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Off label pharmacological therapy in patients with short bowel syndrome

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Abstract. – BACKGROUND: Short bowel syndrome is a disabling disease requiring long-term nutritional support and ancillary drugs. Aiming to analyze the most commonly prescribed drugs, a retrospective analysis was conducted is an outpatient cohort.

PATIENTS AND METHODS: Stable patients (N= 37, 59.5% males, age 51.1 ± 20.1 years, body mass index 20.1 ± 7.9 kg/m^2) with three or more appointments in the Outpatient Service during the last 18 months were retrospectively analyzed. regarding oral pharmacologic prescriptions. Medications were classified as on label or off label.

RESULTS: A total of 257 oral prescriptions were retrieved from computer files, encompassing 17 different preparations. The majority was employed on label however 28.8% (74/257) were classified as off label and scrutinized with regard to indications. The main categories were pharmacologic modulators of gastrointestinal secretions and motility, along with antibiotics. Virtually all patients required one or more of such drugs, without differences regarding demographic or clinical variables. Adverse effects or premature drug discontinuation were not observed.

CONCLUSIONS: This is the first study to our knowledge highlighting the importance of adjuvant drugs, particularly with unconventional indications, in the management of short bowel syndrome. Antidiarrheic agents, pancrelipase micropellets, antacids and antibiotics represented the most relevant off label prescriptions for this population.

Key Words:

Short bowel syndrome, Intestinal insufficiency, Intestinal resection, Chronic diarrhea, Off label drugs, Proton pump inhibitors, Antibiotics, Pancrelipase, Home nutrition, Enteral nutrition.

Introduction

Short bowel syndrome (SBS) is an infrequent, however, disabling and life-threatening condition, with major clinical, social and financial costs. Intestinal insufficiency, which is the hallmark of SBS, may occur with 50-150 cm of residual small bowel, depending on the presence of the colon and functional status of the gut[1,2].

Cases with intact intestine may also fit such diagnosis, which is fundamentally functional and not anatomical, if hindrance of digestion and absorption is sufficient to trigger intestinal failure. Chronic pseudo-obstruction, familial polyposis, radiation enteritis and Crohn's disease are representative examples, even in the absence of any enterectomy. Although these are models of intestinal insufficiency only, not of short bowel, traditionally such designations are used as synonyms and encompass all mentioned abnormalities.

Incidence and prevalence are estimated as 3 per million and 4 per million respectively[1]. In Western Europe at least 10,000-15,000 patients require permanent nutritional support for SBS and a similar number is estimated in the USA[3]. However, such calculations do not reflect the total burden of the disease, which is several times higher.

Indeed major enterectomy is not rare in surgical practice, notably for advanced cancer, severe trauma and inflammatory bowel disease. As many as 70% of all patients undergoing resection of 2/3 or more of the small intestine, especially involving the terminal ileum and ileo-cecal valve, may progress with clinical manifestations indistinguishable from SBS including persistent diarrhea, malabsorption, dehydration, weight loss and nutritional deficits[4,5]. Specialized dietary assistance and pharmacologic treatment may be needed for variable periods, until clinical course points toward either spontaneous recovery (no SBS), or alternatively overt intestinal insufficiency (true SBS).

It has been affirmed that diet manipulation alone will reduce stool output and enhance fluid and nutrient absorption[6]. Indeed one should not underestimate the importance of careful titration of enteral nutrient and fluid input during all phases of the disease, with or without combined par-

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enteral feeding, both for nutritional and metabolic compensation and for stimulation of long term intestinal regrowth and adaptation.

Nevertheless, virtually 100% of the patients with SBS will require additional medications, particularly in the form of vitamins and mineral supplements, modifiers of intestinal secretion, motility and absorption including pancrelipase (Creon), as well as antibiotics for occasional bacterial overgrowth[1,2].

Indications and dosage schedules for some of them are suggested in the literature however consensus is lacking. Many of these drugs will be prescribed off label, as randomized trials targeting adjuvant drugs for SBS are virtually nonexistent, and such diagnosis is mostly overlooked by official regulatory panels. Therapeutic routines for difficult or non-responding patients need, therefore, to be improvised or borrowed from related classic illnesses such as chronic diarrhea, malabsorption and undernutrition. To the best of our knowledge, no investigation has hitherto attempted to define the prescription profile in this context, little being known regarding requirements of either standard or uncoventional medications.

Aim of the Study

Given the relevant role of ancillary pharmacologic agents, a retrospective study was conducted with patients on home nutritional support because of intestinal insufficiency. The objectives were to unveil the most employed drugs, the frequency of prescription, and the occurrence of off label use.

Patients and Methods

Ethical Considerations

This investigation was approved by the Ethical Committee of Hospital das Clinicas (Protocol 0540/11, August 22, 2011).

Study Type

This was a retrospective observational cohort protocol, targeting patients on home nutrition because of intestinal insufficiency (short bowel syndrome).

Inclusion criteria: Males or females, age 18-80 years, undergoing outpatient nutritional support for at least 3 years, and submitted to enteral feeding, associated or not with parenteral and oral nutrition.

Exclusion criteria: Critical disease, active cancer, surgical procedures for SBS (intestinal lengthening, valves, segment reversal, transplantation), discontinuation of nutritional therapy, liver cirrhosis, other organ failures, less than three outpatient appointments in the last 18 months.

Experimental Design

Information about all prescribed oral drugs was collected from the hospital system during the most recent 18 months. Injectable medications are uncommon in this context, and in order to keep the investigation homogeneous they were not considered. Uses were classified as on label and off label, according to officially approved indications. Each drug registered at an outpatient appointment was counted as one prescription. General demographic and clinical features of the cohort were transcribed as well.

Statistical Analysis

Results are shown as mean ± SD or percentage. Chi-square test and linear regression analysis (Pearson) were employed to assess use of additional prescriptions according to age, gender and diagnosis. A significance level of 5% ($p < 0.05$) was adopted.

Results

A total of 37 patients that fulfilled the criteria of the study were analyzed. Clinical features of the population may be followed in Table I along with Figure 1. As demonstrated, all age brackets were represented, however children were not addressed in the current investigation. Mean body mass index (BMI) was acceptable; however, as

Table I. Demographic and clinical profile of the cohort.

Variable	Resuts
Age (years)	51.1 ± 20.1
Gender (males)	22/37 (59.5%)
Body mass index (kg/m^2)	20.1 ± 7.9 (14.5-32.0)
Hemoglobin (g/dL)	12.0 ± 2.7
Lymphocyte count (/mm^3)	1550 ± 694
Estimated small bowel length (cm)*	94 ± 51 (20-150)
Ileo-cecal valve absent	18/37 (48.6%)
Follow-up period (years)	5.5 ±2.2 (3-14)

*Excluding patients with intact small bowel and functional intestinal insufficiency.

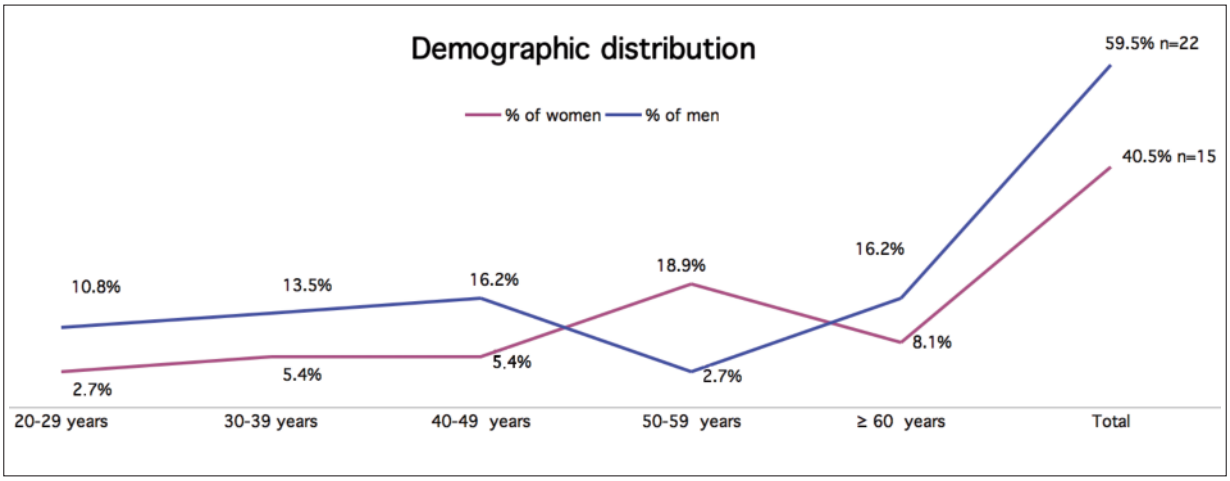

Figure 1. Demographic features of the cohort.

many as 43.2% of the patients (16/37) were underweight (BMI < 18.5 kg/m^2), despite intensive nutritional care. Pattern of small bowel length and absence of ileo-cecal valve corresponds to the expected proportions in this population. Figure 2 depicts baseline diagnosis of the cohort. Mesenteric thrombosis and Crohn's disease predominated; however, multiple etiologic mechanisms were detected.

A total of 257 individual prescriptions of supplementary drugs was identified, encompassing 17 pharmacologic preparations. These represent 6.9 prescriptions/patient, or nearly one very other month. Prescriptions were classified as on label or off label according to the directives of the Ministry of Health. Most prescriptions followed approved guidelines; however, 28.8% (74/257) infringed such rules (off label use).

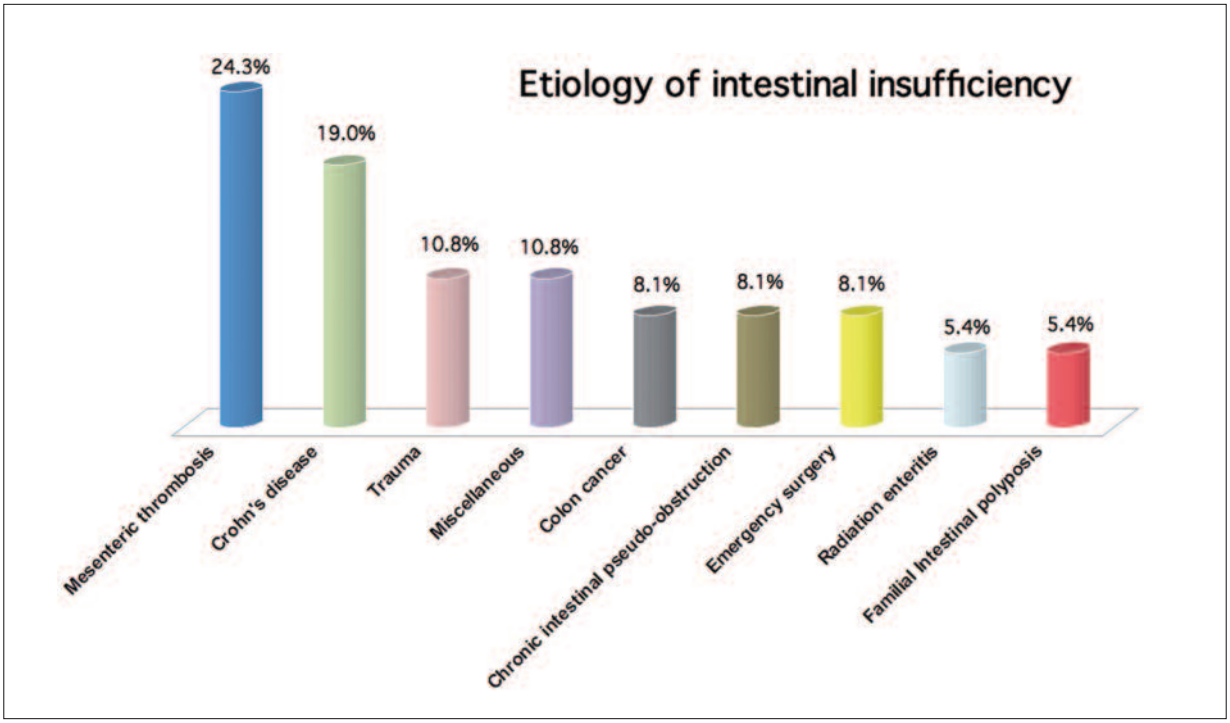

Figure 2. Causes of intestinal insufficiency.

Such exceptions encompassed two antibiotics (ciprofloxacin and metronidazole), three medications aiming at reduction of gastrointestinal fluid output (omeprazole, calcium carbonate and amitryptiline), along with one targeting enhanced food digestion and absorption, in association with diminished enteral residues (pancrelipase minimicrospheres/Creon®) (Table II).

Pharmacokinetics and effectiveness of these medications was beyond the goals of the study, yet a safe profile emerged. Side effects were not reported nor was premature drug discontinuation observed in the patient files.

Statistical analysis failed to associate specific on-label or off-label prescriptions with age, gender, etiologic mechanism or follow-up period (results not shown).

Discussion

Short bowel syndrome is not a mere reduction of the bowel length triggering impaired nutrient absorption, increased fecal losses and malnutrition. It is a systemic disease with numerous digestive and extradigestive aberrations including hepato-biliary, renal, metabolic, infectious and immunologic derangements[1,2,7].

In the analyzed series, ancillary medications were commonly required, as expected in a condition with severe ongoing derangements and an array of possible complications. Most of them were used on label and will not be addressed because indications are obvious, the discussion focusing instead off label prescriptions.

Table II. Supplementary pharmacological therapy (total prescriptions = 257).

Drug	On-label	Off label
Ascorbic acid	3 (1.2%)	0
Alendronate	6 (2.3%)	0
Amitryptiline	0	3 (1.2%)
Calcium carbonate	17 (6.6%)	15 (5.8%)
Ciprofloxacin	0	5 (1.9%)
Cholestyramine	5 (1.9%)	0
Ferrous sulfate	13 (5.1%)	0
Loperamide	24 (9.3%)	0
Metronidazole	0	2 (0.8%)
Omeprazole	0	31 (12.1%)
Pancreatic enzymes	1 (0.4%)	18 (7.9%)
Polyvitamins	24 (9.3%)	0
Potassium citrate	11 (4.3%)	0
Vitamin A	7 (2.7%)	0
Vitamin A + D	22 (8.6%)	0
Vitamin B (B complex)	18 (7.0%)	0
Vitamin B12	32 (12.5%)	0

Antibiotics may be required in short bowel syndrome for a number of complications. Catheter sepsis in those receiving intravenous fluids is well-known; however, this is a classic indication for antibacterial products, typically substantiated by positive microbiological assessment and sensitivity tests.

Off-label use is generally directed towards nonspecific diarrhea with suspected bacterial translocation, featuring fever, weight loss, accelerated gastrointestinal transit and abdominal pain. In rarer circumstances, colonic bacterial fermentation of dietary carbohydrates with excessive D-lactic acid production may elicit both metabolic acidosis and episodes of encephalopathy[1,7,8]. Pathogenic bacteria may not materialize in fecal samples or blood culture and species isolation is elusive, rendering empirical therapy necessary because of the serious and occasionally life-threatening symptoms.

Proton-pump inhibitors such as omeprazole are administered in the early months after intestinal resection to antagonize the typical gastric hypersecretion secondary to acute loss of inhibitory enteral hormones, nevertheless such phenomenon tends to disappear in the late folow-up period which was the focus of this study. Off-label prescription occured in connection with the antidiarrheal properties of omeprazole in short bowel syndrome. Though increased bowel water absorption was documented in a series of SBS[9], this indication is not yet endorsed by regulatory agencies.

Amitryptiline is a tricyclic antidepressant endowed with mild anticholinergic action, similarly to other components of this family. Small doses of 10-25 mg/day are virtually devoid of central nervous system repercussions, still measurably reduce intestinal output. In this sense the product has been successfully utilized in diarrhea associated with irritable bowel syndrome[10], yet within the SBS context such administration is deemed off label.

Calcium carbonate is an ancient antidiaheal medication, superseded by more modern and effective pharmacologic options. Nevertheless due to its partly physico-chemical therapeutic mechanism, independent of neuroendocrine bowel response, response in the SBS setting is often better than with agents which need to interact with the mucosa, which is severely reduced. It has been successfully adopted in other challenging

and refractory situations such as HIV patients with drug-induced diarrhea[11]. Moreover SBS patients are susceptible to osteoporosis, and this salt represents a calcium source.

One of the most innovative ancillary treatments in short bowel syndrome is micronized pancreatic enzymes. These patients rarely undergo pancreatic resection or suffer from established pancreatic insufficiency; therefore, on label indications are lacking[12,13]. Nevertheless, an adverse milieu for adequate performance of pancreatic enzymes should be admitted. Accelerated food transit leads to increased fecal loss and insufficient food exposure, therefore, limiting macronutrient and notably lipid hydrolysis. Increased gastric acid secretion or insufficient duodenal alkalinization frequently hampers enzyme activation. Finally, though diarrhea is the overarching manifestation of SBS, some degree of steatorrhea may be present as well, justifying external enzymes.

Though not officially recognized, such administration on pragmatic grounds has been advocated when the patient is suffering from diarrhea and weight loss, particularly in the form of highly efficient enterically coated micropellets of pancrelipase (Creon® 40000 MMS), which have replaced older, less reliable preparations[13-15].

Off label drug use is an old and widespread trend in medical routine, obviously not restricted to SBS. In the USA it is estimated that 60 million of the estimated 150 million annual prescriptions for the general population do not comply with established guidelines[16]. Some of the disagreements are comparatively minor, involving dosage schedule, route of administration or age bracket. Other conflicts are potentially more serious such as introduction of completely new drugs, or those which have never been tested for a given disease, rendering one clueless with regard to the risk/benefit ratio.

Regulators are aware that off label use is difficult to control. Outlawing the practice could be draconian because infrequent diseases such as SBS, with relatively scant interest to the pharmaceutical industry or to public health authorities, will hardly achieve funding or recruit enough participants for large scale, rigorously randomized trials. Such are essential to define dose/response curves, tolerance and clinical benefits in comparison with alternative pharmacologic treatments, or in case of intestinal insufficiency where few options exist, with standard handling (no treatment)[16,17].

Safety and effectiveness are key for off-label use[17]. In this sense, France has recently issued Temporary Recommendations of Use (TRU's) for unlicensed prescriptions, allowing legal use during a few years, until a more complete analysis of claims and risks of the new pharmacologic principle can be conducted. Among other purposes the focus of the French legislation is to avert the loss of therapeutic options for eligible patients[16]. In the USA the somewhat different and much debated Orphan Drug Act has been in use since 1983[18].

In the current analysis, nearly 30% of all ancillary prescriptions were off-label, a rather high number which underlies both the serious symptoms and complications of such population, and the scarcity of approved therapeutic options in official guidelines.

Other centers emphasize the need in SBS of additional resources notably for diarrhea, gastric hypersecretion, lipid digestion and bacterial overgrowth, although little clinical experience is reported. Thompson et al[1] advise loperamide, diphenoxylate, cholestyramine and pancreatic enzymes for slowing transit and alleviating diarrhea, quite similarly to our experience. In order to inhibit gastrointestinal secretions, proton pump and H2 receptor antagonists, octreotide and clonidine are advocated antibiotics, probiotics and prokinetics for bacterial overgrowth, besides glutamine and growth hormone as potential enhancers of intestinal regeneration should also be part of the arsenal.

Glucagon-like peptides (GLPs) such as exenatide, a GLP-1 analog, and particularly teduglutide, a GLP-2 analog which has recently received approval by the FDA but not yet elsewhere, should not be overlooked as useful and eventually remarkable trophic agents for the intestinal mucosa[3].

This is the first study to our knowledge, that outlined the utilization of adjuvant drugs for SBS in a well-defined stable cohort, thus revealing the importance of such prescriptions, and notably of unconventional or off label drugs. Further investigations are warranted in order to streamline patterns of administration, positive responses along with side effects, thus improving quality of life and long-term outlook in SBS. Surgical lengthening, valving of the bowel or a reversed segment will help some patients, and intestinal transplantation could be the solution to others[1,2,6,7]. Nevertheless, the majority of such cases will continue to be handled nutritionally and pharmacologically for years to come, and to this purpose a safe and reliable array of adjuvant medications will remain invaluable.

Protocol Registration

NCT01696656.

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Conflict of Interest

Joel Faintuch is a National Research Council Investigator (CNPq 302915/2011-7). None of the Authors have any conflict of interest to declare.

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