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Diagnostic criteria and treatment of patients with short bowel syndrome – consensus statements of the National Society for Clinical Nutrition of Serbia (NUPENS)

Dijagnostički kriterijumi i lečenje bolesnika obolelih od sindroma kratkog creva – konsenzus izjave Nacionalnog Udruženja za kliničku ishranu Srbije (NUPENS)

Mihailo Bezmarević*[†], Ivan Palibrk[‡§], Mirjana Stojšić[‖¶], Natalija Vuković, Marija Djukanović[‡§], Danijela Jovanović[††‡‡], Igor Krdžić[§§], Dušica Simić[‡‖‖], Ivan Pantić*, Marina Panišić Šekeljić*, [¶¶]NUPENS Short Bowel Syndrome Multidisciplinary Expert Group**

***Military Medical Academy, Clinic for General Surgery, Department of Hepatobiliary and Pancreatic Surgery, Belgrade, Serbia; [†]University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; [‡]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; [§]University Clinical Center of Serbia, Hospital for Digestive Surgery, Department of Anaesthesiology and Intensive Care, Belgrade, Serbia; [‖]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; [¶]Institute of Child and Youth Health Care of Vojvodina, Department of Gastroenterology, Hepatology, and Nutrition, Novi Sad, Serbia; **University Clinical Center Niš, Clinic for Anesthesiology, Reanimation, and Intensive Care, Niš, Serbia; [††]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia; [‡‡]University Clinical Center Kragujevac, Center for Anesthesiology, Reanimatology, and Intensive Care, Department of Surgery, Kragujevac, Serbia; [§§]Euromedik Hospital, Department of General and Abdominal Surgery, Belgrade, Serbia; [‖‖]University Children's Hospital, Belgrade, Serbia**

[¶¶]A list of the NUPENS Short Bowel Syndrome Multidisciplinary Expert Group and their institutional affiliations is provided in the Appendix

Key words:
diagnosis; enteral nutrition; intestinal failure; parenteral nutrition; parenteral nutrition, home; quality of life; short bowel syndrome.

Ključne reči:
dijagnoza; ishrana, enteralna; insuficijencija, intestinalna; ishrana, parenteralna; ishrana, parenteralna, kućna; kvalitet života; crevo, kratko, sindrom.

Introduction

Intestinal insufficiency is defined as a decrease in the function of the gastrointestinal tract below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, to such an extent that intravenous (i.v.) supplementation (fluids and electrolites and nutrition therapy which includes macro- and micronutrients) is necessary to preserve life, health, and/or growth [1]. Chronic intestinal insufficiency or failure (CIF) occurs when intestinal insufficiency persists for months or years in metabolically stable patients who do not require hospital treatment. CIF is a consequence of severe gastrointestinal, benign systemic diseases, but it can also occur as a consequence of intra-abdominal malignant diseases [1, 2]. The basis of CIF therapy, which aims to preserve the health and life of patients, is home parenteral nutrition (HPN) [1, 3].

Correspondence to: Mihailo Bezmarević, Military Medical Academy, Clinic for General Surgery, Department of Hepatobiliary and Pancreatic Surgery, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: bezmarevicm@gmail.com; office@nupens.com

CIF, as an organ dysfunction/failure, is the rarest organ failure. The prevalence of HPN due to CIF and resulting from benign diseases in Europe is observed in 5–80 patients/million inhabitants [4, 5]. CIF resulting from benign diseases is included in the European list of rare (orphan) diseases [6] and is registered under ORPHA 294422. In the International Classification of Diseases (ICD) – 10th revision (ICD-10), CIF is listed under the diagnosis code K63.8. In 2021, the definition of CIF given by the European Society for Clinical Nutrition and Metabolism (ESPEN) was accepted by the World Health Organization (WHO) and included in the 11th revision of the ICD (ICD-11) [7]. Based on all this, it can be concluded that CIF is a clearly defined disease that requires timely and proper diagnosis, appropriate monitoring, and therapy. The WHO and ESPEN have determined and defined official recommendations and guidelines for the diagnosis and treatment of CIF [2–4, 7].

According to the functional classification of intestinal insufficiency, CIF represents the third type. CIF is a chronic condition that requires i.v. supplementation for months and years, and the course of the disease can be reversible or irreversible. The most common cause of CIF is short bowel syndrome (SBS) [2]. SBS occurs as a result of congenital diseases of the small intestine and/or extensive surgical resections of the intestine. It denotes a clinical condition of patients where the residual length of the small intestine is less than 200 cm in continuity, with or without the colon [8, 9]. The code for this diagnosis is also included in the ICD-11 as DA96.04 - SBS [10]. If CIF or SBS are timely diagnosed or even suspected, with proper therapy, i.v. supplementation, parenteral nutrition (PN), and appropriate monitoring, long-term survival of these patients cannot be questioned. Nonetheless, in order for the patients to survive, long-term use of PN, either in hospital or at home, is necessary. In addition, it should be emphasized that the progress of the pharmaceutical industry in the 21st century has provided biological therapy for SBS patients. This biological therapy has made it possible to restore enteral autonomy and improve intestinal function, even many years after the loss of colon function. In this way, with biological therapy, most SBS patients become independent of i.v. supplementation for both water and electrolytes, as well as macronutrients, within a period of 6 to 8 months from the first administration [2, 11].

The number of CIF and SBS patients in the Republic of Serbia (RS) is unknown. Recognizing the need to identify and treat patients with CIF and SBS, the National Society for Clinical Nutrition of Serbia (NUPENS) formed two multidisciplinary expert teams for the implementation and realization of the HPN project at the ordinary meeting of the Board of Directors and the Supervisory Board on June 9, 2021, in Belgrade, Serbia. The expert teams cover both the pediatric and adult populations. After this initial step, NUPENS, in collaboration with the teams, conducted a cross-sectional study of patients with an indication for long-term PN. This study included seven healthcare institutions in the RS (six university centers and one general hospital). Data analysis led to the conclusion that in the RS, approximately 150 patients *per* year (pediatric and adult) need long-term PN. Half of these patients include those with SBS [12]. Based on unofficial data from team members employed in the above-mentioned health institutions, it was concluded that over 90% of these patients do not survive even one year after being diagnosed. Lethal outcomes in these patients occur due to malnutrition and dehydration caused by the inability to administer HPN. By the year 2024, there was a need to increase the number of physicians in both pediatric and adult expert teams. At the beginning of 2024, a group of clinicians and clinical scientists was appointed to perform a modified Delphi process, encompassing face-to-face meetings, e-mail communications, in-group discussions, literature reviews, and providing expert opinions on the treatment of patients with SBS in accordance with the capabilities of the health system in the RS. Overall, there were six major sections defined for the development of statements which were included: definitions and criteria for diagnosis and classification of SBS; the role of PN overall and HPN in patients with SBS; types and ways of oral/enteral nutrition in three types of SBS; conservative and drug therapy in SBS and therapy for improving and accelerating intestinal adaptation; criteria and indications for intestinal growth factor therapy in SBS patients and non-transplantation surgical procedures in the treatment of SBS. These six sections were chosen unanimously by all team members because they form the basis for understanding, diagnosing, and treating patients with SBS. After literature review, e-mail communications, and in-group discussions, the most important statements have been highlighted from the official guidelines and recommendations of ESPEN [2]. Also, some of these statements have been modified and adapted in a way that makes them easier to implement at the national level. A total of 32 statements were created, which were voted on for consensus at the joint conference of the Association of Patients with SBS and NUPENS on June 7, 2024, in Belgrade, Serbia. All statements received a consensus agreement of 100%. Thanks to the Ministry of Health of the RS, as well as the Republic Fund of Health Insurance of the RS, an initiative was launched to enable HPN during 2025.

The goal of NUPENS is to establish a registry of patients with CIF and SBS in our country, classify this entity as a rare disease, and educate healthcare professionals about SBS diagnostic procedures and recognition of this entity, its monitoring, and treatment. One of the results of the work of NUPENS, but also a step towards improving the treatment of patients with SBS, is the development of these consensus statements.

Definition, criteria for diagnosis, and classification of SBS

a) SBS is defined as a clinical condition associated with residual small bowel continuity of less than 200 cm.
b) The presence of clinical symptoms and signs of SBS despite residual small bowel length of more than 200 cm is defined as “functional SBS”.
c) Based on the anatomy of the residual intestinal continuity, SBS is classified as SBS with a terminal

small bowel ostomy (SBS type 1), SBS with jejuno-colic anastomosis (SBS type 2), and SBS with jejuno-ileal anastomosis with intact colon and the presence of ileocecal valve (SBS type 3).

Comment. In the adult population, the normal length of the small intestine measured from the duodenojejunal flexure (ligament of Treitz) is 275 to 850 cm. There is no precise analysis of the length of the small intestine in children, but it is known that a residual length of less than 25% of the anatomical length of the small intestine leads to SBS, in contrast to the adult population where a residual length of less than 67% of the anatomical length leads to the occurrence of this syndrome [8, 9, 11, 13–16]. A short intestine can be a consequence of extensive surgical resections or congenital anomalies of the small intestine. In adults, the most common causes of SBS are extensive resections related with Crohn's disease (about 20–40%), mesenteric ischemia (about 30%), complications related with surgical interventions (about 20%), radiation enteritis (about 7%), volvulus (about 4%), intestinal and perivisceral adhesions (about 3%), and other causes (about 10%). In the pediatric population, the causes of SBS are mesenteric ischemia (about 6%), volvulus (about 24%), intestinal malformations (about 28%), necrotizing enterocolitis (about 17%), and other causative factors (about 26%) [17–19]. Clinical characteristics of SBS include malabsorption, diarrhoea, fatty stools, malnutrition, and dehydration [2, 8, 9]. In some patients, SBS may be present even though the post-resection length of the small bowel exceeds 200 cm. This occurs due to inadequate function of the remaining bowel, such as accelerated motility or any form of mucositis/mucosal disease of the small bowel, resulting in a reduced absorptive capacity of the bowel below that expected for its remaining length [20]. This condition is described as "functional SBS" [8, 9, 19, 20]. The anatomical classification of SBS includes three types based on the anatomy of the remaining continuity of the gastrointestinal tract, as follows: SBS type 1 – terminal jejunostomy/ileostomy; SBS type 2 – jejuno-colic anastomosis where the remaining jejunum is continuous with part of the large bowel (most often with the transverse or left colon); SBS type 3 – jejuno-ileocolic anastomosis, where the ileocecal valve is preserved with an intact colon (Figure 1) [8, 9, 21]. The incidence of SBS types is approximately 60% for SBS type 1, 30.9% for type 2, and 9.1% for SBS type 3 [19]. The probability that with the applied therapy (special dietary regimen, conventional drug therapy, and non-transplant surgery) it will be possible to reduce or even completely wean off PN and develop full enteral autonomy is different in all three SBS types. In patients with SBS type 1, the rate of PN weaning is 20%, in SBS type 2, 40%, and in SBS type 3, 80% [22]. The likelihood of reversibility of bowel function in SBS is higher if there is a greater length of remaining bowel continuity. Thus, the reversibility of CIF in SBS is higher if the bowel length is greater than 100 cm in type 1, greater than 65 cm in type 2 (only if it is more than 50% of the colon length), and greater than 30 cm of small bowel in SBS type 3 (Figure 1) [13, 21, 22].

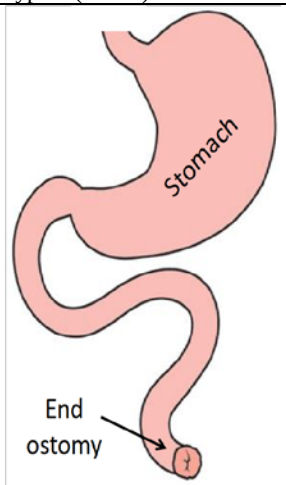
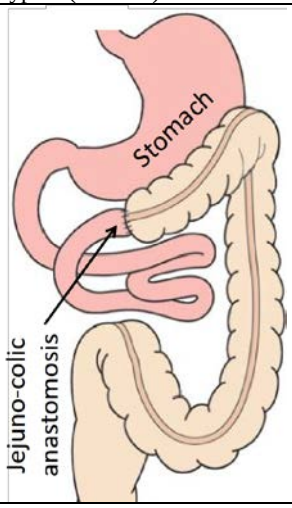
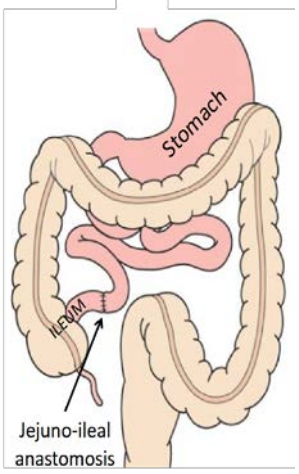
Classification	Type 1 (SBS-J)	Type 2 (SBS-JC)	Type 3 (SBS-JIC)
			
Description	Ileum, colon, and part of jejunum are resected; jejunostomy is created	Ileum, part of jejunum, and portion of colon (mainly right colon) are resected; remaining sections are joined (mainly jejunum and transversal or left colon)	Part of jejunum and ileum are resected, terminal ileum (at least 10 cm of terminal ileum) with ileocecal valve are present; remnant part of jejunum and terminal ileum are anastomosed
Probability of PN and intravenous supplementation dependence	Higher in patients with < 110–150 cm of jejunum remaining	Higher in patients with < 60–65 cm of jejunum remaining	Higher in patients with < 30–40 cm of small bowel remaining

Fig. 1 – Anatomical classification of SBS.
SBS – short bowel syndrome; SBS-J – SBS terminal jejunostomy/ileostomy; SBS-JC – SBS jejuno-colic anastomosis; SBS-JIC – SBS jejuno-ileocolic anastomosis; PN – parenteral nutrition.

The importance of PN and HPN in patients with SBS

a) PN is the first-line therapy that directly saves the life of a patient with SBS.
b) PN is the main therapy for patients with transient-reversible CIF, as well as for irreversible CIF, such as SBS.
c) In metabolically stable patients with SBS, PN can be administered at home because it improves the patient's quality of life (QoL), it is associated with a lower incidence of morbidity and mortality compared to PN in hospital settings, and it is more economical than PN in hospitals.
d) It is preferable to implement an HPN program by a trained and qualified team, as this would ensure the highest level of safety and effectiveness.

Comment. The primary outcome in patients with SBS depends exclusively on PN. Patients with SBS have a high probability of long-term survival if the primary therapy is PN, as it is the only way to provide appropriate amounts of macro- and micronutrients necessary for maintaining the functions of organs and organ systems, and for the growth and development of pediatric patients [3, 4, 18, 19]. In hospital settings and after diagnosing SBS (after surgical resection), the objective of the therapy is to repair electrolyte imbalance and metabolic state. Once the patients are metabolically stable without electrolyte imbalance and proper oral intake has been initiated (but still insufficient), they can be discharged for further home treatment with the use of PN at home. With proper training of patients and close relatives conducted by an expert team, the use of HPN ensures five-year survival in more than 80% of adult and more than 90% of pediatric SBS patients [23]. Properly implemented PN at home increases the QoL of SBS patients, as over 70% of patients achieve complete or almost complete social and occupational rehabilitation, as well as good quality family life [24]. On the other hand, even though the use of PN is also associated with complications, the most common of which is central venous access infection, patients within the HPN program have a significantly lower level of infectious complications compared to those with long-term use of PN in hospital settings [1, 3, 4, 24]. This primarily includes multidrug-resistant nosocomial infections with various bacterial strains in hospitalized patients with SBS. As the mortality rate in patients with long-term use of PN is mainly influenced by infectious complications [25], it may be said that HPN patients might have lower mortality and morbidity rates compared to those receiving PN in hospital settings. The occurrence of multidrug-resistant nosocomial infections and the costs of treating such complications, not counting the costs of hospital days, overall make HPN more economical compared to PN in hospital settings [1, 3, 24]. In order to maximally reduce possible complications, the engagement of a multidisciplinary or trained and qualified expert/expert team for the HPN program is of the utmost importance [2]. The total costs of the HPN program, when compared to the administration of PN in hospital settings, are significantly lower [2, 3]. In the RS, the HPN program still does not exist, but it would be substantially more economical compared to the administration of PN in hospital settings. Namely, if a patient receives PN three times a week, the costs of administering PN in hospital settings amount to approximately 51,120.00 RSD (440.00 EUR), in the case of commercial PN preparations. In the case of PN preparations made by the hospital itself (tailor-made), the cost of administration on a weekly basis, if the patient receives it three times a week, amounts to as much as 87,480.00 RSD (750.00 EUR). These amounts include: one day spent at the hospital ward (not semi-intensive and intensive care), working hours of a specialist, working hours of a medical technician, the costs of laboratory analyses, consumables and services for blood collection, consumables for additional therapy and the additional therapy itself, therapy and PN ordering services, hospital food and the PN preparations themselves. If, on the other hand, a patient receives PN three times a week at home, the cost of this therapy regimen *per* week is approximately 28,560.00 RSD (244.00 EUR), which is about 40% less than the cost of administering the therapy in a hospital setting. These calculations were made in Belgrade, Serbia, during the spring of 2022. Based on data on the safety and efficacy of HPN, it represents the primary form of therapy for CIF and SBS patients. In contrast, intestinal transplantation is a therapeutic approach for patients who are at risk of developing severe, fatal complications associated with PN in general or due to underlying gastrointestinal disease [23, 26].

Types of appropriate oral/enteral nutrition and criteria for oral intake in patients with SBS

a) Patients with SBS require dietary counseling by an experienced dietitian/nutritionist who is trained by or belongs to an expert team.
b) The dietary regimen should be individually tailored to each patient with SBS.
c) All patients with SBS should have their oral fluid intake monitored.
d) Oral fluid intake should be separated from meals in all patients with SBS.
e) The diet of all patients with SBS is based on the intake of solid foods, because liquid and mushy foods accelerate transit through the remaining part of the small intestine.
f) The recommendation for the intake of different macronutrients and their ratio in the meal (carbohydrates, fats, and proteins) differs in some types of SBS.
g) Soluble fiber supplementation (e.g., pectin) is not recommended in patients with SBS, as it does not improve intestinal absorption.
h) The use of enteral nutrition preparations in the form of oral nutritional supplements is indicated in patients with an expected increase in body weight, in order to reduce the volume and number of PN preparations, and should be prescribed and determined by an expert team.

i) In patients with mild dehydration with sodium loss, oral replacement with isotonic rehydration solutions rich in sodium is indicated.
j) In patients with a highly productive terminal jejunostomy, it is necessary to limit the oral intake of hypotonic fluids (water, tea, coffee, or alcohol), as well as hypertonic (fruit juices, carbonated drinks), in order to reduce the "output" at the stoma.
k) Patients who are severely dehydrated or sodium-depleted may be treated with isotonic oral rehydration solutions that are rich in sodium; however, i.v. fluids are the primary form of replacement.

Comment. Patients with SBS must compensate for malabsorption with hyperphagia, as this is the only way, besides PN, that can help with intestinal adaptation and preservation of the metabolic state [27]. The use of oral nutritional supplements, primarily isotonic, can help increase overall energy intake during the day. All patients with SBS should be encouraged to take a larger number of meals with the addition of certain oral nutritional supplements, which are preferably administered between meals. Understanding the physiology and pathophysiology of SBS is an indispensable factor in recommendations regarding the dietary regimen. In this regard, there are different types of counseling and diets, depending on the patient and the type of SBS. In those with a preserved colon, unabsorbed long-chain fatty acids accelerate intestinal transit and reduce water and electrolyte absorption. Fatty acids bind to calcium and magnesium and increase oxalate absorption with the consequent development of nephrolithiasis [2]. On the other hand, mono- and disaccharides draw fluid from the interstitium into the intestinal lumen by an osmotic gradient, which leads not only to accelerated transit but also to greater fluid loss, which is the case especially in SBS type 1. Due to the multifactorial effect of certain macronutrients and the pathophysiology of SBS itself, the optimal dietary regimen differs significantly in all three types of SBS [28]. In general, *per*-oral fluid intake should be limited, especially during the phases of intestinal adaptation. This primarily applies to SBS type 1 with high losses on the stoma. It is recommended that fluids be taken at least 60 min after the last meal [2, 29]. In SBS patients who are considered to benefit from enteral nutrition, either *via* tube feeding or oral nutritional supplements, standard formulas have a similar effect as polymeric formulas on nutrient absorption and water and electrolyte losses [30, 31]. Even though it has been proven that elemental (peptide) formula has better protein absorption in patients with SBS type 1 (90–150 cm of jejunal residuum), overall energy absorption cannot be significantly increased when compared to other types of formulas [32]. In all types of SBS, complex carbohydrate intake is recommended, as simple sugars increase intraluminal osmotic pressure, increase secretion, and accelerate transit, leading to greater losses [2]. It has been shown that maximal sodium absorption in humans occurs when an oral solution containing 120 mmol/L (2,160 mg) sodium chloride and 30 mmol/L (540 mg) glucose is administered [33]. Given that the large intestine has a significant capacity for water and electrolyte reabsorption, this type of oral rehydration is not particularly significant as it is indicated in patients with SBS type 1, and less commonly in those with type 2 [2]. Protein and energy requirements for CIF patients should be based on individual patient characteristics, specific needs, and the adequacy of the regimen should be regularly evaluated through clinical, anthropometric, and biochemical parameters. This refers not only to parenteral supplementation but also to oral/enteral intake. Generally, in stable SBS patients, the provision of 0.8–1.4 g of protein/kg/day is enough to meet daily requirements [1, 2], but this is mostly accomplished by PN. The diet of SBS patients with a preserved colon in continuity (types 2 and 3) can be high in complex carbohydrates, low in mono- and disaccharides, and low in fat [2]. Patients with a preserved colon, who are on the borderline of needing i.v. supplementation (PN and/or i.v. fluid replacement therapy), benefit from medium-chain triglycerides since they are easily hydrolyzed, do not require bile salts, and are easily absorbed across the intestinal mucosa and transported *via* portal vein to the liver [2, 34]. All SBS patients following a low-fat diet, or those in whom long-chain triglycerides have been replaced by medium-chain triglycerides, should be monitored for potential deficiencies in essential fatty acids and fat-soluble vitamins [1, 2]. In all three types of SBS, but especially in type 1, complex carbohydrates are the most important dietary carbohydrates. In SBS type 1, studies have shown that oral food can consist of any fat/carbohydrate ratio, provided that it has a low mono- and disaccharide content [1, 2, 34]. Enteral nutrition in combination with oral feeding can be prescribed in patients with CIF in whom the expected gain with enteral nutrition could allow weaning from HPN. Polymeric isotonic enteral diets may be the first choice [2]. The aim of continuous enteral nutrition is to provide better distribution and maximum exposure of the available intestinal surface area to nutrients while stimulating gastrointestinal secretions and endogenous hormonal secretions that are important for advancing intestinal adaptation [31, 32]. Compared to voluntary oral intake, it is more likely that enteral nutrition will increase intestinal absorption and accelerate adaptation in the immediate post-operative settings [2, 35]. On the other hand, an aggressive approach to enteral nutrition and enteral stimulation in type 1 SBS patients may aggravate gastric hypersecretion and intestinal fluid and electrolyte losses [36]. Regarding administration of oral fluids, as mentioned above, patients with type 1 SBS can use salt liberally and restrict the administration of oral fluids in relation to meals [2]. Those with borderline dehydration or sodium depletion can use an isotonic high-sodium oral rehydration solution to replace stoma sodium losses [1, 2]. In patients with high-output jejunostomy (SBS type 1), oral intake of low-sodium solutions, both hypotonic (e.g., water, tea, coffee, or alcohol) and hypertonic (e.g., fruit juices, carbonated beverages), should be limited in order to reduce the stoma output [2]. All SBS patients are at some risk of dehydration and electrolyte disturbances, especially those with reduced length of jejunum and jejunostomy. Many of these patients tend to secrete more sodium and fluid than they consume orally [29, 37]. Some of these patients even experience losses of water and

sodium when they take nothing by mouth (secretors) [37]. In addition, in these patients, oral intake of food and beverages increases the stomal losses of fluid and sodium. Some of these patients are also subject to magnesium deficiency. In these situations, they often describe an "insatiable thirst", and they are often tempted to compensate by increasing their oral beverage intake. However, since an increase in both hypotonic and hypertonic fluids may stimulate fluid secretion or increase the fluid and sodium influx into the lumen of the jejunum due to the leakiness of the epithelium, this would further aggravate stomal losses. Thus, a vicious cycle of chronic dehydration and excessive beverage intake is believed to be generated [2, 29, 33, 38, 39]. In order to halt this, the general advice has been that the patients should restrict excessive habitual beverages and instead drink oral rehydration solutions [1, 2]. The intestinal fluid and sodium absorption may be evaluated with measurements of 24-hr urine volume and urine sodium excretion. In addition to clinical evaluation, body weight, and standard blood biochemistry, urine sodium excretion may help assess the fluid balance of individual SBS patients and adjust oral fluid intakes [2].

The use of drug therapy in the treatment of patients with SBS, and therapies for improving and accelerating intestinal adaptation

a) Proton pump inhibitors and histamine receptor 2 antagonists are recommended in SBS cases because they reduce sodium excretion and stool loss (contents at the stoma), especially in the first six months after surgical intervention. This is very important if fecal loss is greater than 2 L *per* day.
b) Short-term use of octreotide may be of importance in patients with high-output jejunostomies, for better control of electrolyte imbalance. When using octreotide, proper monitoring of patients is necessary due to their side effects (negative impact on intestinal adaptation).
c) The use of loperamide is recommended in all patients with SBS, because it slows down transit and reduces fecal excretion of water and sodium. When compared to opiates (codeine phosphate, opium, etc.), loperamide is preferred. In SBS type 1, the administration and dosing of loperamide is not difficult, given the easy objectification of its effects.
d) SBS patients who have motility disorders, including those with segmental dilatation of the residual small intestine (e.g., appendix), as well as those with suspected excessive bacterial growth, may benefit from occasional antibiotic therapy, primarily with metronidazole.

Comment. All conditions occurring after small bowel resection are associated with gastric hypergastrinemia and hypersecretion [38]. The etiology of gastric gastrin hypersecretion lies in the loss of hormonal inhibitors in the ileum and colon. Gastric hypersecretion "washes out" the proximal parts of the small bowel, increasing intraluminal volume, decreasing absorption time, and contributing to greater losses. In addition, the associated hyperacidity accompanied by gastric hypersecretion leads to denaturation of pancreatic enzymes and disruption of intraluminal bile salt metabolism, which further reduces absorption [39]. On the other hand, undigested or partially digested nutrients increase intraluminal osmotic pressure and increase intestinal mucosal secretion, which leads to even greater losses at the stoma. Therefore, the administration of histamine receptor 2 antagonists and proton pump inhibitors is an indispensable therapy in patients with SBS [2]. The effects of octreotide and its analogues are reflected in the reduction of gastric, biliary, and pancreatic secretion, as well as the secretion of water and electrolytes (primarily sodium) in the jejunum and colon [40]. Furthermore, octreotide leads to an increase in the absorption of sodium and chlorine in the ileum with a decrease in intestinal motility (by inhibiting the synthesis of secretagogues) [41]. Although octreotide and its analogues can inhibit glucose absorption and reduce the absorption of macronutrients due to the inhibition of pancreatic enzyme secretion, it has been shown that it can temporarily help in the treatment of large losses at the jejunostomy, providing time for the correction of electrolyte and metabolic imbalance [2, 42]. The use of antidiarrheal drugs in SBS is widespread, and it aims at reducing water and electrolyte losses and minimizing symptoms resulting from diarrhoea. The use of these drugs can reduce the need for i.v. fluid and electrolyte replacement. In addition, indirectly, the reduction of the "output" at the jejunostomy prevents damage to the skin around the stoma and facilitates its care. Due to the central effects of some antidiarrheal drugs (codeine, diphenoxylate, opium), loperamide has a significant advantage in SBS. Loperamide inhibits the peristaltic activity of the small intestine, which slows intestinal transit. The result of this is an increase in absorption time not only of water and electrolytes, but also of macronutrients due to more appropriate intraluminal digestion [43]. The optimal dose of loperamide should be individually prescribed and ranges from 3–24 mg *per* day [2]. There is not enough data about excessive bacterial growth in the small bowel of patients with SBS. Patients with post-surgical small bowel dilatation, abdominal pain, and large jejunostomy losses may benefit from short-term metronidazole therapy. However, this therapy is not recommended in patients with preserved colon, i.e., those with SBS types 2 and 3 [2, 44, 45].

Criteria and indications for selection of patients with SBS for intestinal growth factor therapy

a) SBS patients who are absolutely dependent on PN (whether once or several times a week) for a period longer than 12–24 months after surgery should consider the introduction of intestinal growth factor therapy.
b) If intestinal adaptation has been achieved and the patient with SBS is still dependent on PN, the introduction of intestinal growth factor therapy should be considered.
c) Before the use of intestinal growth factors, it is necessary to conduct a thorough diagnosis of the gastrointes-

tinal tract and exclude the presence of malignant or premalignant disease.

d) Recent presence of malignant disease or the presence of malignant disease in patients with SBS is a contraindication for the use of intestinal growth factor therapy.
e) The indication for the use of intestinal growth factors must be determined by an expert team and experts in the field of CIF and SBS.
f) The first choice of intestinal growth factor therapy in SBS is the glucagon-like peptide-2 (GLP-2) analogue, the drug teduglutide, because it is the only one approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).
g) The use of teduglutide requires monitoring of the SBS patient by an expert and/or an expert team.
h) The effectiveness of teduglutide therapy is reflected in the reduction of the need for PN over a period of 3–6 and 6–12 months from the initiation of therapy.

Comment. When all therapeutic options (drug therapy, dietary counseling and specific dietary regimens, prescribing certain enteral nutrition preparations, surgical reconstructive procedures, surgical procedures to increase the length of the small intestine and/or reduce transit through the small intestine) have been exhausted, with maximum intestinal adaptation achieved, and the patient with SBS is still dependent on PN for any period of time, then prescribing PN is the only therapeutic measure to preserve the patient's health and life. The period of intestinal adaptation varies, but it directly depends on the remaining length of the small intestine and the type of SBS. This period can be 6 or 12 months, but never more than 2 years [1–4]. Intestinal adaptation essentially refers to structural and functional changes in the intestinal mucosa, but also to the slowing down of transit and changes in the gastrointestinal microbiome [2]. This process is minimal in SBS type 1, unlike SBS type 3. It has been proven that such intestinal adaptation, which can lead to the independence of patients from PN, is possible only in 20% of patients with SBS type 1, 40% in type 2, and 80% in SBS type 3 [21, 22]. After the initial results in the conducted experimental studies, the clinical studies have shown that intestinal growth factors, primarily GLP-2, lead to increased absorption and reduced need for PN in patients with all types of SBS [46–49]. In addition, it has been proven that ending the therapy with GLP-2 analogues does not lead to a severe deterioration in the condition of patients with SBS, but rather that the effect is long-lasting. Also, treated patients can actually be cured, that is, their health and life do not depend on the use of PN [50]. In an extensive analysis of treated SBS patients [48], the use of teduglutide has been proven safe and effective (in the case of proper indication), and that it does not lead to an increase in the incidence and number of malignancies in treated patients [51, 52]. SBS patients with suspected or active malignant diseases, as well as those with anamnestic data for previous malignant disease of the gastrointestinal tract, including the hepatobiliary tract and pancreas, are not candidates for therapy with intestinal growth factors [2]. The main criteria for determining patients who are candidates for GLP-2 analogues would be the time elapsed since the last intestinal resection, as well as the absence of contraindications for this type of therapy. The time period must be long enough so that the maximum possible intestinal adaptation is ensured. The most reliable way we can use to define the parameters of intestinal adaptation and monitor an SBS patient who is a potential candidate for therapy with GLP-2 analogues is through the work and activities of an expert team [2]. The effectiveness of GLP-2 analogues therapy should be ensured on the basis of standardized protocols that monitor the balance of water, electrolytes, and energy. Teduglutide is the only recombinant analogue of the physiological GLP-2 analogue that is approved in Europe and America for the treatment of SBS in adults and children over the age of 1. The expected effects after initiating the therapy can be seen after 3, 6, 8, or 12 months, and they have a long-lasting effect in terms of complete cessation of PN and in terms of completely curing the SBS [2, 3, 53].

Non-transplantation surgical procedures in the treatment of SBS

a) In patients with SBS, reconstruction of intestinal continuity is indicated whenever possible, with the aim of reducing dependence on PN.
b) Surgical methods of "lengthening" and "augmenting" the intestine and slowing down transit may be considered in certain cases.

Comment. In case of surgical intervention, when extensive resection of the small intestine is indicated, with or without colonic resection, preserving as much of the small and/or large intestine as possible is strongly recommended. One of the main criteria for early identification of patients with CIF is measuring the remaining length of the healthy intestine at the time of surgical resection. The surgeon must register the length of the remaining small and/or large intestine, as well as indicate the exact anatomy of the gastrointestinal tract after surgical intervention [2]. Once the SBS patient is metabolically stable and without electrolyte imbalance, the reconstruction of the gastrointestinal tract and the creation of intestinal continuity between the stoma and the unused distal intestine must be the top priority. Reconstruction can be performed in over 80% of patients while hospitalized, and in 50% of "reconstructed" patients, the need for long-term PN administration can be significantly reduced [26, 54]. There are numerous surgical procedures that can be used for the surgical treatment of SBS. These procedures aim to slow intestinal transit, increase the mucosal surface area, and "lengthen" the remaining part of the intestine. These surgical procedures depend solely on the local condition of the abdomen, underlying diseases (Crohn's disease, radiation enteritis, etc.), the clinical condition of the patient, but also on a proper assessment of potential morbidity and benefits [2].

Conclusion

Bearing in mind that SBS and CIF are chronic diseases, the treatment of which requires a great deal of human, financial, and time commitment, and also the fact

that these are life-threatening diseases, it is absolutely necessary to recognize them as rare diseases and treat them properly as such. Fortunately, there is not a large number of SBS and CIF patients in our country, and therefore it is possible to devise and organize their treatment, primarily through HPN. With such action, the QoL of these patients would be at the highest possible level (outside the hospital, they are at home, active and fully functional). Moreover, such a program would lead not only to an improvement in the quality of their lives, but also that of their family members (the family as a whole becomes functional), and hospital capacities would also be freed up. Therefore, it is necessary to recognize SBS and CIF as rare diseases, to enable the existence and use of home enteral nutrition and HPN, and to ensure the availability of parenteral and enteral nutrition preparations to patients. Enteral and PN preparations should be free of charge and easily obtained from pharmacies (as well as the material for their administration). It is necessary to recognize the HPN program and home enteral nutrition as official legal procedures by the Republic Fund of Health Insurance of the RS. In addition, it is necessary to enable and organize appropriate services to support primarily the patients within the HPN program, but also those dependent on home enteral nutrition. Treatment of SBS requires multidisciplinary and multiprofessional activity. Vigilant monitoring and adequate treatment enable significant life extension of these patients.

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Conflict of interest

The authors declare no conflict of interest.

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R E F E R E N C E S

1. *Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB,* et al. Home artificial nutrition & chronic intestinal failure special interest group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016; 35(2): 247–307. Erratum in: Clin Nutr 2017; 36(2): 619.
2. *Pironi L, Cuerda C, Jeppesen PB, Joly F, Jonkers C, Krznarić Ž,* et al. ESPEN guideline on chronic intestinal failure in adults - Update 2023. Clin Nutr 2023; 42(10): 1940–2021.
3. *Pironi L, Boeykens K, Bozzetti F, Joly F, Klek S, Lal S,* et al. ESPEN guideline on home parenteral nutrition. Clin Nutr 2020; 39(6): 1645–66.
4. *Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C,* et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015; 34(20): 171–80.
5. *Brandt CF, Hvistendahl M, Naimi RM, Tribler S, Staun M, Brøbech P,* et al. Home parenteral nutrition in adult patients with chronic intestinal failure: the evolution over 4 decades in a tertiary referral center. JPEN J Parenter Enter Nutr 2017; 41(7): 1178–87.
6. *Orphanet*. The portal for rare diseases and orphan drugs [Internet]. France: Orphanet; 2025 [cited 2024 April 20; accessed 2025 May 19]. Available from: https://www.orpha.net/consor/cgi-bin/index.php
7. *ICD-11 for Mortality and Morbidity Statistics*. DA96.05 Intestinal failure [Internet]. 2025; [cited 2022 Aug 17; accessed 2025 May 19]. Available from: https://icd.who.int/dev11/l-m/en#/http://id.who.int/icd/entity/778202494
8. *Bering J, DiBaise JK*. Short bowel syndrome in adults. Am J Gastroenterol 2022; 117(6): 876–83.
9. *Buchman AL, Scolapio J, Fryer J*. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003; 124(4): 1111–34.
10. *ICD-11 for Mortality and Morbidity Statistics*. DA 96.04 Short bowel syndrome [Internet]. 2025; [cited 2022 Nov 16; accessed 2025 May 19]. Available from: https://icd.who.int/browse/2025-01/mms/en#780637678
11. *Lauro A, Lacaille F*. Short bowel syndrome in children and adults: from rehabilitation to transplantation. Expert Rev Gastroenterol Hepatol 2019; 13(1): 55–70.
12. *NUPENS*. National Association for Clinical Nutrition of Serbia [Internet]. Belgrade: NUPENS; 2025 [accessed 2025 May 20]. Available from: https://www.nupens.org/ (Serbian)
13. *Pironi L*. Definitions of intestinal failure and the short bowel syndrome. Best Pract Res Clin Gastroenterol 2016; 30(2): 173–85.
14. *Fung JJ*. William Hunter Harridge lecture: The changing face of short-gut syndrome management. Am J Surg 2017; 213(3): 448–51.
15. *Lauro A, Cirocchi R, Cautero N, Dazzi A, Pironi D, Di Matteo FM,* et al. Reconnection surgery in adult post-operative short bowel syndrome < 100 cm: is colonic continuity sufficient to achieve enteral autonomy without autologous gastrointestinal reconstruction? Report from a single center and a systematic review of literature. G Chir 2017; 38(4): 163–75.
16. *Weaver LT, Austin S, Cole TJ*. Small intestinal length: a factor essential for gut adaptation. Gut 1991; 32(11): 1321–3.
17. *Pironi L, Konrad D, Brandt C, Joly F, Wanten G, Agostini F,* et al. Clinical classification of adult patients with chronic intestinal failure due to benign disease: An international multicenter cross-sectional survey. Clin Nutr 2018; 37(2): 728–38.
18. *Lezo A, Diamanti A, Marinier EM, Tabbers M, Guz-Mark A, Gandullia P,* et al. Chronic intestinal failure in children: an international multicenter cross-sectional survey. Nutrients 2022; 14(9): 1889.
19. *Pironi L, Steiger E, Joly F, Jeppesen PB, Wanten G, Sasdelli AS,* et al. Characteristics of adult patients with chronic intestinal failure due to short bowel syndrome: An international multicenter survey. Clin Nutr ESPEN 2021; 45: 433–41.
20. *Jeppesen PB*. Short bowel syndrome - characterisation of an orphan condition with many phenotypes. Expert Opin Orphan Drugs 2013; 1(7): 515–25.

21. *Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C.* Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999; 117(5): 1043–50.
22. *Amiot A, Messing B, Corcos O, Panis Y, Joly F.* Determinants of home parenteral nutrition dependence and survival of 268 patients with nonmalignant short bowel syndrome. Clin Nutr 2013; 32(3): 368–74.
23. *Pironi L, Goulet O, Buchman A, Messing B, Gabe S, Candusso M,* et al. Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. Clin Nutr 2012; 31(6): 831–45.
24. *Baxter JP, Fayers PM, McKinlay AW.* A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clin Nutr 2006; 25(4): 543–53.
25. *Comerlato PH, Stefani J, Viana LV.* Mortality and overall and specific infection complication rates in patients who receive parenteral nutrition: systematic review and meta-analysis with trial sequential analysis. Am J Clin Nutr 2021; 114(4): 1535–45.
26. *Kaufman SS, Avitzur Y, Beath SV, Ceulemans LJ, Gondolesi GE, Mazariegos GV,* et al. New insights into the indications for intestinal transplantation: consensus in the year 2019. Transplantation 2020; 104(5): 937–46.
27. *Messing B, Pigot F, Rongier M, Morin MC, Ndeïndoum U, Rambaud JC.* Intestinal absorption of free oral hyperalimentation in the very short bowel syndrome. Gastroenterology 1991; 100(6): 1502–8.
28. *Austin K, Bonnes S, Daniel H.* Controversy in nutrition recommendations for short bowel syndrome: how type of SBS impacts response. Curr Gastroenterol Rep 2019; 21(12): 64.
29. *Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ.* Oral salt supplements to compensate for jejunostomy losses: comparison of sodium chloride capsules, glucose electrolyte solution, and glucose polymer electrolyte solution. Gut 1992; 33(6): 759–61.
30. *McIntyre PB, Fitchew M, Lennard-Jones JE.* Patients with a high jejunostomy do not need a special diet. Gastroenterology 1986; 91(1): 25–33.
31. *Levy E, Frileux P, Sandrucci S, Ollivier JM, Masini JP, Cosnes J,* et al. Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome. Br J Surg 1988; 75(6): 549–53.
32. *Cosnes J, Evard D, Beaugerie L, Gendre JP, Le Quintrec Y.* Improvement in protein absorption with a small-peptide-based diet in patients with high jejunostomy. Nutrition 1992; 8(6): 406–11.
33. *Sladen GE, Dawson AM.* Interrelationships between the absorptions of glucose, sodium and water by the normal human jejunum. Clin Sci 1969; 36(1): 119–32.
34. *Jeppesen PB, Mortensen PB.* The influence of a preserved colon on the absorption of medium chain fat in patients with small bowel resection. Gut 1998; 43(4): 478–83.
35. *Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB.* Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. Gut 1999; 45(4): 559–63.
36. *Nightingale JM, Kamm MA, van der Sijp JR, Ghatei MA, Bloom SR, Lennard-Jones JE.* Gastrointestinal hormones in short bowel syndrome. Peptide YY may be the 'colonic brake' to gastric emptying. Gut 1996; 39(2): 267–72.
37. *Nightingale JM, Lennard-Jones JE, Walker ER, Farthing MJ.* Jejunal efflux in short bowel syndrome. Lancet 1990; 336(8718): 765–8.
38. *Williams NS, Evans P, King RF.* Gastric acid secretion and gastrin production in the short bowel syndrome. Gut 1985; 26(9): 914–9.
39. *Go VL, Poley JR, Hofmann AF, Summerskill WH.* Disturbances in fat digestion induced by acidic jejunal pH due to gastric hypersecretion in man. Gastroenterology 1970; 58(5): 638–46.
40. *Dueno MI, Bai JC, Santangelo WC, Krejs GJ.* Effect of somatostatin analog on water and electrolyte transport and transit time in human small bowel. Dig Dis Sci 1987; 32(10): 1092–6.
41. *Fuessl HS, Carolan G, Williams G, Bloom SR.* Effect of a long-acting somatostatin analogue (SMS 201-995) on postprandial gastric emptying of 99mTc-tin colloid and mouth-to-caecum transit time in man. Digestion 1987; 36(2): 101–7.
42. *Ladefoged K, Christensen KC, Hegnhøj J, Jarnum S.* Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut 1989; 30(7): 943–9.
43. *Remington M, Malagelada JR, Zinsmeister A, Fleming CR.* Abnormalities in gastrointestinal motor activity in patients with short bowels: effect of a synthetic opiate. Gastroenterology 1983; 85(3): 629–36.
44. *Cole CR, Ziegler TR.* Small bowel bacterial overgrowth: a negative factor in gut adaptation in pediatric SBS. Curr Gastroenterol Rep 2007; 9(6): 456–62.
45. *Ziegler TR, Cole CR.* Small bowel bacterial overgrowth in adults: a potential contributor to intestinal failure. Curr Gastroenterol Rep 2007; 9(6): 463–7.
46. *Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR,* et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagonlike peptide 2 analogue, improves intestinal function in short bowel syndrome patients. Gut 2005; 54(9): 1224–31.
47. *Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ.* Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut 2011; 60(7): 902–14.
48. *O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B.* Safety and efficacy of teduglutide after 52 Weeks of treatment in patients with short bowel syndrome intestinal failure. Clin Gastroenterol Hepatol 2013; 11(7): 815–23. e1–3.
49. *Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'Keefe SJ,* et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology 2012; 143(6): 1473–81. e3.
50. *Naberhuis JK, Tappenden KA.* Teduglutide for safe reduction of parenteral nutrient and/or fluid requirements in adults: A systematic review. JPEN J Parenter Enteral Nutr 2016; 40(8): 1096–105.
51. *Joly F, Zhang P, Allard JP, Genestin E, Gondolesi G, Jeppesen PB,* et al. Long-term safety analysis of teduglutide treatment in adult patients with short bowel syndrome and intestinal failure. Clin Nutr ESPEN 2023; 54: 501.
52. *Joly F, Jezerski D, Pape UF, Crivelli A, Hütterer E, Bergoin C,* et al. Real-world experience of Teduglutide use in adults with short bowel syndrome: A seven-year international multicenter survey. Clin Nutr 2025; 47: 54–67.
53. *Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G. Pape UF,* et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol 2016; 7(2): e142.
54. *Adaba F, Uppara M, Iqbal F, Mallappa S, Vaizey CJ, Gabe SM,* et al. Chronic cholestasis in patients on parenteral nutrition: the influence of restoring bowel continuity after mesenteric infarction. Eur J Clin Nutr 2016; 70(2): 189–93.

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Appendix

Nina Ristić[1], Maja Šujica[2], Branislava Jorović[3], Radmila Popović[3, 4], Olgica Latinović-Bošnjak[5], Vladimir Milivojević[6,7], Dino Tarabar[8], Goran Stanojević[9,10], Velimir Marković[6,11], Ivan Ranković[12,13], Jelena Martinov Nestorov[6,7], Duško Maksimović[14], Nataša Zdravković[15,16], Jovana Stanisavljević[6,17], Jelena Veličković[6,18]

[1]University Children's Hospital, Department of Gastroenterohepatology, Belgrade, Serbia; [2]Institute for Mother and Child Healthcare, Department of Anaesthesia and Intensive Care, Belgrade, Serbia; University Clinical Center of Vojvodina, [3]Clinic for Anaesthesia, Intensive Care and Pain Management, [5]Clinic for Gastroenterology and Hepatology, Novi Sad, Serbia; [4]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; [6]University of Belgrade, Faculty of Medicine, Belgrade, Serbia; University Clinical Center of Serbia, [7]Clinic for Gastroenterology and Hepatology, [11]Hospital for Digestive Surgery, [17]Emergency Center, Department of Anaesthesiology and Intensive Care, [18]First Surgical Hospital, Clinic for Digestive Surgery, Department of Anesthesiology, Belgrade, Serbia; [8]Clinical Hospital Center "Dr. Dragiša Mišović – Dedinje", Department of Gastroenterology Belgrade, Serbia; [9]University of Niš, Faculty of Medicine, Niš, Serbia; [10]University Clinical Center Niš, Clinic for Digestive Surgery, Niš, Serbia; [12]University of Exeter - Medical School, NHS England High Education, Exeter, England, United Kingdom; [13]Royal Cornwall Hospitals NHS trust, Gastroenterology and Liver Unit, Exeter, England, United Kingdom; [14]Military Medical Academy, Clinic for Anaesthesiology and Intensive Care, Belgrade, Serbia; [15]University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia; [16]University Clinical Center Kragujevac, Clinic for Gastroenterology and Hepatology, Department of Internal medicine, Kragujevac, Serbia