Inflammatory bowel disease: long-term therapeutic challenges

**Abstract**

Introduction- Long-term, sustained, remission is the ultimate goal of contemporary inflammatory bowel disease therapy. Avoiding complications, surgery and malignancy, alongside minimising the side effects of medications are vital. However, the reality of treatment involves patients losing response to therapy, or developing complications requiring cessation of medication. The reasons for this are numerous and include medication and host-related influences. Underpinning the response to medication, long-term outcomes and loss of response are individual aetiological factors including the molecular cause of disease and individual pharmacogenomic influences.

Areas covered- In this review we discuss the long-term outcome of inflammatory bowel disease, with a focus on paediatric-onset illness and discuss the factors leading to loss of treatment response and briefly consider the future of personalised therapy as a strategy to improve long-term outcome.

Expert opinion- Research findings are now moving towards clinical translation, including application of new medications targeting new pathways, alongside the integration of biological and multiomic data to predict disease outcome and personalise therapeutic response.

**Keywords**- IBD; Crohn’s disease; ulcerative colitis; personalised therapy; outcome

1. **Introduction**

Inflammatory bowel disease (IBD), consisting of Crohn’s disease (CD), ulcerative colitis (UC) and IBD unclassified, are a group of conditions characterised by acute and chronic bowel inflammation. Typically these are illnesses presenting in early adulthood, although up to 20% of cases will first occur in children, often with severe and extensive disease [1]. Over the last 20 years there have been substantial improvements in the treatment options available, providing effective and sustained remission for many patients whilst appearing to delay or prevent the progression to surgery [2]. However, despite the vast increase in treatment options, significant challenges remain, including maintaining the therapeutic response long-term, avoiding treatment toxicity and preventing the progression of stricturing and penetrating disease [3]. Whilst the precise underlying disease aetiology of IBD remains uncertain for most patients, recent genetic, microbial and immunological findings are now enabling evolution of therapy into an era into personalised medicine. This strategy, based on the underlying disease mechanism, will enable the better prediction of response to medication and potentially pre-empt disease progression and complications [4]. Specifically, the complexity and variation in disease requires more personalisation of therapy, reflecting the heterogenous group of patients which are classified as having IBD [5]. The role of the multi-disciplinary team, including specialist nurses, dietetics and psychological support is vital to provide holistic support to patients.

This review focuses on why patients lose response to therapy in the long-term management of IBD, with an emphasis on paediatric-onset disease. We aim to discuss the long-term challenges in IBD management through consideration of the outcomes of disease and how, through prediction of therapeutic response and disease prognosis, we are likely to improve patient care.

Research methodology

Data for this review were gathered through structured searches of the Medline and PubMed databases. Abstracts were eligible for selection if published between 2000 and 2019. Papers with adequate population size and duration of follow up were selected for inclusion in tables.  Review papers were selected for inclusion to illustrate specific issues.

**2. What are the long-term outcomes of inflammatory bowel diseases?**

The natural history of IBD is one of a chronic relapsing and remitting inflammation, with some patients progressing to significant complications, requiring a multitude of immunosuppressing medications and intestinal resections or perianal surgery. In contrast some will have a quiescent course. Data indicates that paediatric-onset disease is more severe, with higher disease activity, higher immunosuppressant requirements, increased risk of fistulating disease and earlier intestinal resection, compared to adult-onset disease [6,7]. The ability to predict and tailor therapy is currently lacking, leading to the potential for under and over treatment, along with loss of response [8]. A recent study indicated that all-cause mortality in paediatric-onset IBD was 3x higher than the general population, adding significant impetus to the need for improved care, better medication and preventing loss of response [9].

2.1 Long-term remission rates

Long-term remission rates are complex to assess. Over time the goals of therapy have shifted from symptomatic control to mucosal and transmural healing, so called *deep remission* [10,11]. In addition the introduction of new medications, initially anti- tumour necrosis factor-α (anti-TNF) agents, and now the new generation monoclonals/small molecule drugs, have altered the landscape of what can be expected in IBD management [12–14]. Even considering studies from the last 10 years there remains significant variation in remission rates, with key studies summarised in table 1.

Some of the best data comes from prospective North American paediatric cohort studies, published over the last two years. Data from 2017 demonstrated paediatric CD patients treated with standardised therapy, there were remission rates at one year of 85.3% in CD treated with anti-TNF, 60.3% with early immunomodulation and 54.4% with no early immunotherapy [15]. In comparison the 2019 PROTECT study of paediatric UC demonstrated a remission rate of only 38% at 12 months in children treated with standardised induction treatment with pre-defined criteria for escalation to immunomodulation and anti-TNF therapy [16]. Data from beyond 12 months indicates a similarly varied pattern. A recent retrospective European study of nearly 800 patients demonstrated remission of 46% in CD, 64% in UC and 69% in IBD unclassified [17]. The median follow-up duration was 2.8 years. Considering very-early onset disease, data from Ontario appears to indicate that patients diagnosed before the age of 6 years have lower rates of hospitalisation, hazard ratios (HR) comparing VEOIBD to older children were 0.7-1.12 [18]. However, a large North American cohort did not reveal any differences between VEOIBD and older children in terms of 5 year outcomes, although younger children were more likely to have treatment with corticosteroids, immunomodulators and 5-ASAs [19].

When comparing paediatric to adult onset disease, longer-term outcomes in adults appear generally consistent with the milder disease seen at diagnosis. Population-based data from Jakobsen *at al* showed a significantly more severe course in children with UC compared to adults, with mild disease seen in 35% vs 72%, respectively, median follow-up was 5 years [20]. Pigneur *et al* also described increased disease activity year on year in paediatric disease, with higher rates of immunosuppression at 10 years (54% vs 45% in adults). Higher relapse rates have also been described in paediatric-onset disease, adding to the belief that paediatric disease is more difficult to control [21]. Despite this, long-term disease behaviour was not different between adults and children, although complications occurred earlier, with the risk of intestinal resection at age 30 being 48% in paediatric onset disease compared to 14% in adult-onset disease. Adult data from Cosnes *et al* (2012) used a composite score to estimate CD severity over a 15 year period, 46.5% of patients were defined as mild-moderate disease (no active disease for greater than 12 of the 15 years) [22]. The remaining patients were described as severe due to >3 years of active disease, >2 abdominal surgeries, a permanent stoma or death related to CD [22]. Additional studies have estimated up to 73% adult CD patients treated with anti-TNF therapy, at a median of 42 months follow-up, were in clinical remission [23]. In a prospective adult Norwegian UC cohort up to 50% of patients were relapse free within the last five years [24]. Cantoro *et al* compared paediatric-onset Crohn’s disease to disease with onset of >60 years of age, with paediatric disease having a more aggressive disease course and more likely to have ileocolonic (56% vs 21%), upper gastrointestinal (17% vs 3%) and perianal (38% vs 19%) involvement during follow-up.

Overall long-term remission rates in IBD are highly variable, with around 50-60% of patients being described as severe and not entering ‘long-term’ remission. It appears that outcomes typically depend on severity/extent at diagnosis and age of onset, although this is not ubiquitous. The definition of remission is important and which medications were available at the time of study play an important role. Despite this, there are currently no reliable, clinically applicable, predictive features to stratify disease to guide best treatment and predict long-term outcome.

2.2 Surgery rates

Failure of medical management can be defined by the need for intestinal surgery, both in the setting of acute severe colitis in UC or acute obstruction in CD, or as planned surgery for refractory disease or strictures. Over the last 20 years the need for surgery appears to be decreasing in children and adults for both CD and UC [2,25]. A large population-based dataset from Canada published in 2019, showed a significant reduction in intestinal resection rates over a 17 year period [26]. Interestingly the reduction of surgical resection rates in both UC and CD occurred prior to the widespread us of anti-TNF, with the rate unchanged following the introduction of routine use [26]. In contrast, data from other adult cohorts suggests early initiation of monoclonal antibody therapy, as opposed to after complications occur, is key to reducing the need for surgical resection in Crohn’s disease [27,28]. Further evidence of an impact of recent management strategies can be seen in data from the UK indicating a reduction in abdominal surgical rates for CD (2.8% to 1% patients per year) and UC (4.9% to 2.4% patients per year) from 2003-2013 [29]. In paediatric-onset disease, nationwide Canadian data published in 2013 reported an increase in resection rate from 1997-2009 for CD, but not in UC [30]. However, these data have not been replicated.

Considering overall risk of surgical resection, two paediatric series indicate an estimated 9% of UC patients will require colectomy during childhood, compared to 34% in CD, of which 71% were right hemicolectomy [31,32]. More recently, Korean data, published in 2017, reported surgical resection rates at four year of 2% in UC and 13.9% in CD [33]. In contrast a recent Danish adult cohort of CD patients, treated during the era of biological therapy, demonstrated that up to 50% of patients undergo intestinal resection within 10 years of diagnosis with further data on UC from Korea showing rates of colectomy ranging from 7.8% at 10 years to 21.3% at 30 years [34].

The risk of surgery in the specific VEOIBD patient group indicates that these patients have lower rates compared to older onset IBD, at least during childhood, with a hazards ratio of between 0.35-0.59 for CD and 0.42-0.88 for UC [18]. It remains to be seen whether the lifetime risk is different in this group.

2.3 Complicated disease behaviour

Progression to complicated disease phenotype, either stricturing (B2) or penetrating disease (B3), is a key factor in both escalation of therapy and predicting need for surgical resection. Increasingly, management is aiming to pre-empt complications in order to avoid the need for surgical intervention. However, in some patients, progression from an inflammatory phenotype to complicated disease behaviour occurs despite intensive medical management. The impact of stricturing or penetrating disease is considerable, with IBD disease burden negatively impacting on quality of life and economic productivity throughout life [35,36].

The available data on progression to a complex disease phenotype is highly variable. Data from 2008 indicated that up to 59% of paediatric onset CD will develop a complicated disease phenotype during a 10 year follow-up period, B2 (44%) or B3 (15%) disease, contrasting to lower rates of B2 (25%) or B3 (4%) behaviour observed at diagnosis [32]. In contrast more recent estimates indicate only 17% have stricturing disease and 14% have penetrating disease at 7 years post-diagnosis [3]. Older data from 2002, prior to the routine introduction of anti-TNF therapy, reveals comparable 5 year outcomes for the prevalence of stricturing at 12% but a markedly higher prevalence of penetrating complications at 40% [37].

*2.3.1 B2 disease- Strictures*

Up to 10% of patients will present with some element of luminal stenosis, although this can be purely inflammatory, with only a proportion progressing to fibrostenotic disease [38]. This appears to be largely driven by genetic and inflammatory factors, occurring in an estimated 20-30% of patients at 20 years post-diagnosis [37,39,40]. The ability to prevent or reverse fibrotic disease appears to be limited, with little change in the number of patients progressing to B2 disease since the routine introduction of anti-TNF therapy [41].

Prevention of fibrotic complications is an important goal in medical therapy, specifically in Crohn’s disease. Currently we are unable to reverse fibrosis, and once strictures have developed treatment is balloon dilation or surgical resection. Even the most contemporary medications appear to have limited impact the development of fibrosis, and the development of antifibrogenic therapies, alongside targeting the correct patients in order to restrict or prevent the development of strictures are a priority [42,43].

*2.3.2 B3 disease- Fistulae*

In contrast to stricturing disease, many patients with a penetrating disease phenotype will present with this B3 phenotype, occurring in 14-15.5 % of adult CD patients [40,44]. The most common type of fistula is perianal, but patients may also develop rectovaginal, enterocutaneous, or internal fistulae. After 20 years post-diagnosis, progression to a fistulating from inflammatory phenotype was seen in nearly 50% of patients treated prior to routine introduction of anti-TNF therapy [44]. In line with recent Danish data describing only 14% of patients having B3 disease at 7 years follow-up, an additional prospective cohort reported 22.5% of patients developing perianal disease after 10 years of follow-up [3,36]. These data point towards the impact of anti-TNF therapy, delaying progression of an inflammatory phenotype into fistulating disease, in line with the presumed mechanism of fistulae formation being driven by TNFα [45].

2.4 Extraintestinal manifestations (EIM)

The occurrence of EIM can have a significant effect on management, and in some patients, such as those developing primary sclerosing cholangitis (PSC) or enteropathic arthritis, will become the major complaint. In a recent series from Greece up to 33% of patients developed an EIM, including ophthalmic complications, arthritis, liver disease and skin complaints (including erythema nodosum and psoriasis) [46]. These complications, excluding PSC and autoimmune liver disease, were more common in CD patients. A recent prospective European cohort reported 16.9% of patients developing an EIM by 10 years follow-up [47]. In line with the Greek data, the most common complaint was arthritis, seen in 12.9% of CD and 8.1% of UC patients [47].

Outcomes and incidence of EIM are extremely important in relation to switching medication. Whilst there are overlap between treatment of certain conditions, such as inflammatory arthritis and CD with anti-TNF agents, there are also reasons to cease therapy if specific manifestations develop, such as cessation of anti-TNF therapy following development of psoriasis. Specific reasons underlying loss of response, alongside additional treatment options are discussed below.

2.5 Malignancy

The development of cancer has specific impacts on long-term response to therapy, with the potential to avoid or stop therapy due to patients and clinician anxiety surrounding risk. Whilst malignancy is rare during the paediatric-period it is these patients who will live with IBD for the longest time. Balancing therapeutic risks with the costs of uncontrolled inflammation are key to forming the best management strategies.

A recent Scandinavian cohort, covering a 50 year time period, reported the risk of any malignancy being increased in patients diagnosed with IBD as children (RR 2.2). Gastrointestinal cancers had the highest increase in incidence compared to the general population (RR 18.0) [48]. Specifically, UC is associated with increased risk of colorectal carcinoma although rates appear to be decreasing overtime, from a relative risk of 5.4 in the 1960s to 1.7 in the 2000s, with some data indicating that the risk is no greater than the general population [49,50]. However, despite effective management, long-term follow-up data indicates up to 7.6% of UC patients will develop colorectal cancer within 30 years of diagnosis [51]. In the face of this, mortality rates from colorectal carcinoma are now declining and are statistically comparable to the general population [50]. However, patients with longstanding and complex disease, including those diagnosed as children and those with primary sclerosing cholangitis, still have a excess incidence of colorectal malignancy [49]. CD also increases the risk of colorectal carcinoma, RR 2.5, translating to a 10-year risk of developing colorectal malignancy of 2.9%. Small bowel cancers are significantly more common in CD, but remain rare overall (RR 33.2) [52].

An additional, important, consideration is the incidence of malignancy in relation to the therapies used. A large cohort of nearly 200,000 IBD patients demonstrated a small but significant increase in the risk of lymphoma in relation to both thiopurine (HR 2.6) and anti-TNF (2.41) therapy, although absolute risk remained very low at 0.41-0.54 cases per 1000 person years [53]. In contrast, data from North America did not find an increased incidence of lymphoma in paediatric IBD patients exposed to anti-TNF therapy, but did observe that all five patients in the series who developed haemophagocytic lymphohistiocytosis had been exposed to thiopurines [54]. A recent systematic review has identified thiopurines as independently associated with the rare hepatocellular T-cell lymphoma, which was previous thought to occur with anti-TNF therapy, but now appear to be related to thiopurine treatment only [55].

**3- Why is response to therapy lost and treatment discontinued?**

Long-term response is lost due to medication factors- side effects, intolerance or long-term risks, leading to cessation of a medicine, or host factors- immunogenic response, pharmacogenomics or the underlying disease pathogenesis, limiting the effectiveness of therapy. One of the additional host factors, the aetiology of which is multifactorial, is adherence to the medication regimen, alongside additional patient factors. The different aetiologies are summarised in figure 1. Whilst not a cause of loss of response timely de-escalation of treatment is an important consideration to prevent toxicity, complications and loss of treatment options in the longer-term.

3.1 Medication factors

The most common reason for cessation of therapy are factors relating to medications, including side effects and patient adherence. Therapies used in IBD management are frequently systemically acting and not specific to an end organ or dysfunctional pathway, leading to off-target side effects and complications. A summary of key studies reflecting specific factors leading to loss of response in medications used in IBD treatment can be seen in table 2.

*3.1.1 Side effects and complications*

*3.1.1.1 Corticosteroids*

Corticosteroids are used to induce remission, both at diagnosis and during disease flare. Complications are more common in patients having repeated courses or corticosteroids, even when correcting for disease severity [56]. The incidence of low bone-mineral density leading to fractures, venous thromboembolism, infections and poor wound healing are higher in those with increased corticosteroid use [56,57]. In children there are negative effects on growth, with an emphasis on avoiding corticosteroid courses where possible [58]. Beyond this the long-term acceptability of repeated courses of corticosteroids is low, with well-established adverse effects on weight, appearance and psychological wellbeing. Together these factors limit the utility of corticosteroids in long-term management of IBD.

*3.1.1.2 Exclusive enteral nutrition (EEN)*

In paediatric practice the standard induction regimen for CD is with EEN, yielding comparable remission rates to corticosteroids but with a more positive impact on nutritional status and growth [59]. Although there some limited evidence for the long-term effectiveness of EEN in maintaining remission, both long and short-term use is limited in adult practice due to personal and social acceptability [59]. EEN is a highly effective therapy, in which limited tolerability and patient adherence, alongside lack physician confidence and high requirement for patient support, leads to loss of response.

*3.1.1.3 5-Aminosalycylic acid (5-ASA)*

5-ASA medications are used in the treatment of mild-moderate UC as a potential monotherapy, and as an adjunct in more severe disease to reduce risk of colorectal carcinoma [60]. These medications are generally well tolerated but some patients will experience nausea, abdominal pain or rashes, whilst higher doses may result in diarrhoea [61]. Rarely there are more serious side effects such as nephropathy, requiring cessation of the drug [62]. Additional benefits of local preparations, targeted release and safety in pregnancy make 5-ASA generally well tolerated medications for long-term use.

*3.1.1.4 Thiopurines*

Thiopurines are widely used and effective although there a number of relatively common side effects, including bone marrow suppression (1.3-12.6%), pancreatitis (3%), hepatotoxicity (4%) and nausea/vomiting (1.3-6%) [63]. Monitoring lymphocyte count and liver function at the start and regularly throughout treatment is vital [63]. Discontinuation in long-term therapy occurs in up to 1/3 of patients, despite their demonstrable utility in both UC and CD, as a monotherapy and in combination with an ant-TNF agent [63]. Counselling patients of the risks of increased photosensitivity can result in a long-term reduction of skin malignancies [63]. The long-term risks of lymphoma are now beginning to emerge and some clinicians advocate avoiding thiopurines in young EBV-naïve men, due to the increased incidence of lymphoma in this group [64].

*3.1.1.5 Anti-TNF therapies*

Medication-specific factors related to the anti-TNF therapies (infliximab, adalimumab, golimumab) are largely related to infusion reactions and opportunistic infections. Infusion reactions are fairly common, occurring in around 5% of infusions (1/5 of which is a severe reaction), and are typically type 1 hypersensitivity mediated, including, rarely, anaphylaxis [65]. In most cases slowing the infusion rate, alongside pre-medicating with anti-histamine and a corticosteroid will improve tolerance and reduce the reaction, and in the majority this should not prevent further use of anti-TNF therapy. Anaphylaxis require change to another medication.

Approximately 1.5-5% of patients develop anti-TNF induced psoriasis/psoriasiform disorders [65]. In many cases the medication must withdrawn, with Ustekinumab an potential alternative option to treat both conditions in this scenario [66]. Additional anti-TNF induced issues include leukopenia (up to 20%) and other haematological effects (anaemia, thrombocytopenia), which require regular monitoring but not necessarily cessation of therapy. Demyelination and cardiac side effects are well recognised but rare [65].

As with immunomodulators there is increased risk of opportunistic bacterial infection and increase severity of some viral infections (including varicella zoster). Treatment should be directed at the causative organism and this should not always lead to cessation of the anti-TNF therapy long-term. Ascertaining tuberculosis status (including latent tuberculosis) is vital. Active tuberculosis is an absolute contraindication to starting anti-TNF therapy, however once treated anti-TNF therapy may be continued. It is important to discuss latent and active tuberculosis cases with infectious disease specialists to guide treatment.

There is an increased risk of some specific malignancies with anti-TNF therapy, including melanoma, other skin cancers and lymphomas. All should result in immediate cessation of anti-TNF therapy [65].

The host perception of symptoms is important. Symptoms may worsen in 23-46% of patients on anti-TNF therapy, although true loss of response is seen in only 5-13% of by 12 months of treatment [67]. It is also important to note that non-inflammatory mechanisms, such as established fibrostenotic disease, or a shift in disease pathway away from TNFα, will not be controlled by anti-TNF therapy and would constitute a long-term loss of response [67].

*3.1.1.6 Vedolizumab, Ustekinumab and Tofacitinib*

Newer generation IBD treatments introduced more recently now include anti-integrins (Vedolizumab), anti-IL12/23 (Ustekinumab) and JAK inhibitors (Tofacitinib). Long-term outcome data for these medications in IBD is lacking, however safety information is transferrable from dermatological and rheumatological indications for Ustekinumab and Tofacitinib, both of which are associated with increased infections [66,68]. Tofacitinib is associated with a small increase in risk of specific malignancies, including lymphoma[66,68]. Overall long-term safety data from Ustekinumab use in psoriasis, albeit at a lower dose to that used in CD, indicates a safety profile similar to anti-TNF agents [69]. Intestinal-specificity is a potential benefit of Vedolizumab, in theory reducing systemic side effects [70].

3.2 Host factors

Whilst medication-factors are more commonly reported by patients, the actual limitations of long-term therapy more frequently relate to a patient’s underlying disease or their immune response to medication, leading to ineffective (off target) treatment or loss of response to therapy, respectively. Effective and targeted therapy can reduce the impact of an individual’s underlying molecular predisposition to lose response, with the example of concurrent immunomodulation in anti-TNF therapy resulting in reduced anti-anti-TNF antibodies discussed below [71]. It is important to differentiate between gradual loss of response and complete ineffectiveness of medication as these are likely to reflect different molecular processes and inform intra or inter-class therapy switching. Close patient monitoring, through endoscopy and faecal calprotectin can help guide therapy through ascertaining true response, additionally differentiating inflammatory from functional symptoms.

*3.2.1 Underlying disease aetiology*

The underlying cause for IBD in an individual is specific to that person; genetic predisposition to developing disease impacts on immune or intestinal barrier function and interacts with gut bacteria, viruses or fungi, leading to the development of chronic inflammation [72–75].

* **Hyper-immune-** Overreaction to commensal intestinal bacteria
* **Hypo-immune**- Inability to clear pathogenic bacteria leading to ongoing aberrant inflammatory response
* **Normal immune (barrier function)-** Altered epithelial barrier function allowing invasion of bacteria into the mucosa with subsequent immune response
* **Auto-immune**- Inability to recognise self and subsequent inflammatory response

A number of specific immune pathways are implicated in the development of IBD. Whilst there are shared signalling or transcription endpoints in many, some will have distinct features which could be targeted by current and future medications. In some patients, it appears that genetic variation leads to abnormal or insufficient response within a specific pathway which may result in primary non-response to a medication class or progressive loss of response, if a therapy targets only part of the aberrant immune signalling. In addition some patients may shift between inflammatory pathways overtime, resulting in loss of response to treatments that were originally effective [67].

1. *NOD2* signalling- *NOD2* is an intracellular receptor for bacteria and bacterial products (specifically muramyl dipeptide), acting as a pattern recognition receptor. It induces downstream pro-inflammatory response, mainly through *MAPK* and *NFΚB* signalling and may also induce autophagy. Variation leading to reduction in *NFΚB* production is heavily implicated in Crohn’s disease aetiology.
2. *MAPK* and *NFΚB* signalling- common pathways resulting from stimulation of upstream receptors leading to activation of these signalling cascades. Activation of both pathways results in a pro-inflammatory response, inducing transcription of cytokines and chemokines involved in proinflammatory/immune responses against pathogens (or self).
3. JAK-STAT pathway- activated by a variety of cytokines including IL12/23 and interferon-α, downstream signalling results in transcription of genes involved in immune cell survival, activation and recruitment. This pathway is specifically targeted by Tofacitinib, a JAK inhibitor. Additionally, Ustekinumab targets IL12/23 through blockade and reduces downstream pro-inflammatory signalling
4. TNFα signalling- a proinflammatory cytokine key in the acute phase response. Mainly produced in activated inflammatory cells (macrophage, lymphocytes, neutrophils) in response to an infectious insult. Activates downstream pro-inflammatory pathways including *NFΚB* and MAPK, alongside inducing cell death. Excess production is implicated in multiple autoimmune diseases including IBD.
5. Immune cell intestinal trafficking- the movement of immune cells into the intestine facilitates the pro-inflammatory response associated with IBD. Integrins are key in facilitating adhesion and cellular migration, alongside signal transduction. The α4β7 integrin (Gut specific- lymphocyte Peyer's patch adhesion molecule 1) is targeted by the monoclonal antibody Vedolizumab, providing a gut selective medication preventing chemotaxis of lymphocytes into the intestine. Chemokines are signalling molecules secreted to facilitate attraction of (inflammatory) cells to an area. Typically, pro-inflammatory chemokines are formed under stimulus from pro-inflammatory cytokines such as TNFα or bacterially derived products such as lipopolysaccharide.

*3.2.2 Antibodies, drug clearance and drug levels*

Monitoring drug levels and the host immune response to therapy, through anti-drug antibody titres, is important to diagnose the reason for loss of response and to guide therapy where possible. Considering monoclonal therapy specifically, the occurrence of a host immune response against a medication is likely to result in reduced levels and potentially leading to a secondary loss of response.

Up to 30% of patients will be anti-TNF primary non-responders, either reflecting non-TNF driven inflammation or host factors leading to neutralisation of medication. Prior data indicates 2/3 of patients will maintain sustained clinical remission at 12 months post-initiation, but the attrition rate continues over time and at 5 years only 35-40% of patients maintain response [67]. Considering other monoclonals, Vedolizumab appears to have lower immunogenicity than anti-TNF agents, with around 4% of patients developing antibodies and only 3% when used with concurrent immunosuppression [69]. It is important to note that at present there is significantly less long-term data for this drug.

Optimising dose for any medication is an important factor in maintain remission and avoiding loss of response. In secondary loss of response switching to a different medication within the same class (for example infliximab to adalimumab) is ineffective, resulting in the need to switch class [76]. There is increasing data that patients switched from anti-TNF, due to loss of response, have a significantly lower response rate to Vedolizumab and Ustekinumab when compared to monoclonal naive patients [13,70]. This places an emphasis on good drug stewardship, optimising response and reducing immunogenicity where possible. The two main causes of secondary loss of response in anti-TNF therapy are summarised in figure 2, along with appropriate management action.

Preventing loss of response, monitoring treatment efficacy and avoiding toxicity can be facilitated through monitoring of anti-TNF levels and anti-drug antibodies [76]. Ensuring adequate drug levels to meet therapeutic targets whilst using concurrent immunosuppression to reduce anti-drug antibody production [76]. In the event of loss of response, drug levels and anti-drug antibody titres can be determined, this can then be used to decide on dose intensification (increased dose or reduced dosing interval, low anti-TNF levels, no antibodies) will prove effective or whether there is true secondary loss of response (low anti-TNF levels, antibodies present) requiring a change in medication [76]. Increasingly there is a ‘treat to target’ approach used for anti-TNF therapy, requiring close monitoring and a lowered threshold for dose intensification. Acute inflammation resulting in consumption of drug, non-immune mediated clearance and individual pharmacogenomic factors are all reasons for low drug levels, in these scenarios increase dosing frequency or drug dose may elicit response in up to 70% of patients [67]. Increasing drug dose, to target therapeutic levels, may be effective and rescue patients in which loss of response had previously occurred.

Monitoring of thiopurine metabolite levels can similarly shape dosing, ensuring that patients are taking the drug, and that an adequate dose is being used [63]. This typically done through 6-thioguanine nucleotides (6-TGN) levels, although standardising a target range is complex and not-consistent between ages, ethnicities and body types. An option for improving the response for patients who have an underlying pharmacogenetic reason for low levels lies in the use of concomitant low dose allopurinol, which has demonstrated efficacy in both increasing metabolite levels and maintaining clinical remission [77].

*3.2.3 Pharmacogenomics*

There are several established situations within IBD therapy where underlying genetic predisposition leads to adverse outcomes, or limits medication use. Although the clinical translation of these are not yet routine.

An uncommon but significant side effect of 5-ASA is nephrotoxicity, mediated by a genetic predisposition located within the HLA region [62]. Heap *et al* reported 150 cases occurring a median of three years after 5-ASA commencement and identified the SNP rs3135356, lying in the class 2 HLA region [62]. This loci translated to a 3x increase in risk of nephrotoxicity with 5-ASA therapy, although the clinical utility of this is limited by the rarity of this side effect.

Thiopurines are metabolised by the thiopurine methyltransferase or thiopurine S-methyltransferase (*TPMT*) enzyme, the activity of which is altered by variation with *TPMT* gene [78]. In addition around 15 other genes within the thiopurine metabolism pathway have been implicated in reduced ability to metabolise thiopurines resulting in toxicity [78]. The ability to predict which patients are unable to metabolise is key in avoiding bone marrow suppression and hepatotoxicity, whilst this is routinely performed using analysis of TPMT enzyme activity, increased sensitivity may be realised through a targeted gene panel as not all toxicity is mediated by TPMT [4,78]. A further complication of thiopurine use is pancreatitis, observed in up to 4% of users [79]. The IBD pharmacogenetics study group, led from Exeter, UK, identified the HLA-DQA1\*02:01-HLA-DRB1\*07:01 haplotype as increasing risk of developing pancreatitis. This risk for developing pancreatitis was directly linked to the HLA-DRB1\*07:01 genotype and rs2647087 SNP which were thought to be tagging an unidentified causative allele linked to a 9% risk if heterozygous and 17% risk if homozygote [79].

In anti-TNF therapy, the PANTS consortium has identified the HLA-DQA\*5 genotype, present in approximately 40% of people with Northern European ancestry, as conveying a significantly increased risk of developing anti-infliximab (HR 1.92) or anti-adalimumab (HR 1.89) antibodies [71]. However, although antibodies were associated with this HLA genotype, there was no association with loss of response. Interestingly it would appear that preventing antibody formation in patients carrying this HLA allele through concurrent immunomodulator therapy does not prevent loss of response. Monitoring drug levels, alongside clinical and biochemical response, through endoscopy, histology and inflammatory markers, currently appears to be the best course of action in guiding therapy.

3.3 Adherence and patient factors

Adherence to medication regimens is vital to maintain remission. Adherence to medications is difficult for many patients in chronic, incurable disease. Despite this, long-term outcomes can be improved through good adherence, something demonstrable through consistent administration reducing the risk of developing immunogenicity in anti-TNF therapy [67]. Lenti *et al* describe the importance of medication adherence in their recent review, including factors associated with non-adherence and possible interventions to improve outcomes [80].

Long-term worsening of disease, with the perception of losing response to therapy, may be related to additional patient factors such as continued smoking in CD and unhealthy eating leading to obesity, with an increase in concurrent non-communicable disease risk. Additional co-morbidities may require cessation or addition of medications, exacerbating symptoms. Conditions related to obesity, such as type 2 diabetes and non-alcoholic steatohepatitis, are likely to complicate the disease course further.

3.4 Healthcare professional factors

Alongside the multitude of medication-specific aspects leading to loss of response there needs to be consideration of healthcare decision-making. This includes prematurely switching medication class, insurer-driven obstacles or changes (particularly within environments where health care is mostly through insurance), lack of communication or explanation of medications resulting in poor adherence and lack of awareness and infrastructure leading to lack of or delayed referral to support services, including dietetic and psychology [35].

The recognition of these as potential barriers to long-term response, and improved outcomes, is important. In the most part they can be acted upon and relatively simple measures can result in improved long-term adherence, nutritional and psychological wellbeing and trust in healthcare. Fostering a positive relationship between healthcare professionals and patients with IBD must be a cornerstone of preventing loss of response. In addition consensus guidelines and consortium healthcare management systems, such as ImproveCareNow, should result in improved long-term outcomes, alongside benchmarking against other services [81].

**4- How can you predict response to therapy and outcome in inflammatory bowel disease?**

The ability to predict which patients will respond to which medications, who will continue to have active disease regardless and who will develop EIM and fistulating/stricturing complications will potentially revolutionise our approach to treatment [4]. This area of research is in its infancy and requires long-term cohorts and follow up to interventional studies in order to provide evidence to shape management. This includes consideration of what is known about disease outcome and about the response, and loss of response, to therapy. A selection of key studies are listed in table 3.

There are multiple examples of groups attempting to predict response to treatment and therefore tailor the therapeutic approach from diagnosis. The prospective RISK cohort study of paediatric CD was able to predict with a specificity of 71% the outcomes including stricturing and penetrating disease, whilst including specific treatment outcomes in the model [82]. More recently the PROTECT study of paediatric UC used a standardised treatment regimen and clinical, transcriptomic and microbial data to build a model able to predict remission with a 75% accuracy. Further examples of patient stratification can be seen in the study from Marigorta *et al* (2017) where researchers forecast complicated disease based on a gene expression risk score in the RISK CD inception cohort, allowing indolent versus complicating disease to be predicted based on 29 genes [83]. Clinical data has also been used to determine outcome, complications and predict early relapse, with the best predictor of long-term complications and outcome being lack of early response to therapy [84]. Additionally, clinical data has been used to predict the response to specific medication. A recent publication from Dulai *et al* used a pre-treatment scoring system to predict the likely response to Vedolizumab with an accuracy of up to 75%, with previous anti-TNF therapy, no bowel surgery, no B3 disease, high baseline albumin and low C-reactive protein all being significant factors in the model [85].

In adults Lee *et al* (2011) provided the first example of stratifying patients using a molecular biomarker, transcriptional characteristics of CD8+ T cells, allowing risk stratification groups to be determined [86]. Specifically considering response to medication two studies from Arijs *et al* (2009 and 2010) used gene expression profiles to identify differentially expressed genes which were able to predict response to infliximab with up to 95% accuracy [87,88]. Gaujoux *et al* utilised a gene transcription score adjusted for cell type present in histology to develop a prediction for anti-TNF response, with identification of TREM-1 downregulation at baseline as a reproducible predictor of non-response to therapy [89]. Douglas *et al* were able to use microbiome data to identify paediatric CD patients responding to induction therapy with an accuracy (area under the curve) of 94.4% [90]. Additional predictors of response include expression of specific proteins, both in blood and tissue. Oncostatin M is emerging as an attractive potential tissue biomarker, where high expression levels in intestinal tissue is strongly associated with early failure of anti-TNF therapy [91].

**5- Expert commentary**

It is increasingly clear that maintaining long-term and *deep remission* is the consensus approach for reduction of complications, reducing the need for intestinal resection and maintaining quality of life in IBD. Whilst there are an increasing number of medication choices available it is paramount diagnose and attempt to avoid loss of response in order to improve patient outcomes and reduce the risk of treatment-refractory disease. There are several key strategies, discussed in this review, that can be employed including medication dose optimisation and active drug monitoring, close patient monitoring through endoscopy and faecal calprotectin, timely escalation and de-escalation of treatment and moving towards precision therapy from the outset. The role of the multi-disciplinary team should not be underestimated, with specialist nursing, psychological and dietetic support of particular importance.

There are a multitude of reasons underlying loss of response to therapy in long-term management, including medication and host factors. Avoiding medication-exhaustion is vital, something which is particularly pertinent to paediatric-onset disease. Children diagnosed with IBD will have 70+ years living with the condition and keeping a subset of these patients in remission, whilst maintaining options for treatment escalation, is challenging. In a chronic condition such as IBD it is important to consider other factors such as anxiety and co-existing functional gastrointestinal disorders.

In this review we have demonstrated there is potential for considerable morbidity associated with chronic IBD, including frequent relapse, stricturing and penetrating disease behaviour, intestinal resection and increased risk of malignancy. However, it is evident that structured management can response to treatment, with reductions in morbidity and mortality related to the disease state and its complications and improved in long-term outcomes. Key challenges and opportunities remain, including application of a series of exciting new medications, targeting new pathways, alongside the integration of biological and multiomic data to predict disease outcome and therapeutic response.

**6- Five-year view: What does the future hold for predicting response and optimising therapy?**

There are key challenges in managing patients with IBD in the long-term, especially those diagnosed young with severe and extensive disease. An additional challenge over the next 5 years will be the increasing number of elderly people with IBD, who also develop additional age-related comorbidities. The early and successful treatment of disease will have huge benefits on the future wellbeing of these individuals.

The most exciting developments over the next 5 years will be the potential transition to personalised medicine, based on the precise molecular diagnosis of a patient [4]. Predicting response and outcome, based on data from an increasing number of prospective cohorts, for individual patients is likely to result in more targeted use of medications, reducing long-term use in some and promoting the correct molecular pathway to target in others. Prospective, personalised trials such as RISK and PROTECT are now beginning to merge clinical and molecular data to demonstrate this [16,82]. With increased efficacy, an additional benefit of personalised therapy is likely to be increased adherence to treatment regimens as patients experience fewer side effects. Placing IBD at the centre of translational science in complex disease should aid the reduction of stigmatisation of IBD and promote improved quality of life for patients and families.

The development of new drug targets, such as the *RIPK2* inhibitors, may prove clinically advantageous in specific groups, such as those whose disease is due to aberrant *NOD2* signalling [92]. The addition of effective antifibrotic drugs, and stem cell therapies for perianal disease may change the landscape of long-term therapy, enabling medical rescue where surgical intervention has previously been required. The combination of new therapeutic targets, and focussed management based on the underlying molecular cause of disease, provides a hugely exciting future for predicting outcome and preventing long-term loss of response.

**7- Key issues**

1. The long-term outcomes of inflammatory bowel disease are extremely varied. Some patients will have quiescent disease, whereas some will have a severe course with multiple relapses.
2. A significant number of patients will develop complications (such as strictures or fistulae) and require intestinal resections for disease refractory to medical management.
3. Many patients will be primary non-responders to therapy, lose response to medication within a year of starting or find efficacy gradually reducing overtime
4. Whilst some patients may relapse or worsen whilst on a therapy, increasing dose, reducing dosing interval or commencement of concurrent therapy can rescue response in selected cases
5. Active patient monitoring, including drug levels, antibodies and regular assessment of disease activity (faecal calprotectin, endoscopy) are vital to promote disease monitoring to assess long-term response to treatment.
6. The reasons underlying loss of response include medication side-effects, long-term sequelae of therapy such as malignancy or bone marrow suppression, and patient tolerance
7. Host-factors influencing loss of response relate to the molecular causes underpinning chronic inflammation, fluctuating activation of different immune pathways, microbial influences and the modifying effects of medicines
8. Pharmacogenomics will become increasingly important to prevent side effects and toxicity, and to promote medication-stewardship to ensure long-term remission
9. We are moving into an era of precision therapy where prediction of outcome and response to medication will shape personalised outcomes, improving long-term treatment response

**Tables and Figures**

**Table 1- Long-term outcomes of inflammatory bowel disease**- specific situations and key studies.

**Table 2- Why is response to therapy lost in specific medications?** Studies reporting outcomes (including adverse events) of at least 25 or more paediatric patients at 1 year

**Table 3- Key studies in personalised therapy for IBD**- adapted from Ashton et al

**Figure 1- Factors associated with long-term loss of response to therapy in inflammatory bowel disease.**

**Figure 2- Schematic representation of loss of response in anti-TNF therapy.** Loss of response is most frequently due to production of anti-drug antibodies or to reduced levels in the target tissue. Actions to attempt to address this loss of response are detailed.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study name | Year of study | Specific consideration + Location of study | Disease subtype(s) | Population size | Follow-up duration (median) | Remission rate at maximal follow-up | Surgery rates- intra-abdominal  | Surgery rates- perianal | Stricturing rate (B2 disease) | Fistulae rate (B3 disease) |
| Long-term Outcomes of Paediatric Patients Admitted with Acute Severe Colitis - A Multicenter Study from the Paediatric IBD Porto Group of ESPGHAN [93] | 2019 | **Outcome after acute severe colitis-**25 paediatric gastroenterology centres across Europe and North America. | IBDU | x | x | x | x | x | x | x |
| CD | x | x | x | x | x | x | x |
| UC | 141 | 5 years | x | 36.4% | x | x | x |
| Clinical and biological predictors of response to standardised paediatric colitis therapy (PROTECT): a multicentre inception cohort study [16] | 2019 | **Paediatric Ulcerative colitis-**29 Centres in USA and Canada | IBDU | x | x | x | x | x | x | x |
| CD | x | x | x | x | x | x | x |
| UC | 467 | 1 year | 38% | 5% | x | x | x |
| Outcomes of a National Cohort of Children with Acute Severe Ulcerative Colitis [94] | 2018 | **Outcome after acute severe colitis** -Our Lady's Children's Hospital, Crumlin, Dublin | IBDU | x | x | x | x | x | x | x |
| CD | x | x | x | x | x | x | x |
| UC | 55 | 29 months | 53% | 38% | x | x | x |
| Clinical Characteristics and Long term Outcomes of Paediatric Crohn's disease: A single centre experience [95]  | 2016 | **Paediatric Crohn’s disease-** Asan Medical centre, Seoul 3 temporal cohorts | IBDU | x | x | x | x | x | x | x |
| CD | 594 | 10 years | x | 33.9% | 22.7% | 32.9%  | 57.6% |
| UC | x | x | x | x | x | x | x |
| Treatment Options and Outcomes of Pediatric IBDU Compared with Other IBD Subtypes: A Retrospective Multicenter Study from the IBD Porto Group of ESPGHAN [17]  | 2016 | **Paediatric IBDU-**23 paediatric gastroenterology centres across Europe and North America. | IBDU | 260  | 2.8 years | 69% | 4% | x | x | x |
| CD | 250 | 2.8 years | 46% | 20% | x | x | x |
| UC | 287 | 2.8 years | 64% | 22% | x | x | x |
| Incidence, outcome, and health services Burden of Very Early Onset Inflammatory Bowel Disease [96] | 2014 | **All paediatric onset disease (diagnosed <18 years)** Ontario, Canada | IBDU | 506 | 10 years | x | x | x | x | x |
| CD | 1991 | 10 years | x | 35.6% | x | x | x |
| UC | 1123 | 10 years | x | 16.8% | x | x | x |
| Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease – a population-based [20] | 2011 | **Adult-Paediatric comparison-**Copenhagen county and City | IBDU | x |  x | x | x | x | x |  x |
| CD | 29  | 5 years | 45% | 18% | x | x | x |
| UC | 20  | 5 years | 35% | 5% | x | x | x |
| Natural History of Crohn's Disease: Comparison between Childhood and Adult onset disease [6] | 2010 | **Adult-Paediatric comparison-**MICISTA registry, Paris | IBDU | x | x | x | x | x | x | x |
| CD | 206 | 14.7 years | x | 60% | 43% | 24.7% | 24.7% |
| UC | x | x | x | x | x | x | x |
| Natural History of Pediatric Crohn's disease: A population-based Cohort study [32] | 2008 | **Paediatric Crohn’s disease-** Northern France, EPIMAD registry | IBDU | 26 | 5 years | x | x | x | x | x |
| CD | 472 | 5 years | x | 44% | x | x | x |
| UC | 151 | 5 years | x | x | x | x | x |
| Long-term prognosis of early-onset Crohn's disease diagnosed in Childhood or adolescence [97] | 2004 | **Paediatric Crohn’s disease-** North American database | IBDU | x | x | x | x | x | x | x |
| CD | 224 | 12 years |  x | 56.3% | x | 28.6% | 46.4% |
| UC | x | x | x | x | x | x | x |

Table 1- Long-term outcomes of inflammatory bowel disease- specific situations and key studies.

Searches were conducted using medline and pubmed databases. Abstracts were eligible for selection if published between 2000 and 2019. Papers with adequate population size and duration of follow up were selected. Data were collected for remission rates, surgical rates, stricture and fistula rates, growth reduction and all cause malignancy and mortality wherever available, ‘x’ indicates lack of data for that outcome.

**Table 2- Why is response to therapy lost in specific medications?** Studies reporting outcomes (including adverse events) of at least 25 or more paediatric patients at 1 year

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study name | Year of study | Medication | Study location | Disease subtype(s) studied  | Patient number | Follow-up duration | Remission rates- 1 year | Remission rates- 2years | Loss of response rate- overall | Significant\* side effects reported | Most common side effects | Malignancy rate  | Antibody rate (Monoclonals only) |
| Romeo et al [98] | 2019 | InfliximabAdalimumabGolimumab | Southern Italy. Sicilian Network for IBD | UCCDIBD-U | 93 | 2yrs | CD IFX-73.3% | CD IFX – 54.2 % | Not described | Chest painLaryngospasm | Not described | 0 | Not described |
| CD ADA 71.9% | CD- ADA-56.5% |
| UC-IFX 66.7%UC-ADA 50%UC-Gol 100% | UC IFX 50%UC ADA 33% |
| Dayan et al [99] | 2019 | Ustekinumab | New york | UCCDIBD | 52 | 1 yr | CD- 67%UC/IBD U 60% | Not described | Not described | None reported | Allergic reactionArthralgiaFatigue | 0 | 4% had antibodies |
| Naviglio et al [100] | 2019 | Infliximab | Italy | UCCD | 49 | 1 yr | CD 58%UC 26.7% | Not described | 14% | Anaphylaxis |  | 0 | 20% |
| Alvisi et al [101] | 2019 | Adalimumab | Italy | CD | 44 | 1yr | 78% | Not described | Not described | Bacterial meningitis |  | 2.3% | Not described |
| Ledder et al [102] | 2017 | Vedolizumab | EuropeIsrael | CdIBD UUC | 52 | 1yr | CD- 25%UC/IBDU- 60% | Not described | Not described | ItchingMild shortness of breath | Otitis externa | 0 | Not described |
| Turner et al [103] | 2015 | Methotrexate | Multicentre  | CD | 226 | 1yr | 42% | Not described | Not described | Nausea |  |  | NA |
| Zeisler et al [104] | 2013 | 5-ASA | USA | UC | 213 | 1yr | 40% | Not described | Not described | Diarrhoea | Vomiting rashHeadache | 0 | NA |
| Hyams et al [105] | 2011 | Thiopurines | USA | UC | 133 | 1yr | 49% | Not described | Not described | PancreatitisRaised ALT,AST | Nausea | 0 | NA |
| Boyle et al [106] | 2010 | Methotrexate | Columbus | CD | 27 | 1yr | 33% | Not described | Not described | Nausea | Headache | 0 | NA |
| Wiess et al [107] | 2009 | Methotrexate | Tel Aviv | CD | 25 | 1 yr | 64% | Not described | 4% | NauseaVomitingPancreatitis | Eleveated ALT | 0 | NA |
| Markowitz et al [108] | 2000 | 6-Mercaptopurine and prednisolone | USA | CD | 55 | 1 yr | 89% | Not described | 4% | Low WBCRaised AST and ALT |  | 0 | NA |

\*Leading to the medication being stopped

Table 3- Key studies utilising multi-omic data to predict outcome in paediatric inflammatory bowel disease. Adapted from *Ashton et al* [4]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study  | Multi-omic data type | IBD population | Outcomes measured | Results  |
| Hyams *et al* 2019 [16] | Clinical, serological, microbiome sequencing data and intestinal transcriptome data | 467 Paediatric ulcerative colitis patients  | Steroid-free remission, on 5-aminosalicylic acid treatment only, at one year post-diagnosis | Able to predict steroid free remission in 70% for clinical features only (cross-validated on a separate cohort) and 75% when multi-omic data was added |
| Weiser *et al* 2018 [109] | Ileal transcriptome data | 201 Paediatric Crohn’s disease patients | Disease extent, ulceration, needs for colectomy or biological therapy  | Colon-type had greater disease extent and ulceration, plus inferred need for colectomy. Ileal-type had inferred greater need for biological therapy |
| Douglas *et al* 2018 [90] | Microbiome sequencing data | 20 Paediatric Crohn’s disease patients  | Treatment response to induction agents | 94.4% accuracy at predicting response to induction therapy |
| Denson *et al* 2018 [110] | Whole Exome Sequencing data | 543 Paediatric inflammatory bowel disease patients  | Perianal disease, stricturing complications, need for surgery  | Those patients with significant NADPH oxidase gene variants had increased risk of perianal disease and stricturing disease (both 3x). Surgery was conducted in 31% of those with variants compared to 9% of those without  |
| Kugathasan *et al* 2017 [82] | Clinical, serological and Ileal Transcriptome data | 913 Paediatric Crohn’s disease patients, 243 with ileal gene expression  | Development of stricturing or penetrating disease | AUC 0.7 (0.72 with ileal gene expression data) |
| Marigorta *et al* 2017 [83] | Ileal transcriptome data | 215 Paediatric Crohn’s disease patients,  | Development of stricturing or penetrating disease | Significantly higher transcriptional risk score in those progressing to complications (P=5×10-5) |
| Kolho *et al* 2015 [111] | Microbiome sequencing data | 32 Paediatric IBD patients  | Response to anti-TNF therapy  | Patients whose microbiota changed to resemble controls were significantly more likely to respond to therapy compared to those who remains dysbiotic (p=<0.01) |