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## Management of the short bowel syndrome after extensive small bowel resection

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Short bowel syndrome (SBS) is a global malabsorption syndrome that results from extensive intestinal resections. It used to be a typical complication of repetitive bowel resections in patients with Crohn's disease. However, due to improved medical and surgical therapies for these patients it currently occurs more frequently as a consequence of vascular disorders in adults (intestinal infarction) and congenital aberrations in children, respectively. Adequate therapy depends on the degree of (small) bowel losses and on resulting functional disturbances. Moreover, it must be adjusted to the postoperative adaptation process, which consists of three phases: The immediate acute phase lasts less than 4 weeks and serves to stabilise the patient. The subsequent year should be used to induce maximal adaptation by gradually increasing nutrient exposure. When maximal stimulation of nutrient absorption has been achieved, permanent maintenance nutrition treatment should be defined individually, dependent on extent and quality of nutritive deficits. In patients with Crohn's disease, optimal treatment of the underlying disease is of pivotal importance in order to avoid a further reduction of absorptive capacity or other complications. Current investigations aim at improving the adaptation process by administration of specific diets and growth hormones. With these, it appears possible to treat even some patients with very short bowel, i.e. less than 50 cm of small intestine left, with oral nutrition, only. Still, a considerable proportion of patients will need long-term parenteral nutrition. If young patients experience intolerable complications of parenteral nutrition, intestinal transplantation may be considered as a high risk therapy of last choice.

**Key words:** short bowel syndrome; malabsorption; intestinal resections; Crohn's disease; acute phase; intestinal adaptation; maintenance treatment; oral/enteral/parenteral nutrition; vitamin supplementation; growth hormones; glutamine; drug therapy; intestinal transplantation.

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The short bowel syndrome (SBS) is a global malabsorption syndrome due to insufficient absorptive capacity and/or disturbed gastrointestinal regulation resulting from extensive small bowel resections. SBS may occur after resection of more than 50% and is obligatory after resection of more than 70% of the small intestine or if less than 100 cm of small bowel are left. It is particularly severe after resection of the ileocecal region or if the colon has been removed additionally. Apart from global malnutrition, clinical symptoms may be caused by specific deficiencies depending on the site of intestinal loss.

In the past, repetitive intestinal resections in patients with Crohn's disease were the main cause of SBS. However, because of the improvements of conservative and surgical therapy of Crohn's disease, SBS in adult patients now occurs more frequently as a result of vascular disorders (embolism/thrombosis of the superior mesenteric artery/thrombosis of the mesenteric veins) or intestinal strangulation (volvulus, incarceration). Rarely, traumas necessitate extensive bowel resections. In children congenital aberrations (e.g. intestinal atresia, aganglionosis, malrotation) or necrotising enterocolitis are the predominant causes of SBS.

There are no exact current data regarding the incidence and prevalence of SBS. However, data derived from patients receiving home parenteral nutrition (which in about one-third of the cases is necessary because of SBS) indicate an incidence of severe SBS of 1–2 cases per 100,000 inhabitants per year.<sup>1</sup>

Progresses in modern surgery as well as in intensive care have crucially improved the prognosis of patients with SBS. The adequate therapy depends on the degree of (small) bowel losses and of resulting functional disturbances and is adjusted to the postoperative adaptation process, which comprises three phases:

*A. Acute phase:*

- starts directly after resection
- generally lasts less than 4 weeks
- serves for the patient's stabilisation.

*B. Adaptation phase*

- lasts 1–2 years
- maximal stimulation of intestinal adaptation is achieved by gradually increasing intestinal nutrient exposure.

*C. Maintenance phase*

- follows adaptation phase
- permanent dietetic treatment must be individualised
- effective therapy of acute exacerbations and optimal maintenance therapy of Crohn's disease are of pivotal importance.

Not surprisingly, SBS is associated with low quality of life.<sup>2</sup> Longtime therapy, which should aim at the patient's social reintegration, is a demanding challenge to the treating physician. This is due to severe and interacting metabolic changes after extensive small bowel resection which may be even more severe in patients with preexisting inflammatory bowel disease. An additional impairment of

the absorptive capacity by progression of the underlying illness must be avoided, if possible.

- ◆ The short bowel syndrome (SBS) is a malabsorption syndrome due to insufficient absorptive capacity and/or disturbed gastrointestinal regulation resulting from extensive bowel resections.
- ◆ The incidence of severe SBS is estimated to be 1–2 per 100,000 inhabitants.

## PATHOPHYSIOLOGICAL BASIS

### Quantitative loss of absorptive capacity

The small bowel owns a large functional reserve capacity. Thus, resection of up to 50% of the small bowel is usually tolerated without any symptoms, and in most patients resection of up to 50–70% leads to transient malabsorption, only. However, a residual length of the small bowel of less than 200 cm may result in SBS, and if less than 70–100 cm of small bowel are left (resection of more than 70–80%) almost all patients develop SBS. Moreover, almost all patients with less than 60 cm of small bowel need long-term parenteral nutrition. However, not only the length of the remaining small bowel decides about the severity of symptoms but also the absence or presence of the colon. In SBS patients, the colon adopts important digestive functions (absorption of short-chain fatty acids as an energy source) and increases absorption of water and electrolytes so that more extensive small bowel losses can be tolerated.

- ◆ SBS is obligatory after resection of more than 70% of the small intestine or if less than 100 cm of small bowel are left.
- ◆ Additional resections of the ileocecal region or the colon increase severity.

### Qualitative loss of absorptive capacity

Moreover, not only overall extension of bowel resections but also the resection of specific intestinal sites influences the development of SBS. Losses of the duodenum or the terminal ileum, in particular the ileocecal valve, impair absorption much more than loss of other parts of the small bowel. This is due to the fact that both, the duodenum and the ileocecal region possess specific absorptive functions and play a crucial role in the regulation and integration of postprandial gastrointestinal motility and secretion. These functions may not or only partly be replaced by other parts of the small bowel.

Diarrhoea and steatorrhoea, the cardinal symptoms of SBS, are caused by low absorptive capacities for water, electrolytes and nutrients. In patients with 60–100 cm of small bowel left and preserved colon, about 70% of applied energy is reabsorbed, but absorption of individual food components may vary.<sup>3,4</sup> While proteins are absorbed by 60–70%, malabsorption of fat and carbohydrates may reach 50% of ingested nutrients. Carbohydrate malabsorption is of limited importance in patients with preserved colon because up to 80% of carbohydrates not absorbed by the small bowel can be absorbed after bacterial metabolism to short chain fatty acids and thus contribute to energy supply.<sup>5</sup> By contrast, fat malabsorption not only leads to steatorrhoea and malnutrition but is also associated with deficiencies of the fat soluble vitamins A, D, E and K.

Vitamins B1, B2, B6 and C are absorbed by the entire small bowel, therefore deficiencies of these vitamins are relatively rare. Lack of trace elements, in particular zinc and selenium, occurs in patients with SBS and results in epithelial and mesenchymal dysfunction as well as immunodeficiency.<sup>6</sup>

About 60% of SBS patients show hyperoxaluria with an increased risk of calcium-oxalate kidney stones as a result of increased oxalate absorption. This is a consequence of decreased intraluminal availability of calcium caused by binding of calcium to malabsorbed fatty acids. In healthy subjects calcium binds to oxalate to form unabsorbable calcium oxalate. In SBS patients, lack of free intraluminal calcium allows increased absorption of unbound oxalate.

Calcium, magnesium and iron as well as folic acid are predominantly absorbed by the duodenum and deficiencies are a typical consequence of expanded proximal small bowel resections. Malabsorption of calcium may be particularly severe because absorption is further hampered by binding of calcium to malabsorbed fatty acids and by vitamin D deficiency. In contrast, the specific uptake mechanisms allowing absorption of vitamin B12 and of bile acids are limited to the terminal ileum. The loss of the ileum leads to a vitamin B12 deficiency and to spill-over of unabsorbed bile acids into the colon, which causes choleraic diarrhoea. After resections of more than 60–100 cm of the ileum the loss of bile acids usually exceeds synthesis and the bile acid pool decreases. This increases the risk of cholesterol gall stones and causes or deteriorates steatorrhoea. On the other hand, increased colonic bile salt levels may solubilise unconjugated bilirubin, prevent calcium complexing, and promote its absorption and enterohepatic cycling, thus explaining the 3–10 fold increase in bilirubin levels observed in the bile of patients with ileal Crohn's disease.<sup>7,8</sup> Putatively, increased bilirubin levels in the bile following extensive distal small bowel resections may lead to the formation of pigment gallstones. In patients with Crohn's disease affecting the terminal ileum additional functional losses due to chronic inflammation may further impair vitamin B12 and bile acid absorption even if small bowel resection is limited.

In addition, the duodenum plays an important role in the stimulation of digestive responses, in particular of pancreatic enzyme output. Thus, the loss of the duodenum may lead to maldigestion of nutrients which further impairs absorption.

In healthy humans, exposure of the terminal ileum to nutrients induces inhibition of digestive secretory and motor functions (the so-called ileal brake).<sup>9–11</sup> The lack of the 'ileal brake' following ileal resections causes gastric hypersecretion and accelerated small bowel transit. Both mechanisms may substantially deteriorate diarrhoea in patients with SBS.

- ◆ Losses of the duodenum or the terminal ileum impair absorption much more than loss of other parts of the small bowel because specific absorptive and regulatory functions of these intestinal sites cannot be replaced by other parts of the small bowel.
- ◆ Absorption of major food components varies in SBS. Fat malabsorption is usually particularly severe, not compensated by colonic mechanisms and associated with deficiencies of the fat soluble vitamins A, D, E and K.
- ◆ Deficiencies of the water soluble vitamins B1, B2, B6 and C are relatively rare.
- ◆ By contrast, hyperoxaluria with an increased risk of nephrolithiasis is observed in 60% of patients.
- ◆ Calcium, magnesium and iron as well as folic acid deficiencies are a typical consequence of expanded proximal small bowel resections.
- ◆ The loss of the ileum leads to vitamin B12 deficiency and to spill-over of unabsorbed bile acids into the colon, which causes choleraic diarrhoea.

In addition, such patients have an increased risk of gallstone formation (cholesterol and pigment stones).

- ◆ In patients with Crohn's disease functional losses due to chronic inflammation may further impair absorptive functions even if small bowel resection is limited.

### Adaptation

Adaptation of the remaining intestine is mainly stimulated by exposure of the residual mucosa to macronutrients and occurs on several levels.<sup>12,13</sup> In particular, the remaining bowel increases in length and diameter and there is hyperplasia of small intestinal mucosa with increased number and size of crypts and villi. In addition, individual cells can increase certain absorptive functions (e.g. for sodium and calcium), though not all.<sup>14,15</sup> The overall result of these adaptive mechanisms is an increased mucosal surface, and an increased absorptive capacity per surface. In addition, intestinal motility is slowed which increases contact time of nutrients with the mucosa and thereby improves absorption. Important neurohormonal mediators which are released by the terminal ileum and which at least partly also have trophic effects are glucagon-like peptide 1 and 2 (GLP-1 and GLP-2), peptide YY (PYY) and neurotensin.<sup>16–22</sup> However, this important mechanism is only operative if the ileocecal region is preserved, which at least partially explains why these patients fare so much better. In combination, adaptive responses increase absorptive capacity by several hundred percent and are the basis of long-term management. They develop over 1–2 years following onset of SBS or even beyond, as is suggested by a longitudinal study on calcium absorption.<sup>23</sup>

Animal studies and preliminary uncontrolled studies in SBS patients suggested that growth hormones might accelerate and improve the adaptation process.<sup>24–28</sup> However, controlled clinical trials did not confirm this fully.<sup>29–31</sup> Moreover, in patients with active Crohn's disease a disturbed or delayed adaptation process has to be expected. This is also true for patients with radiation enteritis, carcinoma or chronic intestinal pseudo-obstruction.

- ◆ Adaptation of the remaining intestine requires exposure to macronutrients. Adaptive responses develop over 1–2 years following intestinal resection and increase absorptive capacity by several hundred percent as a result of increased mucosal surface, increased absorptive capacity per surface and slowed intestinal motility.
- ◆ Important neurohormonal mediators involved are glucagon-like peptide 1 and 2 (GLP-1 and GLP-2), peptide YY (PYY) and neurotensin.

### THERAPY

In concert with the adaptation process, the treatment of the SBS involves three phases. The immediate acute phase lasts less than 4 weeks and serves to stabilise the patient. The subsequent year should be used to induce maximal adaptation by gradually increasing nutrient exposure. When maximal stimulation of nutrient absorption has been achieved, permanent maintenance nutrition treatment should be defined

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