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REVIEW

The current therapeutic options for Crohn's disease: from medical therapy to intestinal transplantation

Augusto Lauro[a], Francesco D'Amico[b] and Gabriel Gondolesi[c]

[a]Liver and Multiorgan Transplant Unit, St. Orsola University Hospital, Bologna, Italy; [b]Hepatobiliary Surgery and Liver Transplant Unit, University Hospital of Padua, Padua, Italy; [c]Intestinal Failure, Rehabilitation and Transplantation Unit, Fundación Favaloro University Hospitals, Buenos Aires, Argentina

ABSTRACT

Introduction: Crohn's disease (CD) has an annual incidence per 100.000 person-year of 20.2 in North America and 12.7 in Europe, and the purpose of this review is to evaluate its medical management, from diagnosis to transplant. Pharmacologic manipulation with nutritional care aims to achieve and maintain remission, but more than half of patients will undergo an intestinal resection, very often repeated over time. They could experience short bowel syndrome (SBS) requiring total parenteral nutrition (TPN). Intestinal transplantation (ITx) represents an alternative in case of irreversible intestinal failure (IF) with life-threatening TPN complications. Patient survival after ITx is 79%, 53% and 43% at 1, 3 and 5 years respectively, with no differences among ITx for other disorders.

Areas covered: The research discussed medical therapy with nutritional support, evaluating the role of endoscopy, surgery and transplant in CD. A systematic literature review was conducted using the PubMed search engine up to May 31th, 2017 without restriction of the language. The decision on paper's eligibility was reached by consensus between the 3 screening authors.

Expert commentary: CD treatment is mainly medical, leaving endoscopy and surgery for a complex course. ITx represents a therapeutic option if TPN complications with IF arise.

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Crohn's disease; intestinal transplantation; surgical management; medical therapy; TPN

1. Introduction

Crohn's disease (CD) is a chronic and progressive inflammatory disorder of the gastrointestinal tract. Seldom patients with a complicated CD course experience malabsorption due to intestinal failure (IF) and short bowel syndrome (SBS), and it could represent an indication for total parenteral nutrition (TPN) [1]. Despite the availability of powerful immunosuppressive drugs, patients experience high recurrence rate, and more than half undergo an intestinal resection within 10 years after diagnosis and a third of them requiring a repeat resection within 5 years [2,3]. Nutritional care, together with pharmacologic manipulation plus surgery, is often successful in front of type 2 IF, and with type 3 IF, the patients are confined to TPN all life long, and, if complications arise, intestinal transplantation (ITx) is the only life-saving treatment, making CD an indication for ITx in adults [4]. Type 1 is an acute, short-term, and usually self-limiting condition of IF; type 2 is represented by a prolonged acute condition, often in metabolically unstable patients, requiring complex multidisciplinary care and intravenous supplementation over periods of weeks or months, while type 3 is a chronic condition, in metabolically stable patients, requiring intravenous supplementation over months or years, reversible or irreversible [5]. Among the 1115 adults who underwent ITx in the USA between 1990 and 2014 [4], 75% were transplanted because of SBS including 13% of CD patients, representing the second indication together with functional bowel disease (13%). The aim of this literature search is to give a comprehensive overview of CD treatments, especially focused on ITx.

2. Epidemiology and pathogenesis

CD represents a cause of IF [6]: the highest annual incidence per 100,000 person-year is 20.2 in North America, 12.7 in Europe, and 5.0 in Asia and the Middle East [7], but there are no recent data in the English literature addressing the overall prevalence of IF among CD population [8], even if they represent nearly one-third of the home parenteral nutrition population following those with cancer and AIDS [9,10]. There are multiple subtypes of CD, which contributes to its observed clinical heterogeneity. This concept has been reinforced by recognition of the complexity of the genetic, microbial, immune, and environmental factors that affect risk for the disease [11], and, although the etiology is not fully elucidated, CD is nonetheless classified as an inflammatory bowel disease with an autoimmune pathophysiology [12]. Autoantibodies are activated against intestinal epithelial barrier function, and circulating antibodies are present in front of a range of autoantigens including lymphocyte antigens [13]. Tumor necrosis factor (TNF) has a central role, and specific inhibition of this pleotropic cytokine by biological anti-TNF agents has been a major advancement in the treatment of CD [14]. Recently, an association has been demonstrated between CD and nucleotide oligomeric domain 2 (NOD2) mutation: the defect is responsible for an inappropriate immune response, impaired mucosal barrier function, and microbial dysbiosis [15], and it was hypothesized that NOD2 deficiency leads to a specific and transmissible mucosa-associated microbial dysbiosis which is independent of the mucosal barrier defect.

CONTACT Augusto Lauro augustola@yahoo.com; augusto.lauro@aosp.bo.it Liver and Multiorgan Transplant Unit, St. Orsola University Hospital, Bologna, Italy

3. Childhood-onset CD

Childhood-onset CD seems to be an aggressive phenotype of the disease. In a recent literature review [16], up to one-third of children with CD developed bowel complications more than 5 years after diagnosis, and, among them, 44–88% underwent at least one corticoid steroid treatment course, becoming one-third of the children steroid dependent. Immunosuppressive medications were used earlier and more frequently in newer than older cohorts (68% vs. 32% at 5 years), and more than one-third of children received biological treatment early in the disease course. A decrease in the surgery rate was observed in more recent unselected populations compared with older ones, but the relative risk of cancer as well as the risk of mortality seemed to have increased: mortality was recently evaluated in two population-based studies from France and Hungary including both children and adults, and the published data indicated that relative but not absolute risk of mortality is higher in patients with an early-onset disease [17].

4. Diagnosis and prognosis

The diagnosis [18] is confirmed by clinical evaluation and a combination of endoscopic, histological, and radiological investigations. Symptoms commonly include abdominal pain, weight loss, and chronic, sometimes bloody, diarrhea. Physical examination could show abdominal distention and tenderness and previous episodes of perianal abscess or anal fissure. Laboratory tests and stool samples could contribute to diagnosis, but ileum colonoscopy with biopsies represents the first-line procedure to establish the diagnosis and follow-up of the patients. MRI, CT enterography, and trans-abdominal ultrasonography are complementary to endoscopy and offer the opportunity to detect and stage inflammatory, fistulizing, and stricturizing CD. Small bowel capsule endoscopy should be reserved for patients in whom the clinical suspicion for CD remains high despite negative evaluations with ileum colonoscopy and radiological examinations. Device-assisted enteroscopy may be performed if histological diagnosis is needed or when endoscopic therapy is indicated, including dilatation of strictures, retrieval of impacted capsules, and treatment of bleeding. Prognosis is related to age and location of the disease: a French retrospective study found that those patients with an age of diagnosis below 40 years were more likely to have 'very short bowel' (<100 cm) [19], while ileum-colonic involvement carries the greatest risk of IF because of more frequent stricturizing disease that leads to resection of the ileocecal valve, the absence of which increases the risk of TPN dependence [20]. Perianal CD seems also to be predictive of a less favorable prognosis, usually associated with higher number of bowel resections [21]. It is important to rule out a familiarity of CD because a family history of inflammatory bowel disease is associated with an increased risk of IF [22]. Smoking is indeed associated with poor prognosis: smokers tend to be younger at CD diagnosis and have more bowel resections than nonsmokers [19], and extraintestinal manifestations of the disease are more frequently encountered [23]. Corticosteroids (CS) have side effects and also increase the risk of postoperative complications, such as anastomotic leaks and septic complications, requiring urgent reoperation and further resection [24], while elective surgery itself could represent a negative prognostic factor, especially in case of an earlier treatment of enterocutaneous fistulae [25] or repeated surgical revisions of end stomas [22], conditions leading to repeated bowel resections and SBS. A large multicenter cohort study [26] has found several genetic factors influencing the clinical course of CD: the NOD2 gene mutation was the most important genetic factor, being an independent predictive factor for ileal location, stenosing and penetrating CD behaviors and need for surgery.

5. Medical management

5.1. Overview on medical treatment

At least 30–40% of patients with CD require surgery at some point during their lifetime, with higher risk of type 3 IF and subsequent need for home TPN [27], so it is worthwhile at first to elucidate medical treatment and strategy to fight CD before surgery occurs. *Sulfasalazine* (SASP), which consists of 5-aminosalicylates (5-ASA) and sulfapyridine joined together by a diazo bond, was the first aminosalicylate used for the treatment of inflammatory bowel disease (IBD) [28]. The overall use of 5-ASA in CD remains controversial [27], but 5-ASA are commonly used in the treatment of CD and a role for 5-ASA therapy in adult patients may be in front of mild-to-moderate Crohn's colitis [29], even though it is not effective in maintenance of medically induced remission [30]. In North America, CS are still widely used to treat CD, but they are contraindicated as maintenance agents: oral *budesonide*, a CS targeted to the gut with lower systemic bioavailability, is used to treat CD and is thought to have fewer systemic side effects than prednisone [27]. Growing evidence supports the notion that intestinal bacteria may be one of the etiological factors playing a role in the pathogenesis of chronic inflammation in CD, and antibiotic therapies could be considered efficacious in the treatment of active CD, such as *metronidazole* and *ciprofloxacin* considered appropriate for septic complications of CD or in presence of perianal disease [28]. The role of antibodies in the pathogenesis of CD has been underlined, and the first two immunomodulators widely used were *azathioprine* (AZA) and *6-mercaptopurine* (6-MP), both thiopurines (TPs) so chemically quite similar (6-MP is the active metabolite of AZA), but their limitation is a slow onset of action (3–6 months for full effect) [16]. Other immunomodulators are calcineurin inhibitors like cyclosporine A and tacrolimus [31], even if the evidence of their efficacy is limited. *Cyclosporine A* is working only when given intravenously and at high doses (the dose is managed by drug level in the blood) because oral cyclosporine is not effective for the induction of remission [32], and t*acrolimus* can be used in CD when CS are not effective or when fistulas develop, but both are not suitable as maintenance agents. *Methotrexate* (MTX) works more rapidly than AZA or 6-MP and is given by weekly injections: it is an effective option for people with CD who have not responded to steroids and cannot tolerate other immunosuppressants [33]. Increasing concern over the safety of TPs, particularly in combination

with anti-TNF-α agents, has increased the use of MTX [27]. *Thalidomide* is an oral immunomodulatory agent with anti-TNF-α properties that has been used in the treatment of CD in adults and children [27]; however, toxicity limits its use as a maintenance therapy [34]. Remission of CD is best obtained through initiation of combination therapy with immunomodulators and biologics (anti-TNF-α agents like infliximab, adalimumab, and certolizumab pegol) within 18–24 months of diagnosis in patients with moderate-to-severe CD [35]. Biologics are antibodies that target particular proteins and cells and then block the process that causes inflammation in the gut: TNF and other inflammatory cytokines are raised in the secretions by normal-appearing mucosa from patients with CD, providing evidence for a sustained immune stimulation in CD even in the absence of patent inflammation [36]. *Infliximab* is a chimeric monoclonal antibody, while *adalimumab* is a fully humanized monoclonal antibody, and both are targeting TNF-α. *Certolizumab pegol* is a recombinant, humanized, polyethylene glycol-conjugated antigen-binding antibody fragment (Fab') with specificity for human TNF-α [35]. Infliximab and adalimumab have been considered the mainstay of biological therapy in IBDs for the last decade; they have been shown to induce clinical and endoscopic remission in both CD and ulcerative colitis (UC) to diminish exacerbations and surgery rates [37]. Certolizumab pegol has been approved in 2008 for both induction and maintenance of remission in moderately-to-severely active CD, including patients who have previously lost response to infliximab, showing that lower drug levels and existence of antidrug antibodies correlate with loss of clinical and endoscopic response [37]. *Integrin antagonists (anti-integrin* or *anti-adhesions molecule therapies)* are antibodies which target the leukocyte adhesion and trafficking in the gut, thereby reducing inflammation: natalizumab and vedolizumab [27] have been approved for adult use. *Natalizumab* is a monoclonal antibody directed against the α4β1 and α4β7 integrin receptors, and *vedolizumab* [38] is directed against the α4β7 integrin receptor. There is an issue of safety related to natalizumab employment because progressive multifocal leukoencephalopathy has been associated with its use [39]. In contrast to natalizumab, which nonspecifically binds the α4 integrin on leukocytes so preventing them from migrating into the gut, vedolizumab is a gut-specific antibody binding only to α4β7 integrin. *Anti-interleukin therapy* is represented by *ustekinumab* [27,37,40], an antibody directed against interleukin (IL)-12/23 which undergone successful clinical trials in adults with CD, while *Jak kinase inhibitors* like *tofacitinib* [40,41] are oral inhibitors of JAK 1, 2, and 3 (thought to block signaling involving gamma-chain-containing cytokines including IL-2, -4, -7, -9, -15, and -21) and are under evaluation for both UC and CD. The microbiota in the lumen of patients with CD is characterized by reduced diversity, particularly Firmicutes and Bacteroidetes: the introduction of the intestinal microbiota from healthy individuals (*fecal microbial transplantation [FMT]*) could correct this dysbiosis and reverse mucosal inflammation [42]. In an open-label study, FMT led to an expansion in microbial bacterial diversity in patients with active CD and it was overall safe, although the clinical response was variable. Stem-cell therapy through the use of *mesenchymal stem cells* (MSCs) is a promising therapeutic option for severe refractory cases, especially when surgery is not feasible [14,43]. In perianal CD, the objective is to deposit MSCs locally in fistulizing tracts to downregulate the local immune response and induce wound healing [14]. With *hematopoietic stem-cell transplantation*, the objective is to destroy the 'autoreactive' immune cells responsible for disease chronicity and to reestablish bowel tolerance to gut microbes. In a recent randomized clinical trial [43], autologous hematopoietic stem-cell transplantation was evaluated among adult patients with refractory CD, not amenable to surgery who had impaired quality of life: it did not result in a statistically significant improvement in terms of sustained disease remission at 1 year and was associated with significant toxicity, not supporting its widespread use for patients with refractory CD. For patients with mild-to-moderate CD, *exclusive enteral nutrition* (EEN) has been shown to be an effective, non-pharmacologic approach to induce remission and is often used as an alternative to CS [27,44]. EEN involves the use of a complete liquid diet, with the exclusion of normal dietary components for a defined period of time, as a therapeutic measure to induce remission in active CD. This very efficacious approach leads to high rates of remission, especially in children and adolescents newly diagnosed with CD. This intervention also results in mucosal healing, nutritional improvements, and enhanced bone health [45]. For an average length of 6–8 weeks, patients are committed to a diet consisting only of a polymeric or elemental formula. EEN treatments typically achieve remission rates of over 80% in pediatric population, and importantly, they seem to be associated with a high rate of mucosal healing, far superior to steroids, which is prognostic of improved long-term health outcomes [27,44]. The central role of *TPN* as the treatment of choice in CD patients suffering from SBS and IF [46] is beyond doubt, allowing bowel rest while supplying adequate calorific intake and essential nutrients. This approach is better regarding survival and quality of life because parenteral nutrition management has improved dramatically over the last 10 years, and the rate of related complications has notably decreased: the outcome and prognosis of CD-related SBS on TPN seem to be comparable to that of SBS due to other causes [47]. Apart from nutritional support, TPN utility in CD is restricted to certain cases involving efforts to close enterocutaneous or other complicated fistulas in patients with fistulizing CD, when EEN is not possible [46].

5.2. Current pharmaceutical strategy

Pharmaceutical treatment for CD has two main goals, achieving and subsequently maintaining remission. In the 1980s and most of the 1990s, treatment of moderate-to-severe CD was based on TPs with the use of CS for symptom reduction: nowadays budesonide [16] is considered an option in the treatment of acute, mild ileocecal CD, while conventional CS [16,28] are considered the treatment of choice for induction of remission in moderate-to-severe ileocecal CD, in colonic disease, and in extensive small bowel disease. The role of immunomodulators like TP or MTX is more important as steroid-sparing and maintenance treatment after remission [16,28]. Therapy with TPs is associated with an increased risk of

lymphoma, non-melanoma skin cancers, and cervical dysplasia [16]. The introduction of biologics in the new millennium has dramatically revolutionized the therapeutic approach of CD [27]: patients with objective evidence of active disease, refractory to CS, should be treated with an anti-TNF-based strategy, although surgical options should also be considered [16]. Biologic therapy is also indicated in patients with fistulizing CD: early therapy with anti-TNF agents may be considered in patients with severe disease [28]. Biologics increase the risk of melanomas and in combination with TPs significantly increase the risk of lymphoproliferative diseases [16].

6. Endoscopic and surgical management of CD

CD-related complications are the most common indications for surgery, but over the last 25 years, surgery has been limited by the significant increase of medical treatment alternatives. The choice of intervention, such as endoscopic balloon dilatation (EBD), stricturoplasty, or bowel resection (laparoscopic or open), is mainly based on severity, activity, and type (stricturizing or fistulizing) of local and generalized disease plus patient (nutritional and septic) status [48]. The role of the surgeon is to evaluate the best approach, in consideration of the future quality of life. More than 50% of CD patients will require surgery within their lifetime to minimize the impact of the disease [49,50]; complications occur in 10–25% of the cases [51,52]. Surgical interventions should represent an alternative tool to be combined with pharmacological therapy or the only alternative in cases of acute complications like bowel obstruction and/or perforation. Resections should be limited to a segment of intestine (e.g. ileo-colonic resection, minimal small bowel resection, and segmental colectomy). In fact, one of the major concerns regarding surgery for CD is to avoid loss of bowel length and the consequent SBS, particularly when the disease is diagnosed in the childhood: the surgical principle to measure the remnant small bowel length before resecting the affected bowel must be always relevant whenever possible, and a residual small bowel longer than 100 cm in adults should be the goal, especially when colonic continuity is not achievable [53]. When CD starts with perianal abscesses and fistula, the most appropriate procedures are fistulectomy, fistulotomy, abscess drainage, and seton placement with possible 'glue filling' of the fistula; in sporadic cases, more invasive interventions involving the whole perineal region are required. CD-related fistulae are often complex and 'dangerous' in this area, and surgical procedures should be performed by experienced surgeons. The treatment of CD-related perianal disease is mainly medical, and the pharmaceutical treatment of CD-related perianal disease by antibiotics, calcineurin inhibitors, biologic agents, or mesenchymal stem cells has been already discussed in Section 5. Surgery should be considered as limited to local control: in case of perianal fistula, surgery is allowed only to correct one internal and maximal two external openings, considering that simple subcutaneous and low inter-sphincteric fistulas can be treated easily as outpatients [54]. If the upper two-thirds of external sphincter is involved by a fistula in women, it must be carefully treated in particular through the anal fistula plug, using the ligation of inter sphincteric fistula tract procedure [55,56] or the fibrin glue after setons [57]. A relationship between severity of the disease and postoperative complications has been analyzed, considering preoperative risk factors such as the presence of perforating disease, prolonged duration of preoperative symptoms, malnutrition, and steroid assumption among others [51,58]. Lee et al., in a retrospective study of small bowel CD, compared three scores: the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) score, the Seoul National University Bundang Hospital Screening Tool (SNUBH-NST) score, and the Crohn's Disease Activity Index (CDAI) score; they found that the extent of operation and the method used were marginally related to the severity of postoperative complications, except for CDAI [59,60]. Based on these findings, it has been proposed that EBD might be considered as an important adjuvant to surgery.

6.1. Endoscopic balloon dilatation

Endoscopic approach is necessary to diagnose CD. EBD is also usually the first-line therapy with a success rate of 80% but is absolutely contraindicated in the case of fistula or abscess. EBD should be performed after radiological evaluation, to define the diameter, the length of the strictures, and the presence of multiple stenosis or concomitant fistulas. It is usually performed under sedation and fluoroscopic control [61]. A balloon through a guide-wire is placed at the level of the stenosis and is inflated with high pressure through the scope, using saline solution or contrast agent, to obtain a hydrostatic dilation of the stricture. Success of dilatation is represented by the ability to pass the regular scope across the stricture. In clinical practice, it is recommended to perform a biopsy prior to dilatation, particularly in the transverse or rectosigmoid colon to rule out the presence of an underlying malignant process [62]. EBD is mainly used in strictures developed after ileocecal resection, while the role of dilatation in the area of ileocecal valve is controversial and not recommended in the colonic area. A systematic review of 353 strictures showed in a multivariate analysis that the single predictor of a surgery-free outcome was the existence of a short stricture [63]. Tortuous strictures and the need for using a balloon longer or equal to 5.5 cm were predictors of higher failure rate after endoscopic dilation. The use of intralesional injection of CS or infliximab, to avoid stricture recurrence, showed unconvincing results [64–67]. It must be noted that the median rate of major complications is about 3% after EBD [61–68]. EBD could be considered a mini-invasive bridge to surgery, and is complementary to it [63]. Generally, EBD is the perfect technique for treatment of short stricture, but it should only be attempted in institutions where it is available a surgical backup [69].

6.2. Bowel stenting

The use of bowel stents in the management of benign intestinal stricture is a new modality in its early stages, but it is a controversial and not currently recommended approach. Recent literature showed a technical success rate between 86% and 100% and a clinical success rate between 45% and 100%, defined as the absence of occlusive symptoms post-stent placement and ability to pass the

regular scope across the stricture. One of the most described problems is the early stent migration with an incidence up to 30% [70,71]. The complication rates of colonic, fully covered, self-expandable metal stents are prohibitively high [72], while more promising are the ones with specific ileo-colonic anti-migratory design: 6–18-month follow-up did not show any migration and was related to an immediate relief of symptoms (only in two out of seven cases, symptoms came back and in one case required another EBD) [73].

6.3. Stricturoplasty

Stricturoplasty procedure is mainly employed to preserve small bowel length in order to reduce the risk of SBS, and the rules used to perform surgery, in the aim to reduce the risk of SBS, have been previously discussed. Stricturoplasty is indicated when segments of intestine have signs and symptoms of obstruction: the contraindications are perforation, fistula, abscess, significant inflammatory changes in the stricture site (as in suspected carcinoma) [74], the total length of the stricture (related to the presence of several strictures in close proximity), and a stricture close to an area of resection. There is a negative recommendation for stricturoplasty in the colon because of serious concern for increasing risk of cancer [69,75,76]. The most common surgical procedure is the Heineke–Mikulicz stricturoplasty according to a meta-analysis by Yamamoto et al. [77,78], consisting in a longitudinal incision all over the anti-mesenteric border of the stricture site, sutured in a transversal fashion. It is indicated for short stenoses (<10 cm). For middle-length strictures (10–20 cm), if multiple ones are present close to each other over a long segment of small bowel, the side-to-side stricturoplasty by Finney or Jaboulay is more indicated [78,79]. The side-to-side isoperistaltic stricturoplasty consists of placing the proximal and the distal loops (before and after the stricture, obtained by the incision of the mesentery) in a side-to-side fashion and then making a longitudinal enterotomy. In the literature, this technique has been performed for strictures up to 64.3 cm and with a 5-year disease-free rate of 77% [80]. Reese et al. in their study observed a benefit of stricturoplasty over resection, with an overall early complication rate in favor of the stricturoplasty group (p = 0.09) for bowel obstruction, hemorrhage, septic complications, and medical recurrence. At the contrary in favor of the resection group, there was the surgical recurrence (p = 0.09) [81]. In general, all the different kinds of stricturoplasty have been associated with a risk of stricture relapse in 30–35% of patients at 4–8 years [82,83] with perioperative complications of 10–15% and major complications of 5% [68,82–84].

6.4. Resections

In the last 30 years, the surgical treatment for CD has changed. In 1980s, ileal pouch appeared as a procedure with the advantage of preserving body image, avoiding permanent stoma; but this kind of surgery was employed as a 'prophylactic colectomy.' The importance of colonoscopy surveillance, and the decreased risk of cancer, thanks to new medications, have both modified this approach. Now it has been recommended to perform a small resection rather than to bypass an inflammatory bowel segment, which increases risk of carcinogenesis. This new vision reflects the change in approaching CD patients, in particular considering their nutritional and performance status. Over the last years, bowel resections in CD were described to be performed open or laparoscopic. For laparoscopic approach, a single or multiple port access has been used, having the same indications as open surgery does [63,85–87]. The laparoscopic approach is preferable in the ileo-colonic resections and in patients without previous surgeries [85,86], giving the advantage of lesser postoperative adhesions, shorter recovery, lesser abdominal pain, and better cosmetic results. Resections should be as limited as possible: two randomized studies by Fazio et al. and by McLeod et al. [88,89] showed that neither the microscopic presence of inflammation at the anastomosis site nor the type of it influences the postoperative recurrence. As it was explained above, there is no statistically significant difference between stricturoplasty and resection as regards to re-intervention, recurrence, and complications [90–92]. A meta-analysis, including 661 patients with ileocolic resection, showed a significant difference in anastomotic leak rates, favoring side-to-side anastomosis versus end-to-end (p = 0.02) [93]; no statistical difference was reported [94] comparing stapler versus manual sewing, in order to perform the side-to-side anastomosis. If an intra-abdominal fistula with a consequent abscess is present, the current guidelines recommend a percutaneous drainage, considering that surgery has a higher risk of stoma creation [69,95,96]; abscess resolution is related to early intervention and not to the involved technique (percutaneous or open surgery) [97]. More than 25% of CD patients will undergo a second intestinal resection within 5 years from the first operation; the risk of the second surgery in CD has decreased in the last 10 years probably due to the increased utilization of immunosuppressant and anti-TNF therapies and with endoscopic postoperative disease surveillance [98].

7. Transplant management of CD

In spite of the advances in medical and surgical therapy, a small bowel shorter than 75 cm in adults will be at higher risk for IF as previously reported, and some patients with CD will develop SBS becoming TPN dependent: in appropriate centers, TPN is giving much better results regarding quality of life and survival rate, but failure to continue on TPN could represent the primary indication for ITx. It has been previously reported that, following the first small bowel resection, the described risk of IF in CD patients at 5, 10, 15, or 20 years is 0.8%, 3.6%, 6.1%, and 8.5%, respectively. As shown, predisposing factors to irreversible or type 3 IF include younger age at diagnosis, stricturizing disease, family history of IBD, and the recent addition of a genetic mutation in the NOD2 protein. NOD2 is a critical regulator of intestinal microbiota, and the human intestine harbors a large bacterial community, constantly interacting with the immune system. NOD2 is highly expressed in ileal Paneth cells, which provide critical mechanism for the regulation of the ileal microbiota through the secretion of antibacterial compounds, and the mutation of

this protein becomes one of the most critical genetic factors linked to ileal CD [9,99]. Paneth cells are responsible for the production of defensins, and this production is reduced in CD. Furthermore, NOD2 is responsible for autophagy of intracellular and extracellular microorganisms, an important defense mechanism of the GI tract, and moreover, NOD2 is believed to regulate toll-like receptor 2 which is related to the recognition of commensal intestinal flora. When CD patients require multiple operations with consequent intestinal resections, they could evolve to IF, later failing TPN due to life-threatening complications like lack of central venous accesses, catheter-related sepsis, or progressive liver disease leading to severe fibrosis: in such cases, ITx appears as a valid alternative, which has slowly increased over the last years [100] (Figure 1). CD ranks among the indications for ITx in adults (in few reports as second or third) [9,100–103], but it is still quite a seldom procedure in CD patients apart from North America, accounting for not more than 15–20 patients per year worldwide; it comprises a unique subgroup of patients with several clinical presentations, due to an impaired immune regulation as a baseline disorder [100,103–105]. In spite of the current experience, very little data are available regarding the long-term posttransplant clinical course. As it was previously mentioned, it has been recently described a genetic association between NOD2 and CD. The understanding of this association has been useful to better review some of the pathophysiological findings of the disease, including the interplay between the microbiota and intestinal immune cells, the role of Paneth and dendritic cells as well as the increased risk for developing IF; but also it could be translated into the transplant field in order to be used as 'potential marker' or 'predictor' of the posttransplant outcome for the whole population of ITx patients. The mutant NOD2 gene encodes an intracellular protein that acts as an innate immune system microbial 'sensor' in macrophages, dendritic cells, and certain epithelial cells. Few papers [103–105] reported the presence of CD-associated polymorphisms in the NOD2 gene of the ITx recipients like a risk factor for intestinal allograft rejection, and graft loss was up to 97-fold higher in recipients with NOD2 mutation than recipients with wild-type NOD2 loci. This statement is not confirmed by all authors [106], so it will require multicenter studies to be validated. The presence of a mutant NOD2 is responsible for a reduced ability to prevent bacterial adherence and for an impaired antimicrobial response from its Paneth cells [104,107]. CD patients have multiple special challenges that will influence their short- and long-term outcome as transplant candidates and future recipients. They usually present a past medical history with multiple abdominal surgeries that could lead to type 3 IF. CD ITx candidates will not only require isolated intestinal transplants, but some of them will evolve into a parenteral nutrition-associated liver disease, so requiring a combined liver and bowel transplant or a multivisceral graft [102,103,108]. Furthermore, few CD candidates will require the removal of a significant portion of the abdominal wall to be able to remove their complex enterocutaneous fistulae, determining the need for an abdominal wall transplant or rectus fascia as part of the allograft. The role of the colon as part of the intestinal graft has been recently revalued, and it has stimulated the development of novel procedures including an endorectal sphincter preserving pull-trough operation in CD patients with a stricturized anal–rectal segment: this technique should be offered utilizing en-block intestinal and full-length colonic grafts [109]. Table 1 summarizes the different therapeutic options in case of CD. In general, posttransplant outcomes and complications have not been reported specifically to this subpopulation of ITx [111] although some of them have been described, i.e. a case report of graft versus host disease in a CD recipient with abdominal wall as a consequence of a fistulizing disease: this report provides information regarding the extension of the primary CD disease in relation to the need of abdominal wall transplant [112]. A clinical concern after ITX, unique to these CD patients because of the immune nature of the disease, is the increased risk for early posttransplant recurrence (in spite of having a completely new intestinal phenotype after the ITx), in addition to the usual risk of posttransplant

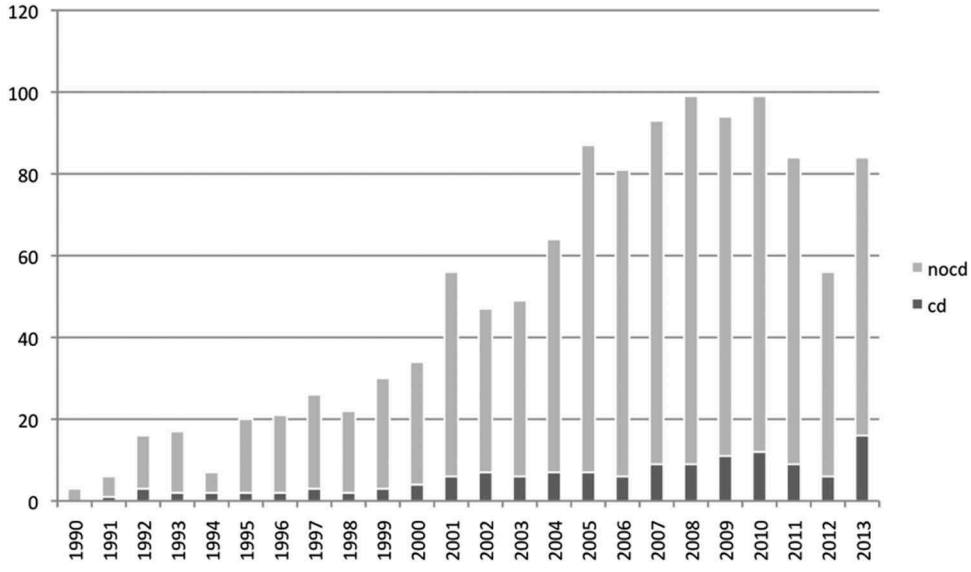

Figure 1. Number of ITx/year for CD and non-CD in USA.

Table 1. Therapeutic options in Crohn's disease (**ref**).

Medical management	Endoscopic management	Surgical management	Transplant management
Aminosalicylates 5-ASA [29]	Balloon dilatation [61]	Stricturoplasty [74]	Isolated bowel transplant [110]
Steroids Budesonide [27]	Bowel stenting [73]	Open or laparoscopic bowel resection [87]	Combined liver–bowel transplant [103]
Immunomodulators Thiopurines [16], methotrexate [33], calcineurin inhibitors [31], and thalidomide [34]			Modified or full multivisceral transplant [108]
Biologics (anti-tumor necrosis factor-a agents) Infliximab, adalimumab, and certolizumab pegol [37]			
Integrin antagonists (anti-adhesion molecules) Natalizumab and vedolizumab [38]			
Exclusive enteral nutrition [44]			

infections and rejection [100,101,110,111,113]. However, the risk of posttransplant CD recurrence is based on limited numbers of case reports, and this finding is only relatively important, but it should be mentioned for the benefit of the transplant community. The first report of posttransplant CD recurrence was in 1997 [110], followed by a second case in 2004 [113]. The first reported case began 7 months after transplantation and progressed to obstructive granulomatous enteritis and allograft failure; the second case involved the native and the transplanted intestine, started 8 years after ITx, but was successfully managed with steroids. Harpaz et al. reported for the first time in a 2005 paper [101] information in terms of recurrence risk and pathological findings, based on systemic endoscopic follow-up of six ITx (four isolated and two combined grafts) recipients with CD. The mean age at ITx was 40.5 years (range: 33–57); none of them had extraintestinal manifestations of CD. The four ITx long-term survivors had surveillance endoscopic biopsies for a mean time of 29 months, and in two cases, a granulomatous enteritis (containing Langhans cells), characteristic of CD, was found few weeks after transplantation and persisted intermittently throughout the follow-up period. It is important to highlight that in the early stages of CD recurrence, there were no specific or suspicious endoscopic findings (Figure 2). At the end of the follow-up, CD recipients did not show worsening disease, and they all had rejection that responded to conventional therapy [99]. Recently [114], four more cases were reported by Pittsburgh group as well (Table 2). The rapid emergence of CD histological manifestations in Harpaz et al. cases offers insights into its pathogenesis. CD is regarded as a systemic disorder wherein immunological factors, microenvironmental stimuli, and tissue constituents of the bowel cause tissue damage by upregulation of the inflammatory response. It continues to be unclear which conditions are necessary to take place in a new engrafted bowel: the complete recipient lymphocyte repopulation of the graft lymphoid tissue, or the early migration of certain cell subsets before the overall repopulation is complete, or the response can involve the graft only secondarily. Fishbein et al. [115] proposed to consider ITx rejection as the fourth IBD after celiac disease, UC, and CD, and although there are clinical, endoscopic, and pathological similarities, probably the most compelling clinical evidence of an association between IBD and ITx comes after the clinical observation of a favorable response to the administration of

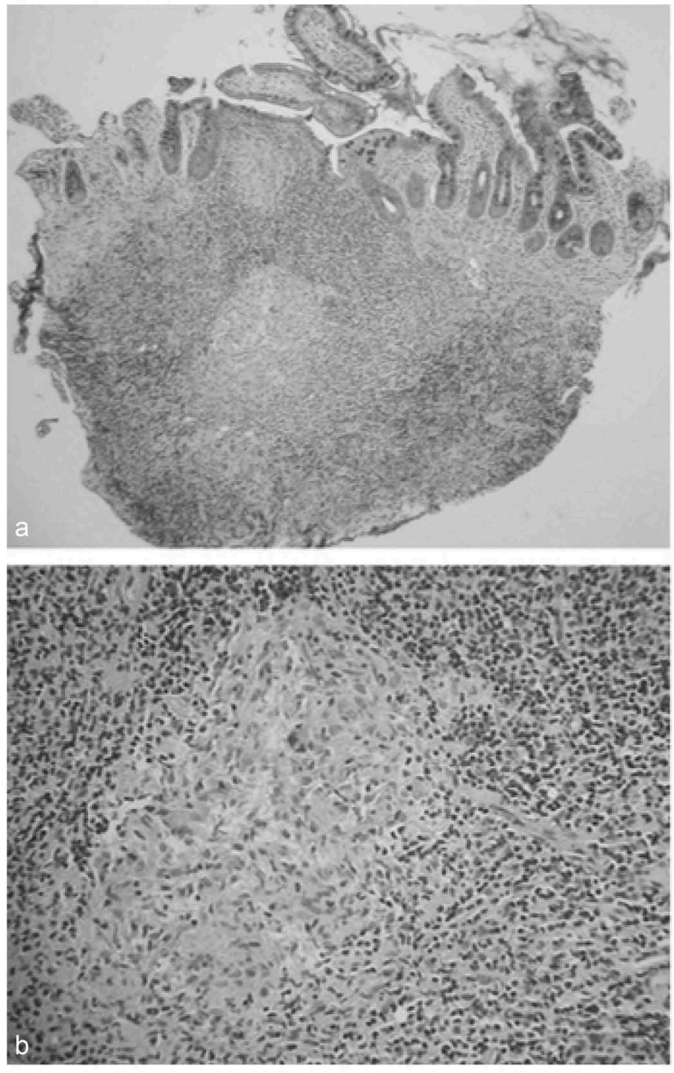

Figure 2. (a) Small intestine biopsy of a patient with recurrent CD, 20 days post-ITX, containing non-necrotizing epitheloid and Langhans cell granuloma. (b) Granuloma at higher magnification (PAS stain, x200). From Harpaz N, Schiano T, Ruf AE, Shukla D, Tao Y, Fishbein TM, Sauter BV, Gondolesi GE 'Early and Frequent Histological Recurrence of Crohn's disease in Small Intestinal Allografts' Transplantation 2005; 80: 1667–1670 (reproduced with authorization of main author *Gondolesi G*).

TNF inhibitors: they have been used to treat chronic intestinal transplant ileum ulcers and exfoliative rejections after ITx, refractory to antithymocyte therapy [116,117], subsequently

Table 2. Crohn's disease (CD) recurrence after intestinal transplantation (ITx).

Reference	Type of graft and no. of recurrences	Treatment of CD recurrence post-ITx	Outcome post-ITx
Sustento-Reodica et al. [110]	One isolated bowel	One surgical treatment	One graft loss
Kaila et al. [113]	One isolated bowel	One prednisone therapy	One responsive
Harpaz et al. [101]	Two isolated bowels	Two no treatment	Two responsive
Nyabanga et al. [114]	Four isolated bowels and one liver–bowel	Four no treatment and one biologic therapy	One graft loss and four responsive

providing new insights in the pathophysiology of the intestinal transplant rejection. The finding of having CD recurrence after changing the whole intestinal phenotype, and the described early timing for recurrence, opened new physiological questions regarding the primary mechanisms related to the origin of CD and is still under study. But in spite of these novel approaches, there has not been any scientific report or clinical experience regarding a different mechanism of rejection or a different immunosuppressive protocol described in CD intestinal transplant recipients; since the beginning of new millennium, the most common immunosuppressive protocols used worldwide in all ITx (CD and non-CD) recipients include preconditioning of the recipient through antilymphocyte and antithymocyte drugs and maintenance by tacrolimus (which it is used also in non-transplant CD patients resistant to corticoids or with fistulizing disease), and moreover, episodes of mild acute rejection in CD recipients respond to common immunosuppressive strategies used in all ITx recipients, mainly based on steroid recycle and increased tacrolimus therapy. Outcomes of ITx for CD have been reported in multiple single-center series [103,106,118–122], and so far to the best of our knowledge, there are only two multicenter analyses. The first is based on the United Network for Organ Sharing (UNOS) database and was published by Desai et al. [103]: they included adult patients receiving ITx from 1987 to 2009 and a total of 86/1664 (5.2%) ITx were performed for CD; 61 received isolated ITx and 25 combined liver–bowel transplant. The overall patient survival for CD recipients was 79%, 53%, and 43% at 1, 3, and 5 years, respectively, with no differences found among different types of transplanted grafts. These figures do not differ from transplants performed for other disorders. The most common causes of post-ITx death were infections (40.6%) and graft failure (9.4%), mainly due to acute or chronic rejection, but the UNOS database has a shortfall because there is no documentation of disease recurrence. The second manuscript was recently published by Limketkai et al. [100], based on the Scientific Registry of Transplant Recipients data base (SRTR), and it retrospectively analyzed the ITx performed from 1990 to 2014; 142/1115 ITx were performed for CD; the incidence of acute cellular rejection at the end of the first-year post-ITx was 36.9%, comparable to the incidence for ITx performed in non-CD patients. The actuarial risk for graft failure at 1, 5, and 10 years after ITX was 18.6%, 38.7%, and 49.2%, values that are significantly higher than those for non-CD recipients ($p = 0.04$), but the difference lost significance when the comparison was made for patients transplanted beyond year 2000; and the risk of death did not differ between groups. The limitation of this last study is related to the fact that the cohort was not designed for assessment of CD outcomes; therefore, CD recurrence could have been misclassified as rejection or graft failure and therefore could have contribute to the higher rate of graft failure. In the close future, the use of new tools, like the confocal laser endomicroscopy during endoscopic imaging, will allow to perform *in vivo* microscopy of the intestinal mucosa and might help the gold standard graft biopsy to differentiate recurrence (Langhans cell granuloma at biopsy) versus rejection (lymphocyte infiltrate, apoptosis, and villi morphological alterations at biopsy) by performing early diagnosis and characterization of the mucosal changes [121]. In spite of a growing reticence in transplanting patients with CD [122], because of the immune nature of the disease, the past and current available data in international literature support that ITx is a valid but last alternative for CD patients, with type 3 IF when failing TPN [6,123–142]. Disease recurrence and its real long-term impact still require a large prospective multicenter study to be completely described and understood, and, as experience and outcomes in ITx improve, indications for ITx will widen. Until the mysteries of CD are uncovered, every effort should be made to ensure that excellent patient health care is delivered in appropriately and organized multidisciplinary teams.

8. Expert commentary

CD involves immune and microbial dysregulation, induced by environmental factors in genetically susceptible individuals, and the role of autoimmunity is confirmed by circulating antibodies against intestinal epithelial barrier function and by commensal enteric bacterial population involvement: the activity of the immune system is proved, thanks to the benefit due to specific inhibition of cytokine like TNF by biologics as current main therapy in severe CD and, through the genetic mutation of NOD2 protein, responsible for an altered immune response, impaired mucosal barrier function, and microbial dysbiosis among few CD patients. Therefore, it is not surprising that in the 1980s and most of the 1990s, treatment of moderate-to-severe CD was based on concomitant introduction of immunomodulators like TPs with the use of CS for symptom reduction. Nowadays, budesonide is considered an option in the treatment of acute, mild ileocecal CD, while the role of TPs or MTX is more important as steroid-sparing and maintenance treatment after remission. Only patients with disease refractory to CS should be treated with an anti-TNF (biologic)-based strategy, although nonsurgical (endoscopic balloon dilatation and stenting) and surgical (stricturoplasty or open/laparoscopic bowel resections) options should also be considered. The main reason for stricturoplasty popularity among surgeons is the preservation of small bowel length in order to reduce the probability of SBS, but it has been associated with a risk of stricture relapse in 30–35% of patients, consequently requiring recurrent procedures. Whenever medical and surgical treatment fails, due to inability of maintaining

disease remission and/or repeated surgical resections till IF with TPN complications, transplantation could represent a good therapeutic option due to two main reasons: the possibility to replace completely the affected native bowel and the need of immunosuppression. Immunosuppressive drugs like tacrolimus have been used since the 1990 in CD patients, with optimal results as in the case of fistulas or acute colitis. The widespread use of tacrolimus plus steroids as maintenance therapy in ITx recipients could therefore represents 'the ace in the hole' in order to prevent rejection (main cause of graft loss after ITx) and CD recurrence; the reality is that the present immunosuppressive maintenance strategies are not able to prevent rejection (early or late) forever in ITx population, and moreover, genetic alterations affecting few CD/ITx patients (NOD2 mutations) may be responsible for the disease recurrence after the transplant because current immunosuppressive modalities are not able to avoid it. The presence of CD-associated polymorphisms in the NOD2 gene was found in few papers to represent itself a critical immunological risk factor for allograft loss and bowel rejection in ITx recipients, but this data was not confirmed by different authors, while rejection itself has been proposed as the fourth inflammatory bowel disease after celiac disease, UC, and CD. The evidence of an association between IBDs and the ITx recipients is related to the observation of a clinical response to the administration of TNF-α inhibitors, used to treat chronic intestinal transplant ileum ulcers and exfoliative rejections after ITx, refractory to conventional therapies. Notwithstanding, ITx appears as a reasonable alternative, which has slowly increasing over the last years, and nowadays, CD ranks among the indications for ITx in adults. The reported outcomes after ITx for CD are not different among intestinal/multivisceral transplants performed for other disorders, and this therapeutic option must be kept in the armamentarium of any center dedicated to rescue CD patients.

9. Five-year view

Patients affected by CD have nowadays an overwhelming amount of medications able to produce and maintain remission of the disease; few cases are nonresponders or prone to recurrence, and these patients are often subjected to endoscopic treatment. Surgery is usually reserved for unresponsive patients, in form of a conservative treatment as stricturoplasty. Regarding new technologies, robotic surgery has demonstrated to be safe and feasible but not financially advantageous; single-port laparoscopy is limited to the extension and severity of CD, and there are similar considerations for NOTES (natural orifice surgery) and TAMIS (transanal minimally invasive surgery) according to the orifice used. Unfortunately, some of the patients will undergo later many bowel resections in order to control disease deterioration, and it will be necessary to support them nutritionally by TPN. Parenteral nutrition management has improved dramatically over the last 10 years, and the rate of related complications has notably decreased; notwithstanding, some patients will experience TPN complications and, if IF becomes irreversible, they will be candidate to bowel transplantation. Over the last 15 years, intestinal/multivisceral transplantation has gained acceptance in the medical community due to optimal short-term results, especially in high-volume transplant centers. Long-term outcomes are still far from other abdominal organs like kidney or livers, but the introduction, in the immunosuppressive management, of drugs against antibodies and lymphatic cells has improved substantially the high rates of rejection affecting a lymphatic-rich graft like the bowel. Another step towards success has been represented by the understanding of the role of donor-specific antibodies in order to minimize the high rate of early and especially late graft loss affecting ITx. In the next few years, ITx will continue to represent a reasonable option to be offered to unresponsive and complicated CD patients, otherwise unable to treat efficaciously their disease.

Key issues

- Crohn's disease is a multifactorial disorder where the immune system dysfunction plays a pivotal role
- Medical therapy represents the gold standard in CD care
- Endoscopic treatment has gained popularity in the last decade
- Surgery must be evaluated in every patient in context with risk of medical therapy and structural changes
- When irreversible IF is associated with TPN complications, ITx must be considered a feasible therapeutic option
- The outcome of ITx in appropriate CD candidates is similar to other indications
- The role of ITx and related immunosuppression in avoiding the development of CD recurrence is still under evaluation by transplant community
- The role of screening patients for NOD-2 mutations as a prognostic tool for the clinical surveillance of CD ITx should be confirmed by multicenter studies

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Declaration of interest

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