < 0.001$). PN was stopped in 126/139 (91%) patients within 2 ± 8 d. Nutritional status
53 improved ($P < 0.001$): weight ($+4.6 \pm 8.6\%$), BMI ($+3.8 \pm 7.7\%$), plasma albumin ($+6.2 \pm 6.1$
54 g/l), and NRI ($+10.9 \pm 9.5$). The proportion of patients with plasma liver tests abnormalities
55 decreased (88 vs 51%, $P < 0.01$). Home CR was feasible without any serious complications in
56 selected patients.

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

60

61 **Keywords:** malnutrition; succus entericus reinfusion; fistuloclysis; parenteral nutrition;
62 ileostomy; enterocutaneous fistula.
63

ACCEPTED MANUSCRIPT

64 1. Introduction

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

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

100

101 2. Materials and methods

102 2.1. Study design

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

107

108 2.2. Centre description

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

115

116 2.3. Inclusion criteria

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

126

127 2.4. Data collection

128 The clinical and biological data were collected prospectively and recorded in a specific
129 Access (Microsoft) database registered, as required by the French law, at the French
130 Committee for computing and freedom CNIL (N° 1452427). Height was measured at
131 admission and weight twice a week. The enterostomy or fistula output was quantified daily.
132 The biological tests were carried out by the same laboratory. These data were collected for all
133 patients at their admission, before CR was initiated, and repeatedly during CR. Body mass
134 index (BMI) ($\text{weight (kg)/height (m)}^2$), weight loss at admission as compared to usual weight
135 ($100 \times (\text{usual weight} - \text{actual weight}) / \text{usual weight}$) and Nutritional Risk Index
136 ($\text{NRI} = 1.519 \times \text{Alb} + 41.77 \times \text{weight/usual weight}$) where Alb is plasma albumin concentration,
137 were calculated. Severe malnutrition risk was defined as $\text{NRI} < 83.5$, moderate malnutrition
138 risk as $83.5 \leq \text{NRI} \leq 97.5$, and absence of malnutrition risk as $\text{NRI} > 97.5$. Plasma values of liver
139 tests, i.e. alanine amino-transferase (ALAT), aspartate amino-transferase (ASAT), alkaline
140 phosphatase (AP), γ -glutamyl-transpeptidase (γ GT), and total bilirubin, higher than two times
141 the normal values (i.e. for total bilirubin $\geq 30 \mu\text{mol/l}$), were considered as increased. Proximal
142 stoma or fecal outputs were daily measured in all patients before and after the initiation of
143 CR, respectively. During CR, anal stools were not daily weighed when their number was
144 $\leq 2/\text{day}$. Intestinal nitrogen and fat outputs were measured over three consecutive days, before
145 the initiation of CR, and at least three weeks after CR initiation. Nitrogen and fat fecal
146 concentrations were measured according to the Kjeldahl's [19] and the Van de Kamer's [20]
147 methods, respectively. Nitrogen and fat fecal outputs were expressed as the mean daily
148 nitrogen or fat fecal output in g/day. Simultaneously, oral protein and fat intakes were
149 determined using a daily dietary record. Total protein and fat dietary intakes were evaluated
150 by dieticians from: (1) the proportion of food proposed that was consumed (25%, 33%, 50%,
151 66%, 75%, 100%); and (2) food composition tables coupled with the software allowing
152 patient's meal choice (Nutriciel_ SCJ Informatique, Mont Saint Aignan, France). Nutritional

153 food intakes (oral, enteral and parenteral) were expressed as kcal/kg actual body weight/day
154 and g/kg actual body weight/day for energy and protein, respectively. PN formulas consisted
155 of tricompartimental bags delivering 0.62–1.14 kcal/ml of energy (15-20% proteins, 29%
156 lipids (80% olive oil, 20% soy oil), and 51% carbohydrates). PN formulas came from Baxter,
157 USA. The coefficients of nitrogen (CNDA) and fat (CFDA) digestive absorption, expressed in
158 percentage of ingested protein and fat, represent the proportion of oral nitrogen or fat not
159 recovered in stomial or fecal wet weight, and was calculated as: $CNDA = (1 - (\text{intestinal nitrogen (g/day)} / \text{protein intake (g/day)} / 6.25) * 100$ and $CFDA = (1 - (\text{steatorrhea (g/day)} / \text{fat$
160 $\text{intake (g/day)}) * 100$ [21]. Values higher than 85% were considered as physiological.
161
162 Fasting plasma citrulline concentration was determined simultaneously with the CNDA and
163 CFDA within the three days before and after CR initiation. Simultaneously, creatinine
164 clearance was calculated with the Cockcroft's formula for 1.73 m² because alteration of renal
165 function prevents from interpreting plasma citrulline. Plasma citrulline concentration was
166 determined using reverse-phase high performance liquid chromatography (HPLC). As Crenn
167 et al. [22] showed that a plasma citrulline below 20 μmol/l was predictive of IF, we chose this
168 threshold to define a low plasma citrulline.

169

170 2.5. Measurement of small bowel length

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

179

180 2.6. Chyme reinfusion (CR)

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

192 The downstream small bowel was intubated through the efferent enterostomy with a simple
193 lumen polyurethane naso-gastric tube ch 14-16, Levine-typed, without balloon, into the first
194 15-20 centimeters of the small bowel. A radiologic opacification with water-soluble contrast
195 agents checked the tube position and controlled the anatomy and the length of the downstream
196 small bowel until the colon. During the two days before CR initiation, enteroclysis was
197 initiating by instilling one liter of oral rehydration solution, together with laxatives in case of
198 fecal residues or fecaloma in the colon. At the same time, anti-motility drugs, e.g. loperamide,
199 were stopped to prevent ileus. Antispasmodic agents could be useful in case of abdominal
200 pain, and cholestyramine was given by enteroclysis in the event of diarrhea during the first
201 days. In case of persisting diarrhea, loperamide was used. Antisecretory drugs were used in all
202 patients before and during CR. Octreotide was never used. Once the patient has been
203 adequately trained and is capable of correctly adjusting the rate of reinfusion, portable non-
204 autoregulated Enteromate Mobile™ (marketed since 2010 by Labodial, Les Clayes Sous Bois,

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

211

212 2.7. Definitions

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

220

221 2.8. Statistical analysis

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

229

230 3. Results

231 3.1. Patients recruitment and characteristics

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

239

240 3.2. Surgical procedure and subsequent small bowel anatomy

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

244

245 3.3. Intestinal absorption (**Figure 3**)

246 CR was associated with a dramatic improvement of intestinal function. CR reduces from 52 to
247 3% ($P < 0.0001$) the proportion of patients with a remnant length of small bowel below 100
248 cm. The intestinal losses were reduced by 85% ($P < 0.001$) and the number of patients with
249 output higher than 1200 ml/24h decreased from 155 to 9 ($P < 0.0001$). CNDA and CFDA were
250 measured before and after CR initiation in 56 and 36 patients, respectively. CNDA, CFDA,
251 and plasma citrulline were measured with a median \pm IQ follow-up of 27 ± 35 days (range
252 10–186 days) after CR initiation. CNDA and CFDA strongly improved with CR (**Figure 3**).
253 Whereas they were largely below physiological levels before CR, attesting intestinal
254 malabsorption, CNDA and CFDA went back to physiological levels in 47% and 67% of
255 patients, respectively ($P < 0.0005$). The number of patients with plasma citrulline $< 20 \mu\text{mol/l}$
256 decreased from 47 (65%) to 8 (11%) ($P < 0.0005$) ($n=72$). In eight patients with a creatinine

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

259

260 3.4. Parenteral nutrition needs

261 At admission, within a median (\pm IQ) time of 33 ± 25 days after initial surgery, 139 (65%)
262 patients received PN (n=111) or IV hydration (n=28). Despite all patients displayed
263 characteristics of IF and would have to be treated with PN, PN was not initiated in the
264 surgical departments referring the patients. Nevertheless patients with PN at admission had
265 shorter upstream small bowel length, worse intestinal function and lower plasma citrulline
266 than patients who did not receive PN (data not shown). Mean (\pm SD) energy and protein PN
267 intakes were 24 ± 9 kcal/kg/day and 0.9 ± 0.3 g/kg/day respectively, in a mean volume of
268 2110 ± 974 ml/day. During CR, mean energy and protein oral intakes were 31 ± 14
269 kcal/kg/day and 1.4 ± 0.7 g/kg/day, respectively. An additional enteral nutrition was needed in
270 72 (34%) patients (“en Y” enteroclysis, n=46; nasogastric tube, n=17; gastrostomy, n=7;
271 jejunostomy, n=2). The total mean amounts of energy and protein oral and enteral intakes
272 were 36 ± 14 kcal/kg/day and 1.6 ± 0.7 g/kg/day. As a result, PN and/or IV hydration could
273 be stopped in 126 of 139 patients (91%), within a median \pm IQ of 2 ± 9 days after CR
274 initiation. PN was carried on in 17 patients with a maximum of 186 days. Therefore the
275 median (\pm IQ) time with saved PN was 59 ± 57 days per patient. The presumed cumulative
276 median (\pm IQ) number of days with saved PN was 9723 patients-days (or 26.6 patients-years).

277

278 3.5. Nutritional status

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

283

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%), γ GT (n=170, 81%), and total bilirubin
287 (n=11, 6%).

288 Plasma liver tests (ALAT, ASAT, AP, γ GT) 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 $\mu\text{mol/l}$ [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 \pm IQ; ALAT, 44 ± 65 vs. 34 ± 59 UI/l; ASAT, 32 ± 35 vs. 27 ± 29 UI/l; γ GT, $175 \pm$
297 121 vs. 226 ± 231 UI/l; AP, 251 ± 184 vs. 289 ± 258 UI/l; total bilirubin, 11 ± 8 vs. 10 ± 8
298 $\mu\text{mol/l}$), 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

309 <100 cm was lower (32 vs. 56%, $P=0.025$). The median (\pm IQ) follow up of CR from its
310 initiation to the SRIC was 63 ± 51 days. The median (\pm IQ) duration of hospital stay after CR
311 initiation was 22 ± 14 days with a median duration of home CR of 36 ± 40 days, accumulating
312 2697 patients-days or 7.4 patients-years. Fifteen patients (25%) received home CR for more
313 than two months (maximum 170 days). Nine hospital readmissions of eight patients for minor
314 problems were reported, lasting six to ten days. No patient had to stop CR.

315

316 **4. Discussion**

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

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

336 Although first described in 1977 by Etienne Levy, and recently suggested as an alternative
337 therapy in IF patients [10], CR is rarely used, under recognized, and not endorsed, as in
338 France, by most health insurances. At this time, PN remains the gold standard therapy for IF
339 patients with temporary double enterostomy, until the patients underwent the SRIC, i.e. within
340 a minimal duration of three months. The PN and catheter-related complications are well
341 known [27] and their frequency is more important when the patient is not managed by an
342 expertise centre, which is the most frequent situation. PN costs are much higher than those of
343 enteral nutrition and increase with complications [28]. In this study, the presumed cumulative
344 number of days with saved PN could reach of maximal value of almost 10'000 patients-days,
345 i.e. 27 patients-years. In UK, Saunders [7] evaluated the minimal median costs of 25 type 2 IF
346 patients' therapies as: 56'400€ of initial costs, 4'522€ of hospital readmissions costs, 25'892
347 € of SRIC costs, i.e. 520, 551 and 855€/patient/day, respectively. For this author, a great part
348 of the costs resulted from PN-related complications. Therefore, by allowing the PN weaning
349 within a short period, CR could be associated with substantial cost-savings. The prospective
350 randomized controlled trial FRY, supported by the French National Clinical Research
351 Program, will determine the impact of CR compared to PN on the incidence of complications,
352 healthcare costs and quality of life in IF patients with temporary high-output double
353 enterostomy.

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

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

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

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

386 bowel, in the absence of intestinal motility and nutrients, increased intestinal permeability,
387 adherence of bacteria to the intestinal epithelium and release of bacterial toxins can promote
388 bacterial translocation to the liver [30]. In the upstream small bowel, bacterial overgrowth is
389 facilitated by the profusion of unabsorbed nutrients, and the use of antimotility drugs and
390 proton pump inhibitors. The endoluminal production of alcohol and acetaldehyde in the
391 intestinal lumen and in the hepatocytes could also explain in part the plasma liver tests
392 abnormalities [31,32]. Another presumed mechanism is the disruption of entero-hepatic
393 cycles, especially bile salts malabsorption. When entero-hepatic cycles are restored by the
394 SRIC or CR reestablishment of intestinal continuity, plasma liver tests normalized in adults
395 [13] and children [18]. Their improvement seems greater in patients treated by fistuloclysis
396 coupled with succus entericus reinfusion than by fistuloclysis alone [25]. Bile salts are potent
397 signaling molecules, and at physiological state, activate an intracellular bile salt receptor FXR
398 during transcellular passage of the small intestinal and hepatic epithelium [33]. Bile salts-
399 induced FXR activation is in part mediated by endocrine-acting fibroblast growth factor
400 (FGF) 19, a bile salt-induced enterokine. The release of the FGF19 subsequently inhibits bile
401 salt synthesis from cholesterol. In case of IF-induced enterohepatic cycle disruption, bile salts
402 synthesis is not inhibited, resulting in overproduction and liver accumulation that could have a
403 direct toxicity on hepatocytes. CR could act by restoring bile salts enterohepatic cycle and
404 bile salts signalling, decreasing liver inflammation and plasma liver tests. A study is ongoing
405 to demonstrate this hypothesis. Our study has some limitations. The prevalence of CR-related
406 technical problems (e.g. tube disinsertions, chyme leaks, stoma care problems,...) and
407 gastrointestinal side effects were not collected. Their management requires dedicated
408 healthcare staff education. The patients' quality of life was not assessed whereas the
409 permanent obligation of smooth texture food could have affected it. The data collection was
410 prospective but not performed at predefined endpoints after CR initiation. However it has
411 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.

425

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432

433 Statement of authorship

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

438

439 Conflict of interest statement

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

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

Male / female - n	125/87
Age - mean \pm SD (range)	61.4 \pm 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.

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

541

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 ≥ 30 cm – n (%)	147 (69)
Resection SB length (cm) (n=147) [§]	62 \pm 62
Afferent SB length (cm) (n=159) [§]	100 \pm 90
Afferent SB length <100 cm – n (%)	83 (52)
Efferent SB length (cm) (n=161) [§]	100 \pm 100
Total SB length (cm) (n=125) [§]	220 \pm 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)

542 [§]median \pm interquartiles. SB, small bowel

543

544 **Table 3- Evolution of nutritional status between admission (before CR initiation) and**
 545 **discharge (after CR) (n=166).**
 546

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)	

547 Results are expressed as n (%), except[#] mean ± standard deviation (range). Nutritional risk
 548 index (NRI) is calculated as: 1.519*plasma Albumin + 41.77* weight/usual weight.
 549 Malnutrition risk could be categorised as severe (NRI<83.5), moderate 83.5≤NRI≤97.5 and
 550 low (NRI>97.5).
 551
 552

553 Figure legends

554

555 Figure 1- Chyme reinfusion technique with the automated pump Enteromate II[®]

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

562

563 Figure 2- Study flow chart.

564

565 Figure 3- Effects of chyme reinfusion (CR) on intestinal absorption measured before CR

566 **initiation (left boxes) and at discharge (right boxes).** Stomal (before CR) and fecal outputs
567 (during CR) are expressed as dl/24h. Coefficients of nitrogen digestive absorption (CNDA) =
568 $(1 - (\text{intestinal nitrogen} / \text{nitrogen intake})) * 100$. Coefficient of fat digestive absorption (CFDA)
569 $= (1 - (\text{intestinal lipids} / \text{lipid intake})) * 100$. Values are presented as mean (square points), SD
570 (vertical solid bars), quartile 2 and 3 (shaded squares), median (horizontal bar in the shaded
571 squares), extremes (vertical dashed bars). n, number of patients measured twice: before CR
572 and at discharge. ***P<0.001.

573

574 Figure 4- Evolution of the percentage of patients with plasma liver tests abnormalities

575 **defined as higher than two times the normal values between admission (before CR**
576 **initiation) and discharge (after CR initiation) (n=155 for ALAT, ASAT, γ GT, AP; n=91**
577 **for total bilirubin). ALAT, alanine amino-transferase; AP, alkaline phosphatase; ASAT,**

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

579 ***P<0.001.

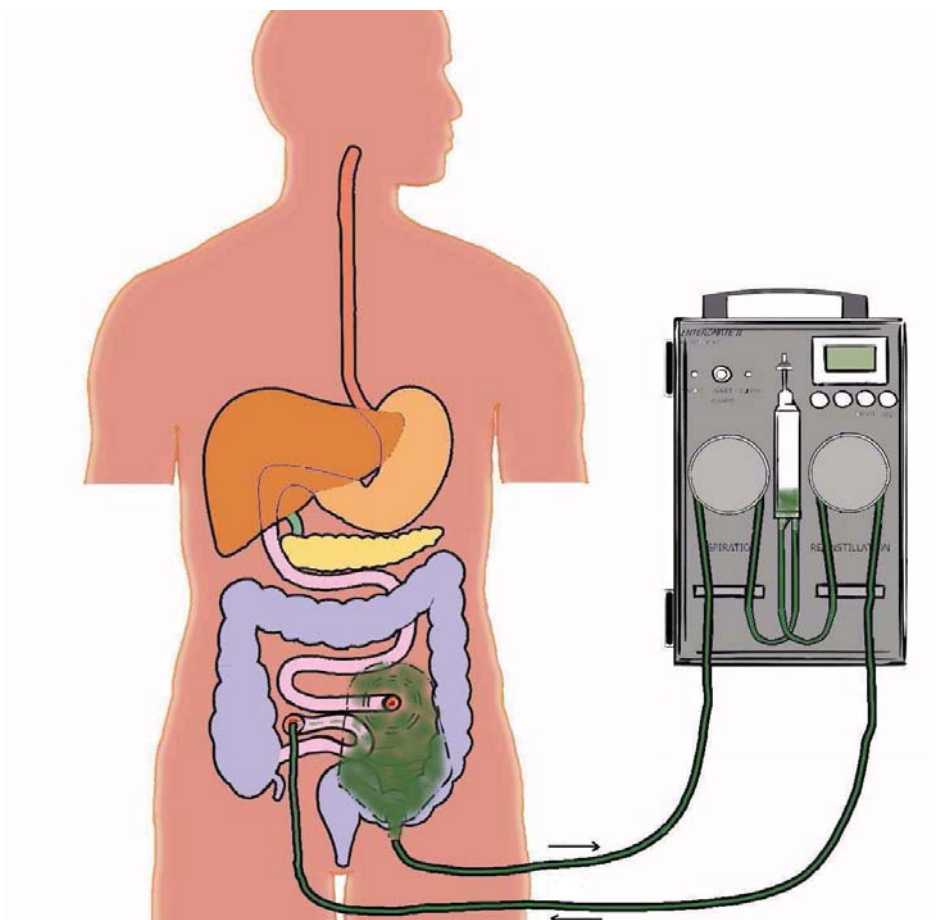
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Figure 1

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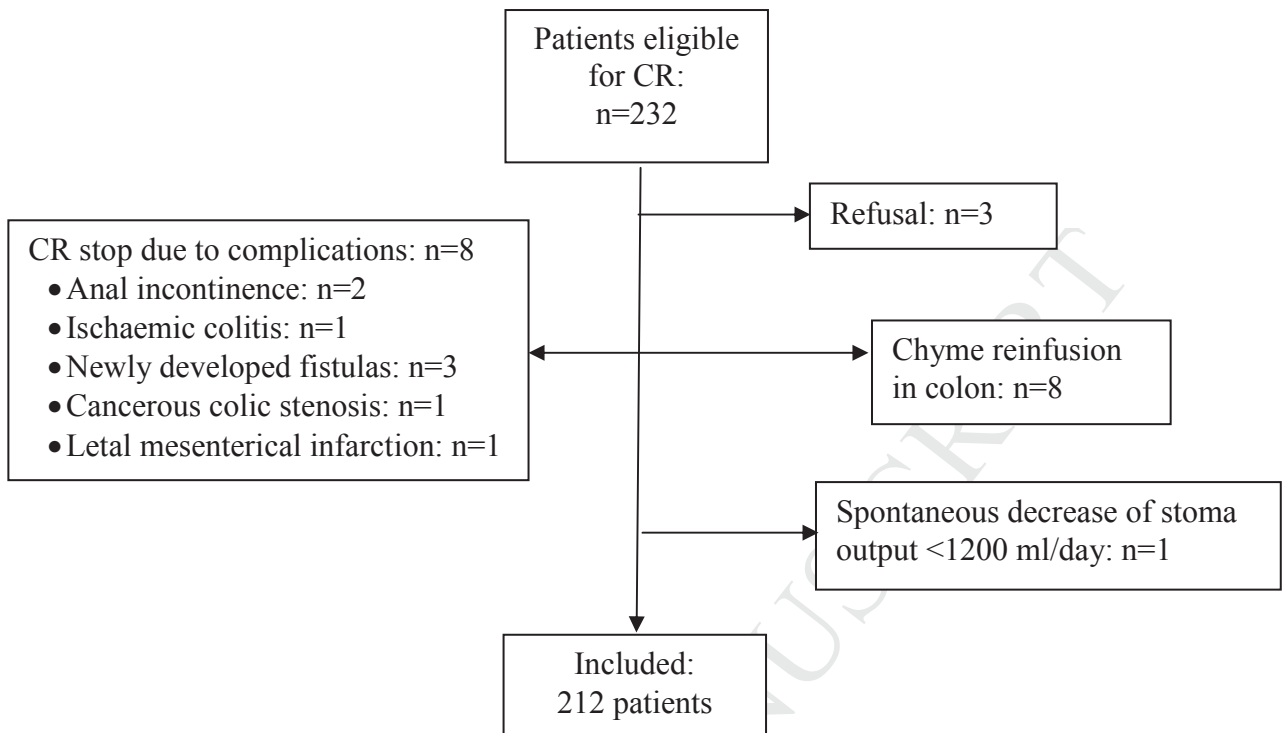


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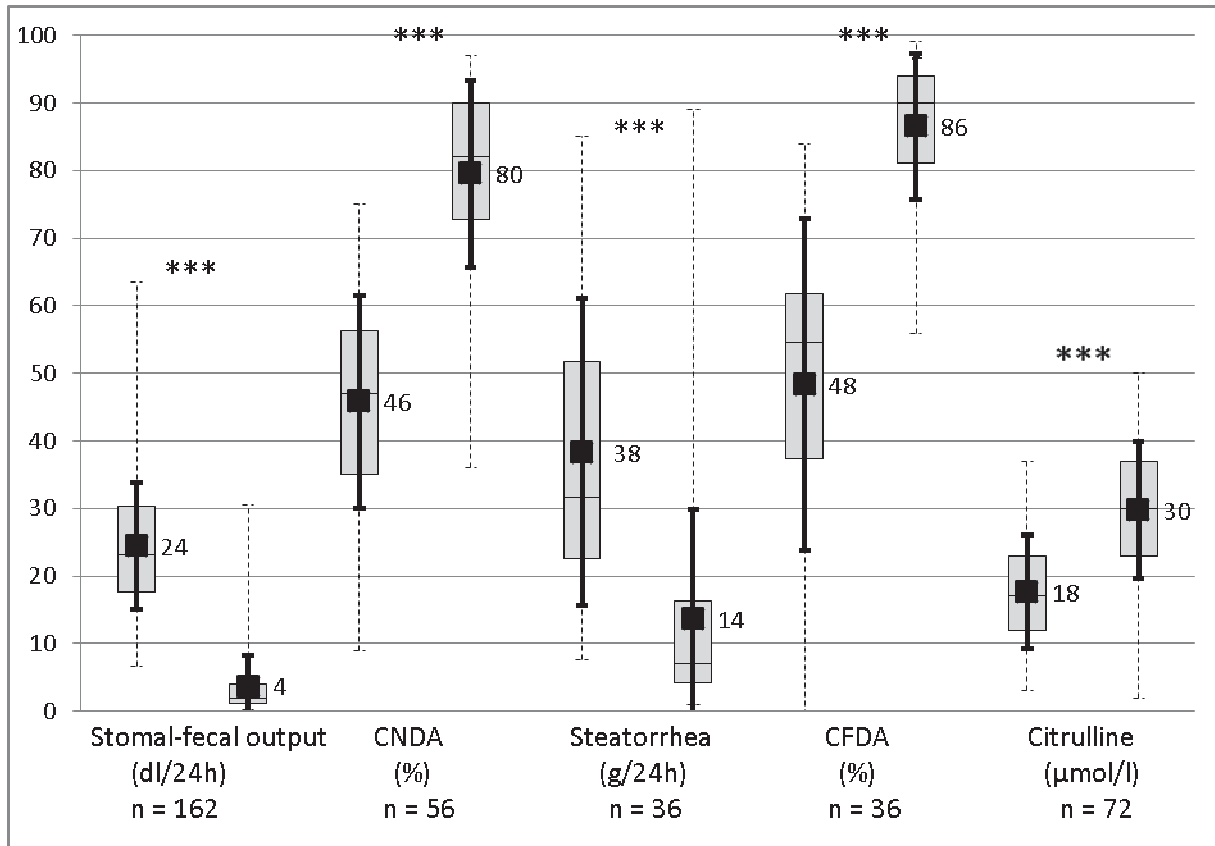
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Figure 2

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Figure 3

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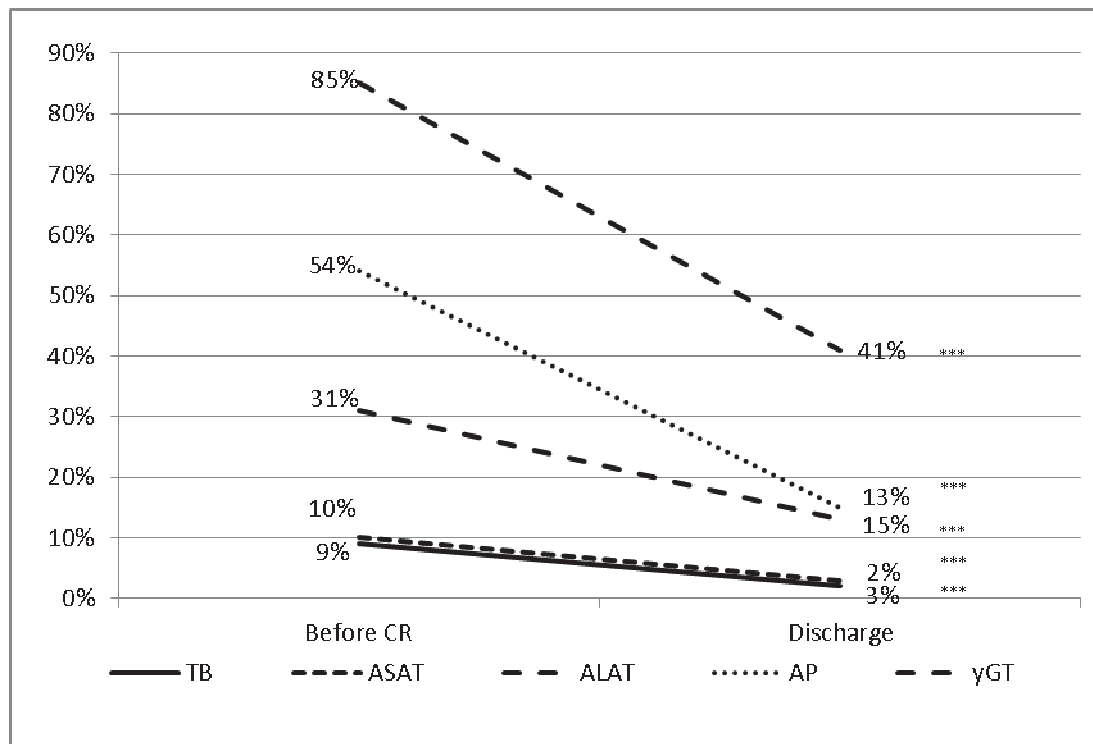
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Figure 4

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