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1 **Chyme reinfusion or enteroclysis in nutrition of patients with temporary double**
2 **enterostomy or enterocutaneous fistula**

3

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5

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22 **Abstract (196 words)**

23

24 **Purpose of review**

25 Patients with double temporary enterostomy or enterocutaneous fistula (ECF) may suffer
26 from intestinal failure (IF). Parenteral nutrition (PN) is the gold standard treatment until
27 surgical reestablishment of intestinal continuity, but serious complications may arise. Chyme
28 reinfusion (CR) or enteroclysis are indicated.

29 **Recent findings**

30 CR corrects the IF by restoring intestinal absorption, allowing PN weaning in 91% of patients.
31 CR contributes to improve nutritional status and reduce plasma liver tests abnormalities. CR
32 is feasible at home without any serious complications in selected patients. Mechanisms
33 underlying CR effectiveness on intestinal function, such as restoration of ileal brake, are
34 suggested but most remain to be demonstrated. When the downstream small bowel is
35 exposed, enteroclysis of enteral nutrition or hydration could be helpful to reduce PN needs, or
36 in case of insufficient food intake during CR.

37 **Summary**

38 CR or enteroclysis are less expensive, safe, and easy-to-use nutrition support techniques, that
39 may allow reducing PN-related healthcare costs. The latter remains to be demonstrated in the
40 setting of a prospective randomized controlled trial. This review may contribute to improve
41 the awareness of intensivists, digestive surgeons and gastroenterologists involved in IF
42 management to spread the use of CR or enteroclysis.

43

44 **Keywords:** intestinal failure; fistuloclysis; gastrointestinal (GI) surgery; EN; parEN

45 **Introduction**

46 In the course of an intestinal surgery procedure, several clinical situations lead the surgeon to
47 undertake a double temporary enterostomy (small bowel resection, peritonitis, fistulae,
48 anastomosis protection...) or could be complicated of enterocutaneous fistula (ECF)
49 (peritonitis, anastomosis leakage, digestive adherences...). These conditions could constitute
50 a type 1 short bowel syndrome and are often complicated with intestinal failure (IF),
51 especially when the stoma output is equal or higher than 1500 ml/24h. These lead to serious
52 complications resulting in hospital readmissions, such as acute or chronic dehydration, renal
53 failure, electrolyte disturbances, micronutrients and mineral deficiencies, and malnutrition,
54 thus increasing healthcare-related costs and affecting patients' quality of life [1]. IF was
55 recently defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) as
56 "the reduction of gut function below the minimum necessary for the absorption of
57 macronutrients and/or water and electrolytes, such that intravenous supplementation is
58 required to maintain health and/or growth » [2]. In case of temporary double enterostomy or
59 ECF, the IF is type 2, and defines as a prolonged acute condition, often in metabolically
60 unstable patients, requiring complex multi-disciplinary care and intravenous supplementation
61 over periods of weeks or months [2]. At this time, the current gold standard therapy indicated
62 until the surgical reestablishment of digestive continuity (SIRC), with a mean duration of 3-6
63 months, is home parenteral nutrition (HPN) [3]. However, HPN has its own morbidity and, in
64 the absence of expertise, the risks of infectious, hepatic dysfunction, mechanical and
65 metabolic complications are increased [1,3]. Therefore, the availabilities of low cost, safer,
66 and easy-to-use nutrition support techniques could be of high added value in these type 2 IF
67 patients. Chyme reinfusion (CR) [4-9] and enteroclysis [5,6,10] could be these techniques.
68 The scope of this review is to describe the technical principles of CR and enteroclysis, to give
69 practical details for their use, review their clinical benefits in clinical practice, and, due to the
70 lack of data, to hypothesize the mechanisms related to their clinical benefits.

71

72 Definitions

73 The interruption of the small bowel by a double enterostomy or an ECF separates the small
74 bowel into an upstream afferent segment and a downstream efferent segment (**Figure 1**).

75 Enteroclysis is an enteral nutrition (EN) technique consisting in the administration of EN or
76 hydration solutions in the downstream efferent small bowel through efferent enterostomy or
77 ECF exposed to the abdomen wall, chyme from the afferent small bowel being thrown out.

78 The term “fistuloclysis” [2,6,10] wrongly used as a synonym of “enteroclysis” should be
79 abandoned since: it is medically inappropriate, referring to a technique of fistula irrigation or
80 washing and not to an EN technique which could be only delivered in the intestine through
81 the fistula, but not in the fistula; it is linguistically inappropriate: one Latina prefix followed
82 by one Greek suffix. CR [4] (or re-feeding enteroclysis [2,5] or succus entericus reinfusion
83 [8,9]) is an EN technique which artificially re-establishes the small bowel continuity by an
84 extra-corporeal circuit of the chyme and mimics the definitive gastro-intestinal function; the
85 chyme, composed of digestive secretions and nutrients from oral food and/or tube feeding, is
86 collected from the afferent small bowel, and reinfused via the enterostomy or the ECF into the
87 efferent diverted small bowel segment. CR could be, at best, in our experience, continuous,
88 through a portable or not automated pump, or, as reported by others [5], sequential by manual
89 chyme decanting.

90

91 The principle of CR with auto-regulated pumps

92 Although first described in 1977 by Etienne Levy, and recently suggested as an alternative
93 therapy in IF patients [2], CR is rarely used, under recognized, and not endorsed by most
94 health insurances. This is partly due to the fact that the materials used for CR were not
95 specifically dedicated to the technique. Indeed, in most centres where it is used, CR is
96 performed by diverting from their first use EN pumps and tubulures, or dialysis material...

97 Usually, and we think that this technique must be abandoned, chyme was collected in a bag
98 thanks to gravity, sometimes refrigerated, often sieved to remove the largest food particles.
99 Chyme is then transferred every 3-4 hours in an EN bag to be reinfused with an auto-
100 regulated EN pump into the downstream efferent small bowel. Others directly reinfused the
101 chyme with a syringe. All these handlings were associated with uncomfortable odours and
102 dirt making the CR technique very unpopular. Spreading the use of auto-regulated pumps
103 dedicated to CR would help to increase CR acceptance and use in IF-specialized centres. At
104 Clinique Saint Yves, Rennes, France, we perform continuous CR using the Entéromate® II
105 system (Labodial, Les Clayes Sous Bois, France), marketed since 1998 (**Figure 2**).

106 Entéromate® II auto-regulates continuous CR without any adjustment or nurse's intervention,
107 and no uncomfortable odour. The dead space volume of the extra-corporeal circuit is lower
108 than 50 ml and does not cause any volemic deprivation. The tubulures are closed and prevent
109 from outside infectious contamination. The automaton has two peristaltic pumps. One pump
110 works permanently and aspirates the jejunal effluent toward a 30 mL disposable plastic
111 container, so that the upper stoma pouch is always empty. The weight of the container is
112 continuously and electronically monitored. When the minimal volume of approximately 10 ml
113 is exceeded, the second pump starts and the contents are infused into the diverted downstream
114 small bowel until the return to minimal volume. The downstream small bowel is intubated
115 through the efferent enterostomy or ECF with a simple lumen polyurethane naso-gastric tube
116 ch 14-16, Levine-typed, without balloon, into the first 15-20 centimetres of the small bowel
117 (**Figure 1**). We advise that polyurethane naso-gastric tubes must be preferred to Foley's
118 because of their higher internal diameter (for a given "ch" calibre) and the absence of balloon,
119 that could injure the small bowel when too much inflated. Ideally a radiologic opacification
120 with water-soluble contrast agents checks the tube position and controls the anatomy and the
121 length of the downstream small bowel until the colon.

122

123 **Indications of CR**

124 In our experience, the patients eligible for CR fulfil the following criteria: IF defined as a
125 theoretical indication to PN, plus a stoma output nihil per mouth of at least 1200 ml/24h;
126 existence of a double enterostomy or at least two orifices of ECF visible on the abdominal
127 wall; theoretical temporary nature of the stoma or ECF in the expectancy of SIRC; presence
128 of efferent small bowel between the stoma and the colon, or a terminal ileostomy; absence of
129 obstruction of digestive fistula between the mouth and the afferent stoma, and in the efferent
130 intestinal tract; ability to catheterize the efferent stoma with a feeding tube on more than 15
131 cm; absence of progressive peritoneal carcinosis; age >17 years; full agreement of the patient
132 to carry out CR and accept the food constraints of ingesting smooth puree meals.

133

134 **CR and enteroclysis in daily practice**

135 CR and enteroclysis should be integrated in a global approach of intestinal rehabilitation.
136 Patients require complex management of opened abdominal wounds, high intestinal outputs
137 and need a multi-disciplinary nutrition team, including specially trained nurses and
138 nutritionist gastroenterologists or surgeons. During the two days before CR initiation,
139 enteroclysis is initiating by instilling one liter of oral rehydration solution, together with
140 laxatives in case of fecal residues or fecaloma in the colon. At the same time, anti-motility
141 drugs, e.g. loperamide, are stopped to prevent ileus. Antispasmodic agents could be useful in
142 case of abdominal pain, and cholestyramine is given by enteroclysis in the event of diarrhea
143 during the first days. In case of persisting diarrhea, loperamide is used. Antisecretory gastric
144 drugs are used in all patients before and during CR. Octreotide is never used. Once the patient
145 has been adequately trained and is capable of correctly adjusting the rate of reinfusion,
146 portable non-autoregulated Enteromate Mobile® pump (Labodial, Les Clayes Sous Bois,
147 France), marketed since 2010, is used secondly to give autonomy to the patient. This pump is
148 autonomous thanks to batteries. During CR, to avoid tubes obstruction, patients are

149 mandatorily orally fed ad libitum with smooth puree meals. In case of insufficient food or
150 hydration intake during CR, EN and additional hydration solutions could be administered
151 classically through a nasogastric feeding tube, gastrostomy or jejunostomy, or, in some cases,
152 by "en Y" enteroclysis in the reinfusion tube into the downstream small bowel [6,8,9].

153

154 **Clinical benefits of CR and enteroclysis**

155 Only a few studies have reported the beneficial effects of CR or enteroclysis in IF patients
156 with temporary double enterostomy or ECF. Only one [4] was published within 18 months
157 and none were prospective randomized controlled trials. These studies are monocentric case
158 series, having included only a low number of patients, and did not report post-SIRC clinical
159 outcomes. In adult patients, CR could restore intestinal absorptive capacities [4,7]. This could
160 allow PN discontinuation a few days after its initiation [4,5], and the improvement of
161 frequently observed liver tests abnormalities [4]. Plasma liver tests improvement seems
162 greater in patients treated by enteroclysis coupled with CR than by enteroclysis alone [6]. In
163 neonates and premature infants with double enterostomies, CR reduces PN dependence and
164 and corrects plasma liver tests abnormalities [9]. CR improved nutritional status [4,6,7]. The
165 larger monocentric (Clinique Saint Yves, Rennes, France) prospective cohort assessing the
166 efficacy of CR in 212 patients with a temporary double enterostomy (86% of patients) or ECF
167 (14%) waiting for SIRC is under publication and confirms these findings, and suggests the
168 feasibility of home CR [4]. Double enterostomy or ECF were mainly due to peritonitis (44%)
169 and cancer (34%). CR corrects the IF by restoring intestinal absorption: reduction in intestinal
170 losses by 85%, strong improvement in nitrogen and fat digestive absorption coefficients, and
171 strong reduction in the proportion of patients with plasma citrulline $<20 \mu\text{mol/l}$ [4]. As a
172 result, PN and/or IV hydration could be stopped in 91% of patients, within a
173 median \pm interquartiles (IQ) of 2 ± 9 days after CR initiation [4], or in 100% of cases within
174 20 days in the little case series of 20 patients reported by Coetzee et al [5]). In addition,

175 nutritional status improved. With CR, the number of patients who had one or several plasma
176 liver tests abnormalities decreased from 87 to 51% ($P<0.001$) [4].

177

178 **Complications and side effects of CR**

179 The management of CR-related complications and side effects requires dedicated healthcare
180 staff education. In our case series of 232 patients [4], eight patients (3%) were excluded
181 because of CR early complications, including one lethal: anal incontinence, $n=2$; ischaemic
182 colitis, $n=1$; newly developed fistulas, $n=3$; cancerous colic stenosis, $n=1$; letal mesenterical
183 infarction: $n=1$. Wu et al reported diarrhoea, vomiting, nausea, abdominal pain, and
184 abdominal distension that could affect until 14% of patients, but were all relieved later during
185 CR course [6]. In other case series [4,5], the prevalence of CR-related technical problems (e.g.
186 tube disinsertions or obstructions, chyme leaks, stoma care problems,...) and gastrointestinal
187 side effects was not collected. In our experience, the most frequent side effects of CR are: the
188 difficulty to accept the food constraints of ingesting smooth puree meals that could impact on
189 mood, quality of life, and nutritional status; obstruction or displacement of the CR tube;
190 spasmodic pains during the resumption of normal downstream intestine function; severe
191 constipation, especially if antidiarrheal drugs are used (this is the reason why loperamide has
192 to be stopped before CR initiation).

193 One considerable advantage of CR is, by using the whole remnant small bowel, to prefigure
194 the post-SRIC intestinal function. Indeed some symptoms occurring during CR, such as pain,
195 fecal incontinence, diarrhoea, would have occurred after SRIC. Thus CR should allow
196 anticipating and even preventing situations that would have occurred after the SRIC with
197 potentially more serious consequences and sometimes would have required a second surgery.
198 For example, in case of fecal incontinence, anal biofeedback could be prescribed before the
199 SRIC.

200

201 **Feasibility of home CR**

202 In 59 (28%) patients of our French case series [4], CR was feasible at home in selected
203 patients after specific training and education, where they must have acquired total autonomy
204 for CR and basic stoma care. The median duration of home CR was 36 ± 40 days,
205 accumulating 7.4 patients-years. For home CR, we have elaborated a dedicated clinical
206 pathway including a thesaurus of solutions facing well defined technical problems. As a
207 result, no patient had to stop CR, only a few were readmitted for minor problems, and none
208 had to go back to PN. Unfortunately, at this time, home CR is not yet recognized by health
209 insurances as a nutrition support technique. More studies, noteworthy multicentric, are needed
210 to demonstrate safety and clinical benefits of home CR.

211

212 **Medicoeconomics benefits of CR**

213 At this time, PN remains the gold standard therapy until the patients underwent the SRIC. PN
214 costs are much higher than those of EN and increase with complications [1]. The quick PN
215 weaning with CR could have avoided 26.6 patients-years with PN [4]. As a great part of the
216 costs of type 2 IF patients' therapies resulted from PN-related complications [11], CR could
217 be associated with substantial cost-savings. The prospective randomized controlled trial FRY,
218 supported by the French National Clinical Research Program, will determine the impact of
219 CR compared to PN on the incidence of complications, healthcare costs and quality of life in
220 IF patients with temporary high-output double enterostomy until a follow up of one month
221 post-SIRC. Thanks to an additional ESPEN Technology grant 2015, the FRY trial will allow
222 determining feasibility of home CR in a multicentric setting.

223

224 **Hypotheses upon the mechanisms of the clinical benefits of CR and enteroclysis**

225 In case of small bowel disruption, the absence of the ileal brake results in a non-inhibition of
226 gastric emptying, gastric hypersecretion and accelerated intestinal motility, contributing to

227 impaired absorption. Supposed mechanisms of CR-induced improvement of intestinal
228 function are the reabsorption of digestive secretions (gastric, pancreatic, and biliary succus)
229 and the restoration of the ileal brake. The latter was first suggested by Levy et al [12] who
230 showed that proximal stoma output was brake down by hydration solution enteroclysis into
231 the downstream small bowel (-20%) and mainly by CR (-33%). Plasma citrulline
232 normalization is the result of the increase in the functional enterocyte mass and of the better
233 extraction of intraluminal glutamine [7]. In case of terminal ileum resection, the enterohepatic
234 cycle of bile acids is disrupted leading to bile salts malabsorption. This results in an increase
235 in bile acid synthesis by the liver which, in turn, enhances hepatic lipogenesis and intrahepatic
236 cholestasis, resulting in plasma liver tests abnormalities. At physiological state, bile salts
237 activate the intracellular receptor FXR in the small intestine and liver epithelium [13]. FXR
238 activation is in part mediated by endocrine-acting fibroblast growth factor (FGF) 19, a bile
239 salt-induced enterokine. The release of the FGF19 subsequently inhibits bile salt synthesis
240 from cholesterol. In case of IF-induced enterohepatic cycle disruption, bile salts synthesis is
241 not inhibited, resulting in overproduction and liver accumulation that could have a direct
242 toxicity on hepatocytes. CR could act by restoring bile salts enterohepatic cycle and bile salts
243 signalling, decreasing liver inflammation and plasma liver tests. A study is ongoing to
244 demonstrate this hypothesis. Other mechanisms such as changes in intestinal microflora or
245 prevention of bacterial overgrowth deserve further investigation.

246

247 **Conclusion**

248 CR or enteroclysis are safe and easy-to-use nutrition support techniques. In case of IF
249 secondary to high output temporary enterostomy or ECF, CR is an efficient and reliable
250 technique of EN which corrects IF by restoring intestinal absorption. CR contributes to
251 improve nutritional status and to reduce plasma liver tests abnormalities, and is feasible at
252 home in well selected patients. By allowing the PN weaning within a short period, CR could

253 be associated with substantial cost-savings. The prospective randomized controlled trial FRY,
254 supported by the French National Clinical Research Program, will determine the impact of
255 CR compared to PN on the incidence of complications, healthcare costs and quality of life in
256 IF patients with temporary high-output double enterostomy. This review may contribute to
257 improve the awareness of intensivists, digestive surgeons and gastroenterologists involved in
258 IF management to spread the use of CR and enteroclysis.
259

260 Key points

- 261 • In case of intestinal failure secondary to high output temporary enterostomy or
262 enterocutaneous fistula, chyme reinfusion is an efficient and reliable technique of enteral
263 nutrition which corrects intestinal failure by restoring intestinal absorption, allowing
264 parenteral nutrition weaning in almost all patients.
- 265 • Chyme reinfusion contributes to improve nutritional status and to reduce plasma liver tests
266 abnormalities, and is feasible at home in well selected patients.
- 267 • Chyme reinfusion allows preparing efferent small bowel and colon to the surgical
268 reestablishment of intestinal continuity.
- 269 • In patients with exposed efferent small bowel, enteroclysis of hydration and/or enteral
270 nutrition solutions could allow improving hydration and nutritional status, as well as reducing
271 parenteral nutrition needs.
- 272 • Multicentre prospective randomized controlled trials are needed to determine the impact of
273 chyme reinfusion compared to parenteral nutrition on the incidence of complications,
274 healthcare costs and quality of life, as well as feasibility of home chyme reinfusion, in
275 intestinal failure patients with temporary high-output double enterostomy or enterocutaneous
276 fistula.

277

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280

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283

284 Conflicts of interest

285 RT declares no conflict of interest regarding this article. DP declares advisory activities
286 without any financial retribution with Labodial, Les Clayes Sous Bois, France.
287

288 **References**

289

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335 to parenteral nutrition, but that bile acids signaling through the FXR-FGF19 axis, should be
336 involved.

337 **Figure legends**

338

339 **Figure 1 – Example of a temporary double enterostomy.** The small bowel continuity is
340 disrupted with two small bowel segments exposed to the abdominal wall: the upstream
341 afferent segment, with impaired digestive and absorptive function, and a downstream efferent
342 segment, totally deprived of digestive secretions, bowel flow and succus entericus. The
343 feeding tube is inserted in the downstream small bowel, and is ready for enteroclysis or
344 chyme reinfusion.

345

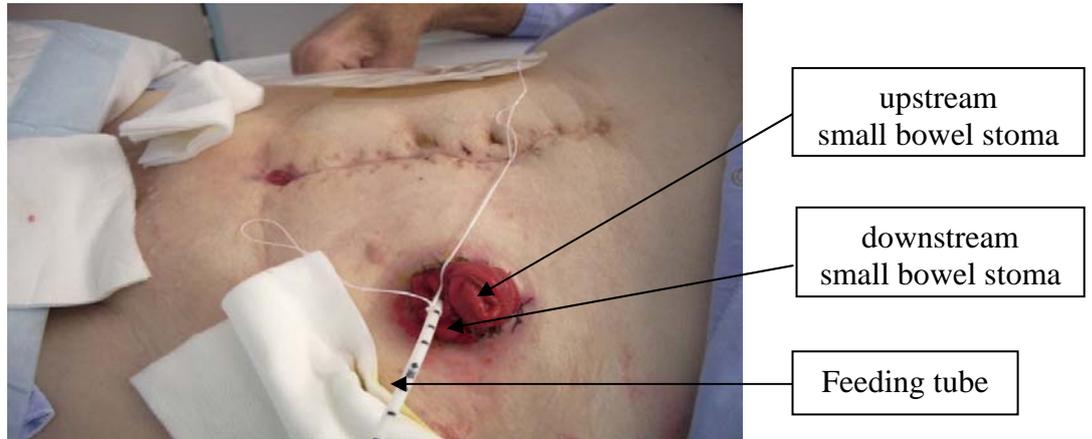
346 **Figure 2 – Chyme reinfusion technique with the automated pump Enteromate II® (A)**
347 **and the portable Enteromate® Mobile (B)** (Labodial, Clayes-sous-Bois, France). (A) The
348 left pump works permanently and aspirates the jejunal effluent from the upstream small bowel
349 afferent stoma toward a 30 ml disposable plastic container, which is hung on an electronic
350 steelyard. The upper stoma pouch is always empty. The weight of the container is
351 continuously and electronically monitored. When the minimal volume of approximately 10 ml
352 is exceeded, the second pump starts and the contents are infused into the diverted downstream
353 small bowel until the return to minimal volume. (B) Once the patient has been adequately
354 trained and is capable of correctly adjusting the rate of reinfusion, portable non-autoregulated
355 Enteromate Mobile® pump was used secondly to give autonomy to the patient during the
356 hospitalization and at home. This pump is autonomous thanks to batteries.

357

358

Figure 1

359



360

361

362

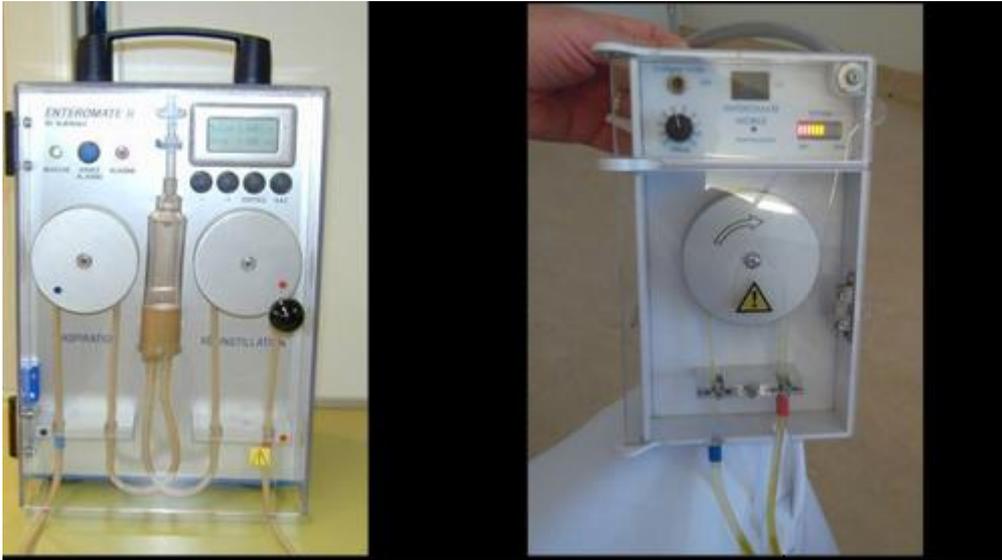
363

Figure 2

364

A

B



365

366

367

368

From upstream
small bowel

To downstream
small bowel

From upstream
small bowel

To downstream
small bowel