Nutritional Therapy In Inflammatory Bowel Disease

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Abbreviations

Inflammatory bowel disease (IBD)

Health-related quality of life (HRQoL)

Crohn's disease (CD)

Ulcerative colitis (UC)

Gastrointestinal (GI)

Nucleotide-binding oligomerization domain 2 (*NOD2*)

Caspase activation and recruitment domain 15 (*CARD15*)

Nuclear factor-kappa B (NF-κB)

Primary sclerosing cholangitis (PSC)

Nonalcoholic fatty liver disease (NAFLD)

Colorectal cancer (CRC)

Computer tomography (CT)

Ultrasound (U/S)

Magnetic resonance imaging (MRI)

ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology, and Nutrition)

ECCO (European Crohn’s and Colitis Organization)

MR enteroclysis (MRE)

Azathioprine (AZA)

6-mercaptopurine (6-MP)

Nausea and vomiting (N\V)

Methotrexate (MTX)

tumor necrosis factor- alpha (TNF- α)

5-Aminosalicylic Acid (5-ASA)

Exclusive enteral nutrition (EEN)

Erythrocyte sedimentation rate (ESR)

C reactive protein (CRP)

Partial enteral nutrition (PEN)

Crohn’s Disease Exclusion Diet (CDED)

Physician’s global assessment (PGA)

Harvey Bradshaw index (HBI)

Non-commissioned officer (NCO)

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1. SUMMARY

Crohn's disease (CD), which can affect any segment of the gastrointestinal (GI) tract from the mouth to the anus, and ulcerative colitis (UC), which is primarily limited to the colon and rectum, are the two kinds of inflammatory bowel disease (IBD). These are chronic relapsing-remitting idiopathic immune-mediated inflammatory illnesses that primarily affect the gastrointestinal system and have potentially life-threatening extraintestinal manifestations.

While clinicians often track the direct impact of disease on their patients, such as changes in laboratory testing or imaging, it's also vital to think about how IBD affects the quality of life. When evaluating a patient's health-related quality of life (HRQoL), all areas of their lives are considered, including psychological and functional domains that a specific disease may impact.

IBD is linked to a slew of unpleasant symptoms, including the need for frequent bowel movements, abdominal pain, lethargy, sleep disturbances, and poor nutrition. Because IBD is a chronic, relapsing disorder with a diagnosis generally occurring at a young, developmentally crucial age, the impact on life quality is likely to be considerable. All of these can harm HRQoL indicators, which have been known for over 20 years.

Diet plays a vital role in the pathogenesis of IBD, with some dietary components having a more significant impact on the gut microbiome and the ability to worsen or alleviate the course of IBD.

The challenges of pharmacotherapy adherence and their loss of response, as well as the realization that all children with IBD require appropriate nutritional assessment and support to avoid growth retardation due to malnutrition, have led to the development of specific diets as the primary treatment for IBD.

Enteral nutrition remission induction in children with Crohn’s disease, without additional immune suppression, is a well-known and effective method, especially in those with mild or moderate disease. Unfortunately, it is not effective for remission maintenance and treatment interruption due to non-tolerance or non-compliance is common.

Novel nutritional approaches with a combination of EN and normal diet with inclusion/exclusion of foodstuffs result in better compliance, absence of side effects and prolonged remission.

Therefore, diet measures could play an important role in IBD treatment in both children and adults, and are subject to many ongoing studies.

2. SAŽETAK

Crohnova bolest (CB), koja može zahvatiti bilo koji segment gastrointestinalnog (GI) trakta od usta do anusa, i ulcerozni kolitis (UK), koji je prvenstveno ograničen na debelo crijevo i rektum, dvije su vrste upalne bolesti crijeva (UBC). To su kronične recidivirajuće idiopatske imunološki posredovane upalne bolesti, koje prvenstveno utječu na gastrointestinalni sustav i imaju potencijalno po život opasne izvancrijevne manifestacije.

Dok liječnici često prate učinak bolesti na svoje pacijente, temeljem promjena u laboratorijskim pretragama ili nalazima slkiovnih metoda , također je važno razmisliti o tome kako UBC utječe na kvalitetu života. Prilikom procjene kvalitete života bolesnika povezane sa zdravljem (HRQoL), uzimaju se u obzir sva područja njegovog života, uključujući psihološke i funkcionalne domene na koje određena bolest može utjecati.

UBC je povezan s nizom neugodnih simptoma, uključujući potrebu za čestim pražnjenjem crijeva, bolove u trbuhu, letargiju, poremećaje spavanja i lošu prehranu. Budući da je UBC kronični, relapsirajući poremećaj s dijagnozom koja se općenito javlja u mladoj, razvojno ključnoj dobi, utjecaj na kvalitetu života vjerojatno će biti značajan. Sve to može štetiti pokazateljima HRQoL-a koji su poznati već više od 20 godina.

Prehrana igra vitalnu ulogu u patogenezi UBC-a, pri čemu neke komponente prehrane imaju značajniji utjecaj na crijevni mikrobiom i sposobnost pogoršanja ili ublažavanja tijeka UBC-a.

Izazovi zbog nepridržavanja farmakoterapiji i gubitka odgovora, kao i spoznaja da je djeci s UBC-om potrebna odgovarajuća nutritivna procjena i podrška kako bi se izbjeglo usporavanje rasta zbog pothranjenosti, doveli su do razvoja specifične prehrane kao primarnog liječenja UBC-a.

Uvođenje u remisiju enteralnom prehranom, u djece s Crohnovom bolesti bez dodatne imunosupresije već je poznata i djelotvorna metoda osobito u onih s blagim ili srednje teškim oblikom bolesti. Nažalost se nerijetko prekida zbog nesuradljivosti ili nepodnošljivosti a nije pogodna niti kao terapija održavanja.

Noviji nutritivni pristupi u kojima se kombiniraju enteralna prehrana i uobičajena prehrana uz isključivanje/uključivanje određenih namirnica (CDED) rezultiraju prije svega boljom suradljivošću, odsustvom nuspojava i duljem trajanju remisije.

Stoga, dijetalne mjere mogu igrati važnu ulogu u liječenju UBC bolesti u djece i odraslih te je utjecaj prehrane na patogenezu i dinamiku bolesti i dalje predmet brojnih istraživanja

3. INTRODUCTION

The medical condition inflammatory bowel disease (IBD) comprises a group of disorders with two main types, Crohn's disease (CD), which can affect any segment of the gastrointestinal (GI) tract from the mouth to the anus, and ulcerative colitis (UC) which is primarily restricted to the colon and rectum. These conditions are chronic relapsing-remitting idiopathic immune mediates inflammatory diseases that primarily affect the GI tract and cause potentially serious extraintestinal manifestations affecting the skin, joints, liver, and eyes. They are considered life-long conditions, and commonly have their onset in late adolescence or early adult years. IBD pathogenesis and etiology are complex and yet partially known but are considered multifactorial with genetic, microbial and environmental components.

Although the presentation of CD and UC are often similar, they can be distinguished in most cases.

3.1 Crohn’s Disease

CD first received widespread recognition in the United States as a syndrome involving the terminal ileum in 1932. It took another few years to recognize that the primary process could involve any part of the ileum and jejunum. Later, in 1954, a larger series of case observations v. However, it was not until 1965 that Crohn's colitis was recognized in the United States. From these early landmark descriptions until nowadays, our knowledge of CD has progressed immeasurably [1,2].

CD is described as chronic inflammation that can appear anywhere along the GI tract, from the lips to the anal canal, although mostly found in the terminal ileum and colon. CD is associated with trans-mural (= full-thickness) intestinal inflammation. Several of the grave complications that can occur as a result of this are strictures that can lead to intestinal obstruction, abscesses and fistulas. Macroscopically, CD appears as a patchy mucosal inflammation and discrete ulcered areas, often described as “cobble-stone". Microscopically, the presence of non-caseating granulomas is a pathognomonic hallmark of

CD [3,4]. Further information regarding the clinical picture and the extraintestinal manifestations of CD will be described later.

3.2 Ulcerative Colitis

The main distinguishing characteristic of UC from CD is that UC only affects the colon. An additional difference pertains to both the macroscopic and microscopic appearance of the gut. Unlike the discrete, patchy and characteristically deep appearance of CD, the appearance with UC is of continuous circumferential inflammation and superficial ulceration. Microscopically the inflammation in UC is limited to the mucosa or sub-mucosal layers only. Another key difference that can distinguish UC is the intestinal complications. unlike the perforation, strictures and fistulas are seen in CD, the main serious complication of UC relates to severe colonic inflammation that leads to toxic megacolon, with a risk of perforation, significant morbidity and even mortality [3,4]. Further information regarding the clinical picture and the extraintestinal manifestations of UC also will be described later.

Crohn Disease	Ulcerative Colitis
Small bowel is involved in 80% of cases.	Disease is confined to the colon.
Rectum is often spared; colonic involvement is usually right-sided.	Rectum is invariably involved; colonic involvement is usually left-sided.
Gross rectal bleeding is rare, except in 75–85% of cases of Crohn's colitis.	Gross rectal bleeding is often present.
Fistula, mass, and abscess development are common.	Fistulas do not occur.
Perianal lesions are significant in 25–35% of cases.	Significant perianal lesions never occur.

Crohn Disease	Ulcerative Colitis
On x-ray, the bowel wall is affected asymmetrically and segmentally, with skip areas between diseased segments.	The bowel wall is affected symmetrically and uninterruptedly from the rectum proximally.
Endoscopic appearance is patchy, with discrete ulcerations separated by segments of normal-appearing mucosa.	Inflammation is uniform and diffuse.
Microscopic inflammation and fissuring extend transmurally; lesions are often highly focal in distribution.	Inflammation is confined to mucosa except in severe cases.
Epithelioid (sarcoid-like) granulomas are detected in bowel walls or lymph nodes in 25–50% of cases (pathognomonic).	Typical epithelioid granulomas do not occur.

Table 1. Differentiating Crohn's Disease and Ulcerative Colitis.
From: Walfish AE, Companioni RAC. MSD Manual Consumer Version. MSD Manuals; 2022 [5]

Regarding therapy, approximately a hundred years ago, the treatment of colitis consisted of bed rest and colon irrigation. From that time until nowadays, there has been major progress in this field and lots of therapy options were discovered, among them are anti-inflammatory drugs, immunomodulators, biological therapies, antibiotics and others.

There were also discoveries about the effect of diet and nutrition on the exacerbation and remission of the disease. The understanding that specific dietary components can affect the inflammatory process together with the perception that there's a need to provide adequate nutritional support to promote normal growth and development of the child, has led to the development of specific nutritional therapy that goes beyond the common dietary modifications.

4. IBD CHARACTERISTICS

4.1 Epidemiology

IBD can affect people of all ages, but the onset is usually before age 30. IBD has a bimodal age distribution, with a peak incidence from 14 to 24, and between the ages of 50 and 70, there may be a second minor peak. About 10% of cases occur in individuals <18 years old. In general, UC appears 5-10 years later than CD [6,7].

IBD usually affects people of Northern European origin and in industrialized nations. It's 2 to 4 times more common among Ashkenazi Jews than non-Jewish whites from the exact location. A lower incidence is seen in central and southern Europe and South America, Asia, and Africa. However, the incidence increases among blacks and Latin Americans living in North America [5,8].

According to M'Koma et al., "the highest annual incidence of IBD in Europe was 24.3 per 100,000 person-years for UC, and 12.7 per 100,000 person-years for CD, that in North America was 19.2 per 100,000 person-years for UC and 20.2 per 100,000 person-years for CD and that in Asia and the Middle East was 6.3 per 100,000 person-years for UC and 5.0 per 100,000 person-years for CD. The highest prevalence for UC was 505 per 100,000 persons in Europe and 249 per 100,000 persons in North America. The annual prevalence of CD was 322 per 100,000 persons in Europe and 319 per 100,000 persons in North America. A time-trend analysis showed that 75% of studies on CD and 60% of studies on UC displayed an increasing incidence with statistical significance ($P < 0.05$)" [9,10].

Looking at this disease from the pediatric perspective, there's an increase in the incidence rates of IBD in children worldwide. The highest incidence of pediatric IBD is in North America and Europe. IBD among children and adolescents accounts for approximately 30% of total IBD [11]. According to Kugathasan et al. reports, "the incidence of IBD in a city of the United States was 5 per 100,000 to 11 per 100,000 children (4.56 per 100,000 for CD and 2.14 per 100,000 for UC), suggesting that CD predominates over UC in

children". Moreover, the incidence of CD is dramatically rising, unlike the steady increase in the incidence of pediatric UC [12].

Additionally, smoking was found to influence the course of IBD. Its association with UC was first described by Harries et al. [13]. They identified a decreased frequency of smoking in UC patients compared to healthy controls. In line with these findings, a meta-analysis conducted by Mahid et al. demonstrated that smoking increased the risk for CD by two folds [14]. According to these results, we can conclude that, generally, cigarette smoking seems to contribute to the development or exacerbation of CD but decreases the risk of UC.

Besides smoking, appendectomy was also found to lower the risk of UC and increase the risk of CD by Kaplan et al. On the contrary, Nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate IBD and oral contraceptives may increase the risk of CD [15].

When comparing gender incidence rates, both sexes are equally affected, although UC is slightly more common in males, whereas CD is more frequent in women.

IBD is known to have a genetic component attributing to the development of the disease, as IBD patients' first-degree relatives are at a 4- to 20-fold higher risk of getting the disease and their absolute risk may be as high as 10%. It also found that familial tendency in CD is much higher than in UC [16].

4.2 Etiology

As previously said, the etiology of IBD is complex and still unclear, but it is widely agreed to be multifactorial, involving the interaction of genetic, environmental, immunological, and microbial factors, which manifest differently in CD than in UC.

Genetic

Several studies demonstrated the role of genetic factors in susceptibility to IBD. However, the conclusion was that the disease is genetically complex, and a single gene cannot give an explanation but several gene models.

It was found that there is an increased prevalence of IBD in first- and second-degree relatives and a higher relative risk among siblings. The familial frequency of IBD ranges from 20% to 30% in referral-based studies [17]

One of the clearest linkages is for IBD-1, a susceptibility locus of chromosome 16 containing mutations in the NOD2/CARD15 gene that have been associated with CD but not UC [18]. This gene is only expressed in monocytes and plays a role in activating nuclear factor-kappa B (NF-κB), a critical mediator of inflammatory responses and leads to the production of proinflammatory cytokines [19]. Patients with NOD2/CARD15 genotype have demonstrated fibrostenosing disease, usually in the ileum, and earlier disease onset [20]. Another gene, IBD5, located within the 5q31 cytokine cluster, has been associated with perianal disease in Crohn's patients.

Immune

In a healthy individual, the relationship between commensal bacteria and the host is symbiotic. Exposure to commensal bacteria, according to Donnenberg and Neish et al. findings, causes down-regulation of inflammatory genes and blocks activation of the NF-B pathway, inhibiting the gut's inflammatory immune response to the massive number of microbes and food antigens to which it is constantly exposed [21,22]. In IBD, this tolerance is lost, so exposure to luminal microflora now triggers an inflammatory response by the

cells lining the mucosa, leading to a chronic, destructive immune response [23].

Environmental

The higher incidence of IBD seen in industrialized countries is postulated to result from dietary changes, smoking, and industrial chemicals which are examples of "westernization" of lifestyles. [24]. One of the most vital environmental risk factors for IBD is smoking. As noted, smoking has a complex relation to IBD as it's known to reduce the risk for UC but increase the risk for CD. Stress is a known factor to affect the development and exacerbation of IBD. Diet is also an essential component. Many studies have found that persons with IBD lower their intake of particular foods containing fibers such as vegetables, fruits, cereals, brown/wholemeal bread, and nuts, and increased intake of high-sugar foods and white bread [25]. This and more will be described in detail below.

4.3 Clinical picture and diagnosis

4.3.1 Signs and symptoms

The clinical picture of IBD shows some common symptoms that arise from intestinal inflammation, such as persistent diarrhea, abdominal pain, rectal bleeding/bloody stools, weight loss and fatigue [26]. Despite the differences in signs and symptoms between UC and CD, it can be challenging to tell the two apart.

Some differences between CD and UC lie in the extraintestinal manifestations of each condition.

In CD, joint involvement is common, can be either peripheral or axial, and can even precede the diagnosis of IBD by several years [27]. Skin changes like pyoderma gangrenosum and erythema nodosum. Ocular involvement can include iritis, uveitis and episcleritis. Patients with CD are more likely to develop osteoporosis, avascular necrosis, and venous and arterial thromboembolism, all linked to the disease and its treatment [28]. Patients with CD may develop liver problems such as primary sclerosing cholangitis (PSC), which can lead to cirrhosis, and nonalcoholic fatty liver disease (NAFLD) [4,29]. Moreover, those patients suffer more often from gallstones and renal calculi. Finally, mood disorders including anxiety and depression are significantly more common in IBD, with psychological manifestations seen in over 50% of CD patients [30].

In UC, the occasional small bowel involvement is known to result from "backwash" from the inflamed colon rather than primary small bowel involvement. Patients with UC tend to have higher rates of colorectal cancer (CRC) [7,31,32]. Fecal urgency and tenesmus secondary to rectal inflammation can be particularly distressing. The extraintestinal manifestations that UC patients are known to suffer from are somehow like those mentioned in CD with specific HLA-B27 associated spondylitis and ocular complications, including uveitis [28]. In addition, pyoderma gangrenosum is more strongly associated with UC than CD [3].

4.3.2 Diagnosis

The broad spectrum of signs and symptoms and the fact that most of them are nonspecific make the diagnosis of IBD very challenging. A thorough and meticulous assessment of all the factors is an integral part of the diagnostic procedure. Nowadays, there's no single diagnostic test to confirm the diagnosis of IBD. The diagnosis, therefore, remains based on combinations of history, examination, imaging, histology and possibly serological findings.

A proposed diagnostic evaluation published in 2010 by the World Gastroenterology Organization [4] includes:

1) Comprehensive history

2) Physical examination

3) Stool analysis to exclude infection

4) Full blood examination (FBE), albumin, ferritin, C-reactive protein (CRP)

5) Human Immunodeficiency Virus (HIV)/Tuberculosis (Tb) testing if from a high-risk population

6) Colonoscopy and biopsy for histology

7) U/S abdomen

8) MRI or CT abdomen

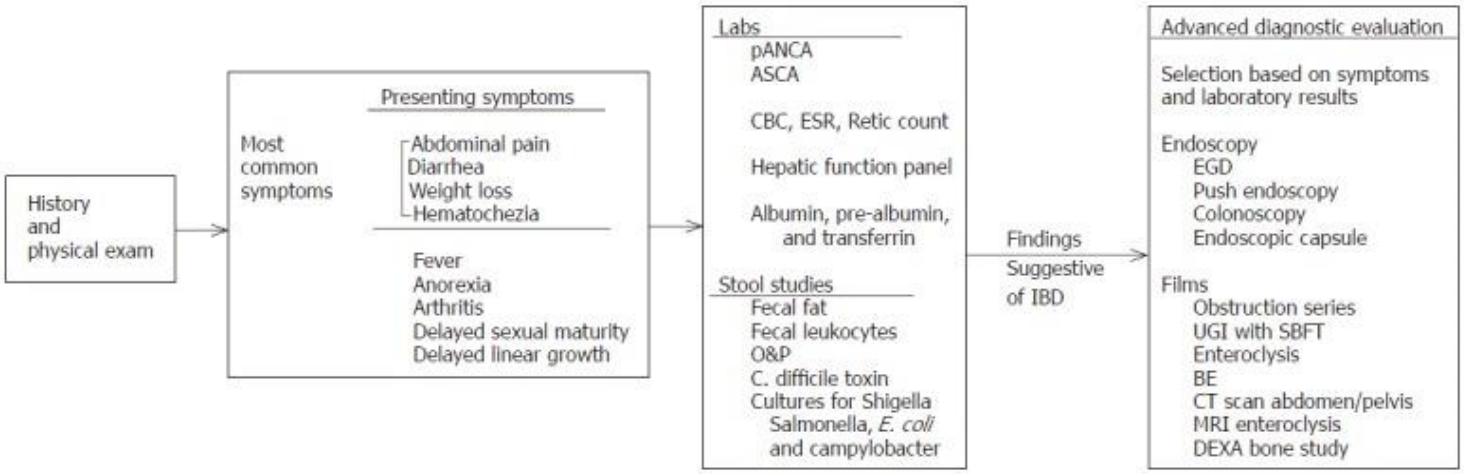

Figure 1. Diagnostic Evaluation for IBD in Pediatric Patients.
From: Diefenbach, K. A., & Breuer, C. K., WJG 2006;12(20), 3204.[33]

Additional criteria made by the ESPGHAN is the Revised Porto Criteria for Diagnosis of IBD, which is the following:

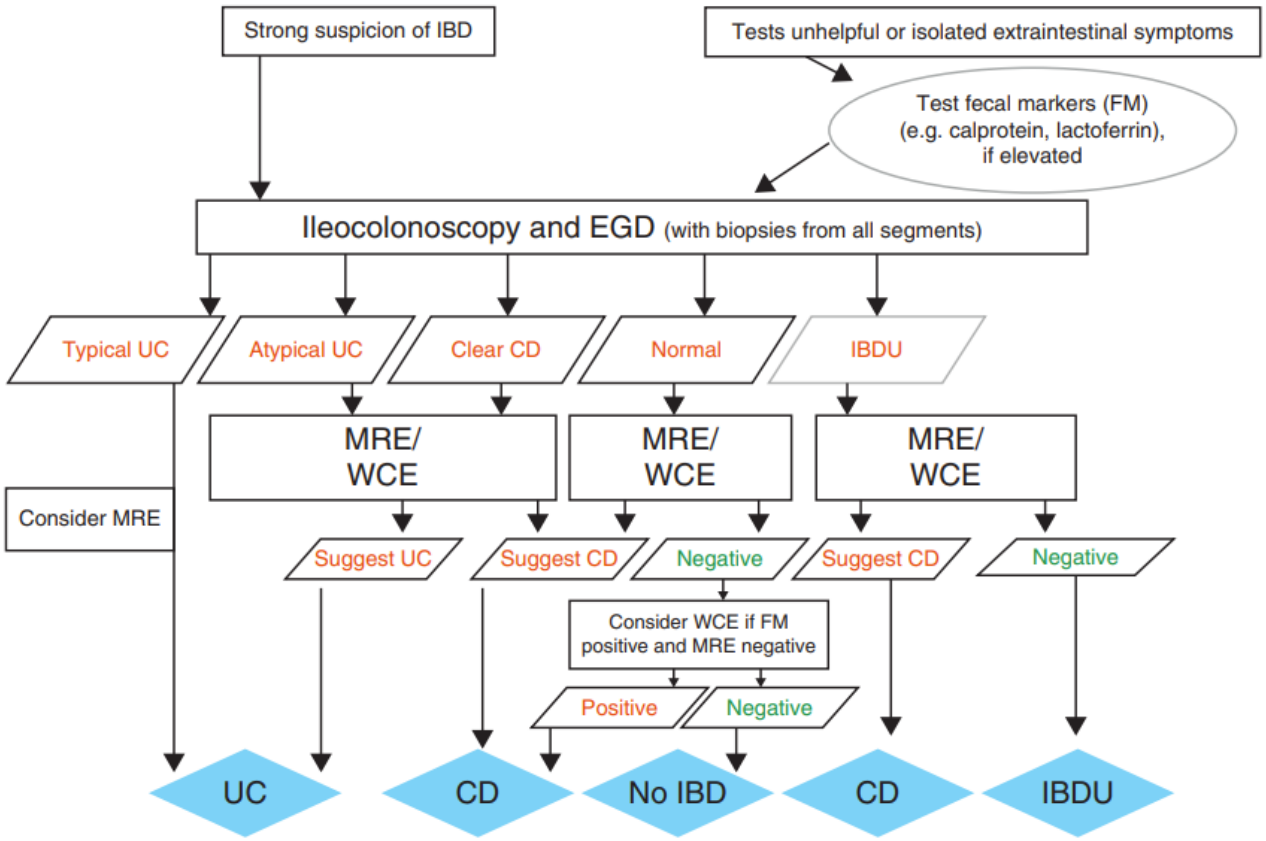

Figure 2. Evaluation of child/adolescent with intestinal or extraintestinal symptoms suggestive of IBD. Atypical UC is a new IBD category consisting of 5 phenotypes, and reflects a phenotype that should be treated as UC. IBD-U may be entertained as a tentative diagnosis after endoscopy, and can be used as a final diagnosis after imaging and a full endoscopic workup. UC is divided into typical UC and atypical UC. CD = Crohn's disease; EGD = esophagogastroduodenoscopy; FM = fecal marker; IBD = inflammatory bowel disease; MRE = magnetic resonance enterography; UC = ulcerative colitis; WCE = wireless capsule endoscopy. From: Levine, A. et al. , JPNG 2014;58(6):795-806. [34]

Endoscopic assessment plays a crucial role in defining IBD phenotype and distribution and guiding severity assessment and prognosis. This procedure allows direct mucosal inspection and tissue biopsy for histopathology [35]. Some of the histopathological differences between CD and UC were mentioned before.

Regarding imaging modalities, Plain films are essential in the acutely ill patient to look for complications such as obstruction, toxic megacolon, or perforation. In the non-acutely ill patient, contrast studies may be more beneficial in making a diagnosis. A CT scan is helpful in the diagnosis and management of patients presenting with acute onset of symptoms or an exacerbation of their disease. CT can assess intestinal abnormality and extraluminal abnormalities such as abscess formation [35,36]. MR enteroclysis (MRE) is a new technique being evaluated to evaluate the small bowel for CD, and initial reports are promising that it is susceptible. Thickening of the bowel wall, skipped lesions, stenotic areas, and fistulas have all been diagnosed with more sensitivity when compared to conventional small bowel follow-through. It has the added benefit of minimal radiation exposure due to the need for fluoroscopy [37].

4.3.3 Differential diagnosis

As previously noted, IBD has a broad and vague clinical picture, therefore the differential diagnosis can encompass a wide range of inflammatory or viral disorders that mimic IBD.

Infectious	Non-infectious (inflammatory)	Non-infectious (toxic)	Non-infectious (malignant)	Non-infectious (other)
Yersinia spp	Diverticulitis	Postoperative diversion colitis	Colorectal cancer	Irritable bowel syndrome
Mycobacterium tuberculosis	Ulcerative colitis	Bile acid loss	Small-bowel cancer and lymphoma	Ischaemic colitis
Atypic micobacterias	Microscopic colitis	Overuse of non-steroidal anti-inflammatory and other drugs		Chronic pancreatitis and malabsorption
	Behçet syndrome Radiation enteritis Sarcoidosis Celiac disease Ulcerative jejunoileitis	Excessive or misuse of laxatives		

Table 2. Differential diagnosis in Crohn's disease.

From: Andres PG, Friedman LS. Gastroenterol Clin North Am. 1999;28:255–281.[38]

5. TREATMENT

Currently, there's no cure for IBD and the goal is mainly to achieve remission, maintain it, and prevent relapses. There are several methods of treatment with a typical role to heal the mucosal inflammation and improve the quality of life. According to ECCO and ESPGHAN, the guidelines for the management of pediatric UC are:

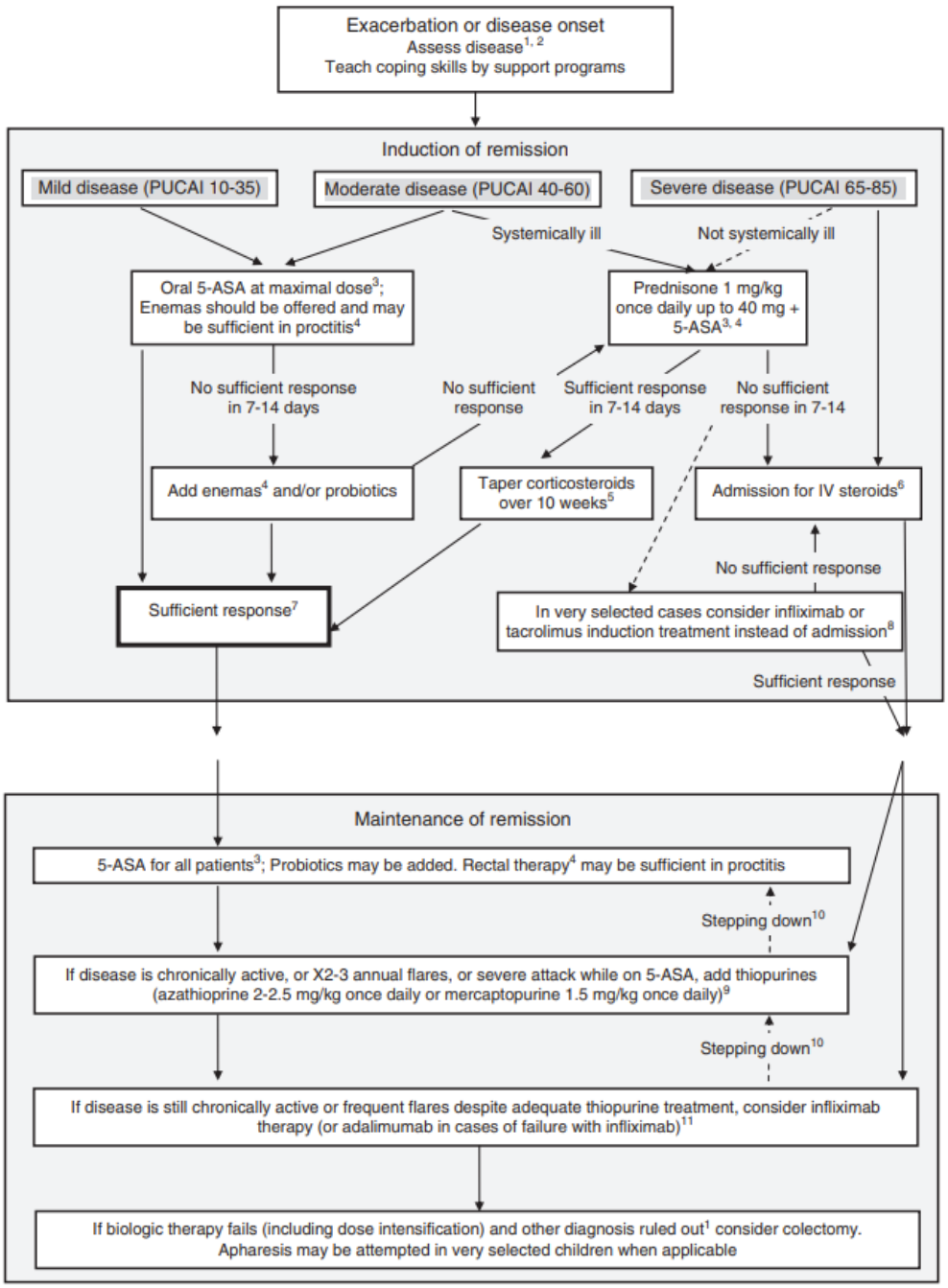

Figure 3. Joint ESPGHAN- ECCO therapeutic paradigm for pediatric UC.

From: Turner D. et al.. *JPGN 2012;55*(3), 340-361.[39]

Their guidelines for the management of pediatric CD are:

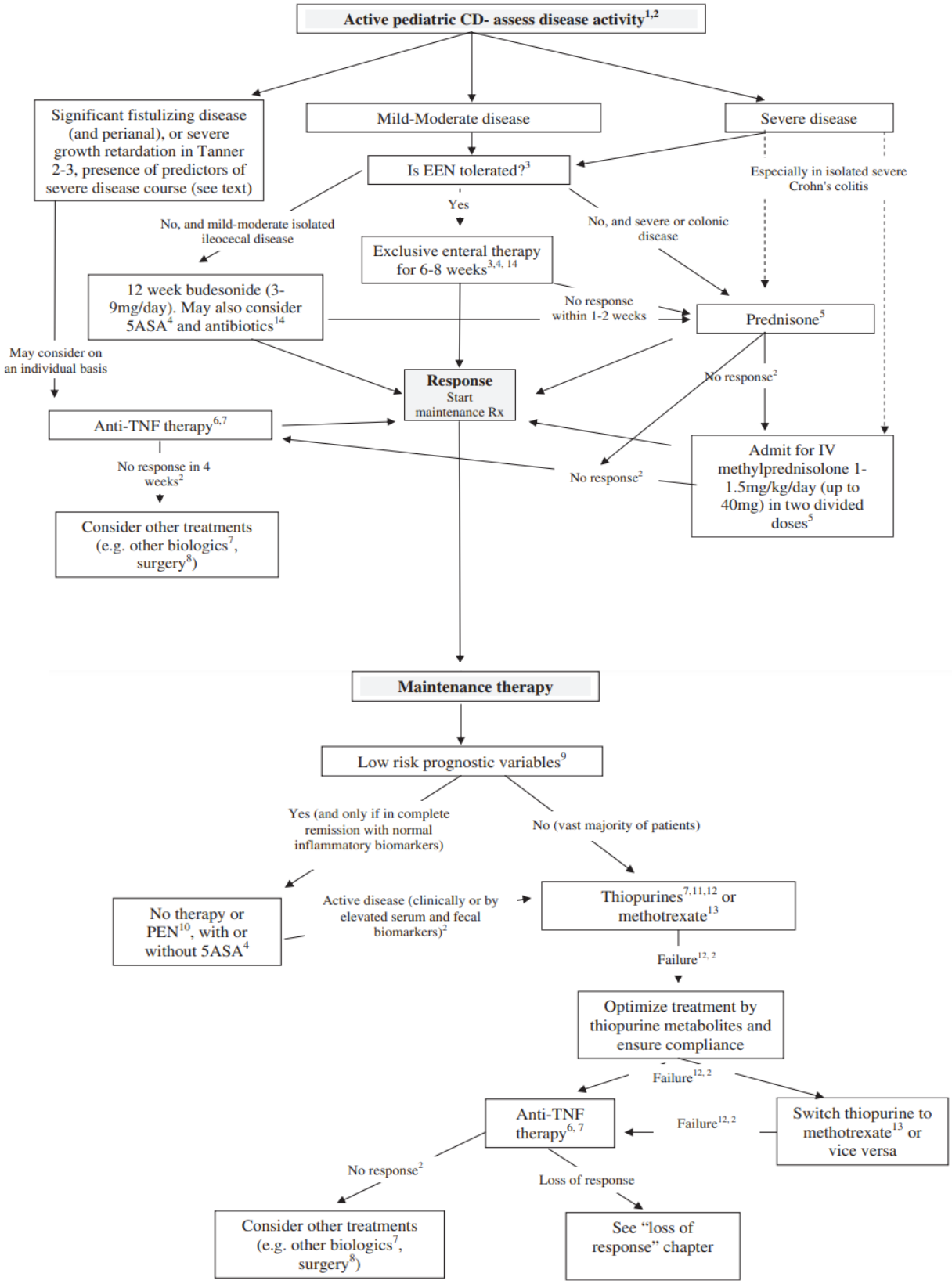

Figure 4. Joint ESPGHAN- ECCO therapeutic paradigm for pediatric CD.

From: Ruemmele, F. et al.M., J Crohns Colitis 2014;8(10):1179-1207. [40]

5.1 Pharmacotherapy

5.1.1 Anti-inflammatory

Anti-inflammatory drugs are usually the first-line treatment for IBD and include aminosalicylates and corticosteroids.

Aminosalicylates (5-ASA agents)

5-Aminosalicylic Acid (5-ASA) blocks the production of prostaglandins and leukotrienes and has other beneficial effects on the inflammatory cascade. The main agents in this class are Mesalamine (the active moiety) and Sulfasalazine (complexing 5-ASA with a sulfa moiety). These drugs are usually used to induce remission in mild IBD or maintain remission in moderate IBD. Nausea, dyspepsia, headache, interference with folic acid absorption, and hemolytic anemia or agranulocytosis are side effects linked to the sulfa component of the medicine [41].

Corticosteroids

Corticosteroids are beneficial for inducing remission in UC and CD and act rapidly to alleviate symptoms. Still, they do not heal mucosal lesions and are therefore of no benefit for maintenance therapy [42]. Moreover, their unfavorable side effect profile makes them unsuitable for long-term use.

5.1.2 Immunomodulators

Some of the agents in this class are azathioprine (AZA) and 6-mercaptopurine (6-MP), which are thiopurines with a complex metabolic pathway. [43]. They've been used in maintaining remission or when the patient became steroid-dependent, but they are ineffective in the induction of remission since they have a prolonged onset of action. Their side effects include hepatotoxicity, myelosuppression, pancreatitis, N/V, and allergic reactions [19]. Another known immunomodulator is Methotrexate (MTX), which is used as an alternative to the thiopurines due to suboptimal results or intolerance of the medications. Unlike thiopurines, MTX can be used for induction and remission maintenance. Its known side effects are nausea, vomiting, diarrhea, stomatitis, rash, arthralgias, leucopenia, and hepatotoxicity [19].

5.1.3 Biologic therapy

Biological agents are the most recent addition to therapy in IBD and they have dramatically changed the approach to modern CD management. They have demonstrated the ability to alter the behavior and complications of the disease. Infliximab and adalimumab, a chimeric monoclonal antibody directed against tumor necrosis factor-alpha (TNF-), are established biological agents in IBD therapy for lowering the inflammatory response seen in CD. They are both effective in luminal and peri-anal CD. They may be used in patients refractory to the other pharmacological agents or steroid-dependent to achieve remission induction and maintenance [19]. It is possible to develop antibodies to infliximab and thus decrease responsiveness, which is preventable by concomitant therapy with immunomodulators. Other downsides to biologic agents are that they are expensive and can be administered by intravenous or subcutaneous injection. Other side effects include flushing, rash, dyspnea, and headache and are typically seen at the time of infusion and opportunistic infections.

5.1.4 Antibiotics

The antibiotics metronidazole and ciprofloxacin have been widely used to treat mild IBD, even though their efficacy is unproven. Antibiotic use for complications of CD, including local abscess formation, is common. Short-term use of metronidazole to prevent recurrence after surgery [44] and ciprofloxacin in combination with biological therapy to treat peri-anal fistulae have both been shown to be effective [45].

5.2 Surgery

If refractory to all other treatment modalities, diet, lifestyle changes, and several medical therapy attempts, the other option is surgery.

Historical data suggested that up to two-thirds of CD patients will likely require surgery along the course of their disease. Common indications are for perforating and stricturing disease phenotypes. However, surgery doesn't cure CD, with high post-operation recurrence and re-operation rates of over 50% [46].

As opposed to surgery for CD, surgical intervention for UC, in the form of removal of the entire colon and rectum, is considered an essentially curative procedure. Colectomy rates vary between studies, ranging from 8.7 – 54% ten years from diagnosis [47]. Common indications are failure to respond to intensive medical therapy or developing complications such as high-grade dysplasia or cancer. However, it should be remembered that colectomy with subsequent restorative ileoanal pouch surgery can provide proper bowel function without stoma in most operated patients, and surgical consultation should occur early in severe disease [48].

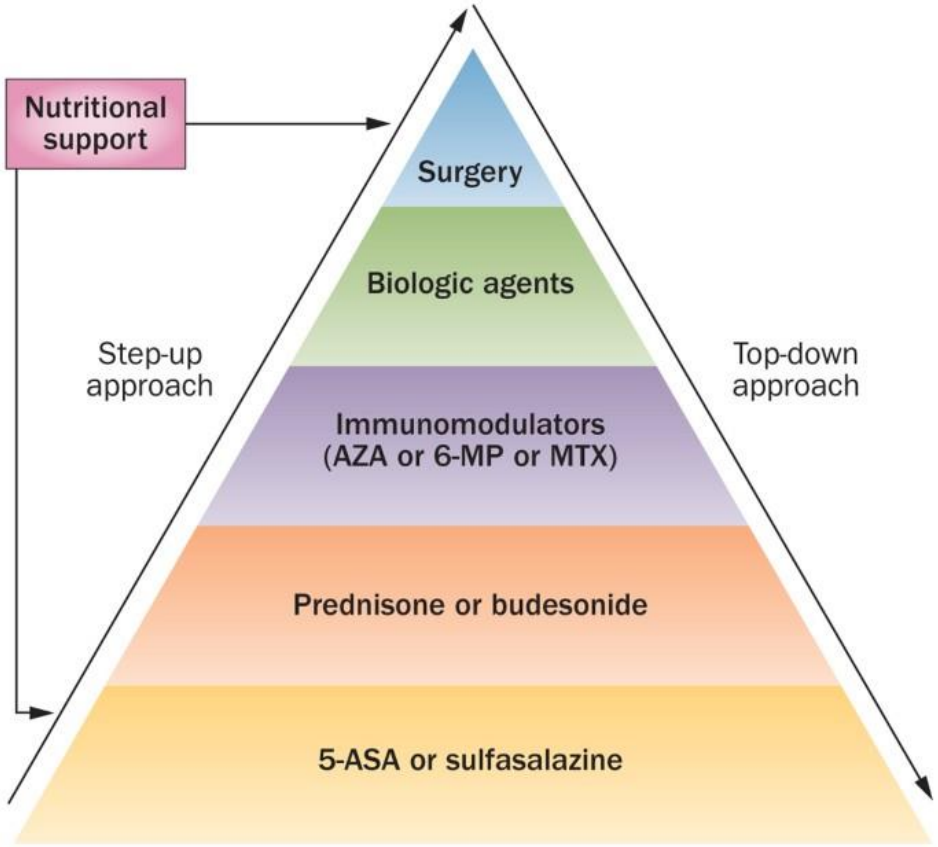

Figure 5. Therapeutic pyramid for pediatric IBD.
From: Aloi, M., Nuti, F., Stronati, L. et al. Nat Rev Gastroenterol Hepatol ,2014; 11, 99–108. [49]

5.3 Nutritional therapy

It is now known that diet has an essential role in the pathogenesis of IBD and that dietary components, some more than others affect the gut microbiome and have the ability to exacerbate or improve IBD course.

Research and trials regarding dietary impacts in IBD in general and the developing of specific nutritional therapies, in particular, are evolving subjects of interest among gastroenterologists.

In general, nutritional therapy can be considered as supportive or primary treatment. Supportive therapy aims to correct malnutrition and macronutrient deficiencies and reverse their metabolic or pathological consequences, in addition to recommendations on specific dietary regimes. This should be considered in all patients with IBD. On the other hand, nutrition as a primary treatment has a more limited selection and can benefit specific subgroups of patients.

The realization that all children with IBD require appropriate nutritional assessment and support to avoid growth retardation due to malnutrition and the need for a more easily adhered to treatment than pharmacotherapy has led to the development of specific diets as the primary treatment for IBD, especially in children.

5.3.1 Dietary modifications

Fruits and vegetables

Fruits and vegetables are diverse foods that generally have high-fiber content. Several studies suggested that patients with IBD consume less fruit and vegetables before disease onset, particularly for CD. Significant dietary restriction of fiber leads to greater bacterial consumption of colonic mucus, contributing to inflammation. [50-52]. A diet rich in fibers was found to decrease the risk of developing CD, and among those wore were in remission, lowers the risk of flare-ups [53].

Carbohydrates

The current data regarding increased intake of carbohydrates and IBD risk is inconsistent. Several studies examining the effect of mono and disaccharides found that a high intake is associated with a higher risk of developing IBD. According to Tragnone et al., a significantly higher relative risk is associated with sugar intake in CD (relative risk: 3.5; 95% confidence interval [CI]:1.5–8.1) [54]. According to those findings, there's insufficient evidence to recommend any specific intake change of complex carbohydrates or refined sugars in both CD and IBD.

Red Meat, Processed Meat, Poultry, and Eggs

The recommendation is to reduce the intake of animal protein in IBD patients. Some studies showed an association between red meat intake and increased incidence, worsening, and relapse of UC in particular and CD (IBD overall hazard ratio: 3.03; 95% CI: 1.45–6.34) [55-57]. According to these findings, there's a recommendation to reduce the intake of red and processed meat, but the guidance regarding poultry and eggs is still inconclusive.

Dairy

Dairy products include a wide variety of natural and processed foods that may vary greatly from one product to another because of differences in processing, fat content, and food additives. Most of them contain lactose, but some do not. Recent studies showed that Odds Ratio for lactose malabsorption in patients with CD (2.29 [1.09–4.80; P ¼ .03]) and in UC (1.14 [0.69–1.86; P ¼ .62] were higher compared to the control group [58]. Unpasteurized milk should be avoided by all patients with IBD, given the potential risk of infections.

Fat

In epidemiological studies, trans and saturated fat consumption was associated with a higher risk of developing IBD [59]. In different studies, it was found that some types of fats, for example, omega-3 fatty acids (DHA and EPA) from marine fish, walnuts, flax, hemp, and chia seeds, but not from supplements, reduce the risk and alleviate active disease in UC [60].

Other dietary products were found to affect the course of IBD and their reduced intake from the patients' diet is recommended. These include alcoholic beverages, artificial sweeteners and emulsifiers and thickeners (found in processed food), among others [61].

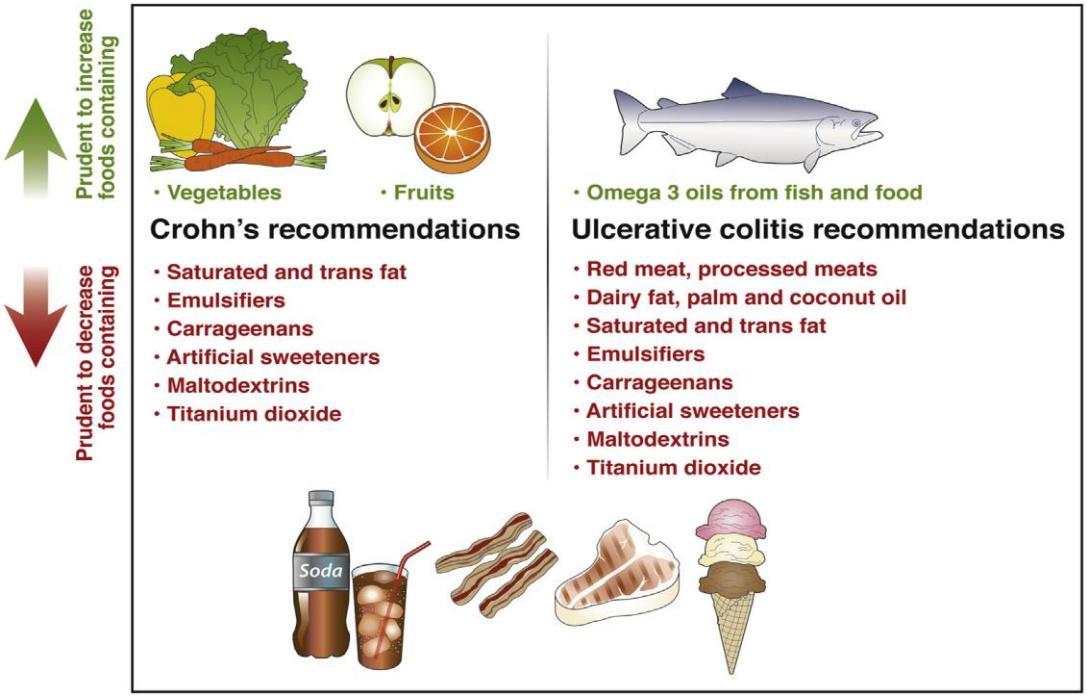

Figure 6. Dietary guidance for patients with inflammatory bowel diseases. From: Pfeffer-Gik, T., & Levine, Dig Dis, 2014; 32(4):389-394. [61]

5.3.2 Exclusive enteral nutrition (EEN)

EEN therapy involves using a standardized restricted diet composed of a single polymeric formula, a nutritionally complete liquid diet given exclusively instead of regular solids and fluids (other than water as required) for a period of 6–8 weeks as the main source of nutrition. EEN is the initial therapy for remission induction in almost every child or adolescent with a newly diagnosed CD. Early in the disease (usually during the first year), this treatment method results in clinical remission in 50 to 80 percent of children by week 8, with no additional pharmacological treatment and a significant reduction in inflammatory markers

like erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and fecal calprotectin. EEN was also found to be as effective as steroids for the induction of remission and improves mucosal healing in mild-to-moderate uncomplicated disease, which makes it a proper substitute considering steroids' side effects [62, 63].

After achieving remission, diet as a sole component of maintaining remission is both convincing and challenging. On the one hand, once remission is established, it is certainly possible that diet will be sufficient to maintain homeostasis and prevent the cascade of pro-inflammatory events leading to flare; on the other hand, long-term studies are challenging to perform, and adherence becomes a serious concern [63].

The use of EEN presents challenges to both physicians and patients, as patients have to deal with the monotony of food and taste fatigue, and some formulas have a distinct taste that prevents patients from adhering to treatment. Furthermore, up to 50% of patients may require nasogastric tubes and many might refuse to start therapy due to these issues. This limits access and availability of the treatment [63].

According to Yamamoto et al., who conducted a study in adults regarding the efficiency of EEN in maintaining remission, 40 patients treated with ileum or ileocolonic resection were allocated to one of two groups: one group (20 patients) received EEN for one year via overnight nasogastric tube feeding, and the other group (20 patients) was allowed to eat a non-restricted diet. Only 5% of the EEN group versus 35% of the free-diet group had a clinical recurrence of the disease in the 1st year of the follow-up. After one year, endoscopy was performed, and 30% of the EEN group and 75% of the nonrestricted-diet group had an endoscopic recurrence [64].

CD can lead to several complications that eventually can result in surgery. Treatment of complications, such as strictures, abscesses and fistulae, has usually been medical or surgical. Recent studies have demonstrated that EEN therapy may have the potential to treat complications and have a 'surgery sparing effect' [63].

Some studies evaluated the efficacy of EEN in complicated CD. Hu et al. conducted a prospective, observational study examining the effects of 12 weeks of EEN on inflammatory bowel strictures. They performed cross-sectional CT before and after therapy. 65% of patients achieved clinical remission, while 54% achieved radiologic remission. Additionally, they noticed a notable increase in luminal diameter and decreased bowel wall thickness [65]. Another prospective study was conducted by Yan et al. to identify the predictors of response to 12 weeks of EEN in 48 patients with CD who had enterocutaneous fistulae. They demonstrated that 62.5% had a successful fistula closure after EEN therapy with an average

closure time of 32.4±8.85 days [66].

EEN has also been demonstrated to reduce surgery in complicated diseases. Heerasing et al. showed in a retrospective case-control study that six weeks of EEN could eliminate the need for surgery in 25% of patients who were scheduled for an elective surgical resection. Moreover, they demonstrated that patients who went to surgery without EEN had a ninefold increase in the incidence of postoperative abscess and/or anastomotic leak (OR 9.1; 95% CI 1.2 to 71.2, p=0.04) [67]. Another study reported that patients with CD suffering from intra-abdominal abscesses, treated with four weeks of EEN and antibiotics, were less likely to require surgical intervention than those who did not use EEN (26.1% vs. 56.3%, p=0.01).

Several studies have confirmed that perioperative EEN can improve surgical outcomes, lower rates of stoma creation, decrease urgent operation requirements, reduce complications and recurrence rates and the need for immune suppression [63].

An uncertainty regarding which part of EEN therapy conveys its efficiency, whether it's the formula content that is beneficial or the exclusion of regular diet that leads to remission, has led to the question, does it have to be exclusive? In a study performed by Johnson et al., 50 children with active CD were randomized into two groups, one was treated with EEN and the other group was given partial enteral nutrition (PEN) with a free diet (meaning that 50% of the diet came from formula and 50% was not restricted). They discovered that the remission rate was lower in the group with PEN combined with the free diet compared with the EEN group (15 vs. 40%, respectively. p = 0.035). Furthermore, the children in the EEN group improved both in clinical symptoms and inflammatory markers. This study has shown that the essential component is the principle of exclusivity, reinforcing the importance of diet in triggering in treating IBD, even though the underlying mechanism of exclusivity is still undetermined [62,68].

Table 3 Key studies and recent advances with EEN in children and adults

Study design	Population	Duration of EEN	Comparator	Number of patients	Outcome	Key findings	Reference
Randomised controlled trial	Adults	3–6Weeks	EEN vs CS and sulfasalazine	EEN: 51 pts Drugs: 44 pts	Improvement in CDAI: EEN: 41% Drugs: 72% p<0.05	Equal effectiveness of EEN compared with drugs per protocol	Malchow. *Scand J Gastroenterol*, 1990[117]
Randomised ccontrolled trial	Adults	4–6Weeks	EEN vs CS and sulfasalazine	EEN: 52 pts Drugs: 55 pts	Remission: EEN: 55% Drugs: 74% p<0.01	Comparison to medications	Lochs. *Gastroenterology*, 1991[118]
Randomised ccontrolled trial	Adults	4Weeks	EEN: n-6 PUFA vs MUFA vs CS with ward diet	MUFA: 20 pts PUFA: 23 pts CS: 19 pts	Remission rates (ITT): MUFA EEN: 20% PUFA EEN: 52% CS: 79% p=0.001	Composition of fat	Gassull. *Gut*, 2002[119]
Randomised ccontrolled trial	Paediatric CD	6Weeks	Elemental formula vs polymeric formula	Elemental fomula: 16 pts Polymeric formula: 17 pts	Remission: Elemental: 69% Polymeric: 82% p=0.44	Polymeric equivalent to elemental	Ludvigsson. *Acta Paediatr*, 2004[120]
Randomised ccontrolled trial	Paediatric CD	6Weeks	EEN vs 50% PEN with free diet	EEN:24 pts PEN: 26 pts	Remission: PEN: 15% EEN: 42% p=0.035	Principle of exclusivity	Johnson. *GUT*, 2006[68]
Randomised ccontrolled trial	Newly diagnosed paediatric CD	10Weeks	Polymeric formula vs CS	EEN: 19 pts CS: 18 pts	Remission: polymeric EEN: 79% CS: 67% p=0.4 Mucosal healing EEN: 74% CS: 33% p<0.05	Mucosal healing comparing EEN with CS	Borrelli. *Clin Gastroenterol Hepatol*, 2006[121]

Retrospective	Paediatric CD	8Weeks	Oral vs continues enteral feeding	Oral: 45 pts Enteral: 61 pts	Remission: Oral EEN: 75% Tube EEN: 85% p=0.157	Oral equivalent to enteral feeding	Rubio. *Aliment Pharmacol Ther*, 2011[122]
Prospective uncontrolled	Adults	4Weeks	–	EEN: 13 pts	Significant improvement in quality of life Clinical remission: 84.6%	Improvement of quality of life	Gou. *Nutr Clin Pract*, 2013[123]
Prospective inception cohort	Newly diagnosed children	6–8Weeks	EEN vs CS mild-to-moderate CD	5-ASA: 29 pts EEN: 43 pts CS: 114 pts	CS-free remission week 12: EEN: 71% CS: 46% 5-ASA: 55% p=0.0006 NCR: EEN: 39% CS: 25% 5-ASA: 24%	EEN superior to CS for reduction of inflammation	Levine. *IBD*, 2014[70]
Prospective cohort	Paediatric CD	6Weeks	EEN vs healthy control	EEN: 15 pts HC: 21 pts	EEN: decreased butyrate, decreased diversity, *Faecalibacterium prausnitzii* concentration decreased	EEN mechanism	Gerasimidis. *IBD*, 2014[124]
Prospective cohort	Newly diagnosed paediatric CD	6Weeks	Mild-to-moderate EEN with thiopurine	34 Children	Clinical remission: 84% Early good endoscopic response: 58% Complete transmural healing ileal CD: 21%	Mucosal healing	Grover. *J Gastroenterol*, 2014[125]
Prospective cohort	Paediatric CD	8Weeks	EEN vs anti-TNF vs PEN with ad libitum diet	Anti-TNF: 52 pts EEN: 22 pts PEN: 16 pts	Clinical response: PEN- 64% EEN- 88% Anti-TNF - 84% p=0.08 FCP<250 mg/g: PEN: 14% EEN -45% Anti-TNF- 62% p=0.001	Comparison with anti-TNF EEN reduced calprotectin	Lee. *IBD*, 2015[69]
Retrospective	Newly diagnosed paediatric CD	8–16Weeks	EEN vs CS	EEN:76 pts CS 35 pts	EEN: 86.6% remission vs CS: 58.1% p<0.01	Reduced need for steroids	Connors. *JCC*, 2017[71]
Prospective inception cohort	Newly diagnosed children	6–8Weeks	EEN vs CS	EEN: 60 pts CS: 87 pts	Remission: CS: 47% EEN: 63% p=0.036	EEN superior to CS	Cohen Dolev. *JCC*, 2018[72]

5-ASA, 5-aminosalicylic acid; CD, Crohn disease; CDAI, Crohn's Disease Activity Index; CS, corticosteroids; EEN, exclusion enteral nutrition; FCP, faecal calprotectin; ITT, intention to treat; MUFA, monounsaturated fatty acids; NCR, normal C reactive protein remission; PEN, partial enteral nutrition; PUFA, polyunsaturated fatty acids.

1733

From: Levine, A., Boneh, R. S, Wine, E. Gut 2018; 67(9), 1726-1738.

5.3.3 CDED + PEN

As mentioned before, diet plays an essential role in the pathogenesis of IBD. The findings around the success of EEN in inducing remission have led to its use as first-line therapy, but over some period, a few difficulties rose that needed an adjustment. The current recommendation is the use over a prolonged period (6-12 weeks), which is challenging to perform and has led to decreased compliance among adults.

The hypothesis that the primary dietary therapy effect is due to the exclusion of harmful dietary components has led to the development of a specialized diet called "Crohn's Disease Exclusion Diet" (CDED), which induced remission and mucosal healing with and without additional use of liquid formulas. Due to these discoveries, the combination of CDED and PEN has replaced EEN as the standard dietary therapy among several patients.

The CDED is a whole food diet consisting of fruits, vegetables, meats, and complex and simple carbohydrates evaluated in randomized controlled trials. As was examined by Boneh and Levine et al. [68], it comprises two stages over 12 weeks. The first stage lasts for six weeks for induction of remission (which was defined by a combination of physician's global assessment [PGA] and Harvey Bradshaw index [HBI] <5) and is more restrictive than the second stage. All patients received dietary counseling regarding the proper use of diet and clear instructions, including mandatory, allowed foods, disallowed foods, and quantities permitted.

The primary guideline was that foods that contain dietary components that could hypothetically be hypothesized to increase intestinal permeability, degrade the mucous layer, or have induced dysbiosis with certain organisms are excluded or limited, depending on the food type. Animal fats, gluten, certain kinds of meats, emulsifiers, sulfites, and specific monosaccharides are restricted on that diet. Alternatively, it entails mandatory consumption of certain fruits, sources of resistant starch, and particular animal protein sources daily. Regarding the results of the trials, “clinical response (decrease of at least 3 points or remission) was obtained in 19/21 [90.4%] patients, and remission in 13/21 [62%]. Improvement in previously elevated inflammatory markers occurred in 17/21 [81%] patients, while normalization occurred in 9/21 [40.9%]. 3/4 of patients who used the CDED alone without any liquid formula supplementation

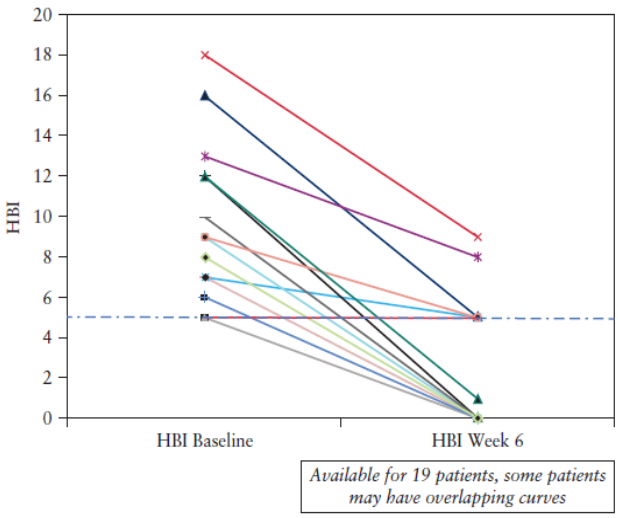

Figure 7. Change in HBI between baseline and week 6 for individual patients.

From: Levine, A., Boneh, R. S, Wine, E. Gut 2018; 67(9), 1726-1738.

entered clinical remission. 9/13 [69.2%] patients with small intestinal involvement obtained remission, compared to 7/13 [53.8%] patients with colonic involvement. The highest remission rate was among patients with Isolated ileal disease [5/6, 83.3%], whereas the lowest remission rate was among patients with isolated colitis [3/6, 50%]" [68].

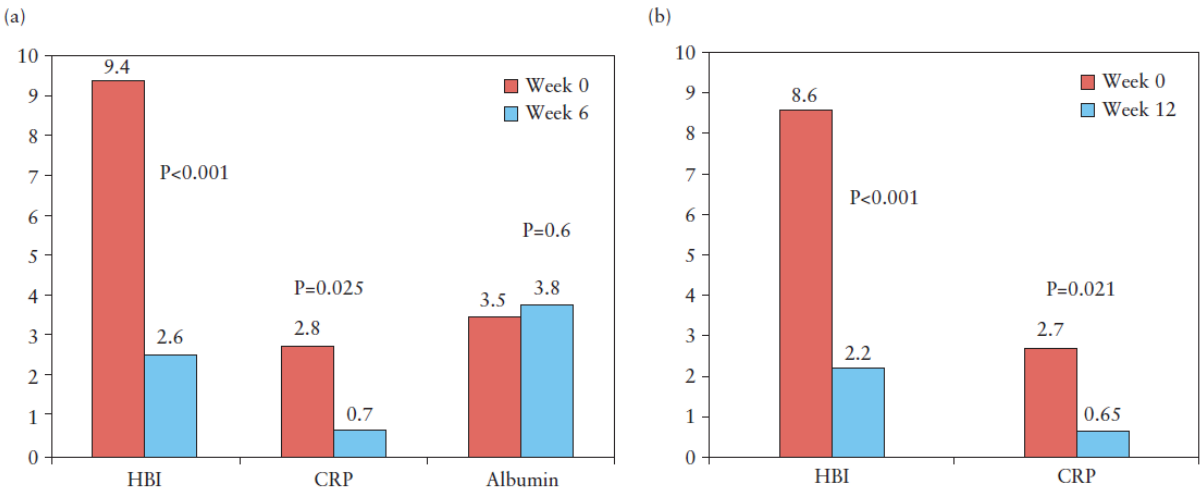

Figure 8. (a) Pairwise comparison of parameters between baseline and week 6. (b) Pairwise comparison of parameters between baseline and week 12

From: Levine, A., Boneh, R. S, Wine, E. Gut 2018; 67(9), 1726-1738.

This current research has demonstrated that a specific feasible dietary strategy may play a crucial role in regaining remission amongst patients failing medical therapy with biologics. It allowed patients to continue biological treatment successfully and served as a bridge to switch strategies. It worked either by directly inducing remission or reducing exposure to factors triggering inflammation, which enabled biological therapies to perform better due to a reduction in inflammation.

The results in this research add to the growing body of evidence suggesting that dietary therapy with PEN or exclusion diets plays a more significant role in the induction of remission and disease control at several points in the course of the disease, and not just in new-onset pediatric disease. The use of dietary therapy should be considered in these difficult-to-treat patients.

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8. BIOGRAPHY

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I was born in Haifa, Israel on July 23, 1995.

In 2013 I graduated from Carmel Zvulun Regional High School and extended the Theater and Physical Education programs and completed 7 units of studies learning English.

Between 2013-2015 I served in the Israel Defense Forces as a non-commissioned officer (NCO) in a classified unit in the intelligence force. I terminate my service as Sergeant.

In 2016 I started the Medical Studies in English program at the University of Zagreb, School of Medicine.

I am fluent in Hebrew and English and am familiar with Spanish and Croatian.

During my studies, I was awarded the Dean's award for the 1st year (2016-2017).