

1 Intestinal failure as a significant risk factor for renal impairment in 2 children

3 Running head: Renal function of children with intestinal failure

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19

20 **Authors' contribution**

21 EY, LM-S, MP and TJ designed the study. EY wrote the manuscript draft, EY, RG, LM-S and MP
22 collected the data. EY performed statistical analysis. EY, LM-S, RG, MP and TJ took part in the
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27 **Abstract**

28 *Objective:* While impaired renal function has been a frequent finding among adult patients with
29 intestinal failure (IF), the data on children is scarce. This study aimed to assess renal function
30 in pediatric-onset IF.

31 *Methods:* Medical records of 70 patients (38 boys) with pediatric onset IF due to either short
32 bowel syndrome (SBS, n=59) or primary motility disorder (n=11) and a history of parenteral
33 nutrition (PN) dependency for at least one month were evaluated. Renal function at the most
34 recent follow-up was studied using plasma creatinine, cystatin C and urea concentrations and
35 estimated glomerular filtration rate (eGFR).

36 *Results:* At a median age of 5.7 and after PN duration of 3.2 years, twenty (29%) patients had
37 decreased eGFR and higher cystatin C and urea concentrations. Patients with decreased renal
38 function had significantly longer duration of PN (3.2 years versus 0.9 years, p=0.030) and
39 shorter percentage of age-adjusted small bowel length remaining (22% versus 32%, p=0.041)
40 when compared to patients with preserved renal function. No other predisposing factors for
41 decreased eGFR were identified.

42 *Conclusions:* Patients with pediatric onset IF are at significant risk of impaired renal function,
43 which associated with the severity of SBS. Further studies using measured GFR are needed.

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45 **Key Words:** intestinal failure; short bowel syndrome; pediatric; parenteral nutrition; kidney

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54 **Background**

55 The European Society of Clinical Nutrition and Metabolism has defined intestinal failure (IF)
56 as the reduction of gut function below the minimum necessary for the absorption of
57 macronutrients, water and electrolytes, so that intravenous supplementation is required to
58 maintain health and growth [1]. In pediatric patients, necrotizing enterocolitis, intestinal atresia,
59 mid-gut volvulus, gastroschisis, Hirschsprung disease and intestinal pseudo-obstruction (CIPO)
60 causing either short bowel syndrome (SBS) or severe intestinal dysmotility are the most
61 common etiologies for IF [2,3].

62
63 Patients with IF are at persistent risk of hypovolemia and electrolyte imbalance due to impaired
64 absorption and increased intestinal losses, recurrent sepsis episodes and nephrotoxic
65 medications, which may have an adverse effect on kidney function. Impaired kidney function
66 and development of chronic renal failure have been reported in adult patients with long-term
67 parenteral nutrition for IF [4-7] whereas data on renal function in children with IF is very limited
68 [8,9]. Chronic renal failure is observed earlier and more frequently following intestinal
69 transplantation when compared to other solid organ transplantations [10]. The golden standard
70 for evaluating renal function is to measure the glomerular filtration rate (mGFR) using either
71 inulin or some other radio-labeled marker, such as ethylenediamine tetracetic acid labeled
72 chromium-51 (⁵¹Cr-EDTA). Due to the costs and complexities of measuring GFR, estimated
73 GFR, plasma creatinine and cystatin C are often used in clinical practice to assess renal
74 function. Renal function is considered to be impaired if GFR is < 90mL/min/1.73m² in adults
75 and children older than two years of age [11]. The aim of the present study was to assess the
76 renal function in children with IF during and after weaning off PN.

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81 **Materials and methods**

82 The study comprised patients with pediatric onset IF treated and followed up at the Children's
83 Hospital, Helsinki University Hospital, between the years 1990 and 2015. All patients with IF
84 due to either SBS or primary intestinal dysmotility disorders and with parenteral nutrition (PN)
85 for at least for one month and a follow-up period of at least one year were included. In total, 78
86 eligible patients were identified; eight of them were excluded from the study because of
87 incomplete laboratory values.

88

89 Patient's age, sex, primary disease, cause of IF, surgical procedures, number of blood culture
90 positive sepsis episodes, anatomy of the remaining bowel, duration of PN, and the amount of
91 current PN as well as weight and height at the most recent follow-up were collected from the
92 patient records. Sepsis episode details could be reliably extracted from the electronic hospital
93 discharge database from the year 1993 onwards. Six out of the 70 patients were born before
94 1993, and data on their early sepsis episodes may therefore not be complete.

95

96 Growth was assessed using the Finnish national growth charts. The height is given as z scores
97 and weight as age-adjusted ISO-BMI scores for patients ≥ 2 years. Height was corrected for
98 gestational age if needed. Age-adjusted weight-to-height percentiles (based on the national
99 data) are reported for those < 2 years [12]. Three patients with cartilage-hair hypoplasia and
100 one patient with Down syndrome-associated growth failure were excluded from the height
101 analysis. The percentage of the remaining age-adjusted small bowel and colon length was
102 calculated based on age-specific normal *in vivo* values [13]. Hirschsprung disease patients with
103 less than 50% of age-adjusted small bowel length remaining were categorized to the SBS group.

104

105 Renal function laboratory parameters (plasma creatinine, cystatin C and urea) measured at the
106 time of the most recent follow-up visit were collected from the medical records; the follow-up
107 time was considered to end at this point. Renal function was evaluated using either the estimated

108 glomerular filtration rate (eGFR) calculated by the CKID Schwartz equation [14], which uses
109 all creatinine, cystatin C and urea values in the formula or the CKD-EPI Creatinine-Cystatin
110 equation [15] for patients older than 18 years of age. In two cases lacking cystatin C value,
111 creatinine-based Bedside Schwartz formula was used [16]. In four cases with decreased renal
112 function, GFR had been evaluated more precisely using ⁵¹Cr-EDTA measurement. Renal
113 function was classified as normal when eGFR was ≥ 89 mL/min/1.73m² (≥ 62 mL/min/1.73m²
114 at the age of 12 to 19 months) [17]. In patients who underwent intestinal transplantation during
115 follow-up, renal function was evaluated before the surgery. Renal ultrasound had been
116 performed on all patients with decreased renal function. The possible presence of structural
117 abnormalities, nephrocalcinosis and/or increased echogenicity was recorded from the medical
118 records and ultrasound pictures.

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120 **Statistical analysis**

121 All statistical analyses were performed using the Statistical Package for the Social Sciences
122 (SPSS/Windows version 22.0, SPSS Inc., Chicago, IL, USA). Data are reported as medians
123 with their interquartile range. A Mann-Whitney U test was used to compare median values.
124 Fisher's exact test was used for comparison of categorical variables. Statistical significance was
125 defined as $P \leq 0.05$.

126

127 **Ethics**

128 The Ethical Committee of the Children's Hospital, University of Helsinki, approved the use of
129 patient's information and the study protocol.

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131

132 **Results**

133 The demographics and clinical characteristics of the patient population are summarized in
134 **Table 1**. The causes of IF included necrotizing enterocolitis (n=20), mid-gut volvulus (n=15),

135 small bowel atresia (n=14), gastroschisis (n=2), CIPO (n=8), and Hirschsprung's disease
 136 (n=11); eight of these were categorized to the SBS group. At the latest follow-up visit, 22 of
 137 the 70 (31%) patients were on PN and received a median 7 (6-7) weekly PN infusions. Five
 138 patients have undergone intestinal transplantation and three are currently on waiting list for
 139 transplantation.

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142 **Table 1. Patient characteristics of 70 patients with pediatric onset IF having either normal or**
 143 **decreased GFR at the end of the follow-up.**

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	All patients	Patients with decreased GFR*	Patients with normal GFR*	P-value
148 N	70	20	50	
149 Boys	38	10	28	0.792
150 Age/Follow-up time (yrs)	5.4 (3.3-12.3)	5.7 (3.0-12.1)	5.4 (3.6-14.2)	0.563
151 Height (z score)	-1.4 (-2.3 to -0.4)	-2.5 (-3.2 to -0.7)	-1.1 (-2.0 to -0.1)	0.027
152 Weight (ISO-BMI)	19.6 (17.3-22.0)	20 (18.9-22.4)	19.2 (16.4-21.9)	0.207
153 Weight (percentiles)	-9% (-11 to -0)	0	-9 % (-11 to -2)	0.667
154 SBS/Dysmotility disorder	59/11	19/1	40/10	0.159
155 Patients weaned off PN	48	12	36	0.397
156 Time after weaning off PN (yrs)	4.5 (2.2-9.7)	4.0 (1.7-7.1)	4.9 (2.3-10.7)	0.338
157 Duration of PN (months)	14.7 (6.3-40.0)	38.7 (11.5-99.2)	11.1 (5.2-32.0)	0.030
158 Amount of curr. PN (kcal/kg/day)	41.5 (30.7-60)	50.5 (35.3-74.7)	38.4 (30.0-45.0)	0.297
159 N of septicemia/patient	1.0 (0.0-2.0)	0.0 (0.0-3.5)	1.0 (0.0-2.0)	0.863
160 Remaining bowel				
161 Small bowel (cm)	50 (30-100)	36 (23-65)	50 (31-103)	0.364

162	Small bowel (%)	26 (17-53)	22 (16-32)	32 (21-75)	0.041
163	Colon (%)	77 (50-100)	72 (3-100)	82 (50-100)	0.462
164	Colon +/-	45/15	14/6	41/9	0.337
165	ICV preserved	34	7	26	0.290
166	Plasma creatinine $\mu\text{mol/L}$	33 (24-48)	43 (28-53)	30 (22-46)	0.062
167	Plasma cystatin C mg/L	0.85 (0.74-0.98)	0.99 (0.90-1.18)	0.76 (0.72-0.86)	<0.001
168	Plasma urea mmol/L	4.9 (3.9-6.6)	6.8 (4.8-7.2)	4.5 (3.7-5.2)	<0.01
169	eGFR mL/min/1.73m ²	100 (86-115)	71 (65-86)	107 (99-124)	<0.001

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171 Curr. = current, eGFR = estimated glomerular filtration rate, ICV = ileocecal valve, ISO-BMI =
172 age-adjusted BMI, N = number, SBS = short bowel syndrome, PN = parenteral nutrition, yrs =
173 years. *Renal function was classified as normal when eGFR was $\geq 89\text{mL}/\text{min}/1.72\text{m}^2$ (≥ 62
174 $\text{mL}/\text{min}/1.73\text{m}^2$ at the age of 12 to 19 months) [17].

175

176 Overall, 20 (29%) patients had decreased eGFR at a median age of 5.7 years after median PN
177 duration of 3.2 years (**Table 1**). Patients with decreased eGFR had also significantly higher
178 cystatin C and urea values. The increase in creatinine levels failed to reach statistical
179 significance. Among patients with decreased renal function, eGFR was 60-89 mL/min/1.73m²
180 in 16 (80%) patients and below 60mL/min/1.73m² in four (20%) patients. **There was no**
181 **difference between patients treated in 1990–2000 to those treated in 2000–2015, the mean GFR**
182 **being 108 versus 97 mL/min/1.73m² (p=0.395).**

183

184 The duration of PN was significantly longer among patients with decreased eGFR when
185 compared to patients with normal renal function (**Table 1**). The duration of PN remained
186 significantly longer among patients with decreased eGFR also after patients with CIPO or
187 Hirschprung disease with more than 50% of age-adjusted small bowel length remaining were
188 excluded from the analysis (p=0.020). The percentage of age-adjusted length of the remaining

189 small bowel was also significantly lower in patients with decreased renal function than in
190 patients with normal GFR (**Table 1**). Patients with decreased renal function were also shorter
191 than patients with normal renal function (**Table 1**). There was no association between the cause
192 of IF, current PN delivery, the follow-up time after weaning off PN, the number of blood
193 culture-positive sepsis episodes, weight, the absolute length of remaining small bowel,
194 remaining colon or the presence of ileocecal valve and decreased eGFR (**Table 1**). None of the
195 patients with decreased renal function had a history of any renal disease or anomaly, renal
196 stones, or had nephrocalcinosis on their last ultrasound.

197

198 Of the eight patients who had received (n=5) or were listed (n=3) for intestinal transplantation
199 after a median of 90 (7–170) PN months, five showed decreased GFR in the evaluations
200 performed at listing. Of the five patients with decreased GFR, four had Hirschsprung disease
201 and one had NEC with 16%, 21%, 25%, 25% and 23% of remaining small intestine,
202 respectively, and the median duration of PN was 99 months (80-153). Among the five patients
203 with decreased renal function, median GFR was 66 (49–67) mL/min/1.73m² measured using
204 ⁵¹Cr-EDTA measurement in four of these cases.

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206

207 **Discussion**

208 In this study, we found that renal function was impaired in 20 out of a total of 70 (29%) patients
209 with pediatric onset IF after a median follow-up time of 5.3 years. Prolonged duration of PN
210 and a short proportion of remaining small bowel were found to be associated with the decreased
211 kidney function, suggesting that the severity of IF plays an important role. To our best
212 knowledge, there are only two previous studies available on renal function in children with IF
213 and/or with prolonged PN. According to the report by Moukarzel et al. including 13 children
214 on long-term PN, all patients had impaired renal function (GFR 65.5±11.9 mL/min/1.73m²) at
215 a mean age of 9.0 ± 4.9 years [9]. The authors also found that in children with long-term PN,

216 the duration of PN was inversely correlated with GFR, similarly to the study carried out by
217 Buchman et al. [5,9]. Recently, Kosar et al. published a study where they evaluated kidneys of
218 54 children with IF using serum creatinine and urea and urine oxalate, creatinine and calcium
219 as biochemical parameters and renal ultrasonography. According to their report, a large
220 proportion of the patients had increased echogenicity/nephrocalcinosis on ultrasonography
221 analysis. Increased echogenicity/nephrocalcinosis was associated with prolonged PN exposure
222 [8]. The authors did not report decreased renal function in any of the patients, but they did not
223 measure GFR or calculate eGFR. Studies among adult IF patients have provided evidence for
224 decreased renal function and a relatively high frequency of chronic renal failure [4-7]. Buchman
225 et al. found a progressive impairment of renal function during prolonged PN. The rate of decline
226 in creatinine clearance was $3.5 \pm 6.3\%$ per year [5]. In another study, renal function was studied
227 in 33 patients on long-term PN and in 22 patients after intestinal transplantation. Chronic renal
228 failure was found in 21% of the PN-dependent patients and in 54% of the transplanted patients
229 [7]. Significant deterioration of kidney function also occurs following intestinal transplantation
230 in children [10]. These findings are reinforced by the present study showing impaired renal
231 function in a significant proportion of children with IF even after weaning off PN and in 5 out
232 of 8 patients at listing for intestinal transplantation.

233

234 The pathophysiology of chronic renal failure in IF patients remains unclear.[4] It is most likely
235 of multifactorial origin. Possible dehydration episodes, nephrolithiasis, repeated septicemias
236 and exposure to nephrotoxic antimicrobial medication may all gradually deteriorate kidney
237 function. The deterioration could be partly due to more novel mechanisms such as chronic low-
238 grade renal inflammation induced by bacterial products, which translocate through leaky
239 intestinal epithelium in SBS. In a study carried out by Lauverjat et al., 21 out of 40 (53%) adults
240 with IF had a significant reduction in renal function, with a hypovolemic component in over
241 70% of the cases [6]. In addition to dehydration, the presence of urologic or nephrologic
242 diseases was also found to be a risk factor for chronic renal failure [6]. There is also some

243 evidence suggesting that episodes of bacteremia and fungemia during PN are associated with a
244 decline in GFR [5]. In this study, the number of blood culture-positive episodes of bacteremia
245 or fungemia was not found to be associated with decreased renal function. The risk of calcium
246 oxalate stones and/or nephrocalcinosis has also been found to be increased in patients with SBS
247 and retained colon, which may lead to impairment of renal function [18]. The role of PN in the
248 genesis of renal stones has been attributed to the acidity of solution and to the presence of
249 vitamin C in PN, which leads to formation of urine oxalate formation [19]. Low calcium intake,
250 vitamin D and hyperparathyreosis and the presence of lipid in the PN preparations can also have
251 an impact on oxalate levels [20]. In this study, none of our patients with decreased renal
252 function had nephrocalcinosis on ultrasonography or a history of kidney stones. Here, decreased
253 renal function was equally prevalent during PN-dependency and after weaning off PN,
254 highlighting the importance of close and continuing surveillance of kidney function in children
255 with IF also after weaning off PN. The role of the amount of protein in the PN has also been
256 studied in one earlier study, but no association between renal function and protein load was
257 found [6].

258
259 In this study, patients with decreased renal function were shorter than patients with normal
260 eGFR, suggesting that the growth of these patients has also been impacted by either the severity
261 of IF or renal impairment. However, most of the patients with decreased renal function were
262 not uremic, indicating a non-renal etiology in most cases.

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264 Our patient material is one of the largest describing renal function in patients with IF. The study
265 has, however, some limitations/weaknesses. As in the earlier study by Pironi et al. [7], we
266 mainly used eGFR to evaluate renal function because measured GFR was not available from
267 majority of the patients. In the recent study by Kosar et al. [8], creatinine alone was used to
268 measure the glomerular function. In patients with IF, growth and muscle mass may be
269 decreased, rendering creatinine alone an unreliable parameter of renal function, as was also

270 shown in this study. Here, we measured plasma cystatin C and urea concentrations almost
271 exclusively and used the CKiD formula, which has been shown to correlate better with mGFR
272 than formulas based only on creatinine or cystatin C concentration [14,21,22]. In the future,
273 further studies measuring actual GFR in these patients are needed. Another caveat is that
274 accurate information about the use of nephrotoxic medication was not available and we were
275 thus unable to analyze possible associations between medication and renal function. Our
276 hospital is a tertiary hospital and many of the study patients were managed at their local hospital
277 between the follow-up visits. The possible impact of nephrotoxic medication has been evaluated
278 in three earlier studies, suggesting that the medication does not have major impact on renal
279 function [5,8,9].

280

281 **Conclusions**

282 In conclusion, patients with pediatric onset IF are at significant risk of impaired renal function,
283 which, associated with the severity of SBS, may promote the development of chronic renal
284 failure after intestinal transplantation. Therefore, evaluation of renal function of these patients
285 is warranted.

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