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The epidemiology and natural history of paediatric-onset inflammatory bowel disease in Scotland

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Dedication

I wish to thank and dedicate this thesis to my amazing loving husband Robert and my parents, William and Linda, their patience, support and encouragement has been crucial and without them I could not have achieved all that I have done.

List of publications arising from this thesis

Primary data articles

(1) Cameron F.L., Al Towati M, Rogers P, McGrogan P, Bisset W, Ahmed S, et al. The effects of anti TNF therapy on growth in Scottish children with IBD. J Pediatr Gastroenterol Nutr 2017;64(1): 47-55

(2) Cameron, F.L., Wilson, M.L., Basheer, N., Jamison A., McGrogan, P., Bisset, W.M., Gillett, P.M., Russell, R.K., Wilson, D.C. Anti-TNF therapy for paediatric IBD: the Scottish national experience. Arch Dis Child 2015;100(4):399-405

Published abstracts

(1) The ongoing rapid and significant rise of incident paediatric-onset inflammatory bowel disease in Scotland. Jagger, FA; Cameron, FL; Henderson, P; Rogers, P; McGrogan, P; Loganathan, S; Russell, RK; Hansen, R; Wilson, DC. Arch Dis Child 2015;**100**:A145

(2) Cameron FL, Henderson P, Russell R, Wilson D. Paediatric Inflammatory Bowel Disease Unclassified In Scotland: Incidence And Natural History. Gut. 2014;63(Suppl 1):A75.

(3) Cameron FL, Henderson P, Wilson D. The prevalence of paediatric inflammatory bowel disease: a systematic review. J Crohn's Colitis. 2014;8:S24.

(4) Cameron FL, Wilson ML, Goudie D, Bisset WM, Russell RK, Wilson DC. Biological Anti-TNF dependency in paediatric IBD-the Scottish experience. United European Gastroenterol J. 2013;1 (Suppl. 1): A529.

Declaration of originality

I declare that the work presented here is my own, unless otherwise indicated, performed at the department of Child Life and Health at the University of Edinburgh from September 2013 until September of 2015. This work has not been submitted for any other professional degree or qualification.

The data collection was performed by Dr Fiona Cameron with the exception of:

- Data collection for the historical cohorts detailed in the incidence of paediatric-onset inflammatory bowel disease in Scotland from 2003-08 was also performed by Dr Richard Hansen for the North of Scotland data, Dr Paul Henderson and Ms Pam Rogers for the South East Scotland cohort and Dr Kostas Gerasimidis for the West of Scotland. For the prospective data collection for 2009-2014, data from the North of Scotland was collected by myself and Dr Fiona Jagger, the South East Scotland from Dr Paul Henderson and Ms Pam Rogers.

- Data for the anti-TNF registry, initial data from 2003-09 was collected by Dr Natasha Basheer and Dr Gamal Madhi forNorth of Scotland, Dr Natasha Basheer and Mrs Michelle Wilson for the South East Scotland and Dr Aaron Jamieson for the West of Scotland although there was not complete accrual.

Advice on statistics was provided by Dr Paul Henderson for the incidence of PIBD and Dr Niall Anderson provided advice on statistical modelling for the anti-TNF growth paper. Prof David Wilson reviewed the papers for inclusion in the prevalence systematic review. Dr Mabrouak Al-Towati who converted the raw growth data on children receiving anti-TNF therapy into standard deviation scores to allow me to perform further statistical analysis on the data.

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Abbreviations

ADA- adalimumab

AZA- azathiprine

BMI- Body Mass Index

CD- Crohn's disease

CS- corticosteroids

EEN- exclusive enteral nutrition

Ht SDS- height standard deviation score

HV- height velocity

IBDU- inflammatoy bowel disease unclassified

ICD- International classification of disease

IFX- Infliximab

IV- intravenous

LOR- Loss of Response

Mg- milligrams

MTX- methotrexate

NCC-non crohn's colitis

NRS- National Records Scotland

PIBD-paediatric-onset inflammatory bowel disease

PCDAI-Paediatric Crohn’s Disease Activity Index

PGA- Physician Global Activity

PGHAN- Paediatric Gastroenterology Hepatology and Nutrition

PISA- Paediatric Inflammatory Bowel Service Audit

PUCAI-Paediatric Ulcerative Colitis Activity Index

RCT- Randomised Control Trial

SB- small bowel

SDS- standard deviation score

T-12- 12 months prior to start of anti-TNF

T-6- 6 months prior to start of anti-TNF

T0- start of anti-TNF

T+6-6 months after to start of anti-TNF

T+12- 12 months after to start of anti-TNF

T+24- 24 months after to start of anti-TNF

T+36- 36 months after to start of anti-TNF

TNF- tumour necrosis factor

UC- ulcerative colitis

UK- United Kingdom

Wt SDS- weight standard deviation score

ΔHt SDS- change in height standard deviation score

Abstract

Background

Inflammatory bowel disease (IBD) is a chronic lifelong condition which comprises Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU). Around 8% of IBD cases diagnosed each year present in childhood (under 18 years)(1) and can cause impairment of linear growth and pubertal development, affecting education and future employment. The incidence of paediatric IBD (PIBD) is increasing both within Scotland, as evidenced by previous publications, but also worldwide as demonstrated in a recent systematic review. As the number of cases are increasing, it has become critical that effective treatments are available to manage symptoms in this patient cohort. Anti-TNF alpha antagonists have been used to treat PIBD and shown in large single centre studies to be effective at the induction and maintenance of remission, however, these studies may not reflect the general PIBD patients' clinicians treat daily so "real life" experience are needed to inform clinical practice.

Aims

The aims of my thesis were 1) to determine if the incidence and prevalence of PIBD continue to increase worldwide and to examine the durability of any incidence rise seen in Scotland, 2) to investigate in a nationwide population-based study the incidence and natural history of IBDU, 3) to examine the efficacy, safety and long-term effects of anti-TNF alpha drugs and lastly 4) to assess the long-term risk of PIBD on cancer and mortality rates in a nationwide population-based study.

Methods

Data was collected from all 4 PIBD centers across Scotland (Glasgow, Edinburgh, Aberdeen and Dundee) from 2009-2014 on new cases of IBD as well as those diagnosed with IBDU from 2003-2013, those treated with anti-TNF drugs from 2000-2012 and cases of cancer/deaths within the PIBD population from 2003-2013.

Results

Thirty-six studies from 18 countries were included in the incidence systematic review, most from North America and Western Europe. The highest incidence was 15.2 per 100,000 in Nova Scotia, Canada with the lowest 0.47 per 100,000 in Saudi Arabia, for CD the highest incidence was 9.2 per 100,000 in Nova Scotia and lowest in Saudi Arabia at 0.27 per 100,000 whilst for UC rates were highest in Finland at 8 per 100,000 and lowest in Saudi Arabia at 0.2 per 100,000. In the prevalence systematic review, 27 studies were included from 12 countries with the highest prevalence of 301 per 100,000 in Israel and lowest in Libya at 3.6 per 100,000. CD was highest in Sweden at 41 per 100,000 and lowest in Libya at 2.0 per 100,000 which was similar for UC with a high of 30.7 per 100,000 in Sweden and lowest at 1.36 in Libya. Most studies that reported on temporal trends saw an increase in PIBD, CD and UC. Significant heterogeneity existed in studies in both incidence and prevalence due to varying methodological approaches, age cut offs and diagnostic algorithms so meta-analysis was not performed.

The incidence of PIBD in Scotland demonstrated a significant and sustained rise from 430 cases in 2003-2008 with an incidence rate of 7.6 per 100,000 (95%CI 7.1-8.6) to 582 cases in 2009-2014 and incidence of 10.6 per 100,000 (95%CI 9.8-11.5) ($p<0.001$); primarily due to an increase in paediatric Crohn's disease. When compared with historical data there was a sustained and durable increase over the last 40 years, again mostly driven by increasing CD. The incidence of IBDU also increased from 2003-2013, accounting for around

20% of new PIBD cases in Scotland. Most children with this subtype had a relatively mild disease course, however 43% required immunosuppression and a small number escalated to anti-TNF therapy. 23% of IBDU patients had their diagnosis changed after endoscopic re-evaluation, most 62%, to CD. A Scottish nationwide registry of all children treated with anti-TNF drugs (infliximab (IFX) and adalimumab (ADA) was created from 2000-2012. 87% had improvement of their symptoms within 3 months post induction to IFX and 86% achieved remission with ADA. Growth was improved after one year of treatment with IFX but only in those children who responded after induction, had been diagnosed for over 2 years with IBD and were in the early stages of puberty (Tanner stage 1 and 2). Anti-TNF agents were generally safe and well tolerated with only 13% having an acute adverse reaction to IFX, ADA was also well tolerated with 16/57 having an adverse event. Death in children with PIBD was a rare occurrence with only 3 cases over 10 years, 2 cases were PIBD related with 2 cases of malignancy were observed, both had been treated with azathioprine with one subsequent death.

Conclusions

The incidence and prevalence of PIBD is increasing worldwide with the highest incidence rates from Nova Scotia, Canada and highest prevalence rates from Israel, although there is a propensity of data from North America and Western Europe.

In these population-based studies of paediatric-onset inflammatory bowel disease in Scotland, the number of new cases continue to rise with IBDU, as a subtype of IBD, more commonly diagnosed compared to other countries. Most children with IBDU had a mild disease course with 23% changing diagnosis following endoscopic reassessment most, 62% to CD. In Scotland, anti-TNF drugs are effective at managing symptoms of IBD with relatively few serious side effects with other benefits including improving linear growth in

those treated with infliximab. Finally, cancer and death are a rare outcome in children with IBD in Scotland. The continued increase in incidence of PIBD with higher rates of IBDU observed in Scotland may suggest environmental factors, such as urbanization or latitude, influencing the onset of PIBD. Prospective case control studies can further explore these environmental risk factors taking advantage of the nationwide collaborative approach to care and research within Scotland.

Chapter 1

1. Introduction: Epidemiology of Paediatric-onset Inflammatory Bowel Disease

Paediatric-onset Inflammatory Bowel disease (PIBD) is a chronic lifelong condition which comprises Crohn's Disease (CD), Ulcerative Colitis (UC) and Inflammatory Bowel Disease Unclassified (IBDU). Around 8% of cases of inflammatory bowel disease present in children and young people(1).The worldwide incidence of PIBD is increasing, with countries which historically reported low incidence rates now reporting more cases, however, the highest rates continue to be from Northern Europe and North America (2). With increasing incidence, further research into pathogenesis and the advancement of therapeutic options is critical given the significant impact PIBD has on growth(3), puberty, employment and mental health(4).

The observed increase in PIBD cannot be explained by genetics alone which evolve over thousands of years with no recent significant population shift to explain this. Many alternative theories have been postulated such as dietary and lifestyle factors, environmental triggers, epigenetics, alteration in the gut microbiota or improved methods of diagnosis(5). Epidemiological research can provide data on temporal trends and clues to pathogenesis and environmental risk factors which can then be more closely examined.

1.1 - What is IBD?

1.1.1 Crohn's disease (CD)

Crohn's disease can affect anywhere in the GI tract from the mouth to the anus and is characterised by patchy transmural inflammation (6). Pathological findings include non-caseating granulomata remote from a ruptured crypt (not always present) and focal

chronic inflammation including in the upper gastrointestinal tract. Macroscopic findings include linear or serpentine aphthous ulcers, cobble stoning, skip lesions, jejunal or ileal ulcers or strictures.

Crohn's is classified by the location (colonic, ileocolonic, terminal ileal or upper GI), disease behaviour (inflammatory, fistulising or stricturing), age at onset (less than 10 years or less than 17 years for paediatric patients) and with a qualifier of perianal disease or not (7). These criteria form the basis of the Paris classification for CD which is a paediatric specific phenotypic classification(7).

1.1.2 Ulcerative Colitis (UC)

Ulcerative colitis affects mainly the colon although can affect the final part of the terminal ileum so called "backwash ileitis". Differing from Crohn's disease it is characteristically a continuous diffuse mucosal disease which is divided into pancolitis (proximal to the hepatic flexure), extensive colitis (affecting up to hepatic flexure), left sided colitis (affecting up to the splenic flexure) or ulcerative proctitis (affecting the final part of the colon only)(7). UC has the qualifier of clinical remission, mild, moderate or severe colitis. These criteria form the basis of the Paris classification for UC which is a paediatric specific phenotypic classification(7). Histologically it displays architectural distortion, worsening disease distally, cryptitis and crypt abscesses whilst macroscopically there is superficial ulceration, friability, erythema and granularity.

1.1.3 Inflammatory Bowel Disease Unclassified (IBDU)

The diagnosis of IBDU has evolved over the years having been first described in 1978 as Indeterminate colitis (IC), a colitis with insufficient evidence to diagnose either Crohn's disease (CD) or ulcerative colitis (UC), but macroscopic and microscopic findings suggestive

of chronic intestinal inflammation after infection had been excluded(8)(**Table 1**). Subsequently, IC was renamed colonic inflammatory bowel disease, type unclassified (IBDU) in the Montreal classification where it was first defined as a IBD subtype, requiring a clinical diagnosis made by clinicians following an inconclusive endoscopy rather than a temporary diagnosis made by pathologists (7, 9). However, the Montreal classification did not provide guidance on how to differentiate IBDU from UC/CD but did emphasise the importance diagnosing it due to the poorer prognosis than UC, including increased risk of chronic pouchitis following surgery. IBDU was ill-defined in terms of diagnostic criteria until recently when described by the Porto group as "Patients with definite IBD wherein inflammation is limited to the colon with features that make the differentiation between CD and UC uncertain even after a complete work up"(10). Despite this new definition, it remains a poorly understood and often underdiagnosed as clinicians doubt it is a sub type of IBD and do not diagnose it, patients are often labelled as CD/UC, even in the presence of atypical features. Figure 1 describes features which suggestive of CD, atypical UC and those which would trigger a diagnosis of IBDU. Evidence used to support the criteria could be improved upon as data is limited by small study numbers and short follow up.

Table 1 Classification of Inflammatory Bowel Disease Unclassified (IBDU) since first described in 1978

Year	Author	Description of IBDU
1978	Price(8)	Colitis with insufficient evidence to diagnose CD or UC but macroscopic and microscopic findings suggesting chronic intestinal inflammation after infection has been excluded
2005	Escher (Porto group)(11)	Histology showing acute and chronic inflammation with architectural changes confined to the colon….. with normal small bowel follow through or enteroclysis where infective colitis has been excluded
2005	Silverberg (Montreal)(9)	IC changed to IBDU but definition same as per Price
2006	Satsangi (Montreal) (12)	Further refined using serological and genetic markers as well as capsule endoscopy and other novel diagnostic tests
2014	Levine (Porto)(10)	Patients with definite IBD wherein inflammation is limited to the colon with features that make the differentiation between CD and UC uncertain even after a complete work up

Figure 1- Diagnostic features suggestive of IBDU (13)

TABLE 3. Diagnostic features in a child with untreated colitis phenotype at diagnosis

Likelihood of occurring in UC	Feature	Diagnostic approach
Class 1: Non -existent	Well-formed granulomas anywhere in the GI tract, remote from ruptured crypt	Diagnose as CD
	Deep serpentine ulcerations, cobblestoning or stenosis anywhere in the SB or UGI tract	
	Fistulizing disease (internal or perianal)	
	Any ileal inflammation in the presence of normal cecum (i.e., incompatible with backwash ileitis)	
	Thickened jejunal or ileal bowel loops or other evidence of significant SB inflammation (more than a few scattered erosions) not compatible with backwash ileitis	
	Macroscopically and microscopically normal appearing skip lesions in untreated IBD (except with macroscopic rectal sparing and cecal patch)	
	Large inflamed perianal skin tags	
Class 2: Rare with UC (<5%)	Combined (macroscopic and microscopic) rectal sparing, all other features are consistent with UC	Diagnose as IBD-U, if at least 1 class 2 feature exists
	Significant growth delay (height velocity <2 SDS), not explained by other causes	
	Transmural inflammation in the absence of severe colitis, all other features are consistent with UC	
	Duodenal or esophageal ulcers, not explained by other causes (e.g., Helicobacter pylori, NSAIDs and celiac disease)	
	Multiple aphthous ulcerations in the stomach, not explained by other causes (e.g., H pylori and NSAIDs)	
	Positive ASCA in the presence of negative pANCA	
	Reverse gradient of mucosal inflammation (proximal >distal (except rectal sparing))	
Class 3: Uncommon (5%–10%)	Severe scalloping of the stomach or duodenum, not explained by other causes (e.g., celiac disease and H pylori)	Diagnose as IBD-U if at least 2–3 features exist
	Focal chronic duodenitis on multiple biopsies or marked scalloping of the duodenum, not explained by other causes (e.g., celiac disease and H pylori)	
	Focal active colitis on histology in more than 1 biopsy from macroscopically inflamed site	
	Non–bloody diarrhea	
	Aphthous ulcerations in the colon or UGI tract	

1.2 Classification of PIBD

Accurate phenotyping of patients is essential to conduct research into disease pathogenesis and the genetic basis of disease to allow the comparison of the same types of patients. There have been several landmark papers which have demonstrated the evolving process of IBD phenotyping as our understanding develops in terms of the disease course, improved diagnostic tools such as small bowel enteroscopy and other imaging modalities, disease biomarkers both serological and faecal. The first classification of IBD was in 1991 by an international working group who reported from Rome a classification for CD which used disease location, behaviour, disease extent and operative history(14). This was then followed by the Vienna classification in 2000 (15) which simplified the 756 potential categories of the Rome criteria. In both of these publications UC was not considered, neither was IBDU, so in 2005 the Montreal criteria were then published (9). Unfortunately, the criteria did not consider the specific differences in paediatric-onset disease so paediatric gastroenterologists met and devised the Paris criteria which were published in 2011(7). The Paris criteria included disease severity, the increased propensity for disease extension(16), impact of disease on growth and further sub dividing ages to include a separate category for those under 10 years of age as opposed to 17 which had been the previous arbitrary cut off. The differences between with Montreal and Paris criteria are listed in **Table 2**.

Table 2 Montreal and Paris Classification for Crohn's Disease and Ulcerative Colitis

	Montreal	Paris
Age at diagnosis	A1: 0-16years A2: 17-40 years A3: >40 years	A1a: 0-10 years A1b: 10-16 years A2: 17-40 years A3: >40 years
Crohn's disease		
Extent	L1: Terminal Ileal disease +/- limited caecal disease L2: Colonic disease L3: Ileocolonic L4: Isolated upper GI disease	L1: Distal 1/3 Ileum disease +/- limited caecal disease L2: Colonic disease L3: Ileocolonic L4a: Upper GI disease proximal to the ligament of Treitz L4b: Upper GI disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum
Behaviour	B1: Non stricturing Non-penetrating B2: Stricturing B3: Fistulating P= perianal disease modifier	B1: Non stricturing Non-penetrating B2: Stricturing B3: Fistulating P= perianal disease modifier
Growth	n/a	G0: No evidence of growth delay G1: Growth delay
Ulcerative Colitis		
Extent	E1: Ulcerative Proctitis E2: Left sided colitis (distal to splenic flexure) E3: Extensive (proximal to the splenic flexure)	E1: Ulcerative Proctitis E2: Left sided colitis (distal to splenic flexure) E3: Extensive (hepatic flexure distally) E4: Pancolitis (proximal to hepatic flexure)
Severity	S0: Clinical remission S1: Mild UC S2: Moderate UC S3: Severe UC	S0: Never severe* S1: Not ever severe*

*Severe defined by Paediatric Ulcerative Colitis Activity Index (PUCAI) >65

1.3- Diagnosis of IBD

The diagnosis of inflammatory bowel disease requires thorough history taking and examination, laboratory investigations of both blood and faeces as well as endoscopic evaluation with upper gastrointestinal endoscopy and full ileocolonoscopy with serial biopsies (**See Figure 2**) (10); clearly infective and other aetiologies should be excluded first. The symptoms of PIBD are varied so it is essential to maintain an index of suspicion in unclear cases(17), the commonest symptoms of abdominal pain, diarrhoea and weight loss, the so called "triad" only occurs in 25% of CD(18). CD can also present with pyrexia, unexplained anaemia or growth failure whilst UC more commonly presents with bloody diarrhoea (10). Extra-intestinal manifestations of IBD can occur at diagnosis including joints, ocular, liver and skin involvement (19, 20).

The current guidelines recommend small bowel imaging, particularly in suspected CD, when ileal intubation was not possible or where IBDU is being considered. Imaging can be either MR enterography, barium meal or capsule endoscopy depending upon the facilities of the centre (10).

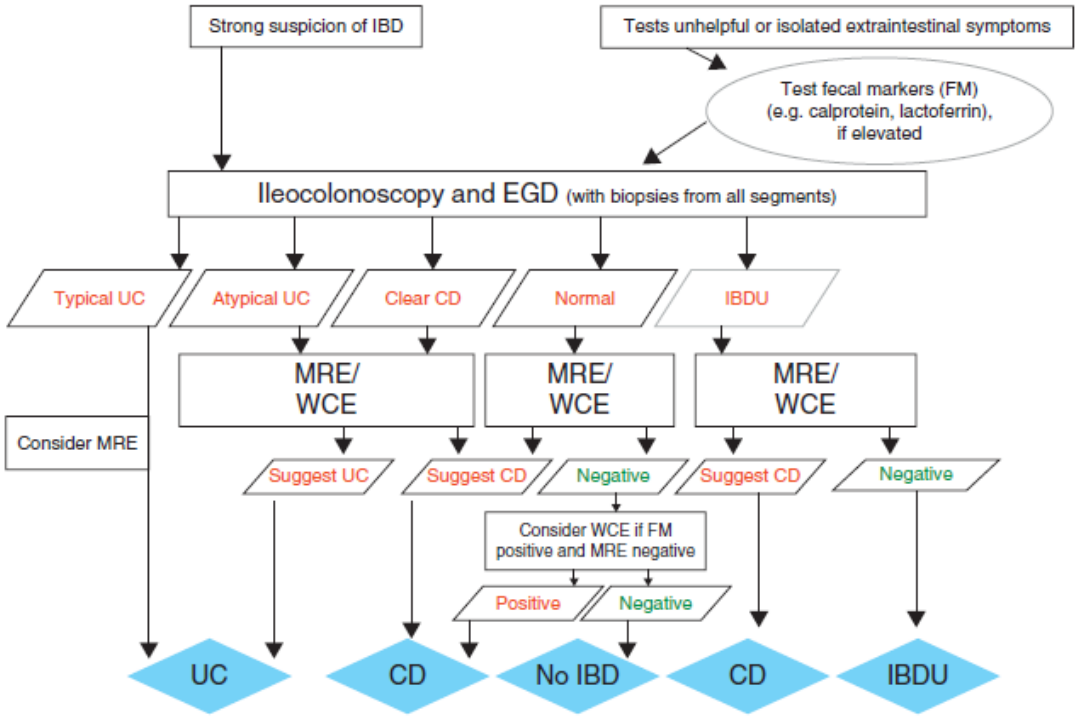


Figure 2: ESPGHAN Revised criteria for diagnosis of IBD

1.4 Treatment of PIBD

The key treatment goals in PIBD are to induce and maintain remission, promote normal growth and pubertal development, minimise drug toxicity and improve quality of life (21). However, recent evidence would suggest that another key target, mucosal healing, should be achieved. By achieving mucosal healing after induction therapy in UC outcomes are improved including longer term remission, decreased colectomy rates and longer term corticosteroid free remission(22). A similar review was published for CD, again demonstrating longer duration of remission, decreased risk of surgery and longer term mucosal healing in those that achieve mucosal healing post induction therapy(22).

Therapeutic options and strategies differ for CD and UC consequently separate guidelines exist for each. However, the evidence basis for many of the treatments used in

PIBD, for either CD or UC, is limited as few placebo controlled trials exist (23). Furthermore, given the ethical issues around withholding potentially effective treatment from children combined with the evidence that children often have an improved response to certain treatments, efficacy from adult data is often extrapolated to paediatric patients (24). Consensus guidelines exist for CD (21) and for UC (25), notably this guidance on UC does not include the management of acute severe colitis which was covered in a separate publication(26).

1.4.1 Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) is used in Europe as the mainstay of induction of remission in paediatric CD and is recommended by European guidelines (21). There is no evidence of efficacy of EEN in UC. Systematic reviews have consistently proved that EEN is as effective as corticosteroids in inducing remission with additional benefits in terms of reducing adverse effects of corticosteroids, improving weight and nutritional status (27-29). The efficacy of EEN is independent of the luminal disease location (30) and has been shown to induce mucosal healing (31). However, only short term improvement in linear growth have been observed (32) with no evidence it does so in the long term(33).

EEN is usually given over 6-8 weeks either orally or via nasogastric tube with both as effective at inducing remission; usually a polymeric (whole protein) feed is given to improve the palatability as it is equally as effective as elemental (amino acid based)(34, 35).

1.4.2 Corticosteroids

Corticosteroids can be used as induction treatment for either UC or CD, although most centres would reserve corticosteroids in CD for those not responsive to EEN or severe

presentations (21). In UC, steroids are first line in the management of acute severe colitis and for moderately active UC with systemic features(25). Corticosteroids should not be used as a maintenance treatment for IBD(21, 25). Adverse effects associated with corticosteroid usage include poor long term growth which is well recognised and can be mitigated by single daily dosing in the mornings(36) and steroid sparing treatments which are preferred. Steroid dependency in paediatric UC can develop in 45% at one year when used as induction agent at diagnosis which is higher than reported in adults(37, 38) making it essential to introduce adjuvant therapies promptly to allow weaning.

1.4.3 5- Aminoacylates

5-aminosalycylates (5- ASAs) are mostly used in the induction and maintenance of remission in UC, there is limited evidence of efficacy in paediatric CD. In UC, oral 5-ASAs are recommended for induction in mild to moderate disease as well as for maintenance(25). If no response to 5- ASA is noted within the first 2 weeks of therapy escalation to oral steroids or adding in enema therapy is recommended. Enemas as an adjuvant in UC have been shown to be effective in improving disease activity in mild to moderate proctitis in children(39). Although oral 5-ASAs are highly effective, their efficacy is enhanced when combined with rectal preparations, which is preferred above corticosteroid enema treatment. Lifelong therapy with 5-ASA is recommended due to the relatively low risk of complications combined with the long term benefits including cancer prevention(25) with once daily superior to twice daily administration(40).

1.4.4 Azathioprine /6-Mercaptopurine

Thiopurines, 6- mercaptopurine (6-MP) or the pro drug azathioprine (AZA), are recommended for both UC and CD for the maintenance of steroid-free remission but not as an induction agent(21, 25). The full efficacy of thiopurines is not reached until 8-14 weeks after commencement which is why they should not be used as an induction agent. In the only placebo controlled trial of the use of thiopurines, relapse rates of 4 and 9% were given for those on mercaptopurine compared to 26 and 47% in the placebo arm(41). Additional benefits of AZA include a decreased risk of surgery(42), reduced corticosteroid use and fewer hospitalisation(43).

A rare and serious complication associated with thiopurines is lymphoma; the relative risk is increased by 4 fold in patients on thiopurines with the risk is higher for males but the absolute risk remains low with 4.5 per 10,000 patient years(44). Furthermore, both AZA and anti-TNF therapy have been associated with the almost universally fatal hepatosplenic T cell lymphoma which occurs mainly in males in the teenage years or early 20s(45). The evolution of this lymphoma has led to a change in practice with some physicians avoiding combination therapy with AZA and anti-TNF preferring to use methotrexate as a co-immunosuppressant or anti-TNF monotherapy.

1.4.5 Methotrexate

Methotrexate (MTX) can be used as an alternative immunomodulator and has been shown to be effective in the maintenance of remission for those with CD who have failed thiopurines(46, 47). Clinical practice varies, some centres would advocate MTX after failure of thiopurines, other would use as a first line immunosuppressant as single agent therapy whilst others would advocate its use as combination therapy with anti-TNF agents. MTX can be given either subcutaneously or orally although most centres would choose

subcutaneously first line(48). In UC, the data regarding MTX use is sparse with one small trial demonstrating efficacy with 50% response/remission at 12 months. Due to the lack of evidence the current guidelines do not support its routine use suggesting only when there are a lack of suitable alternatives in those non responsive or intolerant to thiopurines(49).

The most common reported side effects of MTX include nausea and vomiting, hepatotoxicity and myelosuppression. Folic acid supplementation is recommended but there is no clear evidence to support daily versus weekly administration(21).

1.4.6 Anti-Tumour Necrosis Factor drugs

1.4.6.1 Infliximab

IFX, the first tumour necrosis factor-alpha antagonist (TNF-α) (50) gained UK licences for adult and paediatric CD in 2002 and 2010 respectively(51, 52) having been used off-licence from the late 1990s(23) prior to RCTs in PIBD,(53-55) given the available high quality evidence for IFX use in adult IBD (56, 57). IFX is recommended for use in chronic active luminal CD after failure of immunomodulators, steroid dependency or steroid refractory disease and for first line in management of perianal fistulising disease in conjunction with both a surgical and medical approach(21). It was first described in paediatric patients in a case series of by Hyams with refractory Crohn's and was effective in inducing remission(58). When first licensed, IFX was used on an episodic or "as needed" basis to be administered when patients became symptomatic. However, after the ACCENT trial when episodic was compared to scheduled dosing in adult CD, it was shown to be superior so practice was changed with scheduled dosing as a standard practice; a similar study confirmed this in paediatric patients(55). The REACH study was the first large paediatric cohort which demonstrated both safety and efficacy of IFX in CD (53). The uptake for use in UC followed but was only published in 2012 for the management of acute severe colitis

(54), its use varied between countries and even between centres in each country depending upon expertise and familiarity with its use compared to ciclosporin. However, the recent ECCO/ESPGHAN guidelines recommend it as the first line biological drug of choice for both UC and CD and as a rescue treatment in acute severe colitis(25, 26). In addition to inducing and maintaining remission, IFX has been shown to improve linear growth and promote mucosal healing(59, 60).

However, many issues have yet to be resolved in using anti-TNF drugs to treat PIBD including identifying patients likely to have a prolonged response to treatment and balancing the risk/benefit of combination therapy (anti-TNF and immunomodulator vs monotherapy with anti-TNF therapy alone) and the role of therapeutic drug monitoring. Therapeutic drug monitoring has evolved with evidence supporting a proactive approach to optimising levels rather than awaiting clinical response(61) yet more evidence supports higher trough levels for perianal disease(62). Loss of response to anti-TNFs is a key challenge for clinicians(50), initial loss of response can be regained with dose escalation unfortunately, this is often not maintained and remains a common reason for discontinuation of therapy(63, 64). Several risk factors have been identified including: isolated colonic crohn's disease, lack of remission post induction, increased BMI, corticosteroid use at baseline and strictures(65-68). Despite being widely discussed in the literature, there is no consensus definition on loss of response making it difficult to compare results from various studies(69) and no clear protocol on how to manage although current evidence supports dose optimising and the addition of an immunomodulator if not currently receiving (61, 70).

Anti-TNF therapy has been associated with an increased risk of opportunistic infections including reactivation of tuberculosis and other serious infections such as

abscesses and sepsis (50), and of malignancy, in particular hepatosplenic T cell lymphoma (HSTCL). However, the cases of HSTCL received concomitant thiopurines(71).

Biosimilars to infliximab are now available, which are innovators of the biopharmaceutical products made by different companies once the drug licence has expired. This change has driven down dramatically the costs involved with no observed increase in side effects with similar efficacy(72). Currently studies are ongoing in paediatric IBD comparing biosimilars and originators with promising data emerging to suggest similar efficacy.

1.4.6.2 Adalimumab

Adalimumab (ADA) (Humira) is a fully humanised anti-TNF alpha agent which is administered subcutaneously every other week. ADA was initially used for primary or secondary loss of response to IFX to induce and maintain remission in adult CD and UC(73-77) with efficacy now confirmed by RCT in paediatric CD in 2012(78). ADA was licensed for UK paediatric CD use in 2013 but with prior widespread off-licence usage reported via a UK audit(79). Few case reports exist in the use of ADA in UC which seem to suggest efficacy including UK and Irish data, but the numbers involved are small(79, 80). Less has been published on the side effects of ADA, however, similar risks exist of opportunistic infections(50) and increased malignancy, particularly with co-immunosuppression(50).

1.4.6.3 Golimumab, Certolizumab pegol and other new drugs

Other anti-TNF drugs are available such as golimumab and certolizumab pegol which are not yet licenced in paediatric use. Golimumab was effective in small paediatric UC trials(81) but not in CD(82), it has a licence in adults for moderate to severe UC with certolizumab demonstrating efficacy in adult refractory CD only(83).

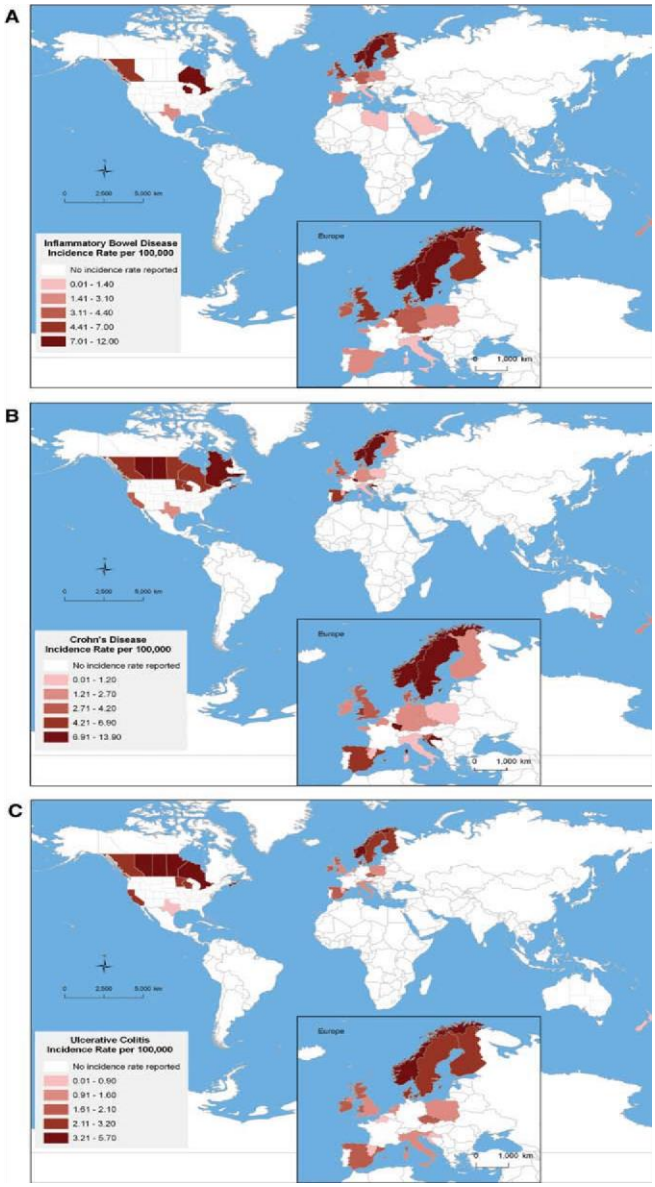
Further drug development is underway targeting other cytokines in the inflammatory pathway such as interleukin 12/23 with ustekinumab or anti integrins with vedolizumab. Both are becoming more common in adult practice with randomised control trials confirming efficacy but limited case reports are available in paediatric patients (84). Other more novel therapies are in development including mesenchymal stem cells for the treatment of perianal CD and the use of T regulatory cell and small molecule drugs (SMD) such as tofacitinib. SMDs, are composed of smaller molecules which can be administered orally, a key benefit in PIBD, with Tofacitinib, a Janus kinase inhibitor, successful in UC(85) but not for CD(86).

1.5 Epidemiology of PIBD

1.5.1 Systematic review on incidence

Systematic reviews on the incidence of PIBD and adult-onset IBD have been published with data on prevalence reported in adults only (2, 87). In the paediatric review, there were key methodological flaws including variable age ranges used to defined PIBD from 14 to 19 years which impacts upon incidence rates the higher the age range as more patients are included. The review reports incidence from 139 studies from 32 countries which are mostly from Europe and North America with a paucity of data from developing countries (**Figure 3**), contrasting with the adult-onset IBD systematic review, which had data from countries which had not previously confirming the increasing incidence of IBD(87). Currently, there is no systematic review on prevalence of PIBD, however, there is an increasing trend in prevalence of adult- onset IBD suggesting a similar trend may be observed in paediatrics.

Figure 3 Worldwide map of countries reporting incidence of paediatric–onset Inflammatory bowel disease(2)



1.5.2 Systematic review prevalence

The systematic review on adult-onset IBD demonstrated an increasing prevalence, which as with incidence, was highest in Europe/North America and lowest in Asia(87). There was a paucity of data in PIBD prevalence, however, increases have been observed in North America(88, 89).

1.5.3 Population–based studies in PIBD

There are few population-based studies of incidence of PIBD compared to referral centre based due to data collection issues. Population-based studies suggest that PIBD is unevenly distributed throughout the world with the highest rates in more industrialised countries in Europe/North America which are (2). However, data is lacking from developing countries which will be discussed further in chapter 3.

1.5.4 Temporal trends in incidence in PIBD

Longitudinal incidence provides key messages about temporal trends and insight into potential environmental factors, informs service delivery and planning, yet few studies report it as evidenced by only 20% of papers in a recent incidence systematic review reporting it. 77% of those reporting temporal data demonstrated an increase with none reporting a decrease (2), this is mirrored in adult IBD with increasing incidence for both CD in 43/57 (75%) and UC 30/50 (60%) in studies that reported data over at least 10 years(87) with none reporting a decrease.

Within the UK, incidence rates have increased in Scotland(90-92), Wales(93-96) and Wessex(97), although the rates were highest in Scotland (**Table 3**). In Scotland, when PIBD incidence was first recorded in 1969, UC was the predominant IBD subtype, however, over the next 40 years the incidence of both has significantly increased with CD now the most common subtype(90-92). This phenomenon has been reported in other western countries(98-100) with UC the predominant subtype when IBD is first reported then CD becomes more common as countries become more westernised with Hong Kong an example(101) .

Table 3: **Recent incidence data for Crohn's disease (CD) ulcerative colitis (UC) in childhood in the UK (incidence rates are provided per 100,000)**

Author	Area	Years	Age range	Incidence (per 100,000)
Barton(90)	Scotland	1968	0-16	CD 0.7 UC 1.9*
		1983	0-16	CD 2.3 UC 1.6*
Armitage(91)	Scotland	1981-1995	0-15	CD 2.5 UC 1.3
Henderson(92)	Scotland	2003-2008	0-15	IBD 7.82 CD 4.75 UC 2.06
Cosgrove(94)	S Wales	1983-93	0-15	CD 2.2 UC 0.7
Hassan(96)	Wales	1995-97	0-16	CD 1.36 UC 0.75
Ahmed(95)	South Wales	1996-2003	0-16	IBD 5.4 CD 3.6 UC 1.5
Gunesh(93)	Cardiff, Wales	1996-2007	0-16	IBD 2.7
Sawczenko(102)	UK	1998	0-15	CD 3.1 UC 1.4
Ashton(97)	UK, Wessex	2002-2012	0-16	IBD 6.39 CD 3.8 UC 2.01

*Rates for 6-16 years

1.5.3 Geographical trends in incidence

A North-South divide within countries has been described in both Europe (103) and North America where more northern states have higher incidences(89, 104, 105). However,

the North American studies are from insurance databases which are not population-based and may influence their results. Population-based studies, such as EPIMAD, have found increased cases in urban verses rural areas(106, 107). In adult IBD, a population-based pan Europe study, an East-West divide was observed, paediatric patients were included but the numbers involved were small suggested incomplete accrual(108).

1.5.4 Incidence of PIBD in Scotland

Incident data for PIBD has been collected across Scotland since 1969 and has demonstrated a continued and sustained increase until 2008(90-92). When incidence data was reported in 1989, incidence rates of CD were higher than UC with a suggestion that rates of UC were decreasing. Disease distribution was similar to adult data with 38% of CD patients having panenteric disease and 50% of UC patients with extensive or pancolitis(90). Armitage reported in 2001 an increasing trend for UC although CD remained higher at 2.3 per 100,000 compared to 1.3 per 100,000 for UC(91) with a 30% increase in IBD. By 2008, the incidence of IBD had continued to rise with a 76% increase from the mid-1990s to 7.82 per 100,000 with CD again more frequently reported with an incidence of 4.75 per 100,000 (92) (**see Figure 4**). Countries which reported higher incidence rates included Canada and Norway (109, 110) (111-113), both of whom have a northern latitude similar to Scotland (**Figure 5**).

Figure 4- Incidence of paediatric onset CD from 1969- 2008 in Scotland(92)

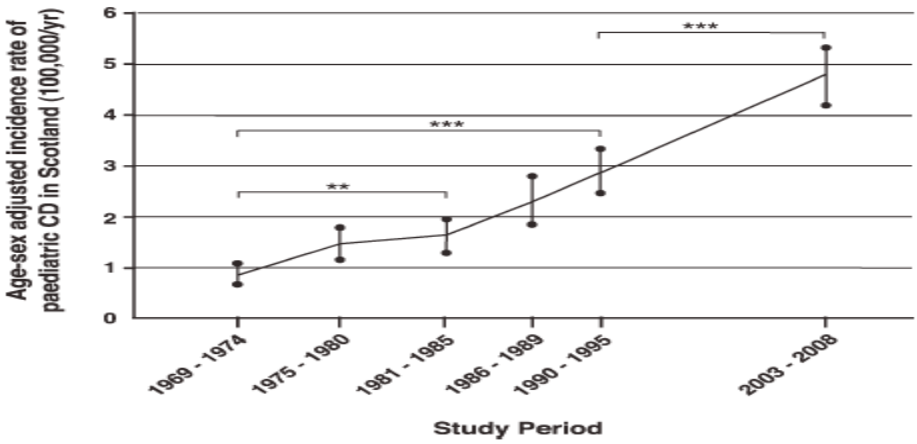


Figure 5 – Temporal trends of worldwide incidence of paediatric-onset Inflammatory Bowel Disease(2)

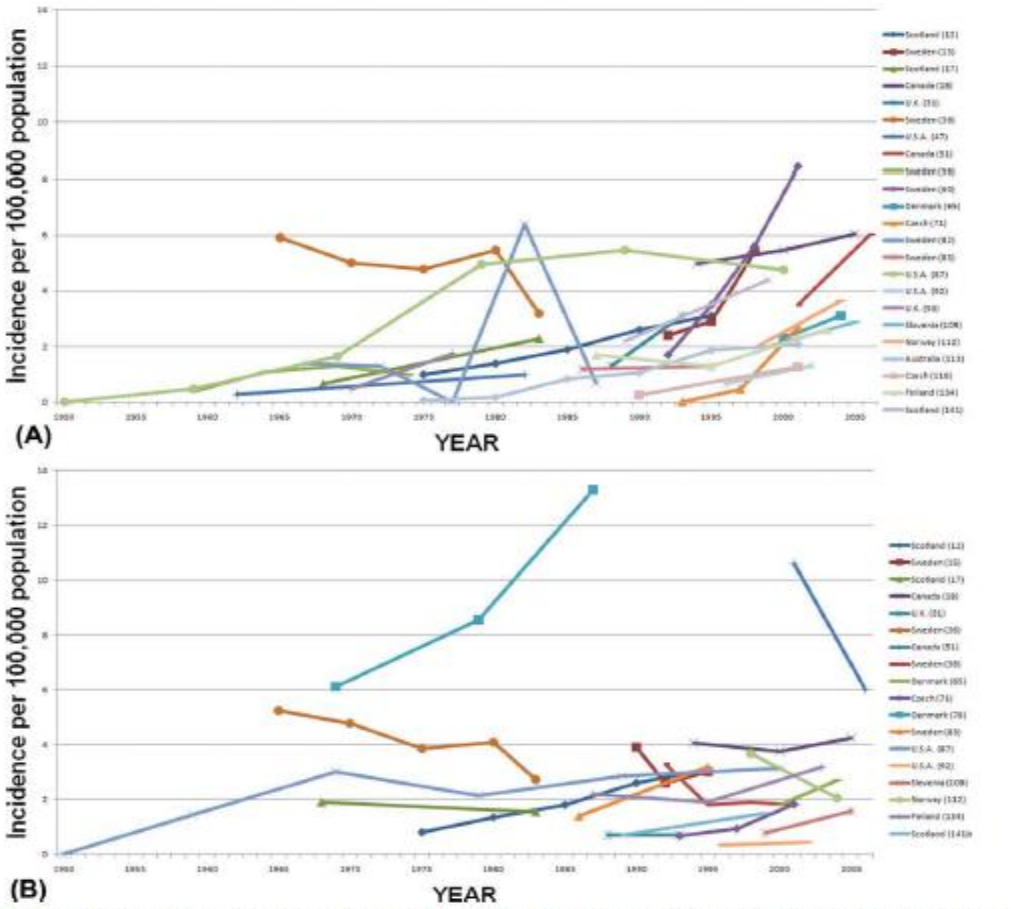


FIGURE 3. Temporal trends of incidence rates for (A) Crohn's disease and (B) ulcerative colitis in studies reporting incidence at multiple timepoints. Where a year range is reported, incidence rate is reported for the final year in the range (e.g., if incidence is reported for 1990–1999, rate is plotted as incidence for 1999).

1.6 Natural history of PIBD

1.6.1 Evidence from population-based studies

Few population-based studies examine the natural history of PIBD due to methodological challenges particularly related to the longitudinal follow up required, however, those that have provide key insights, and how this differs from adult onset disease. Different countries have shown similar and yet conflicting reports which may relate to numerous confounders including environmental factors, differences in diagnostic evaluation, treatment strategies and disease reassessments. However, a review of the published literature on UC reported 50% had disease progression as two thirds with a pancolitis by end of follow up and 20% required a colectomy by 10 years post diagnosis with 50% suggesting an aggressive phenotype (114).

1.6.2 Cancer and mortality

Cancer associated with PIBD is rare but studies report an increased rate in adults who were diagnosed with IBD in childhood(115). Deaths related to PIBD are also relatively low with the highest rates reported in earlier studies due to small or large bowel cancers which were hypothesised to be related to underlying disease activity(116). ESPGHAN published in 2014 European wide retrospective data showing that the leading cause of death was not malignancy as had been previously feared but, infection related to immunosuppression, follow then by cancer and uncontrolled disease(117); an important sequelae as chronic inflammation can lead to immune dysregulation with impaired tumour surveillance(118). The treatment of PIBD has changed significantly in recent years with more aggressive management including early immunosuppression in selected cases (21, 25) as evidenced by Scottish data with 45% of children with Crohn's disease will be on

immunosuppression by 12 months(16). As the incidence of PIBD in both Scotland(92) and the rest of the world increases(2), the number of children on immunosuppression with the associated risks of opportunistic infections and malignancy will consequently increase. Further concern surrounds hepatosplenic T cell lymphoma (HSTCL), an almost universally fatal lymphoma which often occurs in young men with CD treated with thiopurines and/or anti-TNFs(119).

EPIMAD published one of the few population-based studies into mortality and morbidity, reporting a mortality rate of 0.84% which did not differ from the background population. However, it did report a slightly increased risk of cancer which was not dependent upon age or gender, with 4 of 9 who developed cancer receiving prior immunosuppressants or anti-TNF. 1.3% of patients who developed cancer did so after a median follow up of 15 years, so in adult care, which was an increased risk compared to the general population(120). A national population-based study from Sweden supports this finding with an increased risk of gastrointestinal, hepatic, lymphatic and skin cancers in those diagnosed with IBD in childhood compared to those without IBD but with risk factors identified of a family history of cancer, long standing colitis and primary sclerosing cholangitis (121). Those diagnosed with IBD at a younger age had a higher mortality rate although the absolute risk remained low in a Danish population-based cohort(122).

Studies presenting data on the risk of cancer in PIBD are listed in **Table 4** with a summary of mortality studies not listed in a recent systematic review in **Table 5**.

Table 4 Summary of studies of Paediatric inflammatory bowel disease and cancer risk

Study	Study period	Age at onset (years)	No of patients followed (subtype)	Patient years of follow up	No of cancers diagnosed	Incidence per 1000 person years (95%CI)	Relative risk*
Devroede, 1971(123)	USA 1919-1965	<14	396 (UC)	NR, max 43 years	52 (any cancer)	NR	NA
Weedon 1973 (124)	USA 1919-1965	<22 (mean 15)	449 (CD)	7077	12 (any cancer) 8 (CRC)	1.0 (0.5 to 2.1) for CRC	20 for CRC
Goel 1973 (125)	Scotland 1931-71	<14 (mean 8)	25 (UC)	303	1 (CRC)	3.3 (0.2 to 16.3)	NR
Ekbom 1990(126)	Sweden 1945-83	<15	363 (UC)	4220	13 (CRC)	3.1 (1.7 to 16.3)	118 (63 to 202)
Ekbom 1990(127)	Sweden 1983-84	<30	964(CD)	12025	5 (CRC)	0.4 (0.2 to 0.9)	10 (3 to 23)
Ashworth 2012 (44)	USA 1979-2009	<22 (mean 12)	839 (UC, CD)	4441	2 (lymphoma)	0.5 (0.1 to 1.5)	8 (0.7-42)
Jess 2012 (128)	Denmark 1979-2008	<20	4763 (UC, CD)	52100	18 (CRC)	0.3 (0.2 to 0.5)	UC: 44 (27 to 719) CD:2 (0.3 to 17)
Peneau 2013 (120)	France 1988-2009	<17 (median 14)	698 (UC, CD)	NR, median 12 years	9 (any cancer)	NR	3.0 (1.3 to 5.9)
De Ridder 2014(117)	Europe 2006-2011	<19 (median 12)	NA	NA	18 (any cancer)	NA	NA
Kappelman 2014 (129)	Denmark 1978-2010	<20	NR (UC, CD)	NR	NR	NR	UC: 2.0 (1.4 to 2.7) CD: 2.3 (1.5 to 3.4)
Hyams 2017(130)	USA, Europe 2007-2016	<17	5766 (UC, CD)	24543	15 (any cancer) 9 (lymphoid)	0.6 (0.4 to 1.0)	Thio exposed: 2.9 (1.4 to 5.1) Non-exposed: 1.3 (0.2 to 4.7)
Olen 2018 (121)	Sweden 1964-2014	<18 (median 15)	9405 (UC, CD)	148682	497 (any cancer) 122 (CRC) 24(lymphoid)	3.3 (3.1 to 3.6) 0.6 (0.4 to 0.9)	HR for any cancer: UC: 2.6 (2.3 to 3.0) CD: 1.7 (1.5 to 2.1) HR for CRC UC:33(23 to 49) CD: 5.8 (3.2 to 10)
Joosse 2018(131)	Europe 2013-2016	<19	55, 036&	192625	43[£]	171 (120-238)[$]	0.816 (0.57 to 1.18)

CD= Crohn's disease, UC=ulcerative colitis, NA= not applicable, NR= not reported, CRC= colorectal cancer, CI=confidence interval, HR= hazard ratio, Thio= thiopurines
*Standardised incidence ratio, unless otherwise stated; &- patient diagnosed <19 years but developed malignancy by 26 years; £- total number of malignancies reported; $-incidence reported per 1,000,000 patient years based on 33 cancer cases

Table 5 Summary of studies on Paediatric-onset inflammatory bowel disease and mortality risk

Study	Study period	Age at onset (years)	No of patients followed (subtype)	Patient years of follow up	No of deaths	Incidence per 1000 person years (95%CI)	Relative risk*
Jakobsen 2009 (132)	1962-2006	<16	119	NR	4	NR	2.1 (0.6-5.4)
Peneau 2013 (120)	France 1988-2009	<17 (median 14)	698 (UC, CD)	NR, median 12 years	6	NR	1.4 (0.5 to 2.9)
De Ridder 2014(117)	Europe 2006-2011	<19 (median 12)	NA	NA	31	NA	NA
Joosse 2018(131)	Europe 2013-2016	<19	55,036	192625	26	114	

CD= Crohn's disease, UC=ulcerative colitis, NR= not reported, CI=confidence interval,
*Standardised mortality ratio, unless otherwise stated

1.7 Summary of thesis chapters

Further understanding of the current trends in epidemiology of PIBD can be obtained through systematic review which will be explored via the incidence and prevalence in chapters 2 and 3. Temporal trend analysis of incidence provides information on the durability of rise or levelling out cases which is most effective in population-based studies such as Scotland which is seen in chapter 4. Few epidemiological studies have been performed on IBDU, the least common subtype of IBD, so a relative paucity of data exists on the natural history and efficacy of treatments which is explored further in chapter 5. Chapter 6 covers the natural history of anti-TNF therapy in PIBD in a population-based cohort, anti-TNFs are now commonly used despite initial concerns regarding safety and with proven efficacy. However, most studies are either single or multi-centre studies with few population-based studies which limits the generalisability. Lastly, mortality and morbidity are important outcomes to evaluate in PIBD, particularly given the high use of immunosuppression currently in use (Chapter 7) and to counsel families regarding long term course and side effects.

Chapter 2

2. Methodology

2.1 Methodology for incidence and prevalence systematic reviews

2.1.1. Search strategy for incidence and prevalence systematic review

A systematic literature search was performed using a predetermined protocol (**Tables 5 and 6**) using MEDLINE (1950-2017), Ovid MEDLINE® In-Process & Other Non-Indexed Citations (PREM), Embase (1950-2017), and Cochrane Library on the 17th July 2017. The initial search included all languages with abstracts and titles of all eligible studies were reviewed, full text was obtained if appropriate and references cross checked by hand. Finally, a "grey literature" search was performed by hand which involved searching through the abstracts for the previous 8 years (2009-2017) of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition, United Gastroenterology Week, European Crohn's and Colitis Organisation and North American Society of Paediatric Gastroenterology, Hepatology and Nutrition. Once all full text articles were available, they were independently reviewed by FC and DCW for eligibility. A final search was performed using Google Scholar™ using search terms "paediatric" "incidence" "prevalence" and "inflammatory bowel disease" to ensure no relevant papers were missed.

Table 6- Full Medline search for journal article retrieval (1950 to October 2017) for incidence systematic review

1. inflammatory bowel disease/ or colitis, ulcerative/ or crohn's disease/ or ((ulcerative adj2 colitis) or (inflammatory adj2 bowel) or crohn*).mp.
2. morbidity/ or incidence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. 1 and 2
4. inflammatory bowel disease/ep or colitis, ulcerative/ep or crohn disease/ep or (((ulcerative adj2 colitis) or (inflammatory adj2 bowel) or crohn*).mp. and ep.fs.)
5. 3 or 4
6. limit 5 to "all child (0 to 18 years)"
7. (infan* or child* or teen* or adolescen* or paediatric* or pediatric*).ti,ab
8. 5 and 7
9. 6 or 8

Table 7- Search strategy (OVID) for prevalence systematic review (1950-2017):

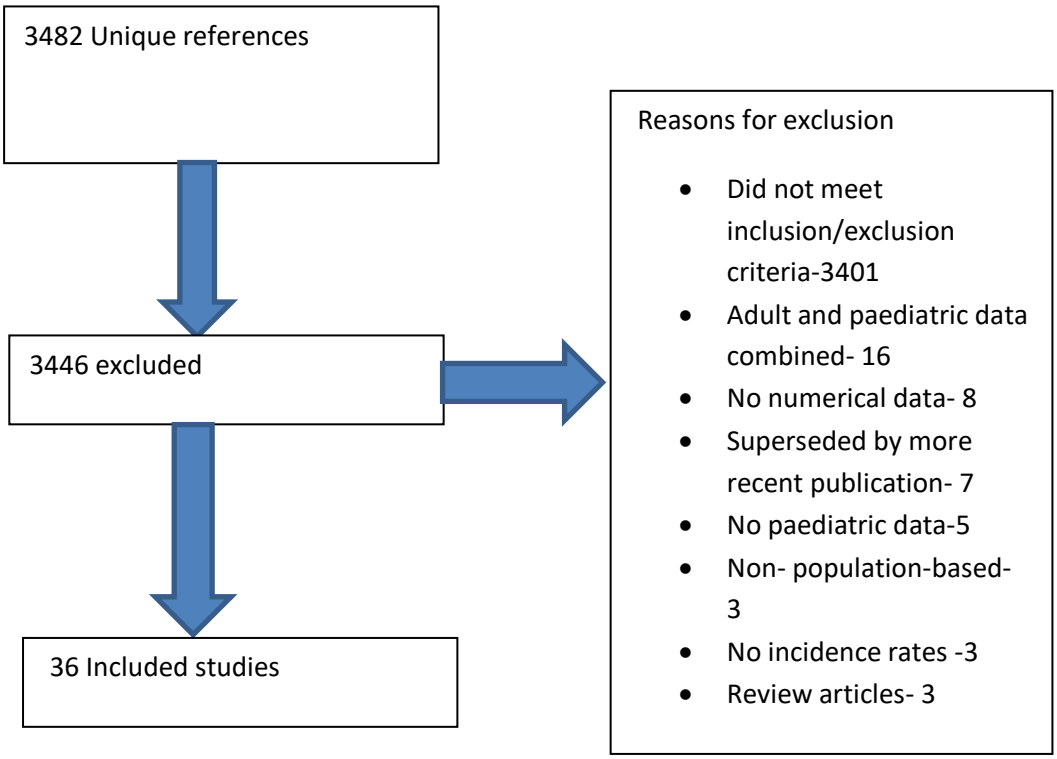
1. exp Inflammatory Bowel Diseases/
2. Colitis, Ulcerative/
3. (inflammatory bowel disease* or ibd or crohn* or ulcerative colitis or indeterminate colitis).ti,ab
4. 1 or 2 or 3
5. Prevalence/
6. Cross-Sectional Studies/
7. prevalence.ti,ab
8. ep.fs
9. 5 or 6 or 7 or 8
10. exp Infant/ or exp Child/ or Adolescent/ or Young Adult/
11. (infant* or newborn or neonate* or child* or adolescent* or teen* or young adult* or young person or young people).ti,ab
12. 10 or 11
13. 3 and 9

2.1.2 Inclusion and exclusion criteria for incidence systematic review

A prior systematic review was performed on the incidence of PIBD, CD and UC which included studies published before 1.1.2010(2), this current review was designed as an update, focusing on longitudinal trends in incidence, to that no eligible studies from the previous search had been missed, the literature was searched from 1950-2017 on studies reporting incidence of PIBD (i.e. CD, UC or IBDU) from 1950-2017. Inclusion criteria were studies with (1) a clearly defined method of diagnosing PIBD including, but not limited to, clinical history, radiological findings, histological changes, endoscopic appearances and physician-confirmed diagnosis (used for healthcare administrative databases); (2) a clearly defined cohort of patients under 18 years of age; (3) incidence data reported; (4) a full manuscript available for review and (5) not included in the previous systematic review. In some studies patients were identified using ICD 10 codes for IBD (K51.0, K51.1, K51.2, K51.3, K51.9, K50.0, K50.1, K50.8, K50.9) from insurance or hospital databases. Studies were excluded (**Figures 6**) if paediatric data could not be clearly differentiated from adult data, where data was presented in graphical form only with no clear numeric values, only male or female incidence reported, hospital-based incidence only, included in the previous systematic review or review articles where no original data was presented (the references were reviewed to ensure all eligible studies were included). Studies were included which reported “possible” and “probable” for two reasons: firstly, to allow comparison with the previous systematic review where these studies were reported and to maximise the number of studies to improve generalisability of the results. Methodological appraisal was hampered by lack of information for certain studies therefore, authors were contacted via e mail to obtain clarification (corresponding author contacted twice, then first author (if different from corresponding author), contacted twice, then senior author if no reply from previous attempts). Five authors replied to provide further data. Eight papers were

excluded that gave no clear paediatric data. Studies in languages other than English were translated using Google Translate™ and their abstracts reviewed, however, upon review none met the inclusion criteria. All eligible studies were included despite the varied methodological approaches to provide as wide a range as possible of the incidence of PIBD.

Figure 6 Flow diagram of included and excluded studies for incidence systematic review

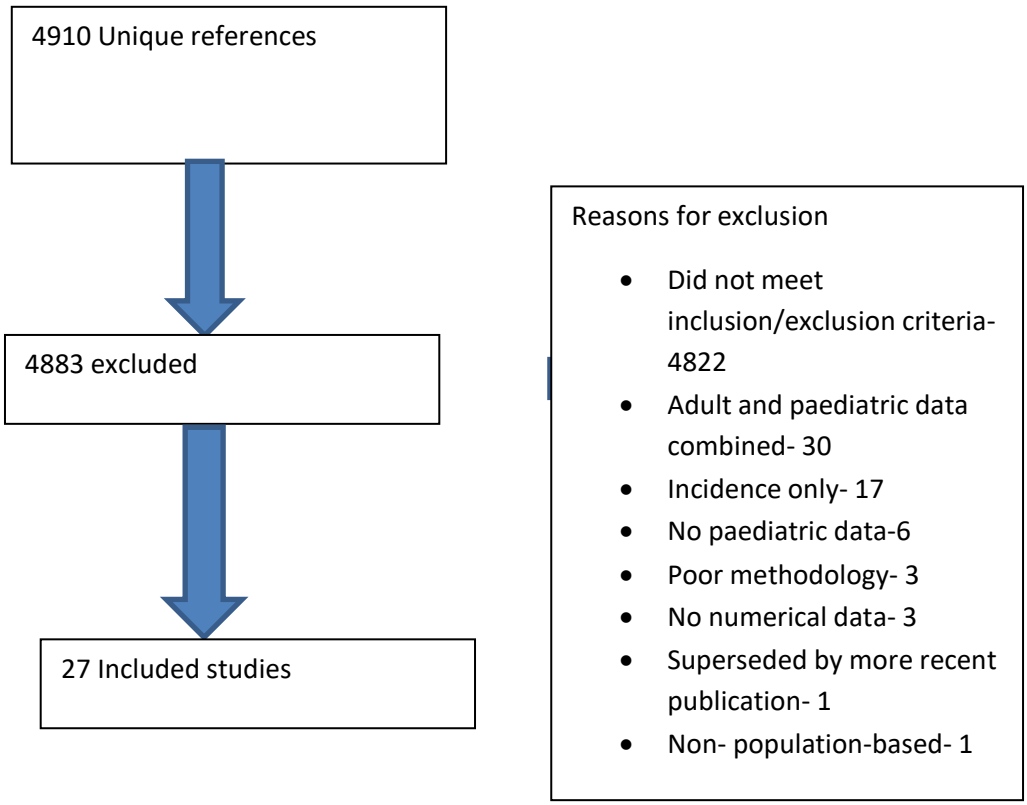


2.1.3 Inclusion and exclusion criteria for prevalence systematic review

Studies were reviewed that reported incidence and/or prevalence of PIBD (i.e. CD, UC or IBDU). Inclusion criteria were the same as for the incidence systematic review other than prevalence data had to be reported to be eligible. Similar exclusion criteria were used (**Figure 7**) with studies excluded that did not include any paediatric specific prevalence data. The same age criteria and methods of contacting authors were applied to this review.

Three authors replied to provide further data with three other papers excluded as no clear paediatric data was provided.

Figure 7 Flow diagram of included and excluded studies for prevalence systematic review



2.1.4 Age criteria for inclusion

Studies were included if there was a clearly defined population less than 18 year of age which is commonly accepted to define the paediatric population. The previous incidence systematic review included studies of patients under 19 years of age to increase the number included but did not consider how this influenced their results. Both incidence and prevalence increase with age so the rates reported may over report the incidence of PIBD. Ideally studies would compare those aged under 17 years according to the Paris

criteria(10), however, due to the diverse methods of data collection if these criteria were strictly applied the number of eligible studies would reduce significantly.

2.1.5 Data collection for incidence and prevalence systematic reviews

Data collected included: incidence/prevalence rates for PIBD/CD/UC/IBDU, year of study, assessment of methodology, methods of disease diagnosis, sources of data and age range of the population included. A time trend analysis was conducted over a 10-year period with a least 2-time points within that period for the incidence systematic review only.

2.1.6 Summarisation of data for incidence and prevalence

Studies were summarised in table format. Geographic maps of incidence and prevalence of IBD, CD and UC were created using Excel 13 (Microsoft Corporation, Redmond, WA™) with rates represented using colour intensity (darker colour indicates a higher incidence/prevalence rate). Incidence/prevalence rates for regions were only shown for United States of America, United Kingdom and Canada which could be clearly defined. In countries where more than one regional incidence/prevalence was reported, the highest rate reported was assigned to the entire country where rates were not reported. Where incidence/prevalence was reported over several time points, the incidence/prevalence was plotted on line graphs for IBD, CD and UC with rates plotted representing incidence/prevalence per 100,000 population. If incidence/prevalence was reported over several years (i.e. 2000-2005) then data was attributed to the final year of that epoch.

2.2 Methodology for data collection of Scottish incidence data for paediatric-onset inflammatory bowel disease

2.2.1. Setting

Scotland has a population of 5.2 million people with approximately 17% aged less than 16 years old (916,103 in 2011) ; the majority of inhabitants are Caucasian(133). It is located in Northern Europe (latitude (55^0-60^0) and covers 30,500 square miles with four cities with a population over 100,000 people(133). In Scotland, specialist paediatric gastroenterology, hepatology and nutrition (PGHAN) is provided through three tertiary regional networks covering all four academic centres (Glasgow, Edinburgh, Aberdeen and Dundee) and all district general hospitals having paediatric units, thus forming a virtual Scottish national network as previously described(92, 134).

2.2.2. Case identification

Data was collected from 1969 to 2014 for all newly diagnosed patients with PIBD in Scotland under 16 years who were diagnosed within paediatric services. In Scotland, children are routinely cared for in paediatric centres until their 16th birthday when they are transitioned to adult services, so this age was used as a cut off. Historically children aged 14 years or above may have been referred to adult gastroenterology or adult surgeons and managed solely in adult care. However, with the advent of an established PIBD network the usual referral pattern now would be to paediatric IBD centres via primary or secondary care if IBD is suspected or to adult services if over 16 years unless extenuating circumstances. Due to changes in recording of new diagnoses during the study period, different methods of data collection were employed. For the most recent cohort, from 1st January 2009 to 31st

December 2014 (hereafter known as Cohort 2), cases of PIBD were identified from each of the three-tertiary paediatric centres and two district general hospitals (Dundee and Inverness) prospectively from PGHAN department-held databases for two centres and retrospectively from the remaining centre. Prospective data was collected using a downloaded excel spreadsheet which was manually cross checked to ensure no duplication or missing data which needed clarification with the local centre. For the previous cohort in 2003-2008, hereafter known as Cohort 1, cases were reported using robust methodology to ensure complete accrual utilizing pathology records, PIBD clinic lists, endoscopy lists and local team knowledge(92). This data was validated in Aberdeen using endoscopy logs from theatre for all children undergoing ileocolonoscopy (all procedures were performed under general anaesthetic), IBD clinic lists, pathology records and local team knowledge. In Inverness, cases were validated using the same methodology with the addition of cross-checking ICD-9 codes for CD/UC (K555-558) for those who would have been aged under 18 years during the study period. The respective collection of data for cohort 2 was performed using the same methodology as for cohort 1, validating local team knowledge against IBD clinic lists, pathology records and endoscopy lists for the duration of the study period from 2009-2013. Data from 1969-1995 cohort was collected using the Scottish Hospital In-patient Statistics which records admission to hospital and classified using the ICD-8/9 codes (CD- 555/0-555.9, UC 556.0). From 1981-1995, these records were all hand examined and validated to ensure diagnostic accuracy(91, 92).However, data from 1968-1983 were limited by the exclusion of those under 5 years with UC, lack of available case records for review and poor coding(90).

Following case identification anonymized data was then collected from a hand search of written case notes/electronic records and entered onto a centrally custom-built database (Access 2007, Microsoft Corporation, Redmond, WA) held at the lead centre.

Cases were individually scrutinized to ensure no duplication from different areas of Scotland using unique identifiers with non-incident cases removed.

When PIBD cases were first collected in 1969, IBDU as a distinct phenotype of PIBD did not exist, even in the later cohort of 1981-1995 the concept of IBDU was not widely accepted or used. In the 1981-1995 cohort, only 2 cases of IBDU was identified so were amalgamated with the UC patients. To allow a clear comparison with the historical cohorts, trend analysis over time and to avoid misclassification bias, two groups will be analysed: CD and non-crohn's colitis (NCC).

2.2.3. Exclusion criteria

Patients were excluded who were diagnosed outside of Scotland or were above 16 years at age of diagnosis if diagnosed within a paediatric centre.

2.2.4. IBD phenotyping

Diagnosis was based on clinical symptoms, laboratory results, endoscopic, radiological and histological assessment in-line with the revised Porto criteria(13) for cohort 2, original Porto criteria(11) for cohort 1 and Lennard Jones(135) for 1969-1995 by the local specialist PIBD team. Investigations performed to confirm the diagnosis of PIBD varied between centres with no unifying diagnostic algorithm but included ileocolonoscopy and/or upper gastrointestinal endoscopy and/or small bowel imaging dependent upon the macroscopic and histological findings. Small bowel imaging was performed by white cell scans, barium meal and follow through or wireless capsule endoscopies dependent upon the centre; MR small bowel was not routinely available in all centres. Faecal calprotectin was also not routinely available in all centres then only latterly in certain centres. Patients were diagnosed as either Crohn's disease (CD), ulcerative colitis (UC) or inflammatory

bowel disease unclassified (IBDU) by the local centres. All ambiguous cases were discussed with senior clinicians (RKR and DCW), both of whom are the lead PIBD consultants in their respective region and have significant experience in IBD phenotyping, with involvement in developing the recent ESPGHAN guidelines on diagnosis of PIBD(13). Within both cohorts, a small number of cases that were diagnosed as IBDU were subsequently reclassified as either CD or UC after full endoscopic re-evaluation, therefore, only the most recent diagnosis was used. Additionally, all incident cases are continually reviewed to ensure the initial diagnosis was correct and non-IBD cases are removed.

IBD phenotyping has evolved over the years with the first classification created in Rome in 1991 for CD based on disease location, behaviour, disease extent and operative history(14). Following the Rome criteria, further modifications were made and the Vienna classification was published in 2000, however, neither mentioned UC or IBDU(15). The

Montreal criteria was published in 2005 and included all IBD subtypes with a separate paediatric IBD classification using age range of less than 17 years for paediatric cases(9). The Paris criteria was developed in 2011 which recognised the specific differences in PIBD verses adult onset disease including the propensity for disease extension, impact on growth and subdivided into those less than 10 years and less than 17 years(7).

When classifying IBD subtypes, certain histological features are pathognomonic including granuloma and strictures in CD, whilst other features, such as ulcers, can be seen in both(11). The 2014 publication from the Porto group provided detailed guidance on differentiating CD/UC and features which would suggest a diagnosis of IBDU(10). The paper has features which are typical of CD/UC as well as atypical of UC but can occur in up to 10% including focal active duodenitis or aphthous ulceration in the colon or GI tract. If there are two or more features which are atypical of UC, a diagnosis of IBDU is suggested. This guidance will hopefully improve IBD phenotyping which, if inaccurate, will impair the

evaluation of treatments and the natural history as patients without similar diseases are compared.

There is no one diagnostic pathway for PIBD as exemplified by the Eurokids registry which included 44 centres from 18 countries representing leading PIBD centres. Newly diagnosed patients were phenotyped according to the original Porto criteria, however, only 64% underwent full endoscopic assessment of upper GI endoscopy and ileocolonoscopy, including 85% with IBDU who had an OGD(136). This highlights that even in leading centres, recommendations are not always followed so a proportion of cases may have been misdiagnosed. Despite not following diagnostic algorithms, it is unlikely that cases of PIBD are missed but that the subtypes are incorrect, most commonly this would favour UC given the lack of consistent upper GI endoscopy. However, the PIBD subtype with the highest incidence remains CD(137) suggesting that this may not occur frequently.

The Eurokids registry published data on IBDU where 16% of cases referred in from reporting centres as IBDU had features not compatible with this diagnosis, such as perianal disease and granuloma(138). Small bowel imaging was performed in 62% of IBDU patients(138) and histology was not reviewed in all due to high patient numbers without complete sets of biopsies, non-adherent to the revised Porto criteria (10). The challenges Eurokids registry faced reflects the daily dilemmas of clinicians in accurately phenotyping patients, some of whom are extremely complex. However, a full diagnostic evaluation including upper GI endoscopy, ileocolonoscopy with small bowel imaging will reduce the number of diagnostic challenges, this used in combination with endoscopic reassessment will improve diagnostic accuracy.

2.2.5. Statistical analysis

Information on the size of the paediatric population were obtained from the National Records of Scotland (NRS) for each year from 2009-2014(133). Allowance for the individual variation in the yearly at-risk population structure was performed by using standardised incidence rates calculated using the 2011 census data. Crude incidence rates were calculated per 100,000 paediatric population at risk per year and 95% confidence intervals were estimated assuming a gamma distribution(139). Trends on incidence over time were performed using Poisson regression using R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). For comparison with our previous published work, age groups of 0-5 years (pre-school), 6-10 years (primary school age) and 11-15 years (secondary school age) were used throughout(92).

2.2.6. Ethical considerations

Ethical approval is not required in NHS Scotland for retrospective case record reviews with examination of departmental databases of service design/delivery as previously discussed as part of the Paediatric IBD Scotland Audit (PISA) (134).

2.3 Methodology for data collection for Inflammatory Bowel Disease Unclassified

2.3.2. Case identification

Cases of IBDU were identified from each of the three-tertiary paediatric centres and two district general hospitals (Dundee and Inverness) from 1st January 2003 to 31st December 2013 with follow up until 30th June 2014 as described in Methods section 2.2.2 then IBDU cases were selected. Context for the number of IBDU cases diagnosed was made to the total PIBD incident cases from 2009-2013 and diagnosis of those under 5 years was

compared to data from a recent systematic review on IBDU(140). Following case identification, data was then collected from a hand search of written case and electronic records and entered onto a centrally custom-built database (Access 2007, Microsoft Corporation, Redmond, WA) as per Methods section 2.2.2.

2.3.2. Inclusion criteria

Patients were included who were less than 16 years old and in paediatric services when a diagnosis of IBDU was made between 01/01/2003 until 31/12/2013 with a minimum of 6 months follow up.

2.3.4. Exclusion criteria

Patients were excluded whose case notes were not available (n=1) or were diagnosed outside of Scotland or in adult centres.

2.3.5. IBDU phenotyping

Diagnosis was based on clinical symptoms, laboratory results, endoscopic, radiological and histological assessment in-line with the revised Porto criteria(13) by the local specialist PIBD team; the same approach as for all PIBD cases (further detail in section 2.2.4). Disease extent was defined as per the Paris criteria(7). Ileal intubation was defined as clinician report of visualization of ileal mucosa with or without ileal biopsy.

2.3.6 Data collection

Data collected included age at diagnosis, diagnostic and ongoing assessment, treatments including corticosteroids, thiopurines, methotrexate and anti-TNF-α therapy (either infliximab [IFX] or adalimumab [ADA]), response to treatment, natural history, surgery and change of diagnosis.

2.3.7. Natural history

Disease course was defined as either: quiescent, very mild, mild, moderate or chronically active as assessed by the lead researcher using definitions as listed below (141). Quiescent disease was disease in continuous clinical and biochemical remission (e.g. normal calprotectin and C-reactive protein [CRP] as defined by normal reference ranges for the hospital laboratory). Very mild disease was mild infrequent disease flares, usually less than twice per year and no evidence of inflammation on laboratory markers (e.g. normal calprotectin and CRP as defined by normal reference ranges for the hospital laboratory). Mild disease involved raised inflammatory markers, mild disease flares only with no escalation of treatment, occurring less than twice a year. Moderate disease was defined as more than two disease flares per year or disease flare requiring escalation of therapy (such as to a thiopurine or methotrexate) with laboratory evidence of inflammation including but not limited to raised faecal calprotectin, CRP, erythrocyte sedimentation rate [ESR] and white cell count. Chronically active disease was frequent severe disease flares requiring escalation of treatment, including anti-TNF-α therapy or the need for surgery.

Response to treatment was divided into remission, response but not yet reached remission and no response. Remission was defined as improvement in physician global assessment (PGA) to inactive disease by the attending physician(142); response but not yet reached remission was defined as improvement in symptoms and/or laboratory parameters (e.g. ESR, CRP and faecal calprotectin) but continued ongoing disease activity. PGA was assessed through history, clinical examination, anthropometry and laboratory values by the clinician after induction treatment.

Steroid dependency was defined as inability to wean steroids despite continuous therapy/rapid recommencement after weaning within 16 weeks; and steroid resistance as no clinical effect despite high doses (maximum 2mg/kg). Thiopurine (azathioprine or

mercaptopurine) and methotrexate intolerance was deemed to have occurred when reproducible symptoms (e.g. headache, nausea, fatigue) or adverse drug reaction led to discontinuation. Thiopurine and methotrexate primary non-response were defined as lack of clinical response despite 16 weeks of therapy. Loss of response to thiopurines and methotrexate was considered when therapeutic effect was lost after initial remission with possible dose escalation. Loss of response to anti-TNF-α therapy was defined as initial clinical response to IFX maintenance treatment but need for surgery or withdrawal of IFX (recurrent acute infusion reactions) and a switch to other medical treatment(143). Primary non-response to anti-TNF-α therapy was defined as no significant clinical improvement when assessed at 10 weeks post first induction dose for IFX and subsequent removal of therapy(143).

2.3.7. Statistical analysis

Paediatric population data were obtained from National Records of Scotland for each year from 2003-2013(133). Incidence rates were calculated per 100,000 paediatric population at risk per year and 95% confidence intervals were estimated assuming a gamma distribution. Trends on incidence over time were performed using Poisson regression using R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.3.8. Ethical considerations

Ethical approval is not required in NHS Scotland for retrospective case record reviews with examination of departmental databases of service design/delivery.

2.4 Methodology for data collection for Scottish Biologicals Registry

2.4.1 Case identification

All PIBD patients within paediatric services were included if aged <18 years at biological therapy start from 01/01/2000 to 31/12/2012 with 10 weeks minimum follow up. Patients were identified using PGHAN department-held records and databases (prospective and/or retrospective), pharmacy lists, nurse practitioner records, and case note review. Patients were given IFX for fistulating CD outside of the licenced indications. Excluded patients were those whose main reason for biological was not primarily IBD (e.g. arthritis or uveitis).

2.4.2. Drug administration

IFX induction dosing was 5mg/kg at 0, 2, and 6 weeks. Prior to 2006, some received episodic IFX dosing (as required, unscheduled) following induction. Maintenance IFX was 5mg/kg administered 8 weekly; dose escalation (increased dose and/or shortened frequency of dosing) and de-escalation occurred. Adalimumab induction comprised 2 doses (160mg/80mg, 80mg/40mg, 40/20mg or 24mg/m^2) followed by fortnightly maintenance dosing (80mg, 40mg, 20mg or 24mg/m^2); dose escalation and de-escalation occurred. No agreed protocol was followed in any of the units regarding dose escalation and was based on clinician's discretion with IFX/ADA levels were not routinely available in all centres and only latterly used in a small number of cases.

2.4.3. Data collection

Not all centres maintained prospective patient databases, data was collected periodically via proforma and entered on the Scottish PIBD biological registry database (held in University of Edinburgh). Data were collected at study end (31/12/2013; transition

to adult services; emigration from Scotland). Demographic information included disease phenotype(9); biological schedule and regimen (induction only; induction-episodic; induction-episodic-maintenance; induction-maintenance); medications (including steroids, thiopurines and methotrexate) and surgery before, at and after biological start. Response to treatment by IFX/ADA was divided into steroid-free remission, remission, partial response, loss of response and no response. Physician global assessment (PGA) was assessed through history, clinical examination, anthropometry and laboratory values after induction treatment. Remission was defined as improvement to inactive disease(142), partial response as improved symptoms but continuing disease activity, and loss of response where initial remission required later surgery or anti-TNF withdrawal during maintenance, and switch to another medication, including second anti-TNF agent(143). The paediatric ulcerative colitis activity index (PUCAI) and the paediatric Crohn's disease activity index (PCDAI) scores were collected at defined timepoints when available (144, 145); PGA was collected and defined as remission, mild and moderate/severe disease activity for all.

Acute infusion reactions occurred during or within one hour of infusion stopping. All serious adverse events (resulting in hospitalisation during or within 90 days of stopping treatment, prolonged hospitalisation, life-threatening or death) and adverse events which investigators thought possibly related to biological therapy were recorded.

2.4.4. Ethical consideration

Ethical approval is not required in NHS Scotland for retrospective case record reviews with examination of departmental databases of service design/delivery, such as in PISA (Paediatric-onset IBD Scottish Audit, comprising epidemiology (2) and biologicals register(134)).Most, but not all patients/families gave written consent for anti-TNF therapy;

this was due to different start points for written consent in two of the networks plus one regional network using mainly oral consent throughout the thirteen year period.

2.4.5. Statistics

Descriptive statistics were median (range) for non-normally distributed continuous results and number (%) for categories. Normally distributed continuous data was displayed as means and standard deviations. Twelve-month CD remission rate was compared with duration of illness and immunomodulator use at baseline by Chi-squared analysis, significance defined as $p<0.05$ using SPSS version 19 IBM™.

2.4.6. Growth cohort

Patients were included who had growth data available for a minimum of 24 months; 12 months prior to commencing anti-TNF therapy and for 12 months after treatment commenced, if further growth data was available this was also captured. One patient was excluded as was receiving recombinant human growth hormone as growth promoting treatment.

Height and weight data were collected for IFX for all PIBD subtypes (CD, UC, IBDU) at the following time points: 12 months prior to commencing IFX (T-12), at start of IFX (T0), 12 (T+12),24 (T+24) and 36 (T+36) months post IFX start. Due to transition and variable length of follow up for each patient, a smaller cohort had growth data available for 24- and 36-months post start of IFX. For ADA, height and weight data were collected over 24 months: at 12 (T-12) and 6 months prior to commencing ADA (T-6) at start of ADA (T0), 6 (T+6) and 12 months (T+12) post ADA. Satisfactory growth data reflects 12 months prior to commencing anti-TNF therapy to 12 months after start date whilst extended growth data covers data collected up to 36 months after starting anti-TNF therapy.

Height was measured using wall mounted stadiometers according to Frankfurt plane position and weight measured wearing minimal clothing using calibrated seat scales to the nearest 100g. These data were converted to standard deviation scores for height (Ht SDS), weight (Wt SDS) and BMI (BMI SDS) using 1990 British childhood standards(146, 147), then Δ height SDS (Δ ht SDS) and height velocity(HV) were calculated for T0 and T+12. Delta ht SDS at T0 was calculated by subtracting the ht SDS at T0 from ht SDS at T-12, for delta ht SDS at T+12 then ht SDS at T12 was subtracted from ht SDS at T0. Pubertal staging was assessed using either a validated self-assessment form(148, 149) or by clinical examination and was documented at baseline, 12, 24 and 36 months where available.

2.4.7. Growth cohort statistical analysis

Descriptive statistics are presented as median with 90th percentiles. Wilcoxon was used to examine differences in height, weight and BMI SDS scores. A standard significance level of 0.012 was adopted due to multiple comparison testing and was calculated using a Bonferroni correction. Analyses were carried out using SPSS (IBM 19, Chicago Ill) IBM^{TM}. Multiple logistic regression was performed using R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and all patients with satisfactory growth data were combined. Confounders including type of IBD, small bowel involvement, azathioprine use, methotrexate use, duration of disease, Tanner pubertal staging, remission, corticosteroid use at baseline, PGA at baseline, height SDS at baseline and whether patients received maintenance therapy with anti-TNF were entered into the model. There was a degree of duplication in the data as certain patients received both IFX and ADA so for those patients, one of the treatment periods was randomly excluded to ensure a robust model with no autocorrelation. A general linear model was used; a correction was performed to minimise the effect of missing Tanner staging data using the adjusted general linear model.

2.4.8. Dependency cohort

Patients who were under 18 years at start of anti-TNF therapy and received at least 12 months of either IFX or ADA in paediatric services in Scotland were included. Patients were excluded for the following criteria: received episodic dosing, did not proceed onto maintenance therapy and those who received anti-TNF therapy for less than 12 months. Dependency was defined as repeated infusions and/or injections to maintain good clinical response per the caring physician for at least 12 months(143). Patients could become dependent on either first or second course of either IFX or ADA. Loss of response (LOR) was defined as initial clinical response to IFX but discontinued maintenance treatment due to need for surgery, recurrent allergies or switch to other medical treatment due to sub optimal clinical response(143). Planned withdrawal was defined as in clinical remission only, clinical remission with normal blood parameters including faecal calprotectin or clinical and endoscopic remission with normal blood parameters including faecal calprotectin classed as “deep” remission.

2.4.9. Dependency cohort statistical analysis

Descriptive statistics were median (range) for non-normally distributed continuous results and number (%) for categories. Differences between groups were analysed using student’s T test. Time to loss of response was calculated using Kaplan Meir analysis using SPSS (version 19 IBM^{TM}), patients were censored on date of last drug administration. Variables associated with loss of response were in the dependent cohort were assessed using Cox proportional hazard modelling using SPSS version 19. Variables included in multivariate analysis were gender, disease duration, corticosteroid usage, perianal disease, panenteric disease, immunomodulator usage, response post induction and remission status at 12 months

Chapter 3

3. The incidence of Paediatric-onset Inflammatory Bowel Disease: An updated systematic review of longitudinal trends

3.1 Background

Inflammatory bowel disease is a chronic relapsing lifelong condition affecting the gastrointestinal tract with around 8% diagnosed in childhood(1) with a more extensive phenotype than adult onset disease(16). The aetiology remains elusive but current hypotheses suggest genetic susceptibility, environmental factors(150) and changes in the gut microbiota resulting in maladaptive responses in the innate and adaptive immunity are involved(151). A comprehensive systematic review of the incidence of paediatric-onset inflammatory bowel disease (PIBD) was performed from 1950 -2009 which included 139 studies from 32 countries(2). In 70% of countries that reported incidence an increase was observed, but only 28 reported temporal trends. Increases were seen in 7/9 for IBD, 15/25 for crohn's disease (CD) and 4/20 for ulcerative colitis (UC) suggesting the increase in IBD is driven mainly by an increase in paediatric CD. Data was mainly obtained from "westernised" countries with a paucity from developing countries which mirrored the systematic review of adult-onset IBD(87). After this systematic review was performed on 1.1.2010, other large nationwide cohort studies have reported new incidence data including the SPIRIT registry from Spain, Scotland and Ireland(92, 152, 153) so an update was required.

3.1.1. Aims and hypothesis

The hypothesis is that the incidence of PIBD continues to rise and the increase is driven mainly by an increase in paediatric-onset CD. This review aims to determine if the

incidence of PIBD worldwide continues to increase, if it is becoming more common in countries that have not yet reported data and to assess longitudinal trends.

3.2 Methods

Details of the methods used are presented in chapter 2, section 2.1.

3.3 Results

3.3.1. Search results

Three thousand four hundred and eighty-two unique references were found using the search strategy in **Table 8**, of those 153 abstracts were reviewed to assess for eligibility with thirty-six included in this review from eighteen countries (see **Figure 6**); 4 of which had not been included in the previous review(93, 132, 154, 155). 24/36 (67%) reported only paediatric incident data(92, 97, 132, 137, 152, 153, 156-173) with the remaining 12/36 (33%) reporting both adult and paediatric data(93, 154, 155, 174-182). Most data were obtained prospectively in 21/36; prospective physician survey in 5/36, prospective patient recruitment in 5/36, government registry in 4/36, national database in 5/36, prospective case review in 1/36 and an insurance database in 1/36. The remainder, 12/36, were collected retrospectively; 8/36 from retrospective case note review, 3/36 hospital database or retrospective physician survey in 1/36. Three studies obtained data from two sources, two used both retro and prospectively case note review(92, 178) whilst the other combined government registry data with prospective physician survey(132).

3.3.2. Incidence rates

Incidence rates of PIBD varied from 0.47 per 100,000 in Saudi Arabia to 15.2 per 100,000 in Nova Scotia Canada(137, 159), whilst for CD incidence ranged from 0.27 per 100,000 in Saudi Arabia to 9.2 per 100,000 in Nova Scotia, Canada (137, 159) and for UC 0.20 per 100,000 in Saudi Arabia to 8 per 100,000 in Finland(159, 173). **Figure 8 A, B and C**

demonstrate world maps of the incidence of PIBD, CD and UC respectively in countries

included in the review whilst **Table 8** summarises the included studies.

Table 8 Summary of included studies for updated incidence systematic review organised by Continent and Country of origin (incidence rates are provided per 100,000)

Reference	Country	Region	Years of data collection	Age Range	Methods of case ascertainment	IBD Incidence (Cases/ 10^5)	CD Incidence (Cases/ 10^5)	UC Incidence (Cases/ 10^5)	Comments
Salkic 2009(155)	Bosnia and Herzegovina	Tuzla region	1995-2006	0-14	RCR			0.4	Trend analysis
Jakobsen 2011(165)	Denmark	East Denmark	2007-2009	0-15	PPS	6.4	3.2	3.1	Multiple time periods reported, mean yearly incidence
Jakobsen 2009(132)	Denmark	Copenhagen county	1998-2006	0-15	GR, PPS	4.7	3.1	1.6	Trend analysis, multiple time periods reported
Mertz Norgard 2014(174)	Denmark		1995-2011 for CD 1995-2011 for UC	0-15	ND		Males- 3.3 Female- 2.8	Males- 2.4 Female- 3.0	
Larsen 2017(171)	Denmark		1995-2013	0-17	ND		M-3.7 F- 3.0	M-3.1 F-5.1	
Lehtinen 2011(162)	Finland		1987-2003	0-18	ND	9.6			Trend analysis, multiple time periods reported
Jussila 2012(183)	Finland		2000-2007	0-14	ND		CD (M, F) 0-7 1.8 1.4 8-14 7.5 5.2	UC (M, F) 0-7 2.5 2.5 8-14 9.55 8.4	
Virta 2016(173)	Finland		2010-2014	0-16	ND	13		8	Multiple time periods reported
Bequet 2017(170)	France	Northern France	1988-2011	0-17	PPS	1988-1990-3.0 2009-2011- 6.3			Multiple time periods reported, trend analysis
Chouraki 2011(175)	France	Northern France	1988-2007	0-19	PPS		Males 0-4-0.1 5-9-0.8 10-14- 3.8 Females 0-4- 0.1 5-9- 0.8 10-14- 2.8	Males 0-4-0.0 5-9- 0.3 10-14- 1.0 Females 0-4-0.1 5-9- 0.4 10-14- 1.3	Trend analysis

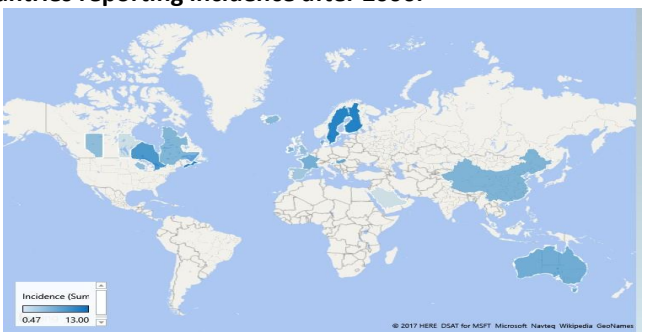
Reference (Table 8 continued)	Country	Region	Years of data collection	Age Range	Methods of case ascertainment	IBD Incidence (Cases/ 10^5)	CD Incidence (Cases/ 10^5)	UC Incidence (Cases/ 10^5)	Comments
Lovasz 2014(166)	Hungary	Western Hungary	1977-2011	0-18	PPR		1977-1981- 0 2007-2011- 7.2	1977-1981- 0.7 2007-2011- 5.2	Trend analysis, multiple time periods reported
Lakatos 2011(179)	Hungary	Western Hungary	2002-2006	0-19	PPR		0-10- 0.5	0-10 1.6	
Muller 2013(164)	Hungary		2007-2009	0-18	PPS	7.48	4.72	3.82	
Agnarsson 2013(167)	Iceland	1951-1989	1951-1989	0-16	RCR	5.0	2.3	2.4	Trend analysis, multiple time periods reported
Hope 2012(153)	Ireland		2000-2010	0-16	RCR	2001- 2.5 2007-4.8 2008-7.3 2010- 5.6			Trend analysis
Urlep 2014(161)	Slovenia	North Eastern	2002-2010	0-18	RCR	7.6	4.6	2.8	Trend analysis
Martin-de-Carpi 2012(152)	Spain		1996-2009	0-18	RPS	1996- 0.97 2009-2.8	1996- 0.53 2009-1.7	1996- 0.39 2009-0.88	Trend analysis
Malmborg 2013(156)	Sweden	Northern Stockholm county	2002-2007	0-16	PPR	12.8	9.2	2.8	Multiple time periods reported, trend analysis
Ronnblom 2010(178)	Sweden	Uppsala	1945-2007	0-19	PCR, RCR			1965-1983 0-9 years -4.3	Trend analysis not specific to paediatrics
Sjoberg 2012(177)	Sweden	Uppsala	2005-2009	0-17	PCR			8.9	Trend analysis not specific to paediatrics
Ashton 2013(97)	UK	Wessex	2002-2012	0-16	HD	6.39	5.85	2.67	Multiple time periods reported, trend analysis
Gunesh 2007(93)	UK	Cardiff, Wales	1996-2005	0-16	RCR		2.7		
Yapp 2000 (154)	UK	Cardiff, Wales	1991-1995	0-16	HD		1.56		

Reference (Table 8 continued)	Country	Region	Years of data collection	Age Range	Methods of case ascertainment	IBD Incidence (Cases/ 10^5)	CD Incidence (Cases/ 10^5)	UC Incidence (Cases/ 10^5)	Comments
Henderson 2012(92)	UK	Scotland	1990-95 2003-2008	0-16	RCR, PCR	4.45 7.82	2.86 4.75	1.59 2.06	Trend analysis, multiple time periods
Abramson 2010(158)	USA	Northern California	1996-2006	0-18	ID		2.7	3.2	Trend analysis
Adamiak 2013(157)	USA	Wisconsin	2000-2007	0-18	PPS	9.5	6.6	2.4	
Benchimol 2017(137)	Canada		1999-2010	0-17	GR	9.7	6.5	2.4	Multiple time periods reported, trend analysis
Benchimol 2014(180)	Canada	Ontario	1999-2008	0-19	GR	0-10- 2.9	0-10- 1.3	0-10- 1.3	Multiple time periods reported, trend analysis
Benchimol 2014(169)	Canada	Ontario	1994-2009	0-18	GR	1994-9.4 2002-8.1 2009-13.2	1994-5.2 2002-5.2 2009-7.9	1994-3.9 2002-2.4 2009-4.1	Multiple time periods reported, trend analysis
El-Matary 2014(160)	Canada	Manitoba	1978-2007	0-17	GR	2003-2007- 6.77	2003-2007-4.68	2003-2007-1.64	Multiple time periods reported, trend analysis
Al-Qabandi 2011(163)	Kuwait		1998-2008	0-15	RCR	2.16	1.53	0.6	No trend analysis
El Mouzan 2014(159)	Saudi Arabia		2003-2012	0-14	RCR	0.47	0.27	0.2	Trend analysis
Studd 2016(181)	Australia	Barwon	2010-2011	0-14	PPR	6.8			
Schildkraut 2012(172)	Australia	Victoria	1950-2009	0-16	RCR			1950-0.15 2009-1.61	Trend analysis
Wang 2013(168)	China	Shanghai	2000-2010	0-18	HD	5.5	2.9	2.5	Trend analysis
Hilmi 2015(176)	Malaysia	Kinta Valley	2011-2013	0-16	PPR	0.63	0.42	0.21	No longitudinal trends

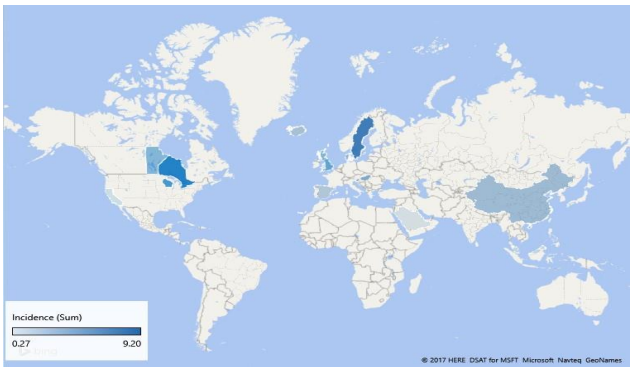
Methods of case ascertainment: ID- Insurance database, ND- National database, RCR- Retrospective case note review, PPS- Prospective physician survey, RPS- Retrospective physician survey, PPR- Prospective patient recruitment, GR- Government registry, Hospital database

Figure 8(A) Worldwide IBD incidence rates for countries reporting incidence after 2000. (B) Worldwide CD incidence rates for countries reporting incidence after 2000. (C) Worldwide UC incidence rates for countries reporting incidence after 2000.

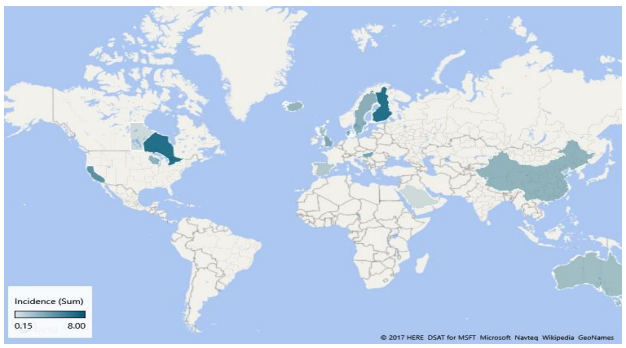
(A)



(B)



(C)



Footnote- except for Canada, United States of America and United Kingdom where a province is reported (i.e. city, state, region) the incidence is extrapolated to the country level.

3.3.3. Temporal trends

Of the included studies, 18/36 (50%) reported temporal trends using a variety of statistical methods to assess the trend. Four studies reported trend data but gave no p value, all studies reported increasing trend in CD and UC(137, 162, 166, 171). Poisson regression was the most commonly used statistical test in 10/18, other methods included linear regression 2/18, chi square 3/18, not specified in 2/18 and Cochran Armitage in 1/18. Temporal trend analysis for IBD in 12/13 had a significant increase in incidence with only one study reporting no increase. For CD 12/15 had a statistically significant increase 2/15 had an increase and 1/15 had a decrease. In UC, 11/16 reported a significant temporal increase with 3/16 reporting an increase and 2/16 reported a decrease with 1/16 reporting no change.

Two studies that combined adult and paediatric data reported an increase in UC and IBD respectively(162, 174). One study reported a temporal increase in UC and CD but no p value (166). **Figure 9 A, B and C** demonstrate temporal incidence rates for IBD, CD and UC respectively with multiple time periods displayed independent of the authors performing statistical trend analysis.

Figure 9A Temporal trends of incidence rates for Paediatric-onset inflammatory bowel disease in studies reporting incidence at multiple time points. (Where year range is reported, incidence in reported for the final year of the range (ie 2000-2010 is reported as incidence for 2010).

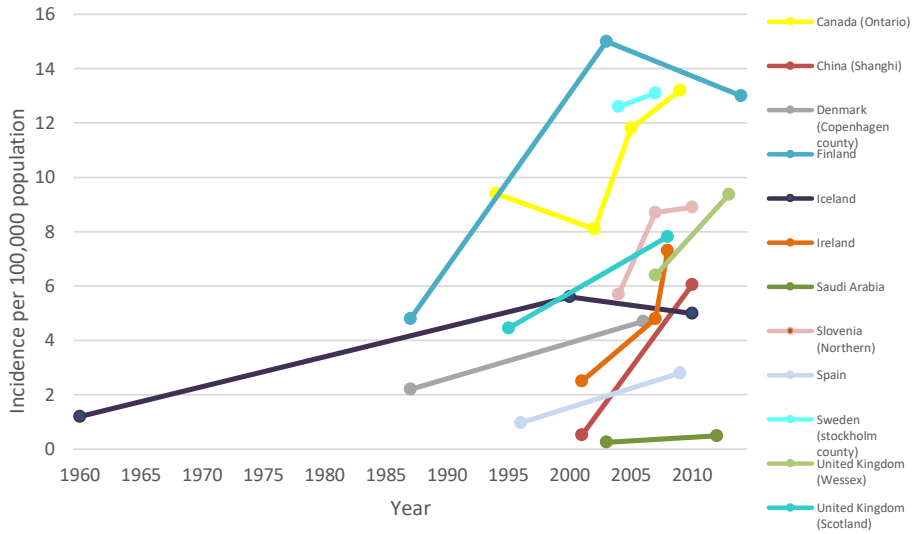


Figure 9B Temporal trends of incidence rates for Paediatric-onset crohn's disease in studies reporting incidence at multiple time points

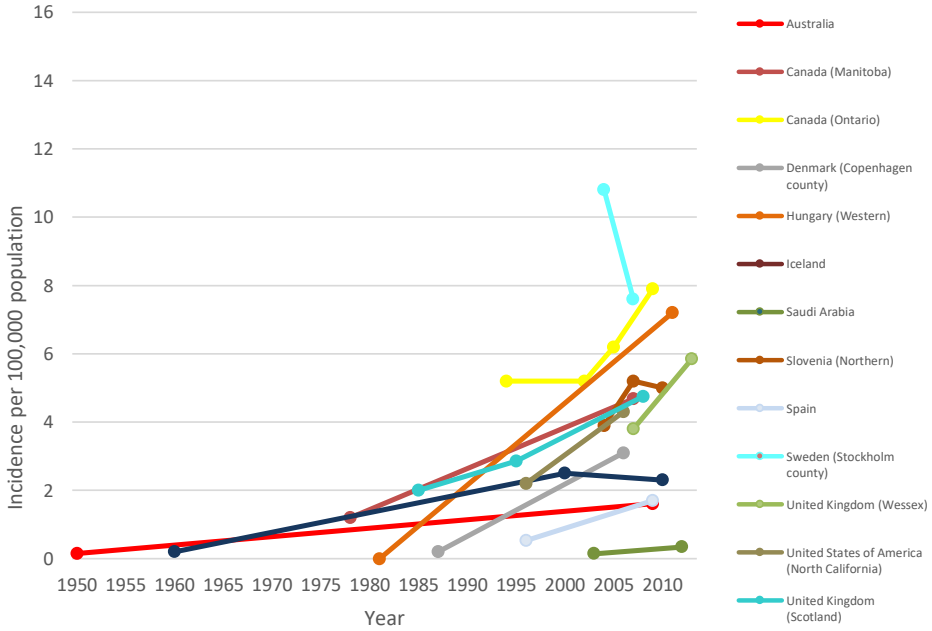
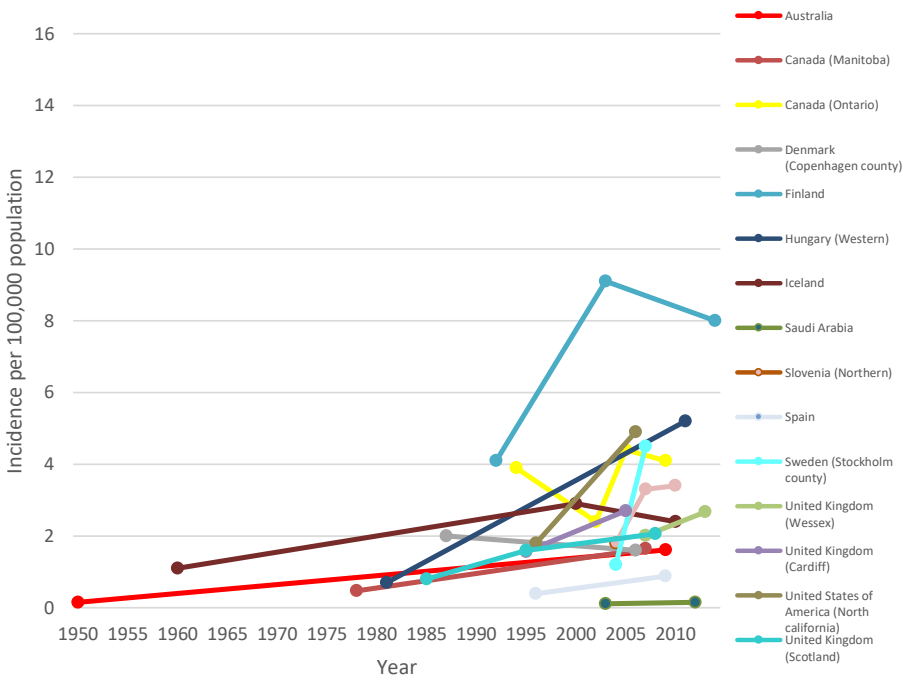


Figure 9C Temporal trends of incidence rates for Paediatric-onset ulcerative colitis in studies reporting incidence at multiple time points



Nine studies reported temporal trends for both IBD subtype and age. In Scotland, a significant increase in incidence was observed for all IBD subtypes in males aged 6-10 years and 11-15 years whilst for females there was only a significant increase in CD in those aged 11-15 years and in IBD/IBDU for those aged 6-10 years(92). Data from Saudi Arabia demonstrated a significant increase in IBD, CD and UC in those aged 10-14 years compared to a significant increase in IBD and CD in those aged 5-9 years, finally only an increase in CD was seen in those aged 0-4 years(159). Ontario, Canada had similar results with an increase in IBD, CD and UC in those aged 10-17 years and 6-9 years compared to an increase in IBD only in those aged 0-5 years(169). Another study from the Ontario group reports a significant increase in IBD, CD and UC in those aged 10-19 years compared to an increase in IBD and UC only in those aged 0-10 years(180). An increase in UC was reported from Finland with increasing incidence in older age groups with a ratio of 1.1 for those aged 0-10 years increasing to 1.4 in 11-15 years and 1.6 for those aged 16-19 years(173). Similar results for UC were seen in Northern California in the 10-14 age group(158) and all IBD(97, 175).

A nationwide Canadian study reported a significant increase in the 6 months to 5 years age category with no significant increase in the older age ranges(137).

3.4 Discussion

The increasing incidence of PIBD persists in this updated systematic review with a propensity of data from North America and Western Europe confirming the hypothesis. The highest incidence of PIBD was 15.2 per 100,000 in Nova Scotia, Canada, the highest to date, with the highest incidence reported so far for UC in Finland at 8 per 100,000. Previously the highest rate of CD was 13.2 per 100,000 in Quebec (2), however, the age range was 0-19 years contrasting with current data from Nova Scotia which was under 18 years meaning the current study may represent a higher incidence. Age ranges varied from under 15 years to 19 years, as the incidence of IBD is higher in those aged 16 to 18 years, the incidence rates reported in **Table 8** may over or underreport current figures. Most studies reporting on longitudinal trends described an increase in PIBD, CD and UC. However, one study reported a decrease in CD(156) and one study reported a decrease in UC which (132). This contrasts with the previous systematic review where, the increase in IBD was thought to be primarily driven by paediatric CD with the rates of UC appearing to level off(2). It is difficult to draw significant conclusions from the relatively few temporal studies published, particularly as the majority from North America and Europe. However, comparison with adult-IBD can be made which has shown that although IBD continues to increase, the rate of rise is not as steep as previously seen(87, 184).

The systematic review by Benchimol (2) on the incidence of PIBD worldwide provided evidence of the increase observed by clinicians with an insight into the globalisation of PIBD. However, wide variation in methodologies were used, a variety of age cut off for paediatric patients from 14 years and under to 19 years were used and differences defining the diagnosis of IBD. By using different age ranges in a condition which varies with age affects incidence rates. All studies that reported on PIBD incidence, regardless of the methods used, so a huge heterogeneity of were cases reported, including “possible” and probable” IBD diagnoses. Although included studies were meant to be population-based, the review included those from insurance databases which may not be a true reflection of the

cases within that geographical area (158). Four studies were identified (2 from the UK, 1 each from Denmark and Bosnia(154, 155)) (93, 132)which were not included within this review but were included within this update.

Health administrative database used to collect cases in Ontario demonstrates a good, robust approaches to collecting incidence data. The database is a mandatory reporting system allowing the treating physicians to be paid, the authors use a variety of database algorithms to collect data then validate their results to ensure full capture of cases. Clear criteria were used to confirm the diagnosis of PIBD which was then validated for a selected period to ensure correct administrative coding. Not all countries have an insurance database but can still collect good nationwide incidence data such as Ireland, Iceland and Scotland. In Iceland, cases were identified retrospectively for the initial part of the study (1951-1989), with charts and pathology specimens reviewed by an investigator to confirm IBD, then cases were prospectively identified (1990-2010). Investigators contacted paediatricians and gastroenterologists to confirm complete accrual of cases and reported on the investigative approach to diagnose IBD. By current recommendations(10) the diagnosis of historic cases was not robust and there may be some diagnostic uncertainty which the authors acknowledge (cases before 1980 did not have an upper GI endoscopy and not all had full ileocolonoscopy)(167). There is a paucity of data from middle eastern countries so the study from Saudi Arabia is crucial to understanding the globalisation of PIBD, however, methodological issues make interpreting this data challenging. Although incidence figures are reported up to 14 years, the authors acknowledge that those aged 13-14 years may be treated by adult gastroenterologists and estimate that they included only 70% of 14 year olds(159). Unfortunately, it is not reported if they tried to contact adult gastroenterology colleagues to identify these cases or private clinics who may have treated these patients. In addition, it is not clear how patients were diagnosed including what investigations or histopathology samples were taken These methodological issues would only increase the incidence rates and support the assertion that PIBD is increasing worldwide.

This review builds on these reports a further increase in PIBD, CD and UC, of which CD continues to predominate. New countries from Europe have reported incidence but, crucially countries from Asia and the Middle East such as Malaysia and Kuwait, have been published supporting the assertion that PIBD is becoming a global disease. However, the highest rates continue to be in Europe and North America which may relate to improved

access to healthcare with robust reporting systems allowing easy capture of new cases within well-established research protocols. The increase in countries which are becoming more "westernised", such as Malaysia, supports the assertion that environment plays a key role in the pathogenesis of PIBD, but specific triggers have yet to be elucidated. 80% of studies in CD and 69% in UC reported an increased incidence contrasting with 60% for CD and 20% for UC in the previous review. The increased rates of UC may reflect the newer countries reporting data or less robust diagnostic accuracy, however, it was not consistent.

Methodological assessment

As with the previous systematic review, methodological issues influence the conclusions drawn from the data presented. A key difficulty for epidemiological research is the definition of IBD and the robustness of initial diagnostic assessment. Few studies reported on diagnostic approach, often relying on data collected for hospital/insurance/government registries so difficult to assess the criteria for obtaining a diagnosis. A historical issue is the use of "probable" and "possible" CD(175). Accurate phenotyping is essential to ensure appropriate comparisons of patients, the publication of ESPGHAN guidance on diagnosis of PIBD(10) will surely improve the process but many of these studies report data collected prior to its publication.

Only studies which contained a clearly defined cohort of paediatric patients under 18 years of age were included so the data accurately reflects paediatric practice. Age ranges reported varied from less than 14 to less than 18 years depending upon the country with differing healthcare systems using varying age cut offs. For example, within Scotland patients are cared for in paediatric IBD centres until the age of 16 years before transitioning to adult services, this contrasts with North America where patients can continue in paediatric services until 19 years of age. The difference of three years affects the incidence rates in a condition which increased with age, potentially North American countries may not have a higher incidence if only those under 17 years were included. Ideally the Paris classification should be used to present incidence of those under 10 years and under 17 years.

Incidence rates for regions within a country were generalised to the entire country, both in this and the previous review to facilitate comparisons between different countries which may have resulted in either over or

under representation of the true incidence. Certain studies contacted adult gastroenterologists whilst others did not which may result in an underestimation of incidence as teenagers may be seen in adult centres.

Temporal trends were reported in thirty-six studies with almost all reporting increases in PIBD, CD and UC incidence rates. A decrease in CD was observed in Sweden with rates decreasing from 10.8 per 100,000 in 2002-2004 to 7.6 per 100,000 in 2005-2007 which is not likely to be significant due to the relatively short time period, this is confirmed by the combined incidence rate of 9.2 per 100,000 from 2002-2007(156) and the increasing prevalence rate(185).Trend analysis was not performed on the results of this review due to the heterogeneity of the data, the various time points used and lack of consistent methodology.

A strength of this study is that newer countries such as Kuwait and Malaysia have been added as have other national registries from Spain, Scotland and Ireland broadening of the current data. More population-based cohorts are included improving generalisability and evidence of the sustained increase in PIBD incidence. Methodological flaws persist of retrospective study design and hospital/regional cohort studies yet he advent of centralised methods of data collection will undoubtedly improve collection of incidence data. A paucity of data reported in Asia, South America and Africa continues where the potential role of environmental and genetic factors could be further developed and comparison with European/North American cohorts could be made.

3.5 Conclusion

The incidence of paediatric-onset IBD, CD and UC continue to rise in almost all countries reporting data most studies from North America and Northern Europe yet more data are now emerging from Asia, Africa and South America improving the generalisability of the results. However, considerable variation and heterogeneity still exists amongst data collection, age ranges and analysis. Prospective national databases in countries that have not previously reported data will enhance knowledge on the globalisation of PIBD and provide insights into environmental factors involved in the aetiology.

Chapter 4

4. Prevalence of Paediatric Inflammatory Bowel Disease: A Systematic Review of trends

4.1 Background

Inflammatory bowel disease (IBD) is a chronic relapsing condition consisting of Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU) with recent data suggesting approximately 8% of cases present in childhood(1). A recent systematic review of adult-onset disease studying incidence and prevalence, found both indices were increasing worldwide, with the highest prevalence in developed countries (particularly in Europe), low prevalence in Asian nations and an increasing trend in developing nations that traditionally had low prevalence rates(87). The incidence of paediatric-onset IBD (PIBD) is increasing worldwide (2, 92) and, although prevalence rates are likely to mirror this increase, accurate data is lacking. Prevalence data is crucial for service planning and delivery to ensure that adequate services provide care exist for children and families with PIBD, it also assesses the burden of disease and facilitates research by allowing accurate power calculations to be performed. Prevalent data is often more challenging to collect due to the changing of the population moving into and out of the catchment area requiring regular monitoring to ensure it is correct.

By understanding why areas have high IBD prevalence it could help uncover environmental factors involved in aetiopathogenesis such as increased urbanisation causing changes to microbial exposures (186) through epidemiological research. Key areas to examine would be developing nations where IBD is becoming more common to identify other changing environmental or dietary factors.

4.3.1. Aims and hypothesis

The hypothesis was that given the significant increase in incidence of PIBD, prevalence rates would show a similar increase. A systematic review of the literature was performed focusing on the prevalence of PIBD worldwide, describing the patterns seen in different geographical areas and where possible assessing temporal trends.

4.2 Methods

Methods for this chapter are discussed the Chapter 2 Methodology section 2.1.

4.3 Results

4.3.1. Search results

4190 references were found during the initial search with 138 abstracts scrutinized. Following this, 53 full papers were reviewed and 26 excluded as they did not meet the inclusion criteria leaving 27 were included from 12 countries (**Figure 7**). 14 studies had data on the prevalence of PIBD, (**Table 9**) twenty (54%) on CD whilst 21 (57%) had data on UC, (3 (11%) on IBD alone, 3 (11%) on UC only and 4 (15%) on CD alone) (**Table 9**). Twelve studies (44%) included paediatric patients only while 15 (56%) had both paediatric and adult data.

Table 9 Summary of included prevalence studies of paediatric-onset inflammatory bowel disease, Crohn's disease and ulcerative colitis (prevalence rates are reported per 100,000)

Reference	Country	Region	Data collection (year)	Age Range	Methods of case ascertainment	IBD Prevalence (Cases/ 10^5)	CD Prevalence (Cases/ 10^5)	UC Prevalence (Cases/ 10^5)	Population at risk
Benchimol 2017(137)	Canada		1999-2010	0-16	HD, RCR	38.2	25.5	10.7	Prevalence rates given for 5 provinces (Alberta, Manitoba, Nova Scotia, Ontario and Quebec)
Benchimol 2014(180)	Canada	Ontario	1999- 2008	0-9 10-19	HD	16.4 146.2	5.8	1.3 7.6	Population at risk figures not given
Benchimol 2009(111)	Canada	Ontario	1994-2005	0-18	HD	58.3	23.9 31.6	16.2 19.7	IBD prevalence figures given for each year from 1994-2005. Population <15yrs- 936,514
El Matary 2013(160)	Canada	Manitoba	1978-2007	0-17	HD, RCR	29.35	18.9	12.7	
Bernstein 2006(113)	Canada	Manitoba, BC, NS, AB, SK	1998-2000	0-9 10-19	HD		AB15.3 BC 12.9 MB 0.2 NS 4.3 SK 3.7	AB 9.8 50.0 BC 5.2 28.4 MB 1.6 35.7 NS 4.0 47.4 SK 2.3 32.1	1235731 1335537 1439111 1597731 481790 489691 349014 381741 430654 484586
Bernstein-CD 1999(112)	Canada	Manitoba	1984-1994	<10 yrs	HD			0	Total population data only given
Abramnson 2010(158)	United States	Northern California	1996-2006	0-17	ID		12.0	19.5	Population given for age ranges but separated according to gender
Kappelman 2007(105)	United states	4 regions (North east, South, Mid-West and West)	2003-2004	2-<5 yrs 5 to <10yrs 10 to <15 yrs	ID		2.3 (1.0-4.5) 9.4 (7.2,12) 45 (41-50)	5.4 (3.2-8.4) 8.5 (6.4-11) 22 (19-26)	350,986 670,162 785,847
Kappelman 2013(89)	United states	4 regions (North east, South, Mid-West and West)	2008-9	CD: 0-5 5-9 10-14 15-17	ID		5.63 (3.76-8.38) 12.6 (10.4, 15.2) 46.5 (42.5,51.0) 106.3 (98.8, 114.5)	5.4 (3.6,8.1) 10.9 (8.9, 13.4) 29.4 (26.2, 33) 91.3 (82.7, 100.8)	461434 886112 1019459 681610
Bonnevie 1968(187)	Denmark	Copenhagen County	1961-67	0-9 10-19	RCR			3.8 18.3	102,400 92,900 Not clear what registries used
Jakobsen 2008(188)	Denmark	Eastern Denmark	1998-2000 2002-2004	0-15	HD	16.0 24.2	6.7 8.2	8.3 10.5	

Reference (Table 9 continued)	Country	Region	Data collection (year)	Age Range	Methods of case ascertainment	IBD Prevalence (Cases/ 10^5)	CD Prevalence (Cases/ 10^5)	UC Prevalence (Cases/ 10^5)	Population at risk
Jussila 2012(183)	Finland		1993-2008	0-14	GR	M- 44.8 F- 39.9	M-6.5 F-4.8	M-13.1 F-12.0	Population at risk give as whole not broken down by age category
Olafsdottir 1989(189)	Norway	Western Norway	1984-5	0-15	PPS	30.7	18.1	18.1	198,570
Hildebrand 1991(190)	Sweden		1984 1985	0-16	PPS	17.9	6.2*	7.5*	1,506186
Ludivgsson 2017(185)	Sweden	Sweden	2010	0-17	GR	75	29	30.7	Population at risk not given
Lindquist 1984(191)	Sweden	Orebro county	1971-1980	0-16	RCR		41		
Cosgrove 1996(94)	Wales	South Glamorgan	1983-1993	0-16	RCR	20.2	16.6	3.42	Approx. 90,000
Levi 2013(192)	Israel		1998 2010	17	GR	149.4 301.0			2021 cases identified out of 953,684 assessed
Gilat 1974(193)	Israel	Tel Aviv-Jafo	1971-2	0-14	RPS			3.93	76,397
Krawiec 1984(194)	Israel	Beer Sheva	1961-1980	0-14	RPS		2.1		95,827
Jacobsohn 1986(195)	Israel	Jerusalem	1973-78	0-14	RCR			3.5	80799
Ahmaida 2008(196)	Libya		1997-2006	0-<15	RCR	3.62	2.0	1.36	441,371
Higashi 1988(197)	Japan		1984-5	Males 0-4 5-9 10-14 Females 0-4 5-9 10-14	GR			0.30 0.39 3.07 0.17 0.37 2.5	
Yoa 2000(198)	Japan		1986-1998	0-9	GR		Male- 0.2 Female 0.1		Total population given not age breakdown Male and female separate- average given
Gearry 2006(199)	New Zealand	Canterbury	2004-2005	0-4 5-9 10-14	RCR, PPR		0 20.2 18.8		
Lopez 2017(200)	New Zealand		2015	0-16	PPR	21.7	16.5	3.3	
Studd 2016(181)	Australia		2010-2011	0-14	PPR	33			

HD- Healthcare database, ND- National database, RCR- Retrospective case note review, PPS- Prospective physician survey, RPS- Retrospective physician survey, PPR-Prospective patient recruitment, GR- Government registry

*Mean prevalence averaged over 2 years

4.3.2. Data collection and diagnosis

Significant variation was evident in the methods of patient identification between studies and was as follows: national healthcare insurance databases 6 (22%), government registries 5 (19%), retrospective case note review 6 (22%), private healthcare insurance database 3 (11%), prospective physician survey 3 (11%), retrospective physician survey 2 (7%) and prospective patient recruitment 2 (7%) (**Table 9**). Government registries are used in certain countries to allow reimbursement of medical expenses for certain chronic conditions such as IBD. Physicians diagnose patients according to specific criteria completing a medical certificate which is then passed to the government so some or all costs of medications are reimbursed to the patient or family. The method of diagnosis is usually robust as clear criteria must be met to receive the benefits but was often not clearly specified. Dependent upon the registry the robustness of the methodology applied varied, with some registries using validation techniques (111-113, 180). Prospective registries have been set up in certain countries, usually involving a specific geographical area, which include both paediatric and adult gastroenterologists to capture all cases(188-190). Healthcare insurance databases allow prospective accrual of data as records indicate if the patient has the condition when they join the organisation or develop during the coverage(89, 105, 158). Most studies were retrospective and several combined methods including adverts in newspapers/in clinics and local charities(199). The most common retrospective method for data accrual involved searching hospital records for relevant ICD 8/9 codes for IBD/CD/UC with subsequent case note review(94, 187, 193-196).

There was a wide variation in the diagnostic criteria used to define CD and UC which included: clinical history, endoscopic appearances, radiology findings and pathological changes suggestive of IBD. Certain authors used a strict definition to define “definite” and “probable” IBD (187, 190, 193, 195) whilst others used disease classification criteria such as

Lennard Jones, Porto and NASPGHAN (158, 181, 188, 194, 199, 200). Insurance and national databases used diagnostic codes such as ICD 8/9, however, diagnostic criteria were not always provided for these and it was unclear how the diagnosis was made. Healthcare databases, either insurance or government, were searched using diagnostic codes specific for CD/UC for hospital discharge diagnosis or pharmacy claims for medications related to IBD (89, 105, 111-113, 137, 158, 160, 180, 182, 185, 192, 197). Some studies did not define the criteria used to diagnose IBD but referred to clinical, radiological, pathology and endoscopy findings (94, 160, 189, 191, 196, 198). Some studies used the results of their database search and case note review to validate their search strategy(182, 197, 198), whilst others used previously validated methods to verify(89, 105).

Further variation was seen in the age ranges used across studies (**Table 9**), with a total of eight different ranges used. Most reported in either 5- or 9-year age brackets (89, 105, 111, 112, 137, 158, 180, 187, 197-199, 201) but some defined paediatric patients as being aged below 14 to 17 years (94, 160, 181, 182, 185, 188, 189, 191, 193-196, 202). Levi reported prevalence in adolescents attending for obligatory medical assessment for eligibility for military service and defined age as “close to the age of 17” (192) with a mean age of 17.3 +/- 0.5 years.

4.3.3. Prevalence

The prevalence of PIBD ranged from 3.6-301.0/100,000, CD from 2.0-28.8/100,000 and UC from 1.36-30.7/100,000 (**Table 9**). There was a preponderance from developed countries: nine from North America(89, 105, 111-113, 137, 158, 160, 180), eight from Europe(94, 182, 185, 187-191), four from the Middle East(192-195), three from Australasia(181, 199, 202), two from Asia(197, 198) and one from Africa(196) (**Figures 10 A,**

B and C). Prevalence rates of PIBD were highest in Israel at 301 per 100,000 and Sweden at 75 per 100,000 with the lowest in Libya at 3.62 per 100,000.

Figure 10A Prevalence of paediatric-onset inflammatory bowel disease (rates per 100,000)

Figure 10B- Prevalence of paediatric-onset crohn's disease (rates per 100,000)

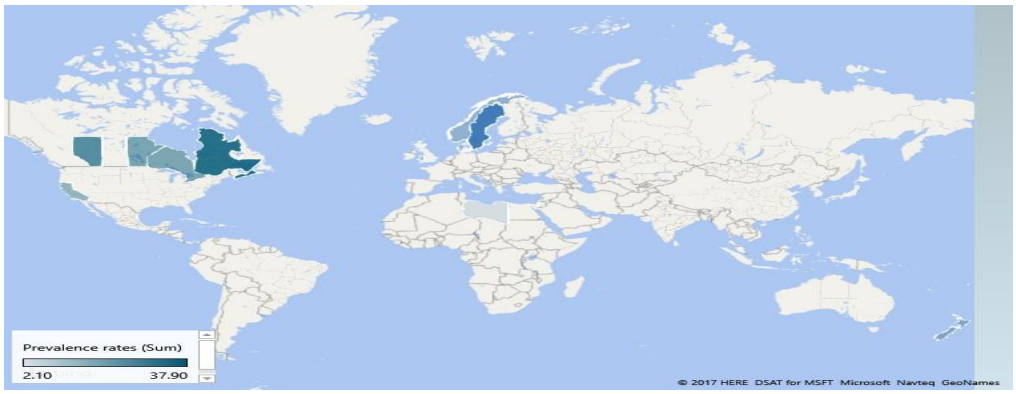


Figure 10C-Prevalence of paediatric-onset ulcerative colitis (rates per 100,000)

Notes: Most recent prevalence rate was used in countries which provided temporal trends. Except for United States of America, Canada and the United Kingdom where a jurisdiction is reported (e.g. city, province, geographically defined region) the prevalence is extrapolated to country level. Studies not included where prevalence rates were presented by age breakdown only or by gender only.

Gender differences were observed in certain studies with 5 CD was common in males than females (105, 112, 158, 197, 198), although only in ages 0-9 years (199) and 6 months to 4 years (111) in 2 respective studies. In UC, the data showed greater variation with two studies demonstrating higher prevalence in males (111, 197) yet two other studies showed a higher female prevalence(112, 158).

4.3.4. Statistical methods

Few statistical methods were performed on prevalence rates and the results were predominantly descriptive. Six studies performed statistics to assess temporal trends and all used Poisson regression (111, 137, 160, 180), however, in one study this covered the whole population and was not limited to paediatric data(182). One studies used a different method to calculate z score to assess trends (196). Kappelman reported a significant variation in prevalence with a North/South divide in the United States of America with more cases in the Northeast compared to the West, with a higher prevalence in males than females(89, 105). Conversely, Bernstein found higher prevalence among females with significantly higher rates in certain provinces ($p<0.0001$) (113). In New Zealand, prevalence was higher in the South Island compared to the North which was statistically significant(202).

4.3.5. Temporal trends

Only six studies provided temporal trend analysis which showed an increase in PIBD prevalence (**see Figure 11A, B and C**). In Libya a significant increase in PIBD prevalence was seen over a 5 year period from 2002-2006(196). In Ontario, Canada, a significant increase in CD and UC over 12 years was reported, from 42.1/100,000 in 1994 to 56.3/100,0000 in 2005 for CD and 16.2/100,000 to 19.7/100,000 for UC)(111) which was maintained in a follow up study (180). Another Canadian prevalence study from Manitoba province

reported increasing prevalence in IBD and all subtypes from 3.1 per 100,000 for CD in 1982 to 14.9 per 100,000 in 2002 whilst for UC an increase from 0.7 per 100,000 to 12.7 per 100,000 over a similar time periods was observed (160). In Israel an increase in PIBD from 149.4 per 100,000 in 1998 to 301.0 per 100,000 in 2010 was observed(192). In Eastern Denmark, an increase was reported in PIBD with an increase in both CD and UC which peaked in 2003 at 28.3 per 100,000 then decreased in 2004 to 24.2 per 100,000(188).

Figure 11A Temporal trends of prevalence of paediatric-onset inflammatory bowel disease (prevalence rates per 100,000)

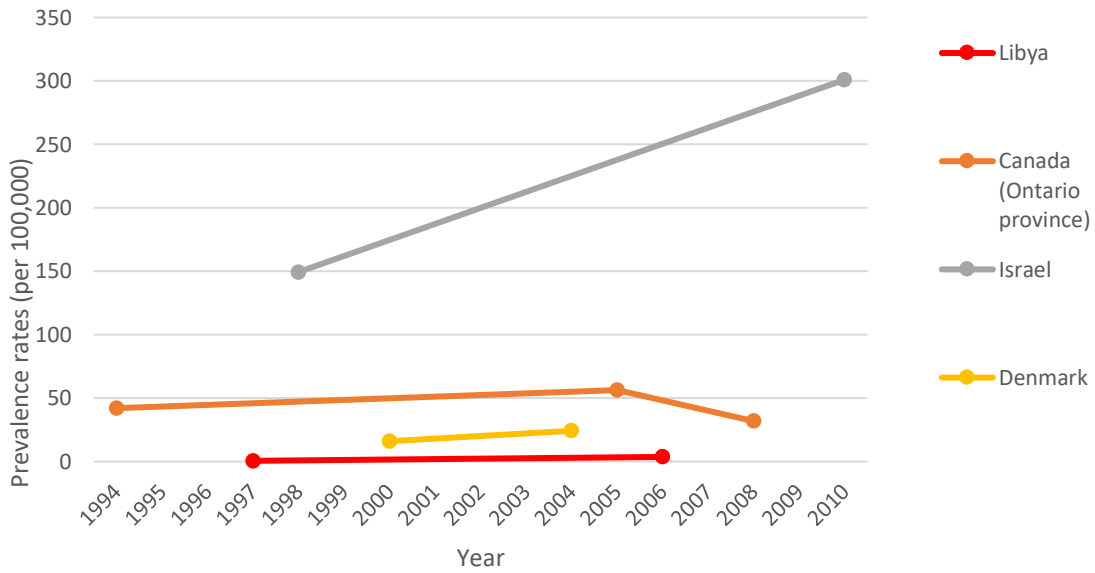


Figure 11B Temporal trends of prevalence of paediatric-onset crohn's disease (prevalence rates per 100,000)

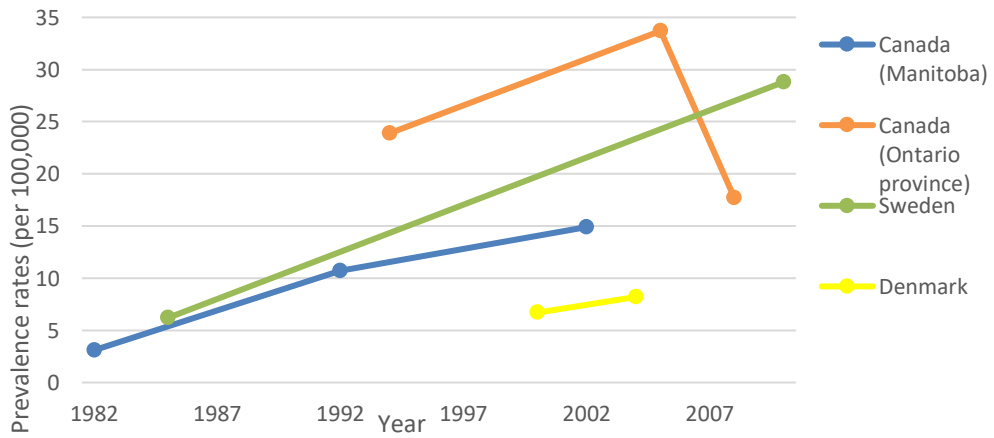
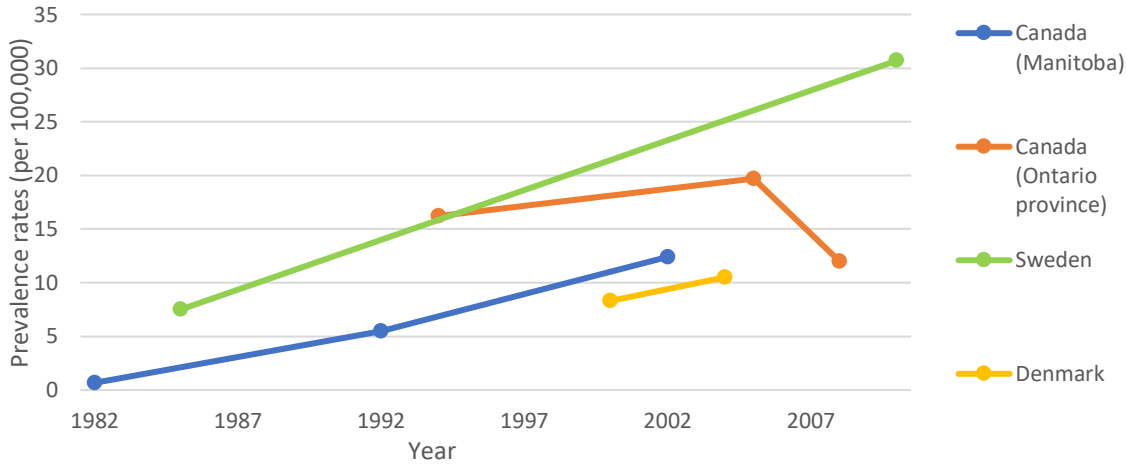


Figure 11C Temporal trends of prevalence of paediatric-onset ulcerative colitis (prevalence rates per 100,000)



4.4 Discussion

This systematic review examined the prevalence of PIBD worldwide indicating a higher prevalence of PIBD in developed countries in North America and Europe with the addition of Israel, confirming the hypothesis. The highest prevalence rates were in Israel for PIBD with 301.0 per 100,000, Sweden for CD with a prevalence rate of 28.8 per 100,000 and for UC 30.7 per 100,000. The results are similar to adult data which demonstrated higher rates in North America and Europe(87). The increase in PIBD prevalence is to be expected given the increasing incidence in systematic reviews in both adult and paediatrics (2, 87). The increase in PIBD incidence has been driven by increase in CD more than UC (2) which again is similar to adult data (87). Temporal trends were difficult to assess as few studies separated paediatric from the adult data including the Finnish study which demonstrated a three-fold increase in the prevalence of IBD over 15 years with the highest prevalence was seen in the 35-44 age category (182). A significant increase in paediatric prevalence over the study period was not reported although this may not be the case. In

contrast, in Libya a significant increase in paediatric prevalence was observed over an eight year period showing yearly increase from 0.53 per 100,000 in 1998 increasing to 3.62 in 2008(196). Similar increases in prevalence rates have been reported in Sweden, Denmark, Canada and Israel over varying epoch lengths (5-26 years), with variable rates of rise seen (111, 185, 188, 190, 192).

All eligible studies were included regardless of the methodology used or age cut offs to ensure a range of countries and data were represented. The methods of data collection were diverse and included: national registries, insurance databases and physician's survey. One study used a variety of sources involving charities, newspaper advertisement and posters at clinics in hospitals then cross checking patients thought to have IBD with pathology and radiology specimens and reports(199). The lack of consistent robust methods of data accrual may suggest that prevalence rates may be under representative of the actual rates. Few studies reported on Indeterminate Colitis or Inflammatory Bowel Disease Unclassified (IBDU) as an IBD subtype, probably as it was not described until the Montreal classification in 2005 before many of the current studies were published. These cases were often excluded or potentially misclassified and as IBDU accounts for 9% of new diagnosis of PIBD(136), if not included then there is potentially a significant under estimation.

Many studies were carried out in the 1970-90s with half from 2000 onwards during which time rates have increased dramatically in both adults and paediatrics suggesting that prevalence has also increased. Most prevalence results included in this review are historical, particularly those from 1970-1990, and are not likely to be true representations of the current rates in their countries. Furthermore, most countries improved access to diagnostic procedures which could result in increasing numbers due to improved diagnosis.

Most studies were hospital based, particularly in developing countries which is often due to centralising of paediatric services. It would be uncommon in most countries for primary care to make and treat IBD in children without secondary or tertiary involvement, therefore, although not population-based, rates may well accurately reflect the population.

Diverse age range were used varying from under 14 to 19 years whilst others broke down further e.g. 5-9, 10-14 years. PIBD prevalence increases with age which influences the prevalence rates reported, for example, studies that used a cut off 17 years could have a higher prevalence rate than those with a cut off 14 years, but, if the same age cut off were used prevalence rates could be similar. Future studies would benefit from using a recognised age cut off, such as 17 years as per the Montreal/Paris classifications(9, 10). However, this may prove challenging as healthcare systems in different countries care for children of certain ages from 14 years to 21 years. A database of all prevalent cases of PIBD regularly updated would aid these problems allowing of those under a certain age to be reported whilst removing those that are no longer eligible for inclusion. Another challenge is patients who present under 2 years with very early onset IBD who often have genetic mutations such as IL-10 deficiency (203) with a different phenotype to IBD, so it is essential to differentiate them which is not clear from some studies.

In adults, as in children, the highest prevalence exists in Northern Europe and North America, with increasing incidence in countries that are becoming more Westernised. Rises in adult prevalence have been reported in Asian countries such as Japan where prevalence has increased 4-fold in 12 years and in developing countries such as South Korea which has seen a similar increase in 8 years(198, 204). The exception to predominance in Europe and North America is Israel which has the highest prevalence of PIBD, this may be due to the age used, 17 years compared to <16 or <14 years in other

studies as more cases were included with an additional 3 years or may be a true reflection of the increased rates in that country. The robust methodology used in the Israeli study ensured good capture of potential patients using government registry for recruitment into national service with only 13.4% excluded on religious grounds(192). The high prevalence rates are consistently increasing over the 13-year study period with the largest number of PIBD cases from Western origin, those living in urban locations and high socioeconomic status. Few studies considered ethnicity which Israel did and found a lower rate of CD in the Arab population compared to the Israeli Jewish population (205). However, others have found higher prevalence's among European/Americans and Asian/African populations respectively when other areas of the country have been studied(195). These studies illustrate the variety that occurs among different within ethnic groups in the same country suggesting genetics as well as environmental triggers are involved. Canada demonstrates an increase in CD and UC in paediatric patients of South Asian origin compared to non-South Asian with an increasing incidence in this group over the 20 year study period (206).

Causation for the increase in PIBD remains unclear with many theories postulated relating to environmental triggers. Both Canada and Israel have demonstrated a higher incidence of PIBD in families with fewer siblings and residing in an urban environment(107, 201). However, other Canadian studies reported different results with less overcrowding in cases of CD than in controls(207). Latitude has been associated with an increase rate of Crohn's disease within a country such as France where an increased rate of Crohn's disease was noted in the North and confirmed by other studies in Northern Europe (91, 182). The same French study found an increased rate of Crohn's in urban areas and those with poor sanitary house equipment, further supporting the hygiene hypothesis(106, 208).

The role of environment in the development of PIBD is supported by the assertion that individuals who immigrate to an area of high incidence of IBD take on the increased risk of developing the condition with the most critical time being childhood(209). Rates of CD were higher in children of non-immigrants compared to immigrants with the age of entry into Canada a critical risk factor with increasing age at arrival associated with a decreased risk of developing IBD(88). Further evidence for an environmental factors can be seen in adults in the United Kingdom where higher rates of UC have been reported in South East Asians, particularly in second generation migrants, compared to the UK population (210) . Increased risk with emigration would suggest that environment, in particular industrialization, may play a significant role in the development of the disease as well as genetic predisposition(211).

Limitations of this study include is that only full published articles in were reviewed so data presented in solely abstract form was not included due to insufficient data to confirm eligibility. The lack of data available from developing countries limits the generalizability of the results; one study from Africa, none from South America and only two from Asia which. Furthermore, the diagnostic criteria to diagnose PIBD varied enormously, although most studies attempted to verify diagnosis using either physician survey or case note review. The gold standard for diagnosis of PIBD is ileocolonoscopic and upper GI endoscopy(13), however, it is unclear from the paper who underwent these investigations and, particularly in the earlier cohorts and in developing countries, it is unlikely. Diagnosis may be incorrect which is more likely to favour a diagnosis of UC than CD and the degree of certainty varied with “probable” CD/UC based on case record review used in older studies.

4.5 Conclusions

This comprehensive systematic review on the prevalence of PIBD has shown a wide range from 3.8-301 per 100,000 with most data provided by countries in North America and Europe. There is a paucity of data on temporal trends of prevalence consequently it is difficult to assess whither the increase in incidence rates of PIBD has led to an increase in prevalence. However, in studies temporal trends were assessed, an increase was observed but numbers were limited, and the methods differed significantly limiting the generalizability.

Significant methodological heterogeneity exists between studies rendering the results unsuitable for meta-analysis. Key methodological differences issues include different age ranges, variations in diagnostic assessments used/diagnostic criteria used and data mainly from Europe and North America. A clearer understanding of prevalence trends of PIBD must include updated from countries with existing data figures ensuring similar diagnostic criteria and methodological are used.

There are many potential environmental factors associated with PIBD which are often not consistent or easily relatable; the challenge now is to unite these different theories through nationwide epidemiological study, particularly comparing developed and developing countries. By studying countries which have seen a sharp increase in PIBD, environmental factors can be sought out such as vitamin D and urbanisation. Paediatric patients present a unique opportunity to enhance our understanding as children have had shorter exposure to environmental triggers. Accurate prevalence figures could result in better provision of services to support to patients and families with PIBD thereby improving standards and care, even more crucial given the high prevalence rates reported.

Chapter 5

5. The incidence of Paediatric Inflammatory Bowel Disease in Scotland demonstrates a sustained rise over the last 40 years- 1969-2014

5.1 Background

The incidence of paediatric-onset inflammatory bowel disease (PIBD) has been increasing worldwide according to a recent paediatric systematic review(2), however, the reasons for this remain elusive. Current hypotheses for the pathogenesis of IBD suggests that in genetically susceptible hosts there is an immune mediated process leading to gut dysbiosis and so the development of IBD(212).

Scotland has the highest reported incidence within the United Kingdom (UK) of PIBD with a rate of 7.82 per 100,000 reported in 2012 in those under 16 years (92). Other areas of the UK and Ireland have also reported an increasing incidence(93, 97, 153). Scotland also has one of the highest reported rates worldwide with only Canada, Sweden and Finland reporting higher rates with an incidence of 23 per 100,000 in Finland(137, 156, 173).However, only Sweden has reported rates in the under 16 year age group with Finland reporting under 19 years of age, and Canada under 18 years which will have contributed to the higher rates reported. Crohn's disease (CD) is the predominant form of PIBD in Scotland (sustained since 1995), where previously ulcerative colitis (UC) had been more common(90) which is unlike other countries that have reported a predominance of UC (162, 167, 171, 182, 213).

5.1.1. Aims and hypothesis

As the incidence of PIBD continues to increase worldwide, the hypothesis is that incidence of PIBD in Scotland would continue to increase. PIBD incidence data has been

collected and collated in Scotland since 1969, so the aim was to calculate the incidence of PIBD in Scotland from 2009-2014 and to compare that to the historical data from 1969 to ascertain if the temporal increases were maintained.

5.2 Methods

Methods are explained in Methodology chapter 2, section 2.2.

5.3 Results

5.3.1. Incidence of PIBD continues to rise in Scotland in all sub types

In total, 430 patients were diagnosed with PIBD between 2003-2008 (cohort 1) (269 CD, 118 UC, 43 IBDU) compared to 582 children between 2009-2014 (cohort 2) (355 CD, 147 UC, 80 IBDU) (**Table 10**). Crude incidence of IBD was 10.6 per 100,000 [95% CI 9.8,11.5], CD 6.6 per 100,000 [95%CI 6.0,7.3], UC 2.7 [95% CI 2.3,3.2] and for IBDU 1.3 per 100,000 [95%CI 1.0,1.6]. Adjusted age-sex incidence rate for IBD increased between cohort 1 and cohort 2 from 7.9/100,000/year [95%CI 7.1-8.6] in cohort 1 to 10.6/100,000/year [95%CI 9.6-11.5] in cohort 2 ($p<0.001$). A significant increase was also seen for CD (4.7/100,000/year [95%CI 4.2-5.4] in cohort 1 compared to 6.6/100,000/year [95%CI 6.0-7.3] [$p<0.0001$]) for cohort 2 and with UC which increased from 2.1/100,000/year [95%CI 1.7-2.5] to 2.7/100,000/year [95%CI 2.3-3.3] in cohort 2 ($p=0.03$). There was an increase in IBDU from 0.8/100,000/year [95%CI 0.6, 1.0] in cohort 1 to 1.3/100,000/year [95%CI 1.0, 1.6] in cohort 2 ($p=0.15$). There was a slight decrease in the population under 16 years from cohort 2 to cohort 1 (**See Table 11**)

Table 10- Crude incidence of paediatric-onset inflammatory bowel disease demonstrates continues increased from cohort 1 to cohort 2 (incidence rates per 100,000)

Cohort	2003-2008# Males	2003-2008# Females	2009-2014$ Males	2009-2014$ Females
IBD	247	183	354	228
CD	158	111	229	134
UC	66	52	85	64
IBDU	23	20	40	30
Population at risk*	474,299	452,369	467,290	446,027

*Mean number of population <16 years of age at risk for each year of the cohort. IBD- Inflammatory Bowel Disease; CD- Crohn's Disease; UC- Ulcerative Colitis; IBDU- Inflammatory Bowel Disease Unclassified.
Cohort 1, $ Cohort 2

Table 11- Population at risk during cohort 2

Year	Population at risk <16 years
2009	912,340
2010	911,794
2011	916,103
2012	914,671
2013	911,679
2014	911,041

5.3.2. Incidence of PIBD by gender

The incidence of PIBD significantly increased in both males and females from cohort 1 to cohort 2 ($p<0.001$ for males and $p=0.03$ for females see **Table 12**), although when further analysed, the significant increase observed in males was due predominantly to the increase in male CD. The highest incidence in cohort 2 was males with an age-adjusted incidence of 13.4 per 100,000 [95% CI 12.0,14.8] compared to 9.0 per 100,000 [95% CI 7.9,10.2] for females with IBD. Incidence was also higher in males in all IBD subtypes: for CD, 8.6 per 100,000 [95% CI 7.5,9.8] in males vs 5.2 per 100,000 [95%CI 4.4,6.2] for females, for UC 3.2 per 100,000 [95% CI

2.5,3.9] vs 2.5 per 100,000 [95%CI 1.9,3.2] for females and 1.5 per 100,000 [95% CI 1.1,2.1] for IBDU in males against 1.2 per 100,000 [95%CI 0.8, 1.7] for females. When compared to cohort 1, the incidence of all PIBD subtypes has increased but a significant increase was only seen in males with IBD and CD, this contrasts with cohort 1 where a significant increase was observed in CD, UC and non-Crohn's colitis (NCC) (**see Table 12**). In cohort 2, females with IBD showed the only significant increase, although a trend to increase was observed for NCC.

Table 12 Age adjusted incidence of Paediatric-onset inflammatory bowel disease demonstrates sustained increase since 1990 for all males and for females with IBD

	Males					Females				
Cohort	**1990-95**	**2003-08[#]**	**P Value 1990-1995 vs 2003-2008**	**2009-14[$]**	**P value 2003-2008 vs 2009-2014**	**1990-95**	**2003-08[#]**	**P value 1990-1995 vs 2003-2008**	**2009-14[$]**	**P value 2003-2008 vs 2009-2014**
IBD	2.23 (1.89,2.63)	8.73 (7.67-9.89)	<0.001	13.36 (12.0,14.8)	<0.001	1.99 (1.66,2.38)	6.80 (5.85-7.86)	0.007	9.01 (7.88,10.23)	0.03
CD	1.51 (1.22, 1.85)	5.58 (4.74-6.52)	<0.001	8.63 (7.54,9.82)	<0.001	1.20 (0.94, 1.51)	4.12 (3.39-4.97)	0.025	5.24 (4.39,6.21)	0.18
UC	0.72 (.052,0.96)	2.32 (1.80-2.97)	0.001	3.17 (2.53,3.93)	0.16	0.80 (0.59, 1.01)	1.94 (1.44-2.54)	0.47	2.52 (1.94,3.22)	0.21
IBDU	N/A	0.83 (0.52,1.24)	N/A	1.52 (1.08,2.07)	0.16	N/A	0.75 (0.46,1.16)	N/A	1.20 (0.81,1.71)	0.23
NCC	1.46 (1.06,1.96)	3.13 (2.53-3.89)	<0.001	4.46 (3.71,5.31)	0.05	1.71 (1.27,2.26)	2.65 (2.10-3.38)	0.005	3.51 (2.84,4.30)	0.06

IBD- Inflammatory Bowel Disease; CD- Crohn's Disease; UC- Ulcerative Colitis; IBDU- Inflammatory Bowel Disease Unclassified. Incidence rates are per 100,000 population at risk. # Cohort 1 $ Cohort 2

5.3.3 Incidence by age subgroups

Incidence rates were calculated by age subgroups for both males and females then compared from Cohort 1 against Cohort 2. The median age at diagnosis was similar for both males and females with a median age at diagnosis of 12.3 years (range 1.23-15.92) for males and 12.2 years (range 1.26-15.91) for females. Although increasing numbers of IBD cases were diagnosed under 6 years of age, this did not achieve statistical significance for males or females. However, the incidence of IBD and CD in males aged 11-15 years continued to increase from cohort 1 to cohort 2 with incidence of IBD 16.0 per 100,000 [95% CI 13.60,18.16] in cohort 1 to 26.9 per 100,000 [95%CI 23.60,30.56] in cohort 2 ($p<0.0001$) and for CD 10.5 per 100,000 [95% CI 8.59,12.80] in cohort 1 increasing to 17.4 per 100,000 [95% CI 14.72,20.32] in cohort 2 ($p=0.001$). There was an increase in UC in males aged 11-15 years with incidence of 4.4 per 100,000 [95%CI 3.21,6.00] in cohort 1 and 6.5 per 100,000 [95% CI 4.93,8.40] in cohort 2 ($p=0.11$). For IBDU in the older age range of 11-15 there was a significant increased from 1.03 [95% CI 0.5,1.91] to 3.07 [95% CI 2.03,4.48] ($p=0.04$). For females, there was a significant increase in IBD in those aged 6-10 years and those aged 11-15 years, in those aged 11-15 years incidence increased from 11.6 per 100,000 [95% CI 9.53,14.04] in cohort 1 to 17.3 per 100,000 [95% CI 14.58,20.31] in cohort 2 ($p=0.01$). For females aged 11-15 years there was a significant increase in CD from 7.3 [95% CI 5.65,9.26] in cohort 1 to 10.2 [95% CI 8.12,12.55] in cohort 2 ($p=0.05$). There was a significant increase in rates of NCC in those aged 11-15 years from 4.3 per 100,000 [95% CI 3.09,5.90] in cohort 1 to 7.1 per 100,000 [95% CI 5.43,9.16] in cohort 2 ($p=0.04$) (**See Table 13**)

Table 13A: Standardised incidence of PIBD by gender, IBD subtype and age at diagnosis demonstrates continues increased from cohort 1 to cohort 2

	Males														
Age (years)	**0-5**	**0-5**	**Difference between cohorts 1990-95 vs 2003-08**	**0-5**	**Difference between cohorts 2003-08 vs 2009-2014**	**6-10**	**6-10**	**Difference between cohorts 1990-95 vs 2003-08**	**6-10**	**Difference between cohorts 2003-08 vs 2009-2014**	**11-15**	**11-15**	**Difference between cohorts 1990-95 vs 2003-08**	**11-15**	**Difference between cohorts 2003-08 vs 2009-2014**
Cohort	1990-95	2003-08#	P value	2009-14$	P value	1990-95	2003-08#	P value	2009-14$	P value	1990-95	2003-08#	P value	2009-14$	P value
IBD	0.76 (0.35-1.44)	1.91 (1.15-2.98)	0.10	2.14(1.35, 3.21)	0.77	3.44 (2.38-4.81)	8.24 (6.46-10.37)	<0.001	10.97 (8.84,13.45)	0.09	9.72 (7.86-11.9)	16.02 (13.6-18.16)	<0.001	26.91 (23.6,30.56)	P<0.001
CD	0.34 (0.09-0.86)	1.21 (0.62-2.11)	0.13	1.30 (0.71, 2.18)	0.89	2.12 (1.32-3.25)	4.95 (3.59-6.65)	0.008	7.28 (5.57,9.35)	0.12	7.03 (5.46-8.92)	10.54 (8.59-12.80)	0.02	17.35 (14.72, 20.32)	P=0.007
UC	0.42 (0.14-0.98)	0.50 (0.16-1.17)	0.77	0.74 (0.32, 1.47)	0.44	1.32 (0.70-2.25)	2.05 (1.22-3.23)	0.16	2.27 (1.36,3.54)	0.73	2.69 (1.76-3.94)	4.44 (3.21-6.00)	0.06	6.49 (4.93,8.40)	P=0.11
IBDU	£	0.59 (0.21, 1.28)	n/a	0.09 (0.00 2,0.5)	0.29	£	1.24 (0.62.2.34)	n/a	1.42 (0.73,2.49)	0.71	£	1.03 (0.50,1.91)	n/a	3.07 (2.03,4.48)	0.04
NCC	0.42 (0.14-0.98)	1.09 (0.54, 1.95)	0.21	0.84 (0.38, 1.59)	0.66	1.32 (0.70-2.25)	3.30 (2.20,4.74)	0.001	3.69 (2.50,5.24)	0.53	2.69 (1.76-3.94)	5.48 (4.10,7.17)	0.01	9.56 (7.64,11.84)	0.008

£- Previous cohort IBDU did not feature. IBD- Inflammatory Bowel Disease; CD- Crohn's Disease; UC- Ulcerative Colitis; IBDU- Inflammatory Bowel Disease Unclassified; NCC- non-Crohn's colitis. Incidence rates are per 100,000 population at risk. # Cohort 1 $ Cohort 2

Table 13B: Standardised incidence of PIBD by gender, IBD subtype and age at diagnosis demonstrates continues increased from cohort 1 to cohort 2

Age (years)	Females 0-5	0-5	Difference between cohorts 1990-1995 vs 2003-08	0-5	Difference between cohorts 2003-08 vs 2009-2014	6-10	6-10	Difference between cohorts 1990-95 vs 2003-08	6-10	Difference between cohorts 2003-08 vs 2009-2014	11-15	11-15	Difference between cohorts 1990-95 vs 2003-08	11-15	Difference between cohorts 2003-08 vs 2009-2014
Cohort	1990-95	2003-08#	P value	2009-14$	P value	1990-95	2003-08#	P value	2009-14$	P value	1990-95	2003-08#	P value	2009-14$	P value
IBD	0.88 (0.42-1.62)	1.48 (0.81-2.48)	0.25	2.04 (1.27,3.13)	0.50	4.33 (3.11-5.88)	7.36 (5.64-9.43)	0.03	7.60 (5.82,9.77)	0.88	7.78 (6.09-9.8)	11.62 (9.53-14.04)	**0.058**	17.27 (14.58,20.31)	0.01
CD	0.62 (0.25-1.27)	0.85 (0.36-1.67)	0.52	1.46 (0.82,2.41)	0.23	2.43 (1.54-3.65)	4.26 (2.98-5.91)	0.06	4.11 (2.83,5.78)	0.91	4.76 (3.46-6.39)	7.29 (5.65-9.26)	0.005	10.16 (8.12,12.55)	0.05
UC	0.26 (0.05-0.77)	0.42 (0.11-1.08)	0.61	0.49 (0.16,1.14)	0.86	1.90 (1.13-3.01)	2.14 (1.27-3.40)	0.74	2.12 (1.24,3.40)	0.98	3.03 (2.01-4.38)	3.24 (2.18-4.63)	0.80	4.97 (3.58,6.73)	0.11
IBDU	£	0.21 (0.03, 0.77)	n/a	0.13 (0.003, 0.70)	0.52	£	0.95 (0.41,1.89)	n/a	1.36 (0.68,2.44)	0.35	£	1.10 (0.53,2.02)	n/a	2.14 (1.27,3.39)	0.11
NCC	0.26 (0.05-0.77)	0.63 (0.23, 1.37)	0.80	0.76 (0.28,1.65)	0.92	1.90 (1.13-3.01)	3.09 (2.02,4.53)	0.057	3.49 (2.32,5.05)	0.48	3.03 (2.01-4.38	4.33 (3.09,5.90)	0.17	7.11 (5.43,9.16)	0.04

£- Previous cohort IBDU did not feature. IBD- Inflammatory Bowel Disease; CD- Crohn's Disease; UC- Ulcerative Colitis; IBDU- Inflammatory Bowel Disease Unclassified; NCC- non-Crohn's colitis. Incidence rates are per 100,000 population at risk. # Cohort 1 $ Cohort 2

5.3.4 Longitudinal trends from 1969-2014

In Scotland, the incidence of PIBD demonstrates a continued and sustained increase since 1969 to 2014 for all IBD (**Figure 12a**) which is driven by paediatric CD (**Figure 12b**) continuing to show a steep increase**.** Comparison with historical data from before IBDU was introduced and commonly used has been performed by combining UC and IC creating non-Crohn's colitis, which has increased but only latterly has achieved significance (**Figure 12c**).

Figure 12A- Incidence of paediatric-onset IBD demonstrates sustained increase in incidence from 1969-2014 (incidence rates per 100,000)

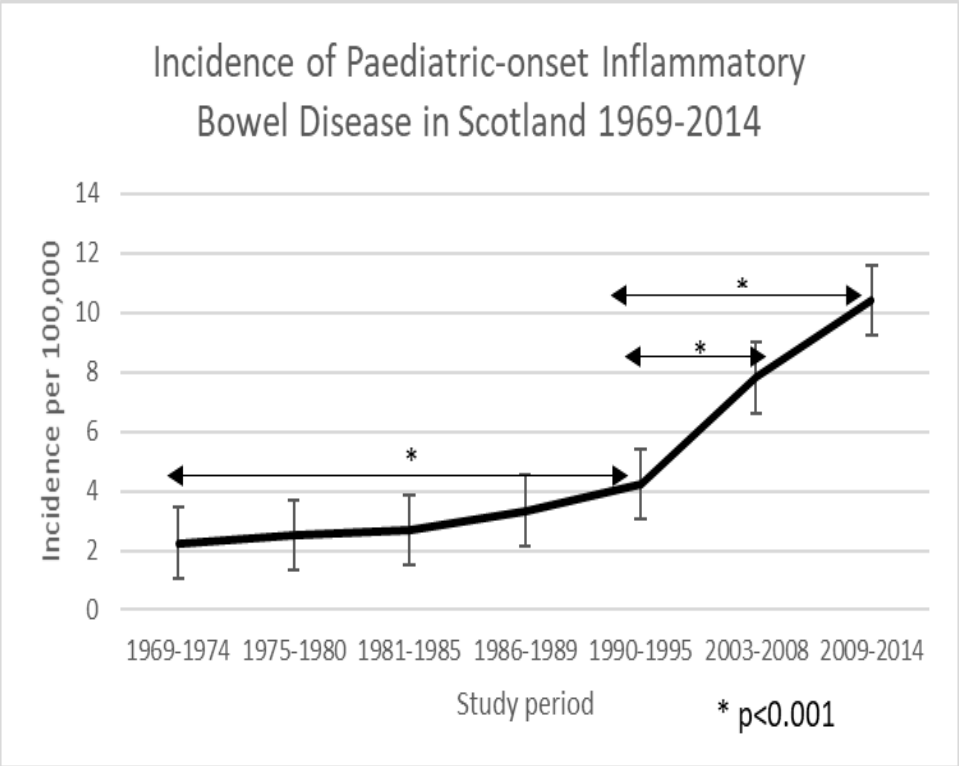


Figure 12B- Incidence of paediatric-onset CD demonstrates sustained increase in incidence from 1969-2014 (incidence rates per 100,000)

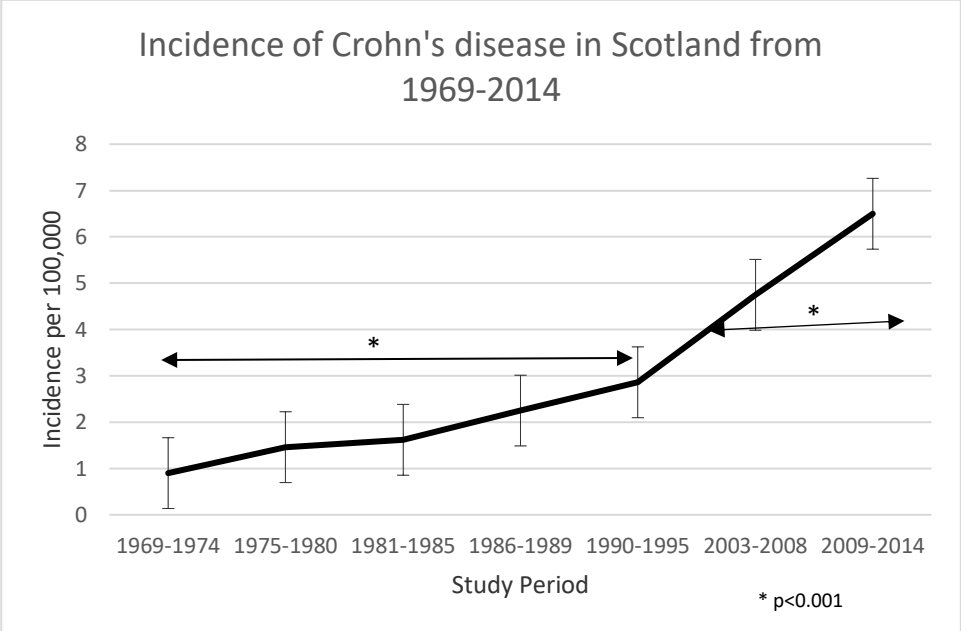
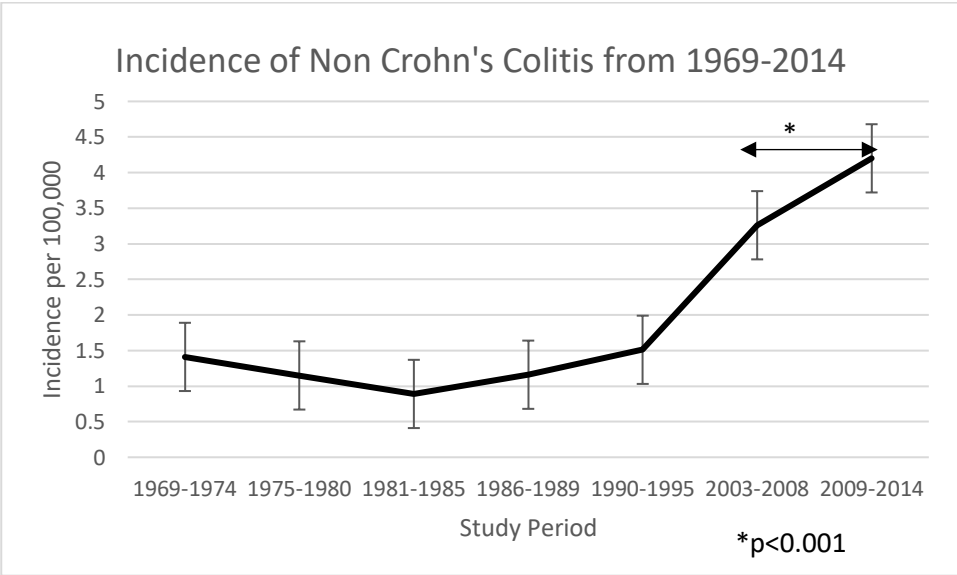


Figure 12C- Incidence of paediatric-onset NCC (non-Crohn's colitis) demonstrates sustained increase in incidence from 1969-2014 (incidence rates per 100,000)



5.4 Discussion

The incidence of paediatric-onset inflammatory bowel disease in this nationwide cohort study demonstrates a sustained and durable increase with a persistent increase in paediatric-onset CD from 1969-2014. Comparing the two most recent cohorts, cohort 2 (2009-2014) and cohort 1 (2003-2008), there was a significant 27% increase in all PIBD incidence, yet the only significant increase in IBD subtypes was in CD in males which has shown an enduring increase since 2003(92). The IBD incidence rate of 10.7 per 100,000 for those under 16 years in Scotland remains one of the highest worldwide and the highest in the UK(97, 153).

In a recent systematic review on the worldwide incidence of PIBD, 70% of countries described an increase, however, few countries reported such a durable rise as observed in Scotland(2). Australia and Sweden also have continued and durable rises in UC over a 60 year period, again with the most significant increases at the end of the study period(172, 178). Both studies compared 20-year epochs (i.e. 1950-1969 vs 1990-2009 in Australia), which if further broken down into 5-year epochs, the incidence may more closely reflect that seen in Scotland. Australian incidence is presented annually in graphical form (no numerical data) where rates vary annually with peaks in 2007-2008 and lower levels in 2006/2009(172). In the Swedish study patients were included up to 19 year which may explain their increase (177). Potential changes in diagnostic pathways or better accrual of data may also explain the increases seen whilst in Scotland these pathways have remained relatively stable over many years with clear established referral pathways.

Ontario Canada has had a sustained increase over a shorter period from 9.5 per 100,000 in 1995 to 13.2 per 100,000 in 2009(111, 180) but includes those under 19 years. More recent Canada-wide incidence data from 2010 included those less than 18 years and reports incidence rate of 9.7 per 100,000(137), which still includes an additional 2 years of

incident data from the Scottish cohort. Unlike our cohort, the Ontario group reported significant increases in all IBD subtypes although, did not report on IBDU, in those aged 6-9 and 10-17 years with a slight decrease in CD in those aged 0-5 years(180). EPIMAD confirms the increases in incidence of CD in those aged 10-19 years with a significant increase from 3.4 per 100,000 in 1988-90 compared to 5.9 per 100,000 in 2006-07 ($p<0.001$), which was not influenced by gender or region(175). A further example from Canada, this time from Manitoba, incidence in PIBD increased from 1.2 per 100,000 in 1978 to 4.68 per 100,000 in 2007 ($p<0.001$). Finland reported incidence over 28 years via a national registry for those under 19 years which increased from 7 per 100,000 in 1987-1990 to 23 per 100,000 in 2011-2014 (173). This is significantly higher than Scotland, however, the additional 3 years of patients from aged 16 to 19 years may explain the higher rates.

Adult systematic review data supports paediatric findings with higher incidence rates reported in Europe and North America(87). Temporal data from this review demonstrates an increasing trend with 56% of CD and 29% of UC studies since 1980 reporting a significant increase, however, 6% of UC studies reported a decrease compared with none for CD. The rate of rise seen at the end of the 20th century in adult IBD has not been maintained (87, 184) and it is possible this may happen in PIBD. The decrease in UC may be related to diagnostic approach with a more robust process associated with an increase in CD, the assertion that in developing countries ulcerative colitis is a more predominant subtype(5) or environmental exposures. Environmental factors have been implicated for many reasons including that as countries become more "westernised", the incidence of IBD increase, as demonstrated in the Asia-Pacific Crohn's Colitis Epidemiological Study, where UC is twice as likely to be reported than CD(101). IBD is increasing in those who immigrate from low risk to high risk countries in either first or second generation exemplars include Canada, UK and Denmark(150, 206, 210, 214) further supporting the role of environment in the

aetiology of IBD. In PIBD, an age related effect was observed with the highest risk of developing IBD in those immigrating at a younger age (88) and potentially the role of the microbiome(215) as infants have higher susceptibility to microbial change in response to environmental factors(216). Immigration is unlikely to have influenced the incidence in Scotland as there is relatively low rates with only 4% of the population belonging to an ethnic minority (16).

Observational cohort studies have suggested several associations with PIBD including cigarette smoking (increases risk in CD) (217), antibiotic usage during childhood (increased risk in Westernised population)(218), breastfeeding (protective)(219), appendectomy (protective against UC)(220), air pollution (increased risk)(221), latitude and urbanisation (89, 221-224). Data from Finland suggests higher incidence in more sparsely populated areas contrasting with Manitoba, Canada which suggests higher rates in urban areas(160, 224, 225) and is supported by Danish data that reported for every 5% increase in urbanisation the odds of having CD compared to UC increased by 34%(208). The hygiene hypothesis may explain the increase and theorizes that childhood infections and poor hygiene are protective against developing CD. Poor hygiene allows the host to develop tolerance or immunity to potential agents that could trigger CD in later life and is been supported by case-control studies(201). Factors found to be protective against IBD support this including having pets, larger family size and greater number of siblings(113, 226). Evidence on the role of diet is conflicting with a recent systematic review, including only one paediatric study, showing an association between high dietary fibre and intake of fruit with a decreased rate of CD(227). In PIBD at diagnosis new CD patients had lower intakes of fruits and vegetables than controls(228) which supports the previous findings. However, caution must be exercised when interpreting these studies are recall bias may influence the results and the effect of confounders cannot be excluded i.e. children restrict their diet as

this influences their symptoms. Another key environmental factor is latitude with a clear north south divide seen in both Europe and North America, including Scotland (89, 106, 223). Scotland has reported higher incidence rates in the North than South for CD only although this may have been confounded by the inverse relationship between socioeconomic status and risk of IBD(223). In the United States of America, higher incidence was reported in Northern states(105), however, this data is not population-based. The diverse results reported illustrate that no single environmental factor can explain the rising incidence which is likely to be a complex interaction between genetics, environment and unknown microbial influences. The effect of the gut microbiota in the pathogenesis of IBD has yet to be fully understood but is associated with innate immunity. Microbial diversity is reduced in IBD when compared to healthy individuals, particularly in CD(229). Additionally, certain types of bacteria are reduced in CD such as *Faecalibacterium prausntizii* which has been shown to have anti-inflammatory properties(230).

The incidence of very-early onset IBD, those aged less than 6 years, remained stable during the study period in our cohort confirmed by the EPIMAD group which also reported a stable incidence from 1988-2011(170). However, this contrasts with other studies which report increasing trend in this age compared to older children(137, 169). EPIMAD reports a stable rate of 5% of all PIBD cases in those under 6 years, similar to a study of 5 Canadian provinces with data collected through health administrative databases. However, there was variation between the Canadian provinces with Alberta reporting 12.5% of all PIBD cases in those under 5 years contrasting with Quebec which reports only 2.4%. IBD diagnosed under 2 years is likely to have a monogenetic cause including IL10 receptor defects and XIAP(231, 232) while those under 6 years are hypothesised to be related to environment(137). The genetics of IBD remains poorly understood, yet recent advances have greatly enhanced knowledge with 200 risk loci now identified suggesting involvement of the adaptive and

innate immunity, autophagy, intestinal epithelial barrier function and microbial defence pathways(151). Genetic shifts evolve over thousands of years and heritability cannot fully explain the risk suggesting that other factors are involved in the increase in IBD including epigenetics. Epigenetic changes occur with increasing age caused by environmental factors(233) and are thought to affect interaction with the intestinal microbiome(234) and immune response(235). Interestingly, differences are reported in DNA methylation between adult and paediatric IBD; 26 dysregulated miDNA associated with PIBD and only 8 overlap identified in adults(234) which is supported by a recent systematic review.

The strengths of our nationwide cohort study are that our most recent cohort was prospectively obtained using the same rigorous and robust methodology used in previous studies(91, 92). The well-established virtual healthcare network set up in Scotland covering all district general hospitals allows for accrual of all cases less than 16 years of age. The established database based in a single centre ensures that cases are regularly reviewed and IBD subtypes are changed if needed after endoscopic re-evaluation and discussion with the lead for IBD for each centre ensuring the phenotyping is robust and evolving. As in our previous study, we have not approached adult colleagues for under 16-year olds who have been diagnosed in adult practice, as there are significantly more adult IBD centres where patients could be seen. A different approach to data collection is required such as a national database to identify cases which would then need to be validated by researchers to confirm the age of diagnosis and the IBD subtype. However, given the well-established paediatric gastroenterology service which is now in place nationwide and has not changed for many years, most cases are seen within this service and the minority are seen in adult service. As these patients are not included, it will only increase the incidence rates observed supporting the assertion that PIBD continues to increase in Scotland. Previous hypotheses the increase was due to improved methods of diagnosis and accrual of data via

the national network of care, are not enough as the current investigations strategies and referral pathways have been in place for sustained period without change, necessitating another explanation for the rise. It is possible that these pathways reduce time to diagnosis through increased awareness and improved access to services but not for the increase in actual numbers diagnosed.

5.5 Conclusion

This population-based nationwide study of incidence of paediatric-onset IBD demonstrates a 27% increase in IBD from 2003-2008 to 2009-2014 which is driven by a sustained and durable increase in paediatric-onset CD, maintained by the increase in males, predominantly aged 11-15 years. The incidence of 10.7 per 100,000 of PIBD under 16 years to our knowledge remains the highest reported in the UK and one of the highest worldwide. Further epidemiological research is needed to establish and explore potential environmental factors using case control studies to explore potential gene-environmental interactions.

Chapter 6

6. Paediatric Inflammatory Bowel Disease Unclassified: a nationwide population-based incidence and natural history cohort study

6.1 Background

IBDU is the least common subtype of PIBD accounting for around 10% of cases (102) yet there is a paucity of population-based data on the incidence with reported incidence figures ranging from 0.03 per 100,000 to 1.0 per 100,000 (152, 236) which has increased over time(152, 188) with United Kingdom incidence in 1999 0.6 per 100,000(102). There is a lack of evidence on the natural history of IBDU but studies do suggest that patients have a rapidly progressing disease in both paediatric and adult patients(237, 238) which evolves over time into CD or UC although with differing frequencies (116, 138). Further research is needed to assess and understand the natural history of paediatric IBDU to gain insight into the disease course and outcomes including efficacy of treatment options.

6.1.1. Aims and hypothesis

The hypothesis was that the rates of IBDU are increasing within Scotland and that most cases have a mild disease course with a similar response to treatments as UC. The aim was to determine the incidence and temporal trends of paediatric IBDU in a well-defined, population-based cohort in Scotland, and to describe their natural history, diagnostic assessment and treatment outcomes.

6.2 Methods

Methods are explained in Methodology chapter 2, section 2.3.

6.3. Results

6.3.1. Basic characteristics

115 patients met the inclusion criteria (66 male; 8% under 5 years old, 36% 6-10 years and 56% 11-15 years) with a median age at diagnosis of 11.4 years (range 2.3-15.9). The median follow-up time was 2.8 years (range 0.5-9.6). 476 cases of PIBD (i.e. CD, UC and IBDU) were diagnosed between 2009-2013; 65 (14%) were IBDU.

Most patients had extensive disease at presentation (**Table 14**) and progression was noted in all categories (**Table 15**). The majority had a relatively mild disease course (when assessed at last follow up; **Figure 13**), however, 16% had severe disease requiring anti-TNF-α therapy and/or surgery. In those that had severe disease at presentation, all remained IBDU at last follow up with 2 requiring surgery with 4/10 having chronically active disease, all of whom required IFX.

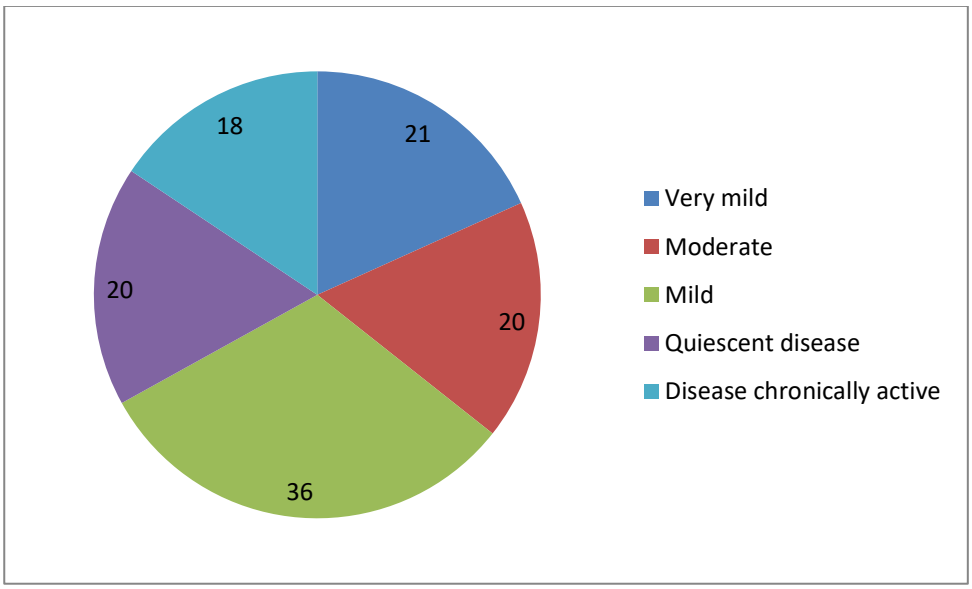
Table 14 Baseline characteristics at diagnosis of patients diagnosed with IBDU

Male (%)	66 (57)
Median age	11.4 years
Disease extent (%)	
-Pancolitis	90 (78)
-Disease distal to hepatic flexure	8 (7)
-Disease distal to splenic flexure	12 (11)
-Proctitis	5 (4)
Colonoscopy performed (%)	115 (100)
-Ileal intubation	75 (63)
Upper GI endoscopy (%)	112 (97)
-Macroscopic involvement	62 (54)
Imaging (%)	
-Barium meal	68 (59)
-MRE	29 (25)
-MRE and barium	1 (1)
-White cell scan	4 (3)
-Capsule endoscopy	1 (1)
-None	12 (11)
Severity (as per PGA) (%)	
-Severe	10 (9)
-Moderate	56 (49)
-Mild	44 (38)
-Remission	5 (4)

Table 15- Progression of disease in those that remained IBDU at last follow up using Paris Classification

Disease extent at diagnosis	**Number of patients (n=115) (%)**	**Disease extent at last follow up**	**Number of patients IBDU at last follow up (n=89) (%)**
E1	5 (4)	E1	2 (2)
E2	12 (11)	E2	6 (7)
E3	8 (7)	E3	9 (10)
E4	90 (78)	E4	72 (81)

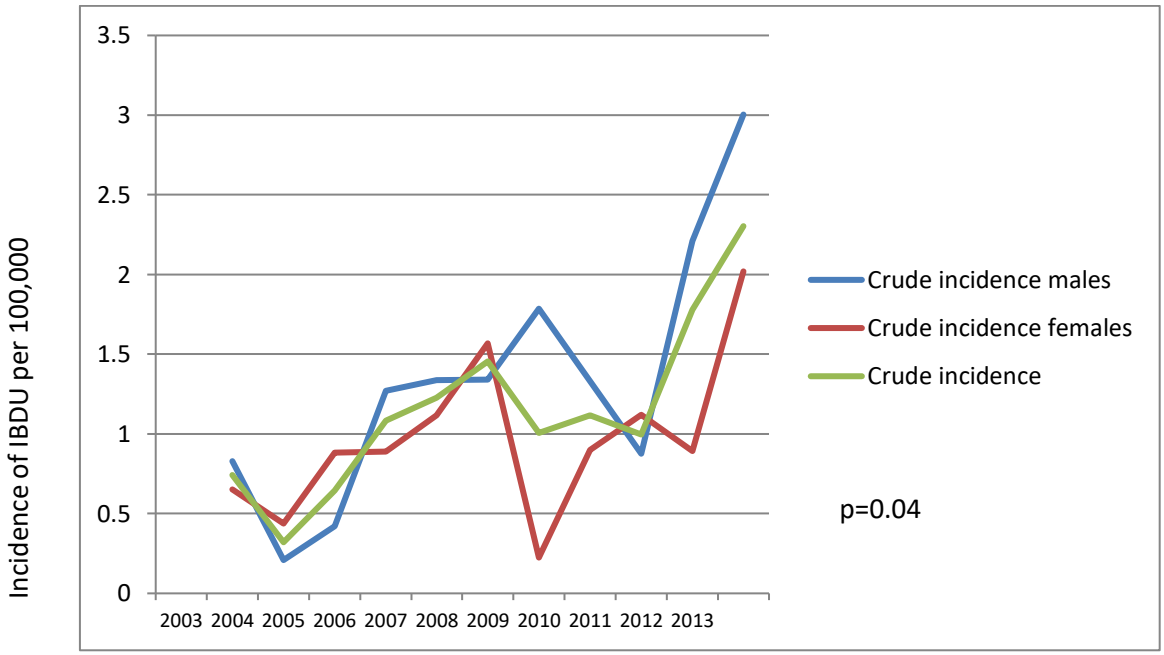
Figure 13 Longitudinal disease course in IBDU demonstrates than most patients have mild or indolent course



6.3.2. Incidence

In 2013, 21% (21/98) of all incident cases of PIBD in Scotland were diagnosed with IBDU, with a crude incidence rate of 1.2/100,000 across the entire study period (2003-2013). Age-sex adjusted incidence rate for 2003-2008 was 0.9/100,000 (95% CI 0.6, 1.2) compared to 1.7/100,000 in 2009-2013 (95% CI 1.3, 2.6) (p=0.04) (**Figure 14**). Following re-evaluation 89/115 had a diagnosis of IBDU at last follow up giving an adjusted 2003-2013 incidence of 0.9/100,000 (95% CI 0.7,1.1).

Figure 14- Incidence of Inflammatory Bowel Disease Unclassified in Scotland 2003-2013 shows significant increase in time between 2003-2007 and 2008-2013 (incidence rates per 100,000)



6.3.3. Baseline investigations

All children underwent colonoscopy at diagnosis and 112 (97%) underwent upper gastrointestinal (GI) endoscopy (**Table 14**). Three children did not receive an upper GI endoscopy. Two were initially investigated in Scottish adult hospitals and on suspicion of IBD were transferred to paediatric services. One was in clinical remission and the other had acute severe colitis which required a colectomy within one month of diagnosis; both patients have subsequently undergone an upper GI endoscopy which was normal both macroscopically and microscopically. The third child did not have an upper GI endoscopy at diagnosis and has not had any requirement for re-evaluation to date.

6.3.4. Induction therapy

75 (65%) received corticosteroids (either intravenous and/or oral) with 65 (87%) achieving remission. Two children received Infliximab (IFX), one child who responded to oral steroids but did not achieve remission and one child who failed to respond at all. Following IFX, one child achieved remission whilst the other had an improvement but subsequently underwent a colectomy.

Exclusive enteral nutrition (EEN) was used in 15 (13%) thought initially to have Crohn's disease based on macroscopic appearances but microscopically suggestive of IBDU. Only two (15%) children achieved remission with EEN one of whom was subsequently reclassified as CD. 5- ASAs were used in 58 (50%) cases; of these 32 (55%) achieved remission and 21 (36%) subsequently received a course of corticosteroids resulting in remission/response in all but one child.

6.3.5 Maintenance therapy

Most children were commenced on a 5-ASA for maintenance 107 (93%). However, with 52 (45%) went on to receive azathioprine and 16 (14%) methotrexate (**Table 16**). Anti-TNF therapy was required in 14 (12%), all initially had IFX and five required ADA after failure of IFX (**Table 16**). Of the 14 patients who received IFX, 11 were discontinued: two for primary non-response, five for loss of response and four as a planned drug discontinuation (two received IFX as a bridge to surgery, one as a bridge to immunosuppression and one entered clinical and endoscopic remission). Five patients changed from IFX to ADA (one primary non-responder and four loss of response), two then had primary non-response to ADA.

Table 16 Prior medications for maintenance for all IBDU patients

Corticosteroids (N, %)	75 (65%)
-Steroid dependency	35 (47)
-Steroid resistance	16 (21)
-Unacceptable side-effects	5 (7)
Azathioprine/6-MP (N, %)	52 (45%)
-Primary non-response	12 (23)
-Loss of response	8 (15)
-Intolerance	14 (27)
Methotrexate (N, %)	16 (14%)
-Primary non-response	2 (13)
-Loss of response	4 (25)
-Intolerance	7 (44)
Infliximab (N, %)	14 (12%)
-Primary non-response	2 (14)
-Loss of response	5 (36)
-Bridge to immunosuppression/surgery	3(21)
-Planned drug withdrawal	1 (1)
Adalimumab (N, %)	
-Primary non-response	2 (40)

6.3.6. Reclassification to alternative IBD subtype from IBDU

Sixty-three patients (55%) had a repeat upper GI endoscopy after a median of 1.5 years (range 0.2-9.6) (**Figure 15**). A further two (2%) underwent repeat upper GI endoscopy for reasons other than IBD (recurrent dyspeptic symptoms despite optimum medical treatment and recurrent H. *pylori* infection) and did not undergo colonoscopy. 2 (2%) underwent repeat colonoscopy only. 18/65 (28%) underwent repeat imaging with one child undergoing a repeat barium follow through then MRE. The most commonly used imaging for reassessment was MRE in 10 (53%) then barium follow through in 6 (32%) then 2 (10%) had wireless capsule endoscopy and 1 (5%) had a white cell scan.

Sixty-five patients underwent 106 colonoscopies most commonly for disease reassessment in 54 (51%), relapse of symptoms in 33 (31%) or steroid dependency in 14 (13%). 41 (36%) had one endoscopic re-evaluation, 16 patients underwent two, three patients had a third re-evaluation, three had four and two had six re-evaluations. One patient who had six re-evaluations had difficult to control disease with a polypoid lesion in his transverse colon which required endoscopic surveillance; he remained IBDU at transition to adult services. Another patient who underwent six re-evaluations had a colectomy and end ileostomy then underwent closure of the loop ileostomy; her colectomy sample was consistent with UC and went on to develop chronic pouchitis and stenosis of her anal pouch.

26 (23%) changed their diagnosis, all after endoscopic re-evaluation, most commonly to CD in 16 (62%) and UC in 10 (38%) after a median of 1.5 years (range 0.6, 5.9) (**Figure 15**). Most, 21 (81%), changed their diagnosis after one endoscopic re-evaluation (14 to CD and 7 to UC). Three patients changed diagnosis after their second endoscopic re-evaluation, one to UC and two to CD. One patient changed to UC after his third endoscopic re-evaluation and one after 5 endoscopies also changed to UC. In those that changed to CD, 5 (31%) did not have ileal intubation at diagnosis but all had small bowel imaging and upper GI endoscopy.

Figure 15 Outcome and treatment for patients who remained IBDU at last follow up

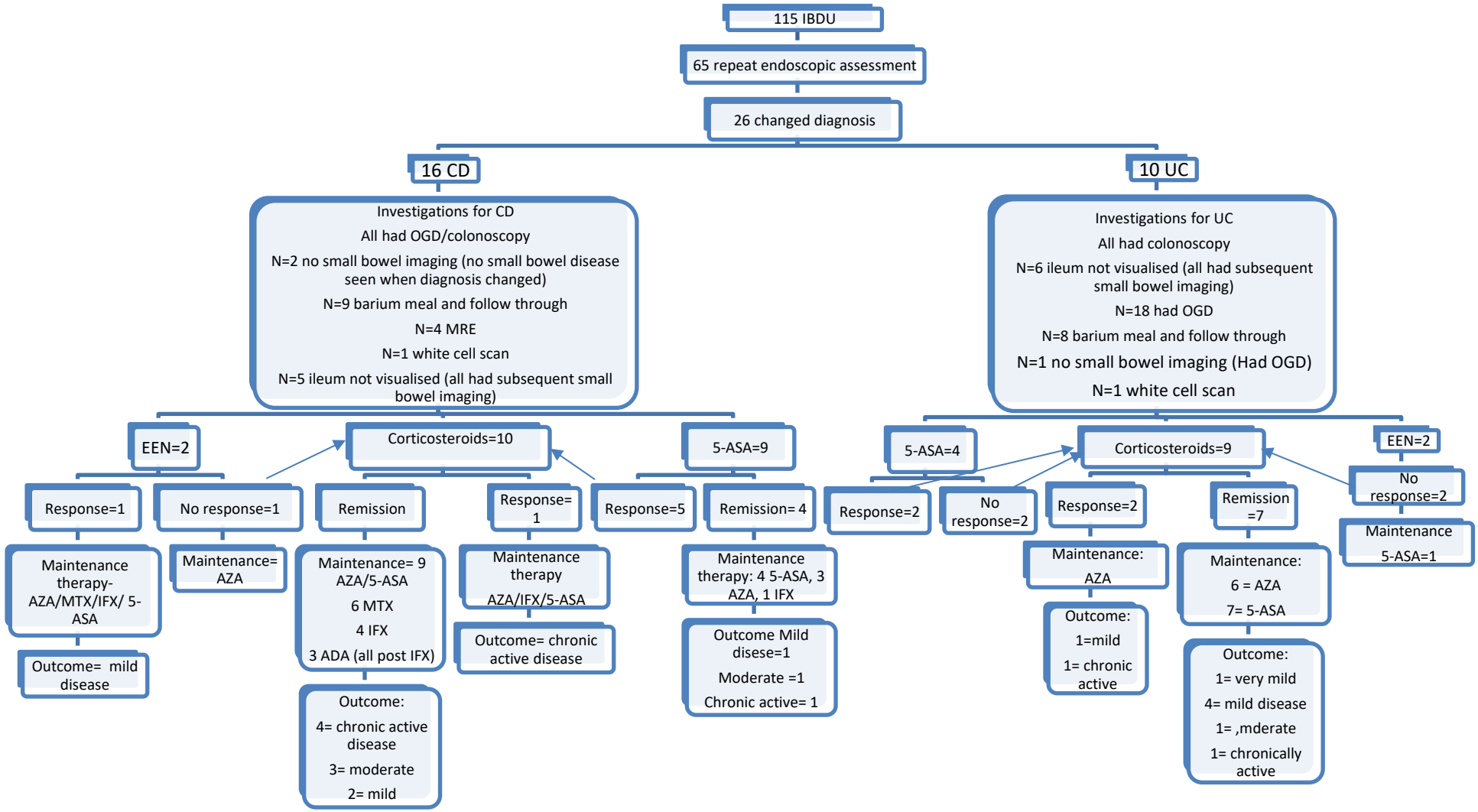
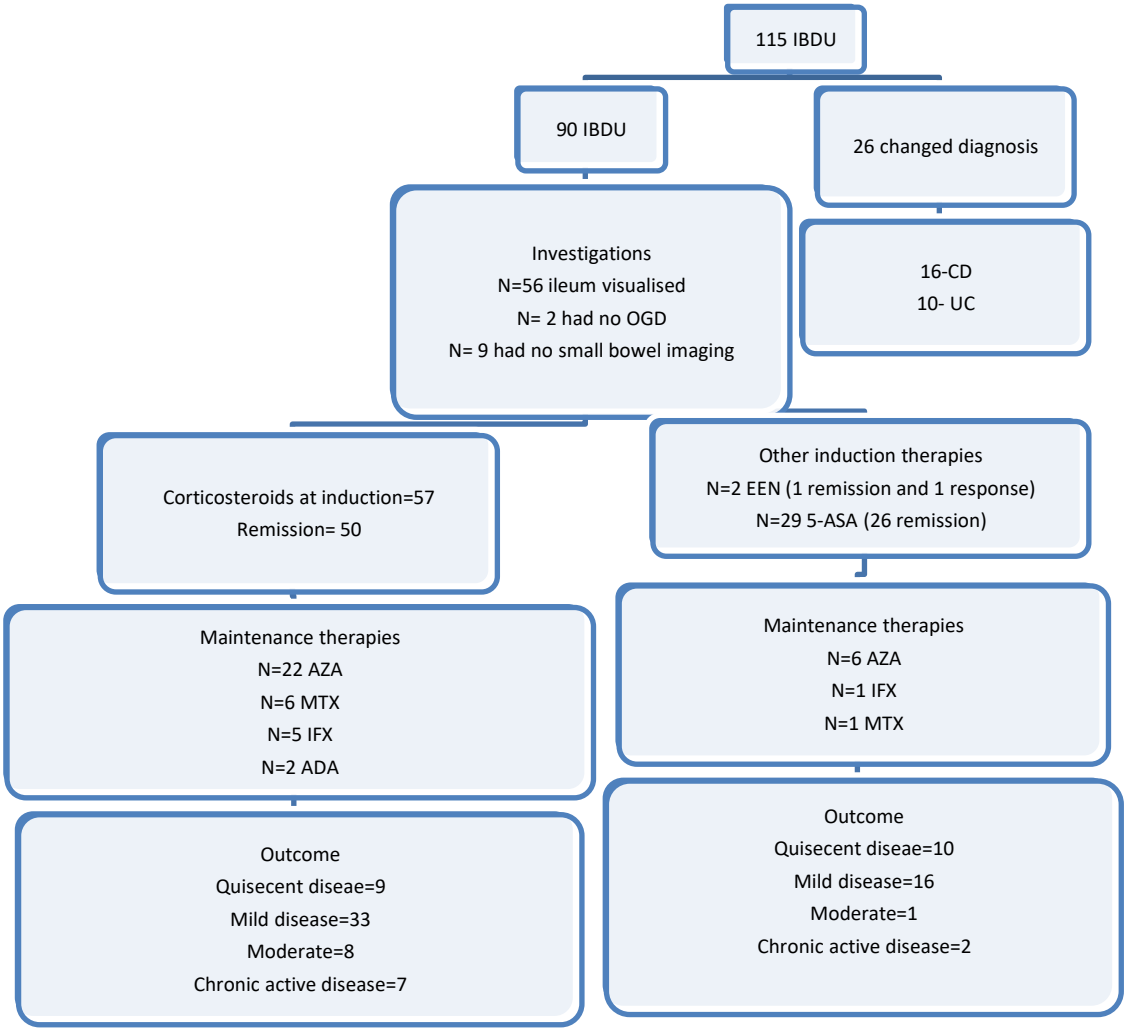


Figure 16 Outcome and treatment for patients who remained IBDU at last follow up



6.3.7 Surgery

Seven (6%) patients underwent IBD-related surgery after a median of 2.1 years (range 0.1-5.4). The most common procedure was colectomy and end ileostomy in 6 of 7 with the final procedure a small bowel resection for a patient who had a changed diagnosis to CD prior to surgery. A further 3 patients had a change of diagnosis; 2 prior to surgery changed to UC whilst 1 had a change of diagnosis to CD following reassessment post colectomy for consideration of pouch formation.

6.4 Discussion

In this Scottish population-based cohort of patients with IBDU, a significant increase was reported over an 11-year study period with an extensive phenotype at presentation, yet a relatively mild disease course, with only 6% requiring surgery and 14% requiring anti TNF therapy. There was a low threshold for re-investigation with 57% having a repeat endoscopy but, despite a high rate of re-assessment, only 40% (26/65) who had a repeat endoscopy changed diagnosis, most commonly to CD in 62% after a median of 1.5 years.

The incidence of paediatric IBDU significantly increased in our cohort over 11 years, as demonstrated in other countries(152, 188). The increase may reflect a more comprehensive diagnostic assessment in this cohort as patients were not labelled CD or UC due to insufficient evidence. All patients in this study underwent colonoscopy and 97% had an upper GI endoscopy, compared to 98% and 89% respectively in the Eurokids registry(138), with 89% of IBDU patients here undergoing small bowel imaging compared to 62% in Eurokids (138). Furthermore, all Scottish patient's histology was reviewed to confirm IBDU prior to inclusion, difficult cases were reviewed by senior IBD clinicians in each centre to confirm eligibility, but biopsies were not reviewed in the Eurokids study. The variation in diagnostic approach may be explained by guidance not being published until 2005 on a recommended approach, when upper and lower GI endoscopy including ileal intubation with multiple biopsies, and small bowel imaging irrespective of ileal disease at endoscopy were recommended (11). Biopsies are crucial for a diagnosis of IBDU with the Porto group defining changes as "histology showing acute and chronic inflammation with architectural changes confined to the colon…. With normal small bowel follow through or enteroclysis"(11). In 2014 further clarification on what which would be considered IBDU and atypical features of UC/CD were published including a child with colitis with significant

growth delay (height velocity <-2SDS), multiple aphthous ulcerations in the stomach not explained by another cause (e.g. non-steroidal anti-inflammatory drugs or *H. pylori*), aphthous ulcers in the oesophagus or duodenum not explained by another cause (e.g. *H. pylori* or coeliac disease) or reverse gradient of mucosal inflammation (i.e. worse right-sided mucosal inflammation)(13).Further validation work on these features have been performed to produce a clearer diagnostic algorithm (239).

A systematic review on the incidence of PIBD(2) did not include IBDU and few other epidemiological studies have covered this area, potentially due to inherent methodological difficulties and relatively recent subclassification. The methodological challenges with any paediatric epidemiological study (heterogeneous data collection techniques, variable age limits defining paediatric populations and diagnostic misclassification) are compounded by the historical lack of diagnostic criteria for IBDU which leads to varying diagnoses of IBDU among countries and even amongst centres within the same country(137). The Eurokids registry exemplifies this, with cases reported from leading European centres yet 16% who were initially classified as IBDU had features more compatible with CD (more likely in those that did not undergo full diagnostic work up)(138). Furthermore, a patient who could have been diagnosed as IBDU previously may now be given a diagnosis of atypical UC(13). True population-based cohort studies such as this, excludes the referral bias inevitable with single centre studies, and with full IBDU accrual the full spectrum of disease severity, from the mildest to the most severe is seen.

In this cohort 8% were diagnosed under 5 years and it became more common with increased age, contrary to the Spanish cohort where IBDU was diagnosed more at a younger age (152). The median age of diagnosis in our cohort was 11.3 years similar the literature (188, 240) yet younger than Eurokids at 12.3 years(138). A systematic review on

IBDU, in adults and paediatrics reported it was more common in younger children with up to 20% of children diagnosed under 5 years of age(116). However, numbers in this age group are small and the diagnosis can often be challenging(140). Heyman performed multivariate regression and demonstrated that compared to CD, children aged below 8 years were 3.5 times more likely to be diagnosed with IC(241). 13% were identified as IBDU in this cohort but it is unclear what diagnostic work-up they underwent (13). Conflicting evidence exists regarding gender propensity in IBDU, we found IBDU to be more common in males whilst Lindberg reported it to be more common in females (240) and others have found no difference(102, 138).

IBDU can evolve over time into either CD or UC and a challenge for paediatric gastroenterologists is that patients transfer to adult care so are often lost to follow up. In our study 23% changed their diagnosis after a median of 1.5 years, is higher than previously reported and mostly reclassified to CD, which is similar to other studies (156, 188). In the Eurokids study, 33% changed diagnosis, most commonly to UC, however, only 44% of the whole cohort of 265 patients were included in this aspect of follow up(138). A different longitudinal cohort study followed IBDU cases for a mean of 3.5 years, 23% of patients changed diagnosis after a median of 4.1 years: 8 (44%) to CD, 5(28%) to UC and 5 (28%) as non IBD. Of the 30% who remained IBDU, 55% reported no symptoms and were on no medication at last follow up with only 30% confirmed IBDU (242). It is not clear from the methodology what baseline investigations were performed or if patients had small bowel imaging which may explain the increased numbers reclassified as CD. Many patients ended up with a non-IBD diagnosis which promotes the need for endoscopic re-evaluation. The importance of longitudinal follow up is illustrated in another single centre study, 33.7% of paediatric patients were reclassified after a median of 1.9 years(237), however, if follow up was extended to 8 years, up to 80% of adult patients had their diagnosis revised(243).

Further support is provided in a systematic review that there was in increase in CD and decrease in indeterminate colitis with time(116). However, this review mentions a decrease in UC s in some studies but not all, so it is then unclear if the increase in CD and decrease in IBDU reflects changes to CD, UC or both.

In those that remained IBDU at last follow up in this cohort, 76% had extensive disease at diagnosis rising to 81% at maximal follow up which is similar to a previous study of Scottish children where74% of UC patient had pancolitis at diagnosis which increased to 82% after a median of 3.9 years(16). The rapid disease progression is especially relevant given the increased risk of surgery in those with extensive disease(13). Disease progression has been observed in both UC and CD in PIBD (16) but little is known about progression in IBDU, recent evidence suggests that it is a genetically different subtype differing from both UC, colonic and ileal CD with a genetic continuum from ileal CD to UC(244). In a single centre study in North America of paediatric IBDU, nearly 80% had pancolitis at diagnosis rising to 100% after 6 years of follow up suggesting rapidly progressing disease(237). In In the Eurokids cohort, 58% had extensive disease at presentation with no comparator at end of follow up although repeat colonoscopy was performed in 50%(138).

The natural history of IBDU in relation to medications is largely unknown as these patients are not included in large studies of immunomodulators or anti TNF therapy. In our cohort, 45% IBDU patients require immunomodulation, mostly azathioprine, and 14% required anti TNF therapy an aggressive disease phenotype. However, 5-ASAs were effective at inducing remission with most patients continuing onto maintenance therapy suggesting a proportion have a milder disease course. Treatment responses are similar to others in the literature with 12% requiring anti-TNF therapy and nearly 90% receiving 5-ASA at diagnosis (245). Future studies would benefit from including these patients to provide

further guidance on how medications should be used in paediatric IBDU and evidence of efficacy.

There were several methodological difficulties in conducting this study which may influence the results. Only children less than 16 years who were diagnosed and managed in paediatric services were included so the number may be an underrepresentation. Patients were identified from either prospective or retrospective databases; however, all data was collected using a standardized proforma by a single researcher to ensure a standard approach. During the 13-year period, practice changed on appropriate diagnostic techniques, so no one standardized approach was used and significant diagnostic heterogeneity exists. However, this study is population-based incidence providing analysis of trends over time with a median of 2.8 years of follow up providing an insight into investigation and treatment of paediatric IBDU. The importance of endoscopic re-evaluation to monitor disease progression and potential evolution to CD or UC has been shown which is not often mentioned in relation to a change in diagnosis(156). The impact of the revised Porto criteria and new diagnostic algorithms may impact upon the incidence of IBDU given more structured diagnostic criteria(13, 239) which may result in an increasing number diagnosed.

6.5 Conclusion

In this national population-based study on the incidence of paediatric IBDU a significant rise over an eleven-year study period was found with 23% changing in diagnosis after endoscopic re-assessment, mostly to Crohn's disease. Low rates of surgery and anti TNF therapy were observed with most patients having a mild disease course despite high rates of extensive disease at presentation and disease extension observed during a median

follow-up of 2.8 years. Further longitudinal follow up is needed to determine if more patients will be reclassified or have further extension of their disease.

Chapter 7

7. The natural history of anti-TNF therapy use for paediatric inflammatory bowel disease treatment in Scotland

7.1 Summary

- ADA/IFX were safe and effective at inducing remission in all subtypes of PIBD with remission in 58% of IFX and 83% response/remission of ADA patients
- Safety- 30 (15%) patients had 35 acute infusion reactions to IFX (either on the first or second course); 2 had anaphylaxis. 21 had an adverse reaction with 14 experiencing toxicity who required hospitalisation. 15 had adverse effects with ADA with 5 hospitalisations. No deaths or anaphylaxis were reported.
- 93% of IFX patients commenced maintenance therapy which they received for a median of 0.9 years (range 0.1-3.7); 56% still receiving IFX at 12 months. The most common reason for discontinuation under 12 months was primary non-response.
- 56/57 commenced ADA maintenance with 34/57receiving at 12 months, the most common reason for discontinuation was primary non-response in 5/11 who stopped before 12 months
- IFX/ADA dependency occurred in 50% of ADA and 34% of IFX patients. Despite dose escalation, 43% discontinued due to secondary loss of response with 56% were still on IFX and 74% on ADA at last follow up. 27% IFX and 39% ADA patients had a planned drug withdrawal, mostly for clinical remission.
- Remission, early stages of puberty (Tanner 1, 2 and 3) and disease duration ≥ 2 years at induction were associated with improved linear growth in IFX

- Significant improvement in linear growth was associated with males, moderate disease at induction of IFX, induction then maintenance and AZA. Corticosteroids at baseline were associated with an improvement in linear growth at 12 months.
- For ADA, improvement in linear growth was in those in the early stages of puberty (Tanner 2 and 3)

7.2 Background

Biological therapy in PIBD is increasing worldwide with Infliximab (IFX) (Remicade, MSD), and Adalimumab (ADA) (Humira, Abbvie) licensed for PIBD use in the UK. Despite widespread usage, no complete nationwide data exist as the UK PIBD audit, a national report on biological therapy, had incomplete reporting both within and amongst UK PIBD centres (246).

As anti-TNF usage has increased, the evidence on long-term efficacy has improved (63, 247) showing reduced inflammation, improved mucosal healing and reduced disease relapse/corticosteroid usage, however improvement in long term linear growth, a key outcome target, has proven more elusive(53, 248, 249). The presence of poor growth and short stature in PIBD, and more specifically, Crohn's Disease (CD) has been described for some time; this can lead to a significant impact on final adult height with varying reports of 20-30% of children with CD having a reduced adult height(250). Evidence on the efficacy of Infliximab (IFX) on short term growth is generally supportive with several studies showing clear benefit (59, 65, 251-253) however other published studies have shown no beneficial effect (33, 254-256). The long term effect of IFX on growth is less widely reported yet a recent retrospective study demonstrated improved height SDS in the short term with 3 year follow up but final adult height at the lower range of their target (257). Fewer growth data exist on ADA, but it does demonstrate an improvement in the short (258)and longer

term growth(78) which is more pronounced in those who have remission/response post induction(259-261). Despite a significant increase evidence on efficacy and benefits of anti-TNF therapy, most data is provided by clinical trials which do not represent the "real life" clinical dilemmas faced by clinicians limiting the generalisability of the results as patients are selected to participate, often from tertiary referral centres, with not all PIBD subtypes included(262).

Dependency was first reported in paediatric CD in 2007 and occurs in 42-66% of CD patients who required repeated infusions to maintain remission (254, 263, 264). In adults on maintenance IFX, relapse on discontinuation is common despite immunomodulator therapy so dependence on anti-TNF to maintain remission is often seen(265). Evidence for ADA dependency is not as clear, possibly related to the length of time it has been available having only recently been licenced for use in paediatric patients with CD in the UK(52).

7.2.1. Aims and hypothesis

The aim of this study was to characterise biological usage, growth and dependency in a population-based cohort of children with all types of IBD, treated with ADA and/or IFX between 2000-2012 in Scotland using data from the Scottish PIBD biologicals register. The hypothesis was that anti-TNFs were safe and effective in all subtypes of PIBD.

7.3 Methods

Methods are covered in chapter 2, section2.4.

7.4 Results

7.4 Efficacy of anti-TNF drugs

7.4.1. All IBD patients receiving anti-TNF agents (IFX and ADA)

One hundred and ninety-five patients were treated with 240 courses of therapy with a biologic, 164 (85%) had CD, 28 (14%) had UC and 3 (1%) IBDU. Most, 115 (60%) were boys with a median age of 11.2 years (range 2.7-17.2) at diagnosis. 191 received IFX and 57 received ADA (4 received ADA alone) (**Table 17 and Table 18**).

Table 17 Baseline characteristics of patient on IFX

	Crohn's Disease (CD)	Ulcerative Colitis (UC)	Inflammatory Bowel Disease Unclassified (IBDU)
Number of patients	160	28	3
Female (%)	63 (39)	11 (39)	2 (66)
Median age at diagnosis (range, years)	11.0 (2.74- 17.2)	12.2 (5.2-14.8)	13.2 (12.0-14.8)
Median duration from diagnosis to start of IFX (range, years)	2.6 (0.02-11.5)	1.34 (0.01-7.7)	0.01
Median age at start of IFX (range, years)	14.0 (5.96-17.5)	13.5 (5.3-17.6)	13.2
Montreal classification (%)	L1 and L4 2 (1) L2 28 (18) L2 and L4 25 (16) L3 36 (23) L3 and L4 67 (42) L5 2 (1) [&]	E3- 25 (89) E2- 3 (11)	E3-3 (100)
Indications to start IFX (%)	-Luminal CD 124 (78) -Immunomodulator failure 102 (64) -Steroid dependency 40 (25) -Bridge to therapeutic immunosuppression 29 (18) -Perianal disease 29 (18)	- Acute severe colitis 17 (61) -Chronic active colitis 11 (39) -Steroid dependency 12 (43) -Immunomodulator failure 9 (32)	- Acute severe colitis 2 (66) -Chronic active colitis 1 (33)
Prior medication usage			
- **Corticosteroids**	138	27	3
- *Steroid dependency*	74	15	1
- *Steroid resistance*	33	16	2
- *Unacceptable side-effects*	26 58 15	3 0	0 0
- **Methotrexate**	58	-	-
- *Primary non-response*	15	-	-
- *Loss of response*	31	-	-
- *Intolerance*	17		
- **Azathioprine/6-MP**	126	16	1
- *Primary non-response*	47	3	0 0
- *Loss of response*	59	7	0 0
- *Intolerance*	16	3	
- **Exclusive enteral nutrition**	122	N/A	N/A
- Adalimumab	0	0	0

Table 17 Continued	Crohn's Disease (CD)	Ulcerative Colitis (UC)	Inflammatory Bowel Disease Unclassified (IBDU)
PGA baseline (%)			
-Moderate-severe	118 (74)	27 (96)	3 (100)
-Mild	36 (22)	1 (4)	
-Remission	6 (4)		
PGA post induction (%)			
-Remission	43 (27)	6 (22)	2 (66)
-Steroid-free remission	51 (32)	9 (32)	0
-Response	50 (31)	9 (32	1 (33)
-No response	16 (10)	4 (14)	0
Post-IFX surgery	51 patients had 95 procedures -30 Colectomy and end ileostomy -1 Small bowel resection -6 Right hemicolectomy -3 Left colon resection -8 Defunctioning stoma -10 perianal/fistula surgery	-14 Colectomy and end ileostomy -1 Defunctioning stoma* -1 perianal surgery **	-1 Colectomy and end ileostomy

&= isolate perianal disease only *family request **subsequently reclassified as CD

.

Table 18 Baseline characteristics of patient on ADA

	Crohn's Disease (CD)	Ulcerative Colitis (UC)	Inflammatory Bowel Disease Unclassified (IBDU)
Number of patients	53	3	1
Female (%)	23 (43)	0	0
Median age at diagnosis (range, years)	10.9 (4.8- 14.9)	12.1 (9.5-12.3)	14.7
Median age at start of ADA (range, years)	14.5 (6.8-18.3)	13.6 (12.2-14.6)	15.5
Duration from diagnosis to start IFX (yrs)	3.86 (0.04-8.3)		0.8
Montreal classification (%)	L2 11 (21) L2 and L4 14 (26) L3 8 (15) L3 and L4 20 (38)	E3- 2 (67) E2- 1 (33)	E3-1 (100)
Concomitant medications at ADA start	24	1	1
Corticosteroids	26	0	0
Methotrexate	7	0	1
Azathioprine/6-MP			
Disease severity at induction:			
Remission	0	0	0
Mild	19	0	0
Moderate/severe	34	3	1
Induction dosing	160/80mg 7 80mg- 1 80/40mg 35 40/25mg- 1 40/20mg 2 24mg/m^2 2 40mg 5	160/80mg 3	80/40mg-1
Number of patients on previous IFX (%)	48 (91)	3 (100)	1 (100)
Reason for IFX discontinuation (%)	16 (33) Primary non-response 26 (54) Loss of response 6 (13) Allergy	2 (66) loss of response 1 (33) allergic reaction	1 Loss of response
Post-induction response at 4 weeks			
- Remission	17	1	0
-Partial response	25	1	0
- No response	11	1	1
Maintenance	40mg 49 25mg 1 20mg 1 24mg/m^2 2	40mg- 2 80mg- 1	
Previous medications (%)			
-Corticosteroids	49 (92)	(100)	1 (100)
-Azathioprine	47 (89)	3 (100)	1 (100)
-Methotrexate	35 (66)	2 (67)	0
-Exclusive Enteral Nutrition	43 (81)	N/A	N/A

Table 18 Continued	Crohn's Disease (CD)	Ulcerative Colitis (UC)	Inflammatory Bowel Disease Unclassified (IBDU)
Prior medication usage			
-Corticosteroids	49	3	1
-*Steroid dependency*	30	2	1
-*Steroid resistance*	10	2	1
-*Unacceptable side-effects*	10	0	0
Methotrexate	35	2	0
-*Primary non-response*	6	1	-
-*Loss of response*	22	1	-
-*Intolerance*	10	1	-
Azathioprine/6-MP	47	3	1
-*Primary non-response*	17	3	0
-*Loss of response*	21	0	0
-*Intolerance*	9	0	0
Exclusive enteral nutrition	43	N/A	n/a
Infliximab	48	3	1
Post ADA surgery (n=12)	12 had 16 procedures -9 Colectomy and end ileostomy -1 dilatation of rectal stricture -1 right hemicolectomy - 1 SB resection* -1 defunctioning stoma** -1 EUA Labia	-2 Colectomy and end ileostomy	-2 Colectomy and end ileostomy

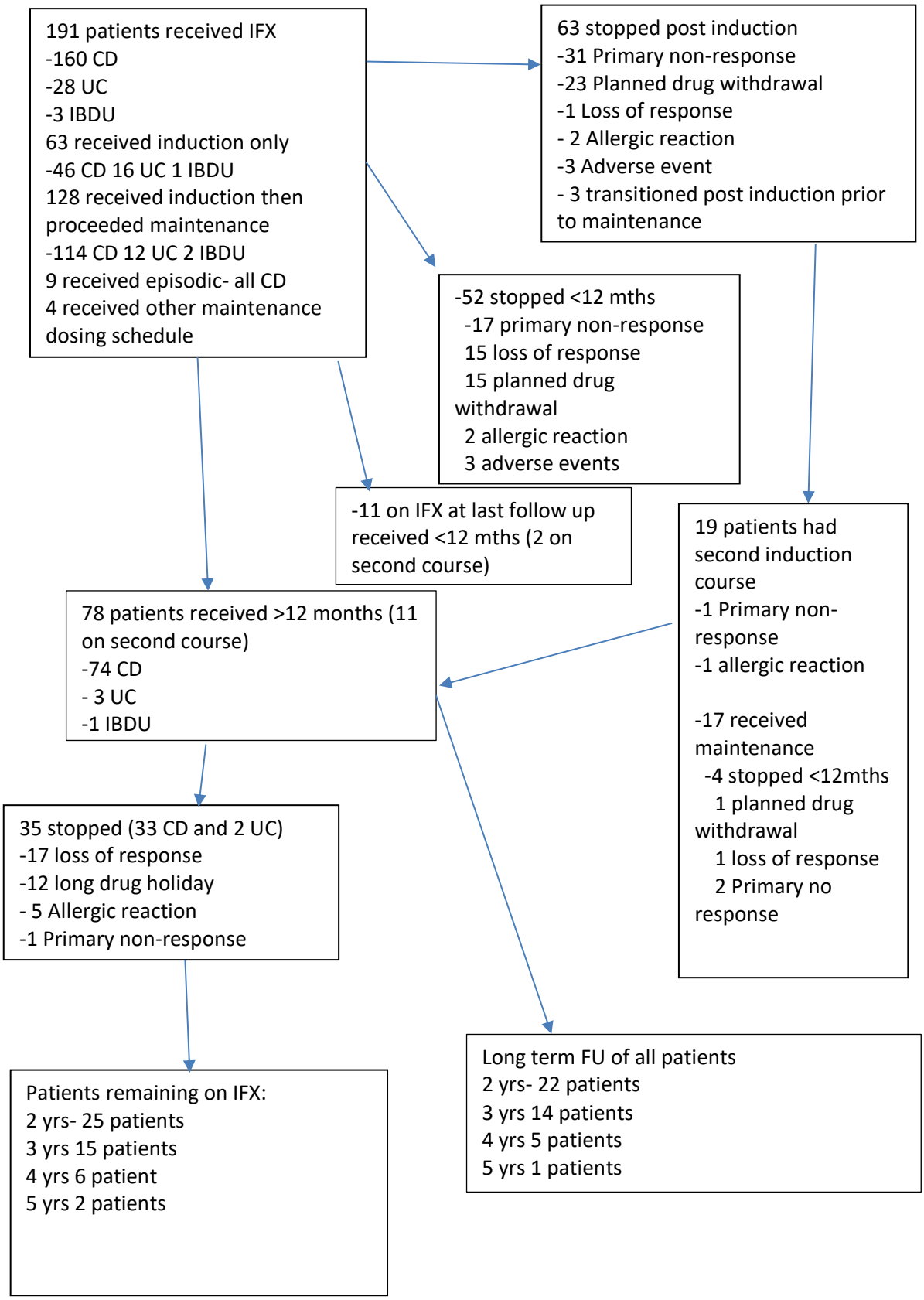
***Small bowel resection ** had defunctioning stoma prior to colectomy**

7.4.2. Details of all patients receiving IFX

7.4.3. Baseline IFX characteristics of all patients

191 patients were treated with IFX, 160 (84%) patients had CD, 28 (14%) had UC and 3 (2%) had IBDU (**see Table 17**). **Figure 17** demonstrates the outcome of all patients treated with IFX. IFX was commenced at a median of 13.8 (range 5.35 to 17.2) years, 2.20 (range 0.01-11.5) years post-diagnosis at 11.2 (range 2.74 to 17.2) years; 115 were male (**Table 17**). Patients received a median of 6 (range 1-41) doses over a median of 5.2 (range 0.67-14.2) years of follow up, a cumulative national total of 1701 doses. Prior corticosteroids, thiopurine and methotrexate had been received by 168, 143 and 58 respectively.

Figure 17 Outcome of patients treated with Infliximab



7.4.4. Planned drug discontinuation

51 (27%) discontinued IFX due to planned drug withdrawal, 23 (47%) received induction only and stopped after a median of 0.3 years (range 0.1-3.5). The most common reason for planned drug withdrawal was clinical remission (clinical examination and biochemical parameters) in 28 (55%) followed by planned withdrawal after achieving therapeutic immunosuppression in 18 (35%). Other reasons were IFX used as a bridge to surgery in 2 (4%) and deep clinical remission (clinical, endoscopic and biochemical) in 2 (4%). One patient with UC discontinued having responded to induction therapy but stopped due to lack of approval for use of maintenance IFX in paediatric UC. Most patients, 30 (59%) were male, and 38 (74%) had CD, 12 (24%) UC and 1 (2%) IBDU. 13 (25%) restarted IFX, 2 failed a second course of IFX and were changed to ADA.

7/18 had planned withdrawal for ADA, all discontinued in clinical remission; 2 of whom relapsed and subsequently restarted ADA, one stopped post colectomy and one remained in remission on anti TNF therapy at study end.

7.4.5. IFX use in Crohn's disease

128 (67%) had further IFX post induction, including 9 (7%) with CD who had episodic dosing, 119 went onto maintenance initial induction (**Figure 17**) and had a median time to discontinuation was 0.9 years (range 0.1-3.7). 67(56%) were still receiving IFX at 12 months; 9 (8%) continued IFX at last follow up but had not yet received IFX for 12 months and 43 (36%) had discontinued. The most common reason for discontinuation under 12 months was primary non-response in 13 (30%), followed by planned withdrawal in 12 (28%), loss of response in 14 (32%) and allergic reaction in 2 (5%) and adverse event in 2 (5%).

Fifty-five required dose escalation; 45 had shortened infusion schedule – most commonly 7 weeks (n=18), then 6 weeks (n=18), 5 weeks (n=2) and 4 weeks (n=1). Thirty subsequently discontinued due to: loss of response in 20, primary non-response in 4, planned withdrawal in 4 and 2 related to infusion reactions. Three patients had their schedule lengthened to 12 weeks, 5 to 10 weekly and 1 to 9 weekly. Thirty-four had increased dose; twenty-three had increased dose and frequency, 11 increasing dose alone. Maximum doses were 10mg/kg (n=25) with 2 each receiving 7mg/kg and 6.5mg/kg. 84 patients underwent surgery either pre- or post-IFX **(Table 17**).

7.4.7. IFX use in UC

Twenty-eight UC patients received IFX with fifteen progressing to surgery (**Table 17**) and 1 having IFX as a bridge to immunosuppression. Twelve had maintenance IFX; 1 continued IFX in remission but 11 discontinuing (2 primary non-response after partial response, 2 loss of response (1 dose increase to 10 mg/kg) and 6 planned withdrawals in sustained remission in 5 with mild disease in one by study end. One stopped due to an adverse event with paraesthesia which resolved upon discontinuation of IFX.

7.4.8. IFX use in IBDU

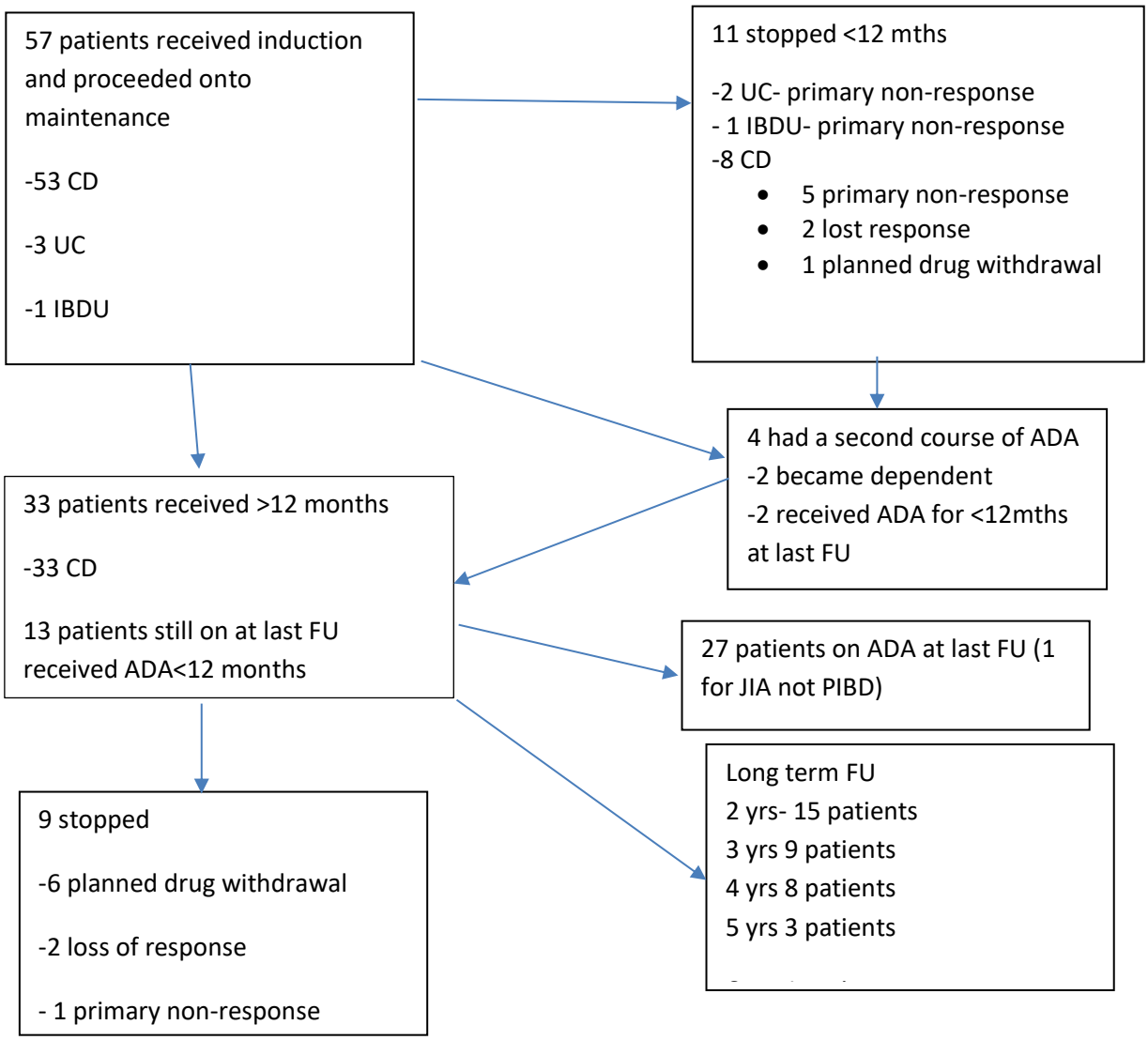
Three patients required IFX, 2 for acute severe colitis and the other for chronic active colitis (**Table 17**). The patient with chronic active colitis entered remission post induction after a bridge to azathioprine but lost response despite dose optimisation so was changed to ADA but unfortunately, they still failed to respond so underwent a colectomy. Two patients with acute severe colitis had IFX, one responded after induction with IFX used as a bridge to azathioprine then entered a prolonged remission on azathioprine monotherapy,

the other patient entered remission post induction with loss of response on maintenance which responded to dose escalation (10mg/kg) and was in remission at study end continuing IFX.

7.4.9. Basic demographics of all ADA patients

57 patients were treated with ADA, 52 (91%) previously received IFX, 53 (93%) had CD, 3 (5%) UC and 1 (2%) IBDU (**see Table 18**). The median age at the start of ADA was 14.5 years (range 6.8-17.2), and patients diagnosed at 10.9 years (range 4.8-17.9), 34 were male. 18 (44%) stopped ADA after a median of 0.9 years (range 0.1-4.6), most commonly for primary non-response in 8 (44%) and planned drug withdrawal in 7 (39%) (**See Figure 18**).

Figure 18 Outcome of patients treated with Adalimumab



7.4.10. ADA use in CD

17/53 gained remission post-induction (**Table 17**) and 22/36 achieved remission on maintenance after 0.33 (range 0.10-1.1) years, totalling 39 achieving remission. Thirty required dose escalation: 5 dose increased to 80 mg and 29 increased to weekly dosing (6/29 increased frequency and dose) with 7 reversing escalation. Fifteen discontinued ADA after 0.94 (range 0.18-4.6) years; 5 primary non-response, 3 loss of response and 7 planned withdrawal. Thirty-eight continued ADA for 1.48 (range 0.1-6.8) years at study end; 22 in remission (17 on co-immunosuppression). Ten of 16 (63%) with primary IFX non-response to IFX gained remission on 2nd biological compared to 21 of 26 (81%) with loss of IFX response. Twenty-six patients underwent surgery.

7.4.11. ADA use in UC

Three patients received ADA, all male for acute severe colitis and were on IV steroids at baseline. One patient who lost response to IFX despite dose optimisation, responded and achieved remission post induction so was commenced on maintenance which continues. One patient stopped IFX due to an acute infusion reaction whilst receiving MTX co-immunosuppression, unfortunately he had no response to ADA so underwent a colectomy and stopped ADA. The final patient had a primary non-response to IFX then had a response to ADA induction but did not achieve remission yet continued maintenance ADA, however, subsequently underwent a colectomy and stopped ADA.

7.4.12. ADA in IBDU

One patient received ADA who had lost response to IFX despite dose optimisation. The patient was on low dose CS and AZA at the start of ADA but failed to respond so stopped ADA and underwent a colectomy.

7.5. Growth

7.5.1. Demographics of the infliximab growth cohort

Satisfactory 24-month growth data were available for 93/191 (49%) (**see Figure 19**); 57 (61%) were boys and 86 (92%) had CD, the remaining 7 (8%) had UC. Median age at diagnosis was 10.4 years (range 2.7-15.2) and median age at start of IFX was 13.8 years (range 5.9-17.6). The most common disease location in CD was panenteric in 28 (33%) with inflammatory the most common behaviour in 76 (88%) whilst 86% had extensive UC. The commonest indication for starting IFX in CD was active luminal disease followed by immunomodulator failure whilst for UC it was chronic active colitis followed by immunomodulator failure (**see Table 18**). At treatment start 18% had Ht SDS <-2, improving to 15% then 7% at 1 year and 2 years respectively after treatment with IFX ($p>0.05$). Forty-one patients underwent surgery (18 pre IFX); all of whom had CD. Most patients had disease for greater than 2 years (n=62) with a median duration of 3.5yrs prior to starting IFX whilst those <2yrs (n=31) had their disease a median of 1.3yrs. Pubertal data were available in 65/93.

Figure 19 Status of patients in Scottish National biologicals registry over study period (2000-2010)

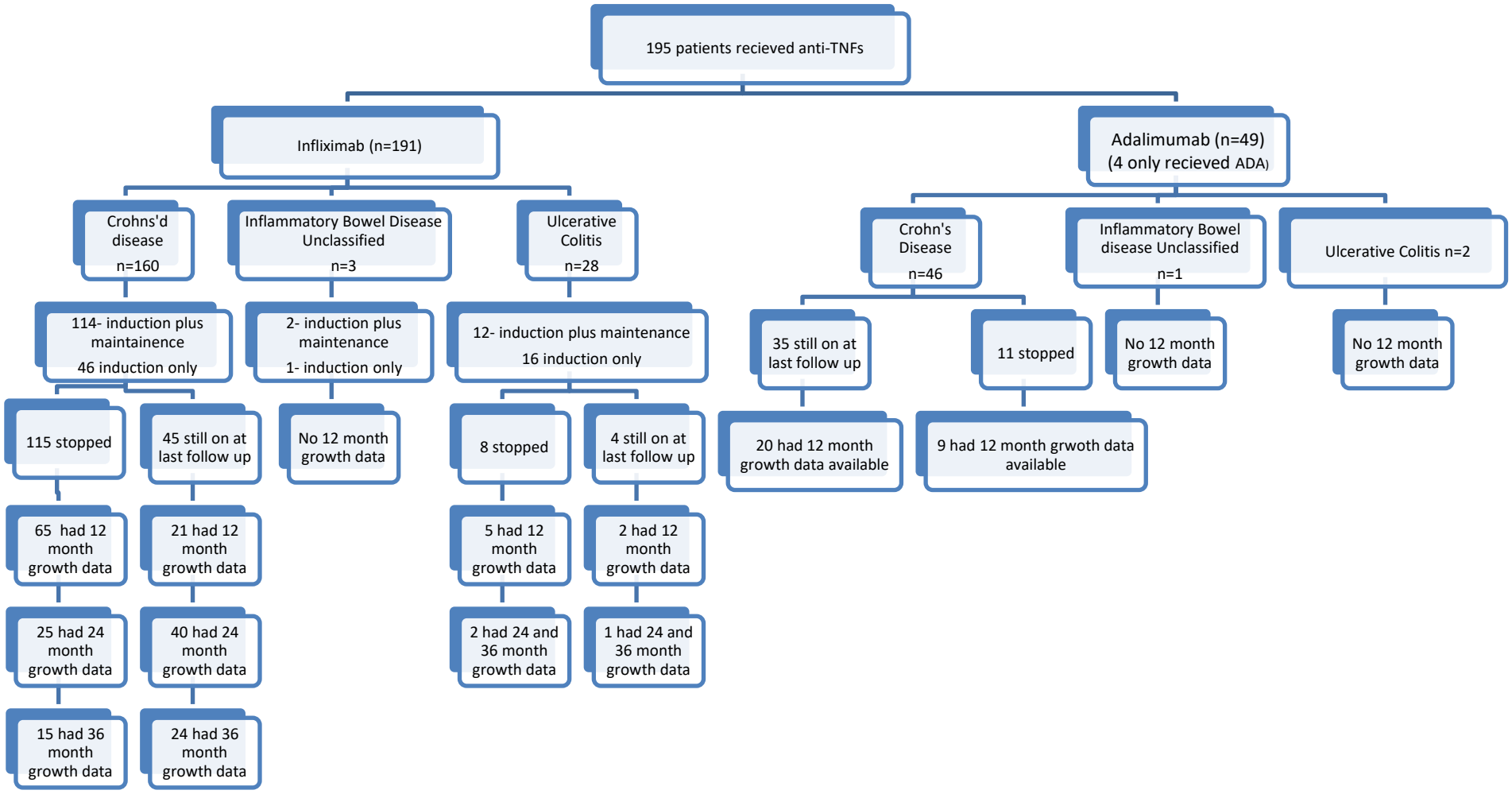


Table 19 Baseline characteristics of 93 patients requiring Infliximab and 28 patients receiving ADA with full growth data for 24 months; results are expressed as median (range) and number (%)

	IFX- Crohn's disease (CD)	Ulcerative colitis (UC)	ADA- Crohn's disease (CD)	Ulcerative colitis (UC)
Number of patients	86 (92%)	7 (7%)	28(97%)	1 (3%)
-Female	38 (44%)	1 (14%)	12 (43%)	1 (3%)
Median age at diagnosis (range yrs.)	10.5 (2.72-15.1)	10.2 (8.48-14.7)	10.3 (4.89-14.9)	12.1
Median Age at start of IFX (range yrs.)	13.8 (5.9-16.9)	13.7 (9.2-17.6)	13.4 (6.8-17.2)	13.7
Median Duration from diagnosis to start IFX (range yrs.)	2.86 (0.15-9.45)	2.66 (0.78-5.6)	3.4 (0.04-8.4)	1.5
Montreal classification	L1 and L4 2 (2%) B1 75 (87%) L2 15 (17%) B2 9 (10%) L2 and L4 12 (14%) B3 2 (2%) L3 20 (23%) L3 and L4 36 (42%) L5 1 (1%)	E1 0 E2 1 (14%) E3 6 (86%)	L2 9 (32%) B1 20 (71%) L2 and L4 3 (11%) B2 5 (18%) L3 6 (21%) B3 3 (11%) L3 and L4 10 (36%)	E1 0 E2 0 E3 1 (100%)
Concomitant medications at IFX start				
- Corticosteroids	40 (47%)	4 (57%)	12 (43%)	
- Methotrexate	40 (47%)	0 (0%)	16 (57%)	1 (100%)
- Azathioprine/6-MP	38 (44%)	4 (57%)	3 (11%)	0 (0%)
				0 (0%)
Indications to start IFX/ADA (more than 1 indication is possible)	Active Luminal disease 72 (84%) Immunomodulator failure 65 (76%) Bridge to immunosuppression 12 (14%) Perianal disease 16 (19%) Growth+/- pubertal delay 4 (5%)	Chronic active UC 5(71%) Acute severe colitis 2 (29%) Steroid dependency 3 (43%) Immunomodulator failure 4 (57%)	IFX primary non-responder 12 (41%) Loss of response to IFX 10 (36%) Allergic reaction 1 (3%) Family choice 2 (7%) Previous JIA 2 (7%) Possible JIA at CD diagnosis 1 (3%)	IFX primary non-responder 1 (100%)
Disease severity at induction				
- Remission	2 (2%)	0	0	0
- Mild	20 (24%)	0	8 (39%)	0
- Moderate/severe	64 (74%)	7 (100%)	20 (71%)	1 (100%)
Response post induction	-Steroid free remission 35 (33%) -Remission 20 (24%) Response not remission 27 (31%) No response 9 (10%)	-Steroid free remission 3(43%) Remission 1 (14%) Response but not yet remission 2 (29%) No response 1 (14%)	-Steroid free remission 1 (4%) -Remission 4 (14%) Response but not yet remission 17 (61%) No response 6 (21%)	-Steroid free remission 0 -Remission 0 Response but not yet remission 0 No response 1 (100%)

Table 19 Continued	IFX- Crohn's disease (CD)	Ulcerative colitis (UC)	ADA- Crohn's disease (CD)	Ulcerative colitis (UC)
Surgery				
Pre IFX	Small bowel resection 4 (5%) Right hemicolectomy 2 (2%) Left colonic resection 3 (3%) Defunctioning stoma 1 (1%) Perianal surgery 12 (14%) Colectomy and end ileostomy 0		Small bowel resection 0 Right hemicolectomy 0 Defunctioning stoma 0 Perianal surgery 7 (25%) Colectomy and end ileostomy 0	
Post IFX	Small bowel resection 0 Right hemicolectomy 4 (5%) Left colonic resection 2 (2%) Defunctioning stoma 5 (6%) Perianal surgery 7 (8%) Colectomy and end ileostomy 10 (12%)	Defunctioning stoma 1 (14%) Colectomy and end ileostomy 3 (43%)	Small bowel resection 1 (4%) Right hemicolectomy 1 (4%) Defunctioning stoma 1 (4%) Perianal surgery 1 (4%) Colectomy and end ileostomy (11%)	Colectomy and end ileostomy 1 (100%)

Sixty-five patients within this growth cohort received further IFX post induction, including 6 patients who received episodic dosing prior to 2007, with 42 subsequently discontinuing maintenance IFX after a median of 1.0 years (range 0.2-3.2) receiving a median of 8 doses (range 1-25) (**see Figure 19)**. The most common reasons for discontinuation of maintenance IFX were loss of response in 15, planned drug withdrawal in 13, primary non-response in 8, allergic reaction in 5 and 1 had an adverse event. Thirty (45%), all with CD, required dose escalation, most commonly increased frequency in 23 (77%) whilst 22 (73%) had an increased dose.

In the 93 children with satisfactory 24-month growth data, median Ht SDS at T-12 was -0.7 (-2.2, -0.7), worsened to median Ht SDS -0.8 (-2.5, -0.5) at T0 and remained similar with a median Ht SDS -0.8 (-2.3,0.7) at T+12 ($p<0.001$). Median Δ Ht SDS was -0.2 (-0.6,0.3) at T0 and increased to a median Δ Ht SDS at T+12 of 0.1 (-0.4,0.6) ($p<0.001$). Median HV at T0 was 3.5 (1.0, 7.2) cm/yr. and which increased to 4.4 (1.2,9.1) at T12 ($p=0.003$). No further sustained improvement in linear growth was seen beyond 12 months post-anti-TNF start in those who were followed up for 36 months, the extended growth cohort (**see Table 19**).

Table 20 Long term follow up to 36 months shows no further improvement in height velocity and delta height SDS beyond 12 months with improvement seen in weight and BMI SDS at 12 months post-IFX treatment.

	T-12 (n=42)	T0 (n=42)	P value for T-12 vs T0	T+12 (n=42)	P value for T0 vs T+12	T+24 (n=42)	P value T+12 vs T+24	T+36 (n=42)	P value For T+24 vs T+36
Ht SDS	-0.9 (-2.4,0.4)	-1.0 (-2.9,0.04)	P<0.0001	-1.1 (-2.6, -0.03)	p=0.39	-0.9 (-2.5, -0.08)	p=0.33	-0.8 (-2.6,0.06)	p=0.29
Δ ht SDS	n/a	-0.25 (-0.7,0.2)	n/a	0.07 (-0.5,0.4)	p=0.009	0.08 (-0.4, 0.6)	p=0.01	0.06 (0.3,0.6)	p=0.90
HV	n/a	3.8 (1.2,7.1)	n/a	4.8 (1.5,9.1)	p=0.04	5.5 (0.9,8.8)	p=0.79	4.8 (0.0,7.8)	p=0.10
Weight SDS*	-0. 5 (-1.9,1.1)	-0.6 (-1.9,1.1)	p=0.001	-0.4 (-2.0,1.2)	p=0.002				
BMI SDS*	0.1 (-1.6,1.5)	-0.3 (-1.9,1.7)	p=0.05	0.1 (-1.5,1.9)	p=0.003				

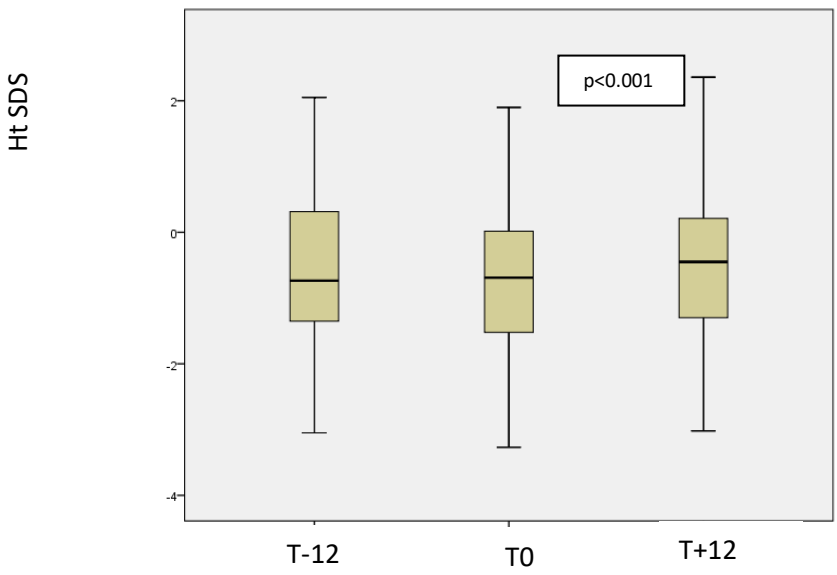
HV= height velocity *n=94

7.5.2. Factors affecting growth

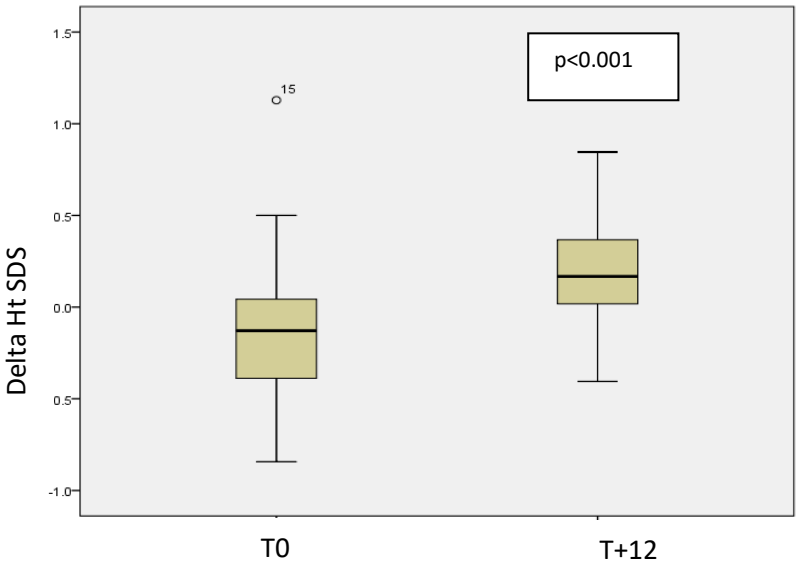
Achieving remission was associated with a significant improvement in median Ht SDS, Δ Ht SDS and HV (**see Figure 20**). Early stages of puberty, Tanner stages 1-3, were associated with an increase in Δ Ht SDS and HV (**see Figure 21**). 22/94 were Tanner stage 4-5 and showed no significant change in Ht SDS and Δ Ht SDS and a decrease in HV; Ht SDS at T0 -0.2 (-1.8,1.1) to -0.3 (-2.0, 1.1) at T+12 (p=0.78), Δ Ht SDS at T+0 -0.14 (-0.5, 0.9) then Δ Ht SDS at T+12 -0.01 (-0.5, 0.9) (p=0.78) and HV at T0 3.5(1.0,9.8) decreased to 2.1 (0.2, 4.4) at T+12 (p=0.001). 60 (65%) of those treated with IFX had a disease duration greater than 2 years at the start of their treatment with IFX and had increased Ht SDS, Δ Ht SDS and HV at T+12 compared to those with disease duration less than 2 years (**see Table 21**).

Figure 20- Improvements in linear growth are seen at 12 months in those treated with Infliximab who achieve remission post induction (n=56)

A. Improvement seen in median ht SDS at T+12 compared to T0



B. Improvement seen in Delta ht SDS at T+12



C Improvement seen in height velocity

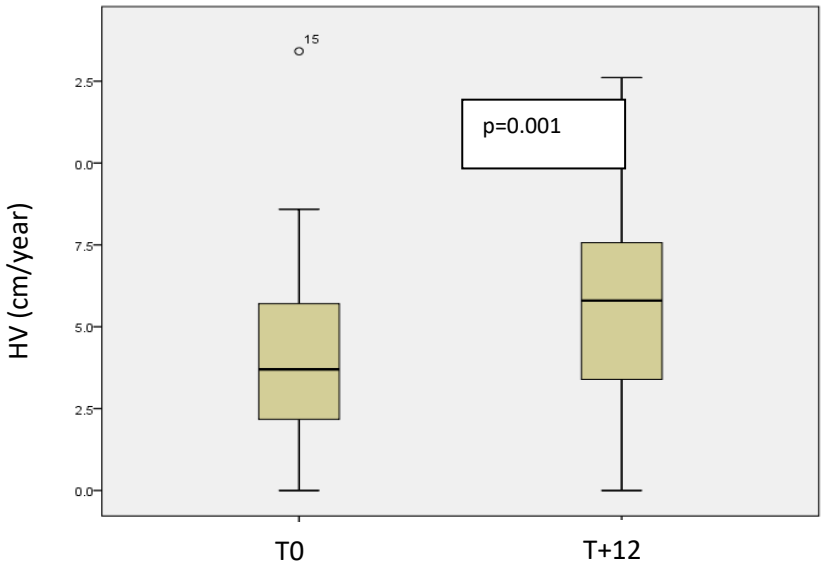
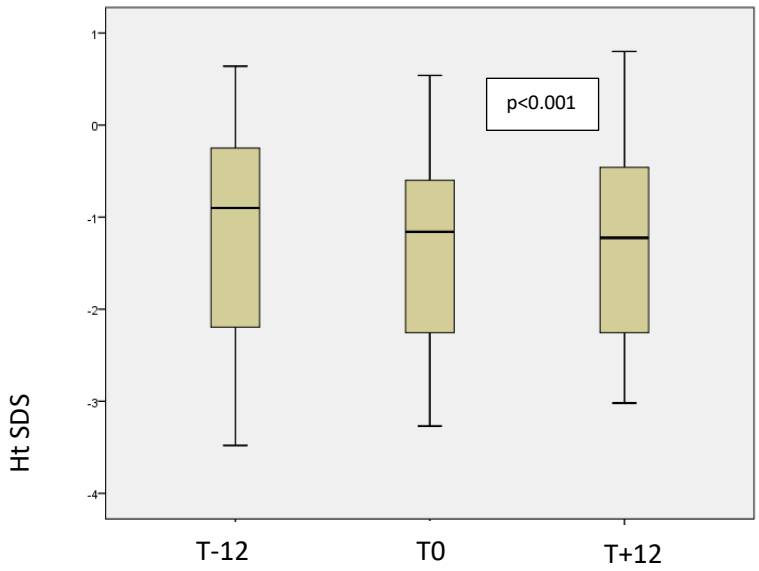
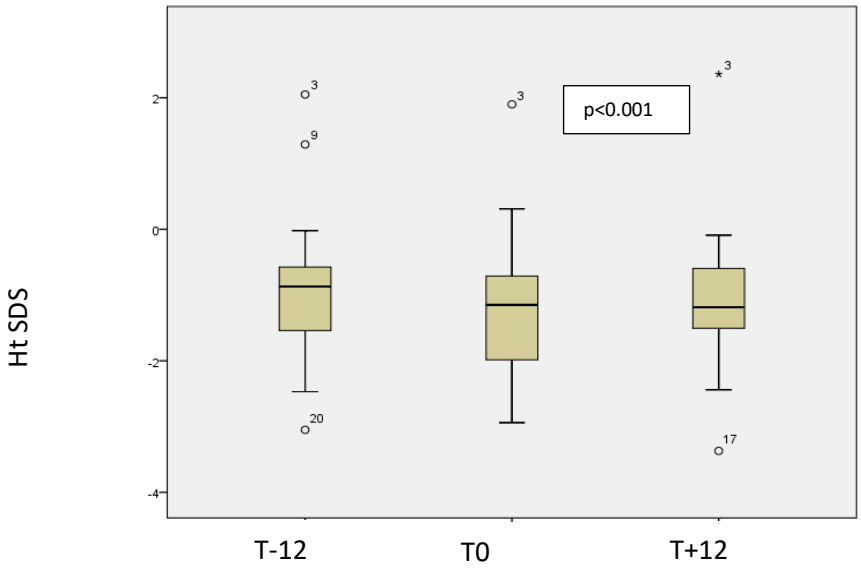


Figure 21. Tanner stage 1-3 shows improvement in height velocity and delta height SDS at T0 to T+12 without improvement in height SDS (n=24)

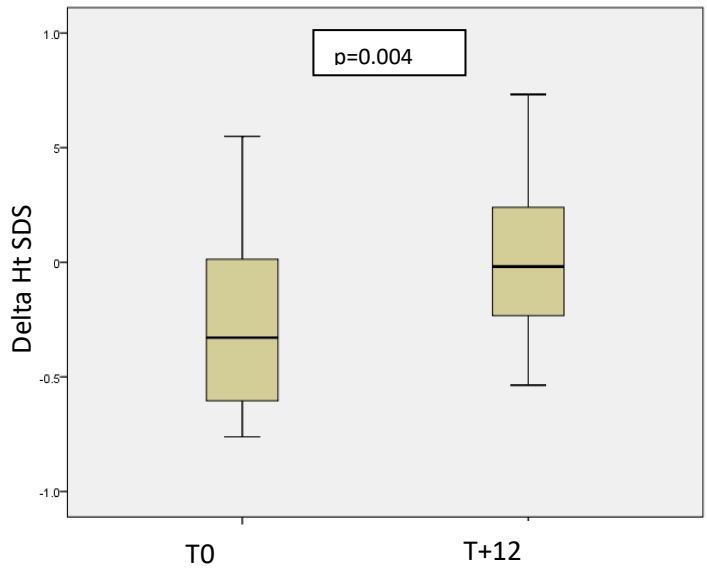
A. Tanner stage 1 ht SDS shows no improvement in ht SDS at T+12



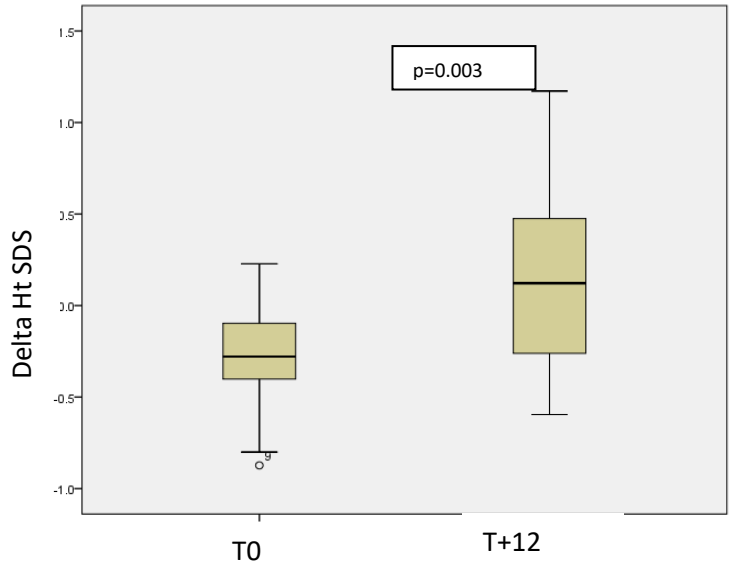
B. Tanner stage 2&3 shows no improvement in ht SDS at T+12 (n=20)



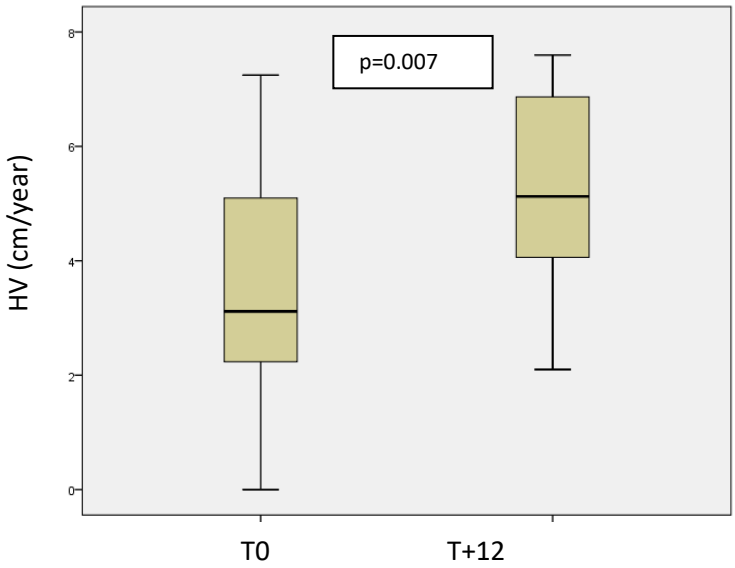
C. Tanner stage 1 shows improved delta ht SDS at T+12



D. Tanner stage 2&3 shows improvement in delta ht SDS at T+12



E. Tanner stage 1 shows improvement in Height Velocity at T+12



F Tanner stage 2 and 3 shows improvement in Height Velocity at T+12

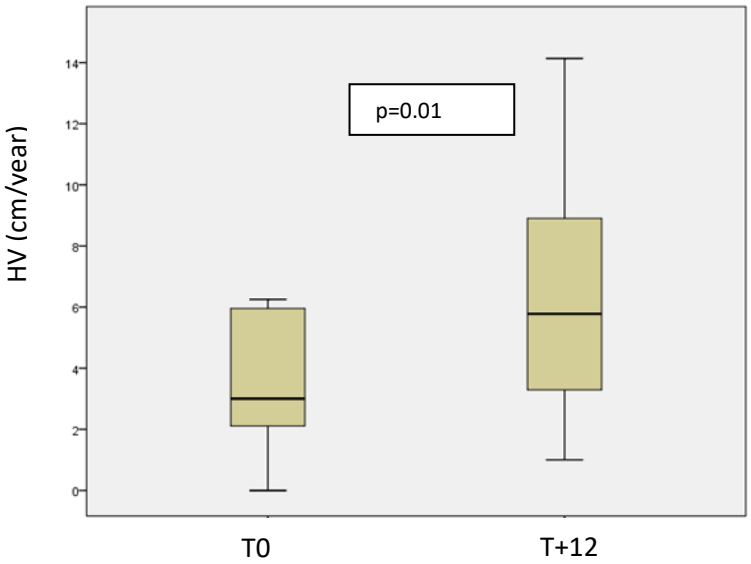


Table 21 Improved growth parameters seen at 12 months in those treated with IFX (n=93)

	Ht SDS T-12 Median (IQR)	Ht SDS T0 Median (IQR)	P value for T-12 vs T0	Ht SDS T+12 Median (IQR)	P value For T0 vs T+12	Delta Ht SDS T0 Median (IQR)	Delta Ht SDS T+12 Median (IQR)	P value for DeltaT0 vs Delta T+12	Height Velocity T0 Median (IQR)	Height Velocity T+12 Median (IQR)	P value for Height Velocity 0 vs Height Velocity 12
Disease duration <2yrs	-0.7 (-2.2, 0.7)	-0.8 (-2.4,0.4)	P=0.002	-0.9 (-2.2,0.4)	P=0.85	-0.3 (-0.8, 0.3)	0.03 (-0.5, 0.6)	P=0.01	3.3 (0.8, 6.9)	4.1 (0.9, 9.4)	P=0.06
Disease duration >2yrs	-0.8 (-2.4,0.7)	-0.8 (-2.5, 0.8)	P=0.007	-0.7 (-2.4, 0.8)	P=0.005	-0.1 (-0.6,0.3)	0.08 (-0.3, 0.6)	P<0.001	3.6 (1.1,7.2)	4.9 (1.3, 9.2)	P=0.01
Gender											
-Males	-0.73 (-2.3,0.7)	-0.81 (-2.5, -0.5)	p<0.001	-0.9 (-2.4,0.6)	p=0.16	-0.2 (-0.7,0.2)	0.1 (-0.5,0.6)	p<0.001	3.8 (1.0,7.3)	5.2 (2.6,9.6)	p=0.001
-Females	-0.8 (-2.3,1.1)	-0.7 (-2.3,1.0)	p=0.07	-0.7 (-2.2,1.1)	p=0.10	-0.1 (-0.5,0.5)	0.10 (-0.3,0.6)	p=0.01	3.2 (0.7,6.7)	3.2 (0.8,8.0)	p=0.41
Moderate disease at baseline	0.7 (-2.2,0.8)	-0.7 (-2.5,0.5)	<0.001	-0.8 (-2.3,0.7)	p=0.23	-0.3 (-0.7,0.2)	0.04 (-0.5,0.6)	p<0.001	2.9 (1.0,7.1)	4.4 (1.1,9.5)	p=0.002
Immunomodulator use	-0.8 (-2.2,0.7)	-0.9 (-2.5,0.5)	p<0.001	-0.9 (-2.3,0.7)	p=0.005	-0.2 (-0.6,0.3)	0.1 (-0.3,0.6)	p<0.001	3.5 (1.1,7.2)	4.9 (1.6,9.3)	p=0.001
No Immunomodulators	0.2 (-2.6,1.2)	-0.1 (-2.5,0.8)	p=0.33	-0.4 (-2.2,0.7)	p=0.16	-0.1 (-0.8,0.3)	-0.2 (-0.7,0.5)	p=0.5	5.0 (0.0,7.1)	3.5 (0.0, 5.2)	p=0.53
Azathioprine at baseline	-0.4 (-2.4,0.9)	-0.7 (-2.8,0.7)	p=0.002	-0.7(-2.4,0.9)	p=0.03	-0.3 (-0.7,0.3)	0.1 (-0.3,0.6)	p<0.001	3.0 (1.0,7.3)	4.6 (1.3,9.3)	p=0.005
Methotrexate at baseline	-0.9 (-2.2,0.3)	-1.0 (-2.4,0.2)	p=0.02	-1.0 (-2.0, 0.3)	p=0.06	-0.1 (-0.5,0.4)	0.05 (-0.4,0.8)	p=0.002	4.1 (1.2, 7.1)	5.3 (1.8,9.4)	p=0.03
Induction only	-0.8 (-2.5,0.9)	-0.9 (-2.6,0.9)	p=0.009	-1.1 (-2.4,0.8)	p=0.93	-0.3 (-0.7,0.3)	0.04 (-0.4,0.6)	p=0.003	3.0 (0.6,6.4)	3.5 (1.1,9.6)	p=0.17
Induction plus maintenance	-0.7 (-1.9,0.6)	-0.8 (-2.3,0.5)	p=0.002	-0.8 (-2.3,0.6)	p=0.02	-0.1 (-0.6,0.3)	0.10 (-0.4,0.6)	p<0.001	3.8 (1.1,7.3)	5.0 (1.2,9.0)	p=0.004
IFX at 12 mths	-0.7 (1.8,0.5)	-0.8 (-2.4,0.5)	p=0.001	-0.8 (-2.0,0.4)	p=0.03	-0.2 (-0.6,0.3)	0.1 (-0.5,0.7)	p<0.001	3.8 (1.4,7.3)	5.8 (2.0,9.7)	p=0.001
Corticosteroid use baseline	-0.4 (-2.0,1.4)	-0.5 (-2.7,1.1)	p<0.001	-0.5 (-2.3,1.1)	p=0.29	-0.3 (-0.7,0.2)	0.05 (-0.5,0.6)	p<0.001	2.7 (0.9,6.1)	4.4 (1.4,9.4)	P=0.001
Corticosteroid free baseline	-0.9 (-2.4,0.4)	-1.0 (-2.4,0.5)	p=0.21	-0.9 (-2.3,0.3)	p=0.05	-0.08 (-0.4,0.5)	0.06 (-0.4,0.6)	p=0.01	4.3 (1.2,7.3)	4.9 (1.1,9.5)	p=0.30
Surgery	-0.74 (-2.4,0.6)	-0.8 (-2.3,0.5)	P=0.006	-1.0 (-2.6,0.3)	P=0.15	-0.20 (-0.7,0.3)	-0.1 (-0.5,0.4)	P=0.065	3.4 (0.9,7.1)	4.0(1.0,8.0)	P=0.17
No surgery	-0.7 (-2.2,0.8)	-0.8 (-2.5,0.8)	P=0.002	-0.8 (-2.2,0.8)	P=0.001	-0.17 (-0.6,0.3)	0.1 (-0.3,0.6)	P<0.001	3.5 (1.1,7.3)	4.9 (1.3,9.5)	P=0.005

Boys growth improved compared to girls, with boys Δ Ht SDS and HV increasing significantly whilst girls only increased Δ Ht SDS (**see Table 21**). In those with moderate disease, improvement was noted in Δ Ht SDS and HV (**see Table 21**). 82 (88%) were on immunomodulators (IM) at baseline and increase in Ht SDS, Δ Ht SDS and HV at T+12 was noted in this cohort compared to no improvement in those not on IM. Further analysis was performed on type of immunomodulator, 42 patients were on azathioprine (AZA) and 40 on methotrexate (MTX); there was no significant difference between the AZA and MTX groups in Δ Ht SDS at T+12 (p=0.64, 95%CI -0.2, 0.1). Azathioprine usage was associated with increased Ht SDS, Δ Ht SDS and HV compared to only improvement in Δ Ht SDS and HV in those on MTX (**see Table 21**).

Patients who received induction and maintenance (n=66 (I&M)) showed improvement in Ht SDS, Δ Ht SDS and HV compared to those who received induction only where only Δ Ht SDS increased (n=37 (I only)). Patients who were established on maintenance IFX for greater than 12 months from first induction dose had significantly increased Δ Ht SDS and HV (**see Table 21**). Corticosteroid use at baseline was associated with significant improvement in Ht SDS and Δ Ht SDS (**see Table 21**). Increase was noted in Ht SDS, Δ Ht SDS, and HV in those who did not have surgery (n=68) whilst no significant improvement was observed in those who underwent surgery post-IFX (n=25) (**see Table 21**). No improvement in Ht was observed in those with Ulcerative Colitis.

7.5.3. Demographics of the Adalimumab cohort

Growth data for 12 months were available for 28 patients treated with ADA; 12 (43%) were girls, 27 (96%) with CD (**see Table 18**) and 18 of whom had IFX growth data analysed previously. All patients treated with ADA increased Δ Ht SDS at 12 months only

(**see Table 22**). Early stages of puberty (Tanner stage 2 and 3) were associated with increased Δ Ht SDS and HV with improvement also seen in Δ Ht SDS in males (**see Table 23**). No improvement was seen in those who were not on corticosteroids at baseline (n=16) or those who achieved remission at week 4 (n= 5).

Table 22 Adalimumab is associated with improved Δ ht SDS at 12 months (n=28)

	T-12	T0	P value for T-12 vs T0	T+6	P value for T0 vs T+6	T+12	P value for T0 vs T+12
Ht SDS	-0.83 (-2.2,0.4)	-0.9 (-2.2,0.3)	p=0.05	-0.8 (2.3,0.0)	p=0.35	-0.7 (-2.2, 0.2)	p=0.75
Δ ht SDS	n/a	-0.1 (-0.5,0.2)	n/a	0.1 (-0.6,0.7)	p=0.06	0.03 (-0.2,0.7)	p=0.01
HV	n/a	3.9 (2.0, 8.3)	n/a	6.3 (0.0,9.2)	p=0.17	5.5 (0.0,8.9)	p=0.18
Wt SDS	-0.4 (-1.6,1.3)	-0.3 (-1.9, 1.4)	p=0.71	-0.2 (-1.8,1.5)	p=0.79	-0.3 (-2.0, 1.1)	p=0.74
BMI SDS	0.1 (-1.5, 2.2)	0.1 (-1.6, 2.0)	p=0.66	0.1 (-1.6, 1.9)	p=0.58	0.1 (-1.3, 2.3)	p=0.72

HV= height velocity

Table 23. Adalimumab is associated with improved Δ ht SDS and HV in those in early puberty and improved Δ ht SDS in males (n=28)

	Ht SDS T-12	Ht SDS T0	P value HtSDS T-12 vs HtSDS T0	Ht SDS T+6	P value HtSDS T0 vs HtSDS T+6	Ht SDS T+12	P value HtSDS T0 vs HtSDS T+12	Δ Ht SDS T-12 to T0	Δ Ht SDS T0 to T+6	P values Δ Ht SDS T0 vs Δ HtSDS T+6	Δ Ht SDS T0 to T+12	P value Δ HtSDS T0 vs Δ HtSDS T+12	HV 0	HV T+6	P value HV0 vs HV6	HV+ 12	P value HV0 vs HV12
Puberty -Tanner 2-3 (median and range)	-0.8 (-1.9, 1.1)	-1.0 (-2.0, 0.4)	p=0.75	-0.9 (-1.3, 0.0)	P=0.40	-0.8 (-1.2, 0.2)	p=0.2	-0.1(-0.7, 0.2)	0.33 (-0.8,2.0)	P=0.09	0.1 (-0.2,1.2)	p=0.04	4.8 (2.0, 6.6)	7.7 (0.0, 17.5)	P=0.12	7.3 (4.1, 11.3)	P=0.04
Disease duration <2yrs (median and range)	-0.6 (-1.7,1.1)	-0.8 (-1.5,0.4)	p=0.04	-0.7 (-1.3, 0.1)	P=0.58	-0.8 (-1.5, 0.04)	p=0.89	-0.3 (-0.7, 0.2)	0.2 (-0.6, 0.4)	P=0.05	0.0 (-0.2, 0.3)	p=0.50	3.0 (2.0, 6.5)	6.1 (0.0, 10.8)	P=0.07	5.1 (0.0, 8.8)	P=0.12
Disease duration >2yrs (median and range)	-1.0 (-2.7, 0.5)	-1.1 (-2.7, 0.01)	p=0.32	-0.8 (-3.0, 0.2)	P=0.55	-0.7 (-3.2, 0.5)	p=0.05	-0.1 (-0.5, 0.8)	0.1 (-0.5, 1.3)	P=0.26	0.0 (-0.5, 1.2)	p=0.05	5.0 (0.0, 9.7)	6.3 (0.0, 17.5)	P=0.58	5.7 (0.0, 11.5)	P=0.58
Males (median and range)	-0.1 (-2.7, 1.1)	-1.0 (-3.0, 0.4)	P=0.15	-0.8 (-3.1, 0.8)	P=0.83	-0.7 (-3.2, 0.5)	P=0.27	-0.1 (-0.7,0.5)	-0.01 (-0.8, 2.0)	P=0.41	0.01 (-0.5,1.3)	P=0.04	5.5 (2.0, 8.5)	6.3 (0.0, 17.5)	P=0.55	6.0 (0.0, 11.5)	P=0.18

7.5.4. Multiple regression

Multiple regression models were used to determine associations of therapy and disease on Δ Ht SDS at T+12 for both IFX and ADA combined. The following variables were inserted into both models: Δ Ht SDS T0, remission, Tanner staging of puberty, azathioprine use, methotrexate use, corticosteroid usage at baseline, type of IBD, PGA at baseline, small bowel involvement, maintenance therapy given and duration of disease until anti-TNF commenced. In the final model, only corticosteroid use at baseline was associated with an improvement in Δ Ht SDS at 12 months (p=0.02) (95%CI 0.03,0.39).

7.6. Dependency cohort

7.6.1. Demographics of IFX dependency cohort

Dependency was defined as repeated infusions and/or injections to maintain good clinical response for at least 12 months(143). 77 (40%) patients developed dependency, 73 (95%) had CD, 3 (4%) had UC and one IBDU. 29 (38%) were female and they received IFX for ≥12 months at last follow up. The median age at diagnosis was 10.6 years (range 4.7-15.5) which was less than those in the non-dependency cohort (p>0.05) (**see Table 24**). Patients received IFX for a median of 1.8 years (range 1.01-5.6) receiving a median of 14 doses (range 8-47).

Table 24 Comparison of demographic of dependency vs no dependency patients on IFX

	Dependency (n=77)	Non-dependency (n=131) [$]
Type of IBD (%)	-CD 73 (95) -UC 3 (4) -1 IBDU (1)	- CD 103 (79) - UC 26 (20) - IBDU 2 (1)
Median age at diagnosis (range, years)	10.6 (4.8-15.5)	11.5 (2.7-17.2)
Median age at start at IFX (range, years)	13.8 (6.1-16.9)	14.0 (5.3-17.6)
Median disease duration prior to IFX (range, years)	2.8 (0.01-10.7)	2.4 (0.03-11.5)
Female (%)	29 (38)	57 (44)
Montreal Classification (%)	L1 and L4 1 (2) L2 12 (17) L2 and L4- 17 (23) L3 12 (17) L3 and L4 31 (42) B1 65 (89) B2 7 (1O) B3 1 (1) E3 4 (100)	L1 and L4 1 (1) L2 17 (17) L2 and L4- 12 (12) L3 28 (27) L3 and L4 43 (41) L5 2 (2) [&] B1 84 (82) B2 15 (14) B3 4 (4) E2 3 (11) E3 25 (89)
Steroids at baseline (%)	44 (57)	75 (57)
Immunomodulators at baseline (%)	68 (88)	112 (85)
Surgery (%)	25 (32) -20 (80) pre IFX had 24 procedures -15 (63) Perianal procedures -3 (13) small bowel resection -4 (18) Right hemicolectomy -1 (4) Left colon resection - 1 (4) Colectomy and end ileostomy -6 (24) post IFX (4 pre-and post IFX) - 2 (33) Perianal procedures -2 (22) small bowel resection - 2 (22) Colectomy -1 (11) Left colon resection	68 (52) 23 (33) pre IFX had 25 procedures - 17 (68) Perianal procedures -3 (12) small bowel resection -3 (12) Right hemicolectomy -2 (8) Left colon resection 51 (75) post IFX had 60 procedures - 11 (18) Perianal procedures - 31 (52) Colectomy & end ileostomy -8 (13) Defunctioning stoma -6 (10) Right hemicolectomy -1 (2) small bowel resection -2 (4) Left colon resection
PGA at induction (%)	Mild 25 (26) Moderate 55 (71) Remission 3 (4)	Mild 24 (18) Moderate 104 (79) Remission 3 (3)
PGA post induction (%)	Remission 56 (77) Response 17 (23) No response 0	Remission 51 (44) Response 49 (37) No response 21 (16)
Reasons for discontinuation of IFX (%)	Primary non-response 1 (3) Loss response 17 (49) Planned withdrawal 12 (34) Allergy 5 (14)	Primary non-responders 51 (44) Long drug holiday 39 (33) Loss of response 17 (14) Allergic reaction 5 (4) Adverse reaction 6 (5)
Previous medication (%)		
-EEN	54 (74)	83(81)
-Corticosteroids	68 (88)	116 (89)
-Steroid resistance	20 (29)	38 (33)
-Steroid dependency	38 (56)	62 (54)
-Side effects	10 (15)	22 (17)
-AZA/6-MP	62 (81)	94 (72)
-AZA resistance	20 (32)	35 (37)
- AZA loss of response	30 (48)	42 (45)
- AZA side effects	8 (13)	11 (12)
-Methotrexate	30 (39)	34 (26)
-MTX resistance	6 (20)	10 (26)
- MTX loss of response	18 (60)	18 (53)
- MTX side effects	10 (33)	10(29)

& isolated perianal disease only $- n=131 includes those who did not develop dependency on either first or second course of IFX

7.6.2. Crohn's disease and dependency- Induction in dependency cohort

At induction 51 (70%) had moderate to severe disease, 19 (26%) had mild disease and 3 (4%) were in remission (**see Table 24**). At baseline, 40 (55%) were on corticosteroids, 30 (41%) on Azathioprine and 36 (49%) on Methotrexate. The most common indications for commencing IFX was luminal disease in 62 (85%), immunomodulator failure in 48 (66%), steroid dependency in 16 (22%) and perianal disease in 11 (15%) (**see Table 24**).

7.6.3. Post induction and dose escalation in dependency cohort

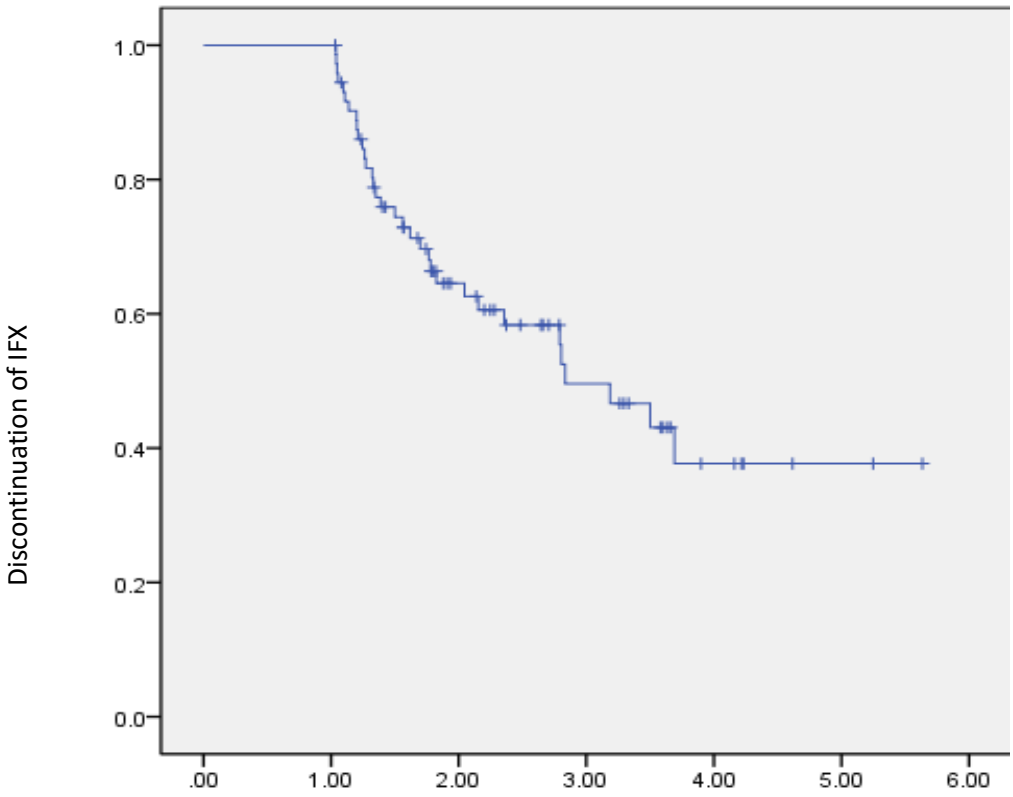
Post induction, 17 (23%) had a response and 56 (77%) were in remission. All patients who received induction proceeded onto maintenance therapy. 46 (62%) required dose alteration with 39 (85%) having a frequency adjustment; 11 (28%) decreased to 7 weekly, 17 (44%) to 6 weekly, 2 (5%) to 5 weekly and 1 (3%) to 4 weekly. 4 (10%) had their dose extended to every 10 weeks and 4 (10%) to 12 weekly. Dose was increased in 25 (54%); 19 (76%) to 10mg/kg, 2 (10%) respectively received 6mg/kg, 6.5mg/kg and 7mg/kg. 16 (34%) had reversal of dose escalation. Of those who required dose escalation, 20 (43%) stopped IFX most commonly due to loss of response 15 (75%) followed by planned withdrawal 3 (15%) and allergic reaction in 2 (10%).

7.6.4. Outcome of CD dependency patients

At 12 months, 47 (64%) were in remission, 16 (22%) had mild and 10 (14%) moderate disease but by 24 months, only 51 (70%) were still in paediatric follow up; 32 (63%) were in remission, 11 (21%) had mild disease and 8 (16%) had moderate disease respectively. By 36 months, 33 (45%) remained in paediatric follow up and 21 (64%) were in remission, 6 (18%) each had moderate and mild disease.

At last follow up 41 (56%) continued IFX with 33 (45%), stopping after 12 months, most commonly due to loss of response in 16 (47%) (**see Figure 17**) and 2 then having surgery (colectomy and small bowel resection). 18 (50%) received ADA, one of whom had undergone surgery after ADA was started.

Figure 22- Time to discontinuation for Crohn's disease in the IFX dependency cohort



The median time to discontinuation of IFX was 2.8 years (range 2.0-3.6) (**see Figure 22**) which was not affected by either immunomodulator usage (p=0.43) or by duration of disease prior to IFX commencing (p=0.76). Median follow up for those that discontinued was 1.3 years (range 0-5.5) years who had received a median of 11 doses (range 8-25). Patients on IFX at last follow up, received a median of 2.3 years (range 1.0-5.6) with 28 (70%) were on immunomodulators at last follow up.

7.7.5. UC and dependency

Three patients with UC received IFX for greater than 12 months with a median age at diagnosis of 9.5 years (range 6.0-13.4); 2 were male. All commenced IFX for acute severe colitis at presentation of UC and failed to improve with intravenous corticosteroids. After induction, all were in remission and commenced 8 weekly maintenance therapy. Two had dose extensions to every 10 weeks and one child received an increased dose of 7.5mg/kg. One child then stopped IFX as a planned drug withdrawal in clinical remission from their disease whilst the other 2 continued until end of follow up. No adverse reactions or infusion reactions were observed with none requiring surgery.

7.6.6. IBDU and dependency

One patient with IBDU received IFX for over 12 months due to chronic active disease and immunomodulator failure having suffered severe side effects secondary to chronic corticosteroid usage. The patient achieved remission post induction but has required subsequent dose escalation to maintain response. Despite repeated endoscopic re-evaluation, the patient has remained IBDU and continues IFX at last follow up.

7.6.7. Demographics of ADA dependency cohort

34 (60%) patients, all with CD, 13 (38%) were female, received ADA for ≥12 months at last follow up (**see Table 25**). Thirty had previously received IFX with one patient developing ADA dependency in their first and second course. Those that had received IFX had a median of 7 (3-22) doses, and 9 (30%) had received a dose escalation. At induction, 23(69%) received 80/40mg, 4 (13%) received 40mg, 2 (8%) received 160/80mg, 40/20mg and 24mg/m^2 respectively and one received 40/25mg.

Table 25 Comparison of demographic of dependency vs no dependency patients on ADA

	Dependency (N=34)	Non-dependency (n=27)[$]
Median age at diagnosis (range, years)	10.6 (4.9-14.9)	12.1(4.8-14.8)
Median age at start at ADA (range, years)	13.5 (6.8-17.2)	15.2 (9.1-18.4)
Female (%)	13 (38)	12 (48)
Type of IBD (%)	34 (100) CD	23 (85) CD 3 (11) UC 1 (4) IBDU
Montreal Classification (%)	L2 8(23) L2 and L4 7 (21) L3 7 (21) L3 and L4 12 (35) B1 25 (74) B2 8 (24) B3 1 (2)	L2 5 (22) L2 and L4- 8 (35) L3 2 (8) L3 and L4 8 (35) E3- 3 (75) E2 1(25) B1 17 (74) B2 5(22) B3 1 (4)
Steroids at baseline (%)	14 (41)	15 (56)
Immunomodulators at baseline (%)	20 (59)	17 (63)
PGA at induction (%)	Mild 11 (32) Moderate 23 (68)	Mild 10 (37) Moderate 17 (63)
PGA post induction (%)	Remission 11 (32) Steroid free remission 1 (3) Response 16 (47) No response 6 (18)	Remission 4 (15) Steroid free remission 2 (7) Response13 (48) No response 8 (30)
Previous IFX (%)	31 (91)	25 (93)
Reasons for discontinuation of IFX (%)	Primary non-response 12 (39) Loss response 17 (55) Allergy 2 (16)	Primary non-response 6 (24) Loss response 14 (56) Allergy 5 (20)
Previous medication (%)		
-EEN	28 (82)	18 (78)
-Corticosteroids	32 (94)	25 (93)
-Steroid resistance	6 (19)	8 (32)
-Steroid dependency	20 (63)	17 (68)
-Side effects	7 (21)	4 (16)
-AZA/6-MP	30 (88)	24(89)
-AZA resistance	12 (40	10 (50)
- AZA loss of response	14 (47)	9 (45)
- AZA side effects	3 (10)	7 (35)
-Methotrexate	25 (74)	15 (60)
-MTX resistance	5 (20)	3 (20)
- MTX loss of response	17 (68)	8 (53)
- MTX side effects	4 (16)	7 (47)
Surgery (%)	17 (50) -9 (53) pre-ADA had 11 procedures - 7 (64) Perianal surgery - 1 (9) Colectomy -1 (9) Defunctioning stoma -1 (9) Left colon resection -1 (9) right hemicolectomy 8 (47) post ADA had 12 procedures - 2 (17) Perianal surgery -6 (50) Colectomy -1 (8) Defunctioning stoma -1 (8) Right hemicolectomy - 2 (17) Dilatation of anal stricture	15 (56) -6 (40) pre-ADA - 3 (50) Perianal surgery - 2 (33) Small bowel resection -1 (22) Right hemicolectomy 13 (87) had 17 procedures post ADA - 11 (64) Colectomy -2 (12) Perianal procedures -1 (6) Defunctioning stoma -1 (6) Small bowel resection -2 (12) Other (EUA labia and resection of ileocolonic anastomosis)

$- number of patients includes those who did not yet reach dependency on either first or second course of ADA

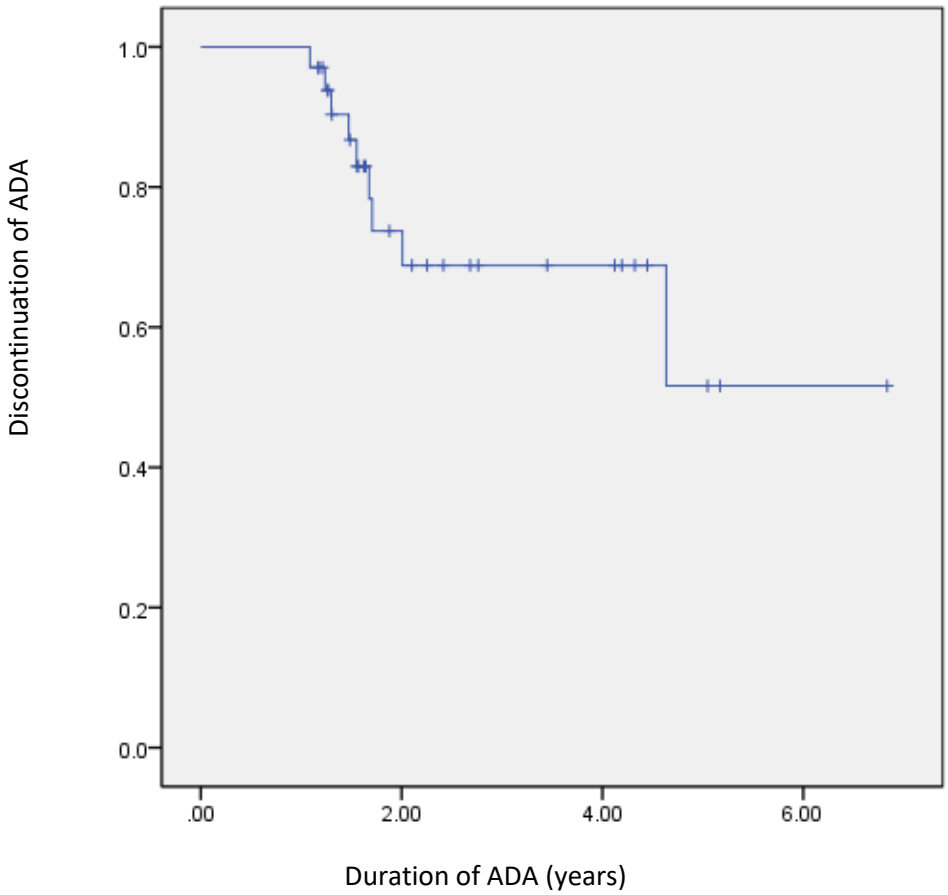
7.6.8. Post induction and dose escalation in ADA dependency cohort

When assessed at 4 weeks, 16 (47%) had a response, 12 (35%) were in remission and 6 (18%) had no response. All 34 patients who received induction proceeded onto maintenance, most 30 (88%) on 40mg, two on 24mg/m^2 and one each received 20mg and 25mg fortnightly. 24 (70%) required increased frequency to weekly after a median of 0.4 (range 0.1-5.4) years, 7 (32%) subsequently had this reversed. 6 (25%) required dose increase to 40mg in 2, 80mg in three and 30mg in one; one subsequently had this reversed.

7.6.9. Outcome of dependency patients

At 6 months, 13(38%) were in remission, 12 (35%) in steroid free remission, 4 (12%) had mild disease and 5 (15%) had moderate disease. At 12 months, 11 (32%) were in remission, 10 (29%) in steroid free remission, 8 (24%) had mild and 5 (15%) had moderate disease. At last follow up 25 (74%) continued ADA with 6 (24%) in steroid free remission, 8 (32%) in remission, 6 (24%) with mild and 5 (20%) had moderate disease having received ADA for a median of 2.1 years (range 1.2-6.8) (**see Figure 18**).

Figure 23 Time to discontinuation of ADA in dependency cohort



9 (26%) stopped after 12 months due to loss of response in 2 (22%), planned withdrawal in 6 (67%) and primary non-response in 1 (11%). The mean time to discontinuation of ADA was 4.8 years (range 2.7, 3.6) (**Figure 23**) which was not affected by either immunomodulator usage (p=0.69) or by duration of disease prior to IFX commencing (p=0.76).

7.6.10. Factors associated with dependency

Lack of steroid use at baseline was the only significant factor associated with dependency at 12 months on univariate analysis (p=0.03) (**see Table 26**).

Table 26 Univariate associations with loss of response in Crohn's disease in those who develop dependency

Variable	Univariable IFX HR (95%CI)	p value	Univariable ADA HR (95%CI)	p value
Male	1.6 (0.8,3.3)	0.16	3.5 (0.9,14.1)	0.08
Panenteric disease (L3 and L4)	1.7 (0.8,3.6)	0.14	2.3 (0.5,12.2)	0.30
Immunomodulator use at baseline	1.8 (0.4,7.3)	0.44	0.76 (0.2,2.9)	0.69
Perianal disease	0.8 (0.4,1.6)	0.53	1.4 (0.4,5.8)	0.61
Corticosteroid use at baseline	2.1 (1.1,4.2)	0.03	1.0 (0.3, 3.9)	0.98
Disease duration (<2yrs vs >2yrs)	1.1 (0.6,2.2)	0.76	1.5 (0.4,62)	0.59
Complete response post induction	1.1 (0.5,2.4)	0.81	4.5 (0.6,36.0)	0.13
Remission at 12 months	0.7 (0.4,1.4)	0.33	3.0 (0.8,11.3)	0.10

HR- hazard ratio; CI- confidence interval

7.6.1. Second course of IFX

19 (10%) patients had a repeated induction course of IFX, 17 were then commenced on maintenance. One child stopped after induction due to primary non-response was changed onto ADA and developed dependency to ADA whilst another stopped after an allergic reaction to the first dose of their second course. 11 (58%) of those commenced on maintenance were still receiving IFX at 12 months, two then discontinued after 12 months due to loss of response. 4(24%) stopped before 12 months: 2 primary non-response, one loss of response and one planned drug withdrawal.

7.7. Infliximab safety

Thirty patients (28 CD 2 UC) had 35 acute infusion reactions with 2 had anaphylaxis requiring adrenaline (**Table 27a**). Twenty-one patients had an adverse event including fourteen patients who experienced toxicity requiring hospitalisation (**Table 27b**)- one with a severe lupus like reaction who needed intensive care and one patient with lupus like joint disease that improved upon discontinuation of IFX. Other adverse events included paraesthesia (3) and non-productive cough (2) (**Table 27c**). Five had a serum sickness reaction occurring between 5 days and 8 weeks post IFX, common symptoms were rash, pruritus, facial oedema and arthralgia, all settled with no treatment. There were 25 infections, 6 serious requiring hospital admission (2-21 days), most commonly infections were bacterial/viral tonsillitis followed by urinary tract infections (**Table 27d**).

Table 27 – Safety of Infliximab

Table 27A- Acute infusion reactions with Infliximab

Patient	Type of IBD	Age at diagnosis (yrs)	Sex	Method of IFX administration	Number of infusions	Type of infusion event;	Concomitant immunosuppression	Response for further IFX	Long term IFX outcome
1	Crohn's disease	11	M	Maintenance	2	Dizziness	AZA	IFX continued	Discontinued- loss of response
2	Crohn's disease	12	F	Induction only	0	Cold and shivery	CS/AZA	IFX continued	Discontinued- primary non-response
3	Crohn's disease	9	F	Episodic	4	Headache/dizziness/nausea/ flushed	CS/MTX	IFX continued	Discontinued- primary non-response
4	Crohn's disease	17	M	Induction only	0	Hypotensive/felt clammy and tongue itchy	AZA	IFX continued	Discontinued- primary non-response
5	Crohn's disease	11	F	Maintenance	6	Hypotensive and short of breath	CS/AZA	IFX discontinued	Discontinued- adverse event
6	Crohn's disease	11	M	Induction only	2	Cannula painful	AZA	IFX discontinued	Discontinued-patient choice
7	Crohn's disease	11	M	Maintenance	4	Swollen lips/flushed and desaturated	AZA	IFX continued	Discontinued- allergic reaction
8	Crohn's disease	14	M	Maintenance	1	Chest pain	CS/AZA	IFX continued	Discontinued- long drug holiday
9	Crohn's disease	10	M	Episodic	3	Felt itchy	CS/AZA	IFX continued	Discontinued- loss of response
10	Crohn's disease	13	M	Maintenance	14	Short of breath and "felt funny"	CS/MTX	IFX discontinued	Discontinued-due to allergic reaction
11	Crohn's disease	14	F	Maintenance	1	Right arm parathesiae	AZA	IFX continued	Discontinued- long drug holiday
12	Crohn's disease	6	M	Maintenance	8	Needed to cough	CS/MTX	IFX continued	Discontinued- primary non-response
13	Crohn's disease	13.6	F	Maintenance	9	Nausea and felt flushed	MTX	IFX continued	IFX continued
14	Crohn's disease	9.6	F	Induction only	2	Shortness of breath/flushed/desaturated-	AZA	IFX discontinued	Discontinued- allergic reaction
15	Crohn's disease	4.9	F	Induction only	2	Short of breath/ gasping/ tachypnoeic/urticarial-	AZA	IFX discontinued	Discontinued- primary non-response &allergic reaction
16	Crohn's disease	13.8	M	Maintenance	22	Chest tightness	CS	IFX continued	IFX continued
17	Crohn's disease	5.7	M	Maintenance	2	Dizziness	AZA	IFX continued	IFX continued
18	Crohn's disease	6.3	M	Maintenance	6	Shortness of breath	MTX	IFX continued	IFX continued

Table 27A (Cont) Patient	Type of IBD	Age at diagnosis (yrs)	Sex	Method of IFX administration	Number of infusions	Type of infusion event;	Concomitant immunosuppression	Response for further IFX	Long term IFX outcome
19	CD	11.9	M	Maintenance	9	“anaphylactic” reaction	MTX	IFX stopped	IFX discontinued due to allergic reaction
20	CD	9.8	M	Maintenance	4	Nausea/urticaria	MTX	IFX continued	IFX continued
21	CD	12.1	F	Maintenance	5	Facial oedema anaphylaxis with chest pain, short of breath	CS/AZA	IFX stopped	IFX stopped due to allergic reaction and PNR
22	CD	14.8	F	Maintenance	15	Dizzy, chest pain, short of breath		IFX continued	IFX discontinued due to allergic reaction
23	CD	10.9	M	Maintenance	8	Chest pain, short of breath, facial erythema	MTX	IFX stopped	IFX discontinued due to allergic reaction
24	CD	14.0	M	Maintenance	0	Nausea	AZA	IFX continued	IFX discontinued due to PDW
25	UC	12.3	M	Induction only	2	Headache, chest pain and “allergic” reaction	CS/MTX	IFX stopped	IFX discontinued due to allergic reaction
26	CD	14.2	F	Maintenance	1	Felt weak, acute malaise, vacant and slurred vision	AZA	IFX continued	IFX continued
27	CD	10.4	F	Maintenance	6	Chest pain, shortness of breath	CS/AZA	IFX continued	IFX discontinued due to loss of response
28	CD	6	F	Maintenance	0	Nausea, short of breath, flushed and sweating	AZA	IFX stopped	IFX discontinued due to loss of response
29	CD	8.8	M	Induction only	1	Nausea, chest pain, short of breath, cyanosis	CS/MTX	IFX stopped	IFX discontinued due to primary non response
30	UC	13.0	M	Induction only	0	Dizzy and short of breath	CS/AZA	IFX stopped	IFX discontinued due to allergic reaction

CS- corticosteroids, AZA- Azathioprine, MTX- Methotrexate. Reactions occurred after a median (range) of 2.5 (0-20) doses, 9 (50%) required treatment, usually with chlorphenamine, but no anaphylaxis occurred, and none required hospitalisation. Clinical features included shortness of breath, chest pain and tightness, headache, nausea and itch. One patient had 2 similar infusion reactions despite premedication with chlorphenamine and hydrocortisone.

Table 27B. Toxicity whilst on Infliximab requiring hospitalisation

Patient	Age	Gender	Toxicity	Management; * hospitalisation for <24 hours	Outcome	Concomitant immunosuppression
1	16	F	Macular rash, varicella	Treated with Varicella immunoglobulin and acyclovir which settled over 48 hrs hospital admission	Stopped IFX due to adverse event	AZA
2	16	F	Labial abscess	Requiring drainage in theatre*	Stopped IFX due to planned drug withdrawal	MTX
3	11	M	Perianal sepsis	Taken to theatre for incision and drainage*	Stopped IFX due to planned drug withdrawal	AZA, CS
3	11	M	Night sweats and fatigue	Required admission for assessment- no treatment needed£	Stopped IFX due to planned drug withdrawal	AZA, CS
4	11	M	Gastroenteritis	Thought to be viral but required PN and admission to hospital for 21 days	Stopped IFX due to loss of response	Nil
5	14	M	Septic arthritis	Required 5-day admission with IV gentamicin and flucloxacillin	IFX continues	MTX, CS
6	13	M	Shingles	Rash spread for 2 weeks then stopped, treated with acyclovir but required 48 hours hospital admission	IFX continues	AZA, CS
7	8	M	Rectal stricture	Required admission for dilatation	Stopped IFX due to rectal stricture	CS, AZA
8	14	M	Rectal stricture	Required admission for dilatation	Continues of IFX	CS, MTX
9	17	M	Impaired memory, headache	Admitted for assessment- MRI normal then transitioned to adult services	Stopped IFX due to planned drug withdrawal	CS, AZA
10	15	M	Lupus like reaction	Prolonged stay in intensive care*$	Stopped IFX due to adverse event	AZA
11	12	F	Central line sepsis	Treated with prolonged course of antibiotics post each episode	Continues IFX	
12	9	M	Gastroenteritis	Likely infective, required IV fluids and admission	Continues of IFX	AZA
13	12	M	Gastroenteritis	Likely infective, required IV fluids and admission	Stopped IFX due to primary non-response	MTX, CS
14	14	F	Rectal strictures	Required admission for dilatation	Stopped IFX due to loss of response	MTX, CS

CS- corticosteroids, AZA- Azathioprine, MTX- Methotrexate. £- patient had two separate toxicity episodes

$Patient had his 4th dose of IFX then developed pyrexia, deranged liver function tests and coagulopathy in conjunction with raised inflammatory markers and immunoglobulins requiring in total a 36-day hospitalisation, including intensive care admission. The patient was initially treated with broad spectrum antibiotics, but his pyrexia continued and serositis developed, so he was commenced on intravenous hydrocortisone (before changing to oral prednisolone) which resulted in a rapid improvement in symptoms, and the working diagnosis of lupus -like syndrome was made.

Table 27C Other toxicity on IFX not requiring admission

Patient	Age	Gender	Event	Management; * hospitalisation required	Outcome	Concomitant immunosuppression
1	15	M	Paraesthesia	Resolved	IFX continues	CS, MTX
2	14	F	Profuse diarrhoea hours after 1st dose	Resolved	IFX stopped due to primary non-response	CS, AZA
3	14	F	Diplopia and Paraesthesia	Resolved	IFX stopped due to primary non-response and adverse event	CS, AZA
4	6.9	M	? hallucinations	Nil	IFX continues	CD/MTX
5	6	M	Perianal abscess	Managed with oral antibiotics	IFX stopped due to loss of response	MTX
6	12	F	Non-productive cough	Self -resolved	IFX continues	
7	15.2	F	Drug induced lupus	Settled on withdrawal of IFX	IFX stopped due to allergic reaction	CS/AZA
8	15	F	Loss of sensation left lower ankle and sole of foot	MRI brain and spine normal	IFX stopped due to adverse event	CS/AZA
9	15	F	Non-productive cough	Self -resolved	IFX continues	MTX

CS- corticosteroids, AZA- Azathioprine, MTX- Methotrexate

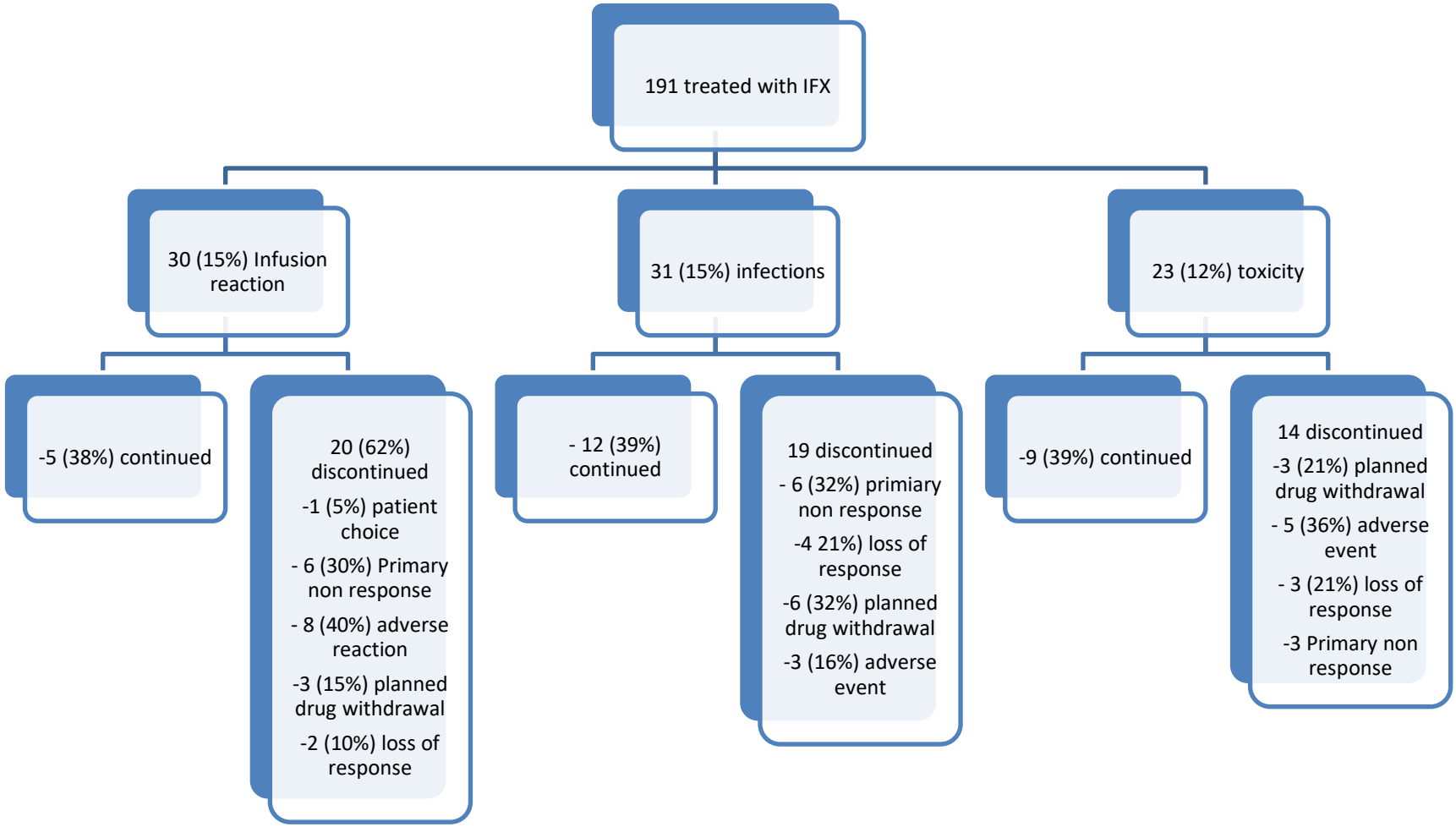
Table 27D Infections whilst on Infliximab

Patient	Age	Gender	Drug	Infection	Management; * hospitalisation required	Outcome	Concomitant immunosuppression
1	15	F	IFX	Macular rash, varicella	Treated with Varicella immunoglobulin and acyclovir which settled over 48 hrs hospital admission*	Stopped IFX due to adverse event	AZA
2	12	M	IFX	Bacterial pharyngitis	Infusion postponed 2 weeks	Continues IFX	MTX, CS
3	13	M	IFX	Viral infection	Settled with conservative management	Continues IFX	MTX, CS
4	10	M	IFX	Shingles	Rash spread for 2 weeks then stopped, treated with acyclovir but required 48 hours hospital admission*	Stopped due to PDW	AZA, CS
5	12	F	IFX	labial abscess	Requiring drainage in theatre	Stopped IFX due to primary non-response	MTX
5	12	F	IFX	Parotitis (viral) and lichenified rash	Resolved	IFX continues	CS, AZA
6	6	M	IFX	Tonsillitis	Treated with amoxycillin, 3rd infusion postponed by 2 weeks	Stopped due to PDW	MTX, CS
7	12	F	IFX	Viral infection sore throat increased diarrhoea	IFX already discontinued	Stopped IFX due to primary non-response	MTX
8	8	M	IFX	Perianal sepsis	Taken to theatre for incision and drainage- no hospital admission	Stopped IFX due to primary non-response	AZA
9	12	M	IFX	Facial candidial infection	Treated topically	Stopped due to PDW	AZA, CS
10	10	M	IFX	Gastroenteritis	Thought to be viral but required PN and admission to hospital for 21 days*	Stopped IFX due to loss of response	Nil
11	6	F	IFX	Candida vulvovaginitis and resistant palmar warts	Topical treatment for candida and dermatology referral for warts	Continues IFX	AZA, CS
12	14	M	IFX	Septic arthritis	Required 5-day admission with IV gentamicin and flucloxacillin *	Continues IFX	MTX, CS
12	14	M	IFX	Viral infection	Self-resolved	Continues IFX	MTX, CS
13	11	F	IFX	Viral illness		IFX stopped due to primary non-response	CS, AZA
14	17	F	IFX	Viral upset		Delayed 3rd dose but IFX continues	MTX
15	15	F	IFX	Feeling unwell, sore throat, coughing, no appetite		IFX stopped due to adverse event	AZA, EEN
16	16	F	IFX	Viral - raised temp, sore throat & lymphadenopathy		IFX stopped bridge to surgery	MTX

Table 27D (cont) Patient	Age	Gender	Drug	Infection	Management; * hospitalisation required	Outcome	Concomitant immunosuppression
17	14	F	IFX	Viral infection, sore throat, increased diarrhoea, around 1/02/08, less than 1 month from stopping IFX		IFX stopped due to PDW	MTX
18	12	M	IFX	Gastroenteritis	Admitted for 1week after IFX for 3 days for IV rehydration	IFX stopped PNR	CS/MTX
19	16	F	IFX	UTI	Treated with oral antibiotics	IFX continues	CS/AZA
20	14	M	IFX	Tonsillitis		IFX continues	AZA
21	14	F	IFX	Influenza A	Self-resolved	IFX stopped LOR	MTX/CS
22	12	F	IFX	Recurrent CVL infections	Treated with broad=spectrum antibiotics	IFX continues	AZA/CS
23	5.3	M	IFX	Viral URTI	Self-resolved	IFX stopped PNR	CS
24	15.5	M	IFX	Acute EBV infection	Self-resolved	IFX stopped due to adverse event	MTX
25	13.2	M	IFX	Chronic colonisation with staph aureus		IFX stopped due to LOR	AZA
26	13.3	M	IFX	Patches of staph aureus infections behind knees		IFX stopped due to LOR	AZA
27	13.3	F	IFX	Recurrent UTIs not confirmed on microscopy		IFX continued	CS/AZA
28	15.5	M	IFX	Tonsillitis	Treated by GP	IFX continued	AZA/CS
29	10.8	M	IFX	Recurrent tonsillitis		IFX stopped due to PDW	AZA

CS- corticosteroids, AZA- Azathioprine, MTX- Methotrexate, EEN- exclusive enteral nutrition

Figure 24 Outcomes of those treated with IFX who suffered an adverse event /infection/infusion reaction



7.7.2 Adalimumab safety

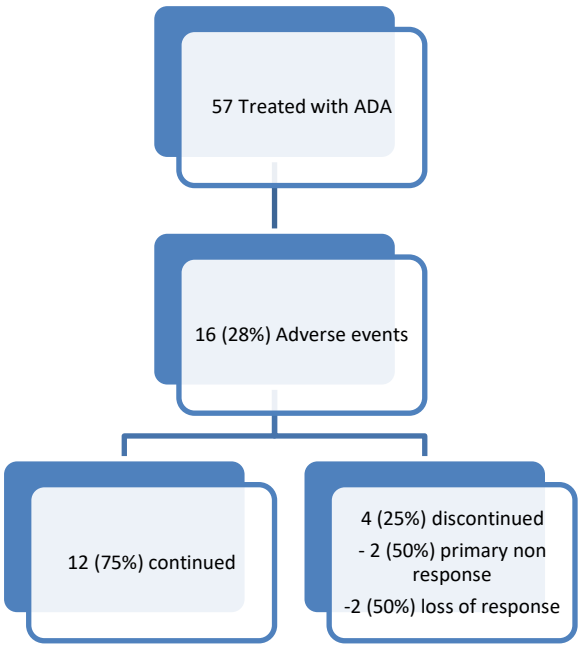
Table 28 Adverse events to Adalimumab

Patient	Type of IBD	Age at diagnosis (yrs)	Sex	Duration of CD to ADA start	Type of adverse event;	Concomitant steroids & immunosuppression	Long term ADA outcome
1	CD	4.9	F	4.0	Viral illness with cough	MTX	ADA stopped due to primary non-response
2	CD	5.4	F	4.8	Neutropenia and leukopenia	CS/AZA	ADA stopped due to loss of response
3	CD	12.4	F	0.16	Chronic right tympanic membrane perforation	CS	ADA continues
4	CD	10.4	F	3.2	Paronychia	MTX	ADA continues
5	CD	14.9	F	0.04	Impetigo	CS	ADA continues
6	CD	8.6	M	6.5	Headaches	-	ADA continues
7	CD	5.4	F	6.3	Neutropenia and leukopenia	MTX	ADA stopped due to loss of response
8	CD	6.5	M	7.2	Perianal abscess required hospitalisation*	CS/AZA	ADA continues
9	CD	7.4	F	8.3	*Clostridium difficile* infection required hospitalisation*	MTX	ADA continues
10	CD	10.5	M	12.7	Recurrent microscopic haematuria and dysuria, no cause found but resolved	-	ADA continues
11	CD	8.4	F	14.9	Vulval swelling/cellulitis required admission and IV antibiotics*	MTX	ADA stopped due to primary non-response
12	CD	13.6	F	16.0	Buttock abscess treated with oral antibiotics	CS	ADA continues
13	CD	4.9	M	9.2	Perianal shingles treated with IV acyclovir*	MTX	ADA continues
14	CD	8.4	F	8.4	Gastroenteritis required IV fluids*	MTX, EEN	ADA continues
15	CD	11.2	M	2.2	Impetigo requiring oral antibiotics	CS, AZA	ADA continues
16	CD	4.7	M	6.9	*Clostridium difficile infection*		ADA continues

CS- corticosteroids, AZA- Azathioprine, MTX- Methotrexate * hospitalisation required

Fifteen had adverse effects, with 5 hospitalisations (1 perianal abscess, 1 *Clostridium difficile* infection, gastroenteritis, perianal shingles and vulval cellulitis) (**Table 28**).

Figure 25 Outcomes of adverse events in those treated with Adalimumab who suffered an adverse event



7.8. Discussion

In this Scottish population-based cohort of children with all subtypes of PIBD treated with either IFX or ADA, both drugs were effective in inducing remission during 'real life' usage with remission rates of 58% for IFX (10-12 weeks) and 83% response/remission of ADA (4 weeks). Both were safe and well tolerated, however, 50% of ADA and 34% of IFX treated patients became dependent on anti-TNF therapy to maintain response. IFX and ADA were associated with improved linear growth which has been demonstrated in other population based cohorts for IFX (266, 267), however, to our knowledge this is the first population-based ADA study for ADA. IFX improved linear growth in those who achieved remission, had disease duration for over 2 years at anti-TNF start and were in the early stages of puberty (Tanner stage 1-3).

Effectiveness of ant-TNF therapy

CD post-induction remission rates reported in this study of 59% with IFX and 26% of ADA are low when compared with published rates of 34-85% (50, 247) and 61-70% (79, 142) respectively. 12 month CD remission rates of 54% for IFX and 47% for ADA compare with published rates of 25-83% (50) and 41-49%(79, 142). A worrying result is the lack of durable response for many on CD maintenance IFX therapy; 66% discontinued for primary-non-response/loss of response/adverse effects after a median of 0.83 years compared to 36% in a recent single centre retrospective study from 2000-2013(247). Reasons for the lower efficacy from our multi-centre 11-year nationwide study with full accrual compared to some published literature, include more liberal use of anti-TNF in some centres (thus better effectiveness rates) than real-life UK practice, where local prescribing restraints and national advice led to a clear top-up policy in everyday practice, only progressing to biologicals if all other therapies failed or became inappropriate. The ability to dose escalate (immediately increasing drug cost) to reverse any loss of response was difficult in many UK centres compared to others worldwide which would influence efficacy. Dose optimisation as a strategy to prevent complete loss of response has been successful as illustrated in Toronto from 2000-2011 in CD which was based on patients symptoms and used in 50% of treated with IFX which resulted in loss of response of just 2-6% per year (68). Most studies on anti-TNF arise from single academic centres, rather than population-based, therefore are subject to referral biases, potentially treating more severe disease, or having more liberal anti-TNF strategies. The retrospective study contains data from 2000 onwards, reflecting how IFX/ADA were first used, with some centres early adopters of strategies now seen as routine for biological therapy (e.g. maintenance rather than episodic IFX dosing in 2000-2005, induction dosing followed by maintenance when bridging to

immunosuppression, strong evidence of prolonged 'deep remission' on biological prior to planned treatment withdrawal, and dose optimisation to rescue loss of response).

Dependency

62% who commenced maintenance IFX became dependent with dose escalation in 44% which was successful in 40%. In a comparable Canadian study of children who were treated in a specialist referral centre from 2000-2011 with IFX, 50% required dose escalation which was successful in 86%. 28% of these children had risk factors for disabling disease at baseline, yet only 10% required alternate therapy by 12 months(68) contrasting with our results. Factors which may explain our increased loss of response include the higher number of patients in this cohort with moderate to severe disease (70%) (median PCDAI was 32.5 in the Canadian cohort) or that the longer median duration of disease to start of IFX (1.3 years in Canada verses 2.8 years in Scotland) may reflect a more severe phenotype and aggressive disease.

The concept of dependency in biological drugs was demonstrated with Infliximab in PIBD in 2006 by a Danish group who found that 71% of children improved with episodic IFX but 42% required further infusions to maintain clinical response(254).Further studies showed dependency rates between 56-60% in paediatrics which was associated with response after induction, inflammatory behaviour, perianal disease and fistulising disease (263, 264). In this cohort, similar rates were reported of perianal disease and inflammatory behaviour with remission post induction and MTX usage was associated with dependency at 12 months on multivariate regression.

There are conflicting results, for co-immunosuppression, it is associated with a reduced risk of loss of secondary response to IFX(68) yet other studies have shown no difference in efficacy, loss rates and endoscopic scores(268). Evidence also differs for ADA

on co-immune suppression with the DIAMOND trial reporting no additional benefit to adding AZA over ADA monotherapy in a multicentre prospective randomised control trial(269). However, two systematic review and meta-analyses differed with one supporting co-immune suppression for induction of remission but with equal rates of remission at 12 months(270) whilst the other reports no difference(271) . However, the adult literature has confirmed no effect of co-immunosuppression with MTX in time to remission(272).

De Ridder found no difference in dependency rates if therapy started 1 or 2 years post diagnosis as was reported here, however, Kugathasan and Lionetti found longer duration of IFX treatment if diagnosed less than 2 and 1 years respectively (273, 274).The differences observed may relate to the disease severity or variations in treatment practices including dose escalation as this population based cohort reflects “real life” clinical practice.

To our knowledge this is the first report of the concept dependency in paediatric ADA in a population-based cohort. 50% who commenced ADA had dependency requiring continued doses to maintain response and/or remission, similar to Imagine 2 with 46% still requiring ADA by week 240 to maintain response/remission(261). 89% in the dependency cohort received prior IFX demonstrating that despite failed response to IFX remission was achieved on ADA in those with moderate to severe CD contrasting with Imagine 2 trial where only 29% had prior IFX(261).

Long term outcomes

Remission rates reported at 12 months vary from 12-64% in those on maintenance IFX(65, 264) which decrease to 30-33% by 3 years reported however the number of patients included also decreases (63, 65, 266). In this cohort dependency, 68% of patients

were still in follow up at 12 months with 50% continuing IFX and 55% in remission. By 3 years, 33% in continuous remission with IFX was reported by Hyams with 90% on immunomodulators and 49% requiring dose optimisation compared to 11% who were dose optimised and 67% were on a form of immunomodulators with Assa. Dose optimisation and co-immunosuppression may explain the improved rates of response in the Hyams study with shorter disease duration, with the median time from diagnosis to start of IFX was 9 months (63, 65, 266). In this cohort 68% were still in follow up at 12 months, 50% of whom continued IFX with 55% in remission but, by 36 months only 37% of dependent patients remained in follow up with 56% of in remission, however, they may not have remained in continuous remission or had disease relapses.

The median follow up in the whole IFX cohort was 59 months which is significantly longer than 33 months for Assa and 32 months for Crombe(65, 266) but is similar to adult studies(275). The increased duration of follow up in this cohort may explain the increase in of loss of response and less planned withdrawal due to changes in practice from 2000 to 2012 with focus now on regularly reviewing therapy and discontinuation if in remission. Adult data suggest that those on immunomodulators had a longer duration until loss of response to IFX(275) which has not been seen in paediatrics(66, 247).

In the ADA dependency cohort, 72% remained in remission at last follow up with a median duration of ADA of 2.41 years. In ADHERE 42% and 50% were receiving every other week and weekly ADA were in remission(276) compared to 75% on every other week and 57% on weekly in this cohort. In ADHERE, 51% of patients had been treated with prior IFX and 43% on immunomodulators compared with 89% prior IFX and 56% on immunomodulators in this cohort. Remission rates were similar with 49% in RESEAT, at 12 months vs 41% in the BSPGHAN audit(79, 142). At 240 weeks in Imagine 2, 41% were in remission with 29% had receiving prior IFX(261). Differing long term remission rates may be

explained by the higher rate of co immunosuppression in PIBD, varying disease status at induction, increased frequency of dose escalation or differing criteria for response/remission.

Second line anti-TNFs

Loss of response

The most common reason for discontinuation of maintenance IFX in those was loss of response in 36%, followed by planned withdrawal in 29% which is in contrast to the Hyams trial where, 46% had a planned withdrawal and 25% discontinued to due to loss of response(63). Significant differences between the 2 cohorts may explain the differing response rates including the prospective and multi centre design of the Hyams study with clear treatment protocols. By contrast, this study was retrospective population based and reflecting “real life” practice with varying treatment protocols by centres. Co-immunosuppression with MTX was associated with dependency which is protective against loss of response in those treated with IFX (68, 277).

Therapeutic drug monitoring has become standard practice with recent evidence supporting proactive monitoring with alteration of doses to ensure optimal drug levels (61). Loss of response may have been related to antibody formation or inadequate drug levels that could have been optimised, or switched to another therapy if high drug concentration or high antibody levels(278); this was only available latterly in some centres.

The most common reason for discontinuation in ADA WAS loss of response in 27% with a mean time to loss of response of 3.6 years which was less common than for IFX, this is supported by the Imagine 2 where 22% stopped due to loss of response. However, other confounding factors may explain this difference including length of follow up or lack of drug/antibody levels.

Anti-TNF and growth

Growth failure in this cohort is comparable to other population-based cohorts such as EPIMAD, the largest population-based multicentre inception cohort from Northern France. In this study, 18% had severe growth failure (HtSDS<-2), improving to 15% then 7% at 1 and 2 years respectively, this is worse than reported by EPIMAD, where around 10% had severe growth failure at diagnosis, improving only slightly to 8% at 1 year and 6.5% at 2 years(266); however, no pubertal data were provided. The increase in growth failure in the Scottish cohort can be explained by the differing median ages at first dose of IFX, in Scottish children the median age was 13.2 years verses 18 years in EPIMAD (data are collected both before and after transition to adult IBD services and time of transition is study end in the Scottish PIBD biologicals register). The younger age in the Scottish cohort may be due to a more severe phenotype who required biological therapy compared to all PIBD patients included in the EPIMAD cohort. Two other nationwide population-based study also examined IFX and growth with differing results; firstly De Ridder observed that in 6 CD patients with ht SDS <1 at initiation of IFX, 3 who remained on IFX post induction, subsequently resumed normal growth velocity (267). However, Wewer showed no improvement in height velocity in 10 CD patients who had IFX in part due to growth failure (no pubertal data or ht SDS were provided for this cohort) (254). Both studies have significantly smaller numbers than the Scottish cohort and the lack of pubertal data makes comparisons challenging. Although improvement was noted in linear height post IFX in this study, follow up was only 5.2 years for the whole cohort so impact on final adult height was not possible to ascertain as others have shown short term improvement but final adult height remained reduced from target (257).

The effect of pubertal stage on linear growth in children treated with IFX remains controversial. In this study, improvement was seen in Tanner 1 -3 in Δ height SDS and height velocity but not height SDS, this suggests improvement in growth is not influenced by pubertal progression as similar improvement is seen in pre-pubertal/pubertal children or that although certain growth parameters improve with IFX, these are insufficient to lead to improvement in height SDS. However, only half who were Tanner stage 1 at start of IFX remained so at 12 months. Malik also demonstrated improved HV SDS 6 months after IFX even after adjustment for pubertal staging(248). However, a large cohort of newly diagnosed patients in North America showed greater improvement in linear height in early puberty (33), yet another showed those in Tanner 1-3 grew but at a suboptimal rate with no improvement in Tanner 4/5 compared to Tanner 1-3 (251).

Growth improves with greater disease control as can be seen in these results with no improvement in those who did not achieve remission post induction, whilst in those that did, all measures of growth improved. Those in clinical remission whose growth parameters improved minimally may not have achieved full mucosal healing which could continue to adversely affect their height. Mucosal healing is associated with prolonged remission after induction treatment with IFX(279) and could potentially be associated with sustained improvement in linear growth. Comparable results for growth in clinical remission are seen in the REACH study extension where a trend towards continued improvement in height SDS score was seen in those with sustained remission(280). Improvement in linear growth was observed in those receiving corticosteroids at induction in this cohort despite most evidence suggesting corticosteroid usage is associated with poor growth(281). Potential explanations include that these children had received steroids prior to anti-TNF therapy which were then able to be weaned leading to improved growth(33), or that corticosteroid usage combined with anti-TNF therapy resulted in remission earlier thereby improving

growth. Alternative hypotheses are that IFX could promote catch up growth once the inflammatory process has been 'switched off' or merely prevents further deterioration in growth trajectory without improving overall height(282).

Disease duration for ≥ 2years had improved height SDS, Δ height SDS and height velocity at 12 months compared to those with a shorter disease duration of less than 2 years. This contrasts with current evidence which suggests shorter disease duration has better outcomes with anti-TNF, exemplars are the REACH study and ACCENT 1 trial. In the REACH study, children had a median duration of disease of 1.6 years prior to IFX with 88% response rate and 59% remission post-induction contrasting with a 66.7% response and 39.1% remission rate in adults in ACCENT 1 trial where the median duration of disease was 7 years prior to initiation of IFX(53, 57). A prospective multicentre North American study observed improved growth and clinical outcome at 12 months in those treated with early IFX (within 3 months of diagnosis) compared with early immunomodulator therapy or no therapy(283) differing for results observed here. Improved growth in those with a longer disease course in our cohort could be related to inflammation being 'switched off' with anti-TNF therapy resulting in normal growth and/or pubertal development.

This study, which included all subtypes of IBD, found a significant improvement in linear growth in those on combination therapy of AZA and IFX contrasting with other studies on the effect of AZA on growth. The only paediatric RCT on the use of AZA from 2000 observed no significant difference in linear growth between those treated with AZA and placebo at 18 months (41). Pfefferkorn also found no improvement in height at 12 or 24 months for AZA(33) yet a UK study did show improved height with AZA although this was not statistically significant. However, this UK study was retrospective, before IFX was commonly used, growth data was only available for 44 patients with confounders including concurrent corticosteroid use, disease severity and pubertal staging data unavailable (284).

Improvement in growth with both MTX monotherapy and used in combination with IFX has been reported with 12 patients receiving MTX and IFX combination therapy showing improved linear growth(248) whilst MTX monotherapy consistently demonstrates improvement in height velocity (47). No mechanism has been proposed as to potential pathways which may explain improvement in growth for either AZA or MTX.

Limited data exists on the effects of ADA on growth which is divided on efficacy. In this cohort no growth improvement was seen in Tanner stage 1 but significant improvement in Tanner stage 2/3 for Δ height SDS and height velocity was observed suggesting that development through puberty may at least partially explain the improvement in height. No improvement was seen in those in Tanner 4/5 which has been previously shown(259). The Imagine trial, only RCT published, found improvement in height velocity z scores at 6 and 12 months with higher and lower doses of ADA, however, no pubertal data was provided(78). More comparable data is provided from a multicentre UK and Irish audit which demonstrated improved short term growth with an improvement in Δ height SDS at 6 months after initiating ADA (259) that continued to 12months but with no increase in height velocity; however, it did show improved growth for Tanner stage 1-3. Contrasting evidence is seen in a single centre study from Israel found no improvement in height at last follow up (median of 17.3 months) with no pubertal data provided (285).

In this study no improvement was seen in those that achieved remission post induction, potentially related to smaller numbers involved with only 5 achieving remission post induction. However, others have reported greater improvement in height velocity if response at 4 weeks post induction was seen which persisted until week 52(260).

UC

This study is the first to report on dependency to IFX in UC which was observed in 14%. IFX was effective in induction and maintenance of paediatric UC and is used as rescue therapy in acute severe UC as previously reported (54) (25). ADA was used in 4% of UC but, was unsuccessful at inducing or maintaining a remission with both patients requiring surgery receiving ADA for a median of 0.16 years. The reasons for the poor responses are unclear, both had moderate to severe disease at baseline having failed IFX for loss of response/allergic reaction and responded initially so not unresponsive to biological therapy. The lack of response may represent the severity of disease when the ADA was commenced or patient preference for the more definitive surgical option than continued medical therapy. ADA has been shown in a small cohort adults of UC to be an effective treatment with 35% in remission at 2 years in those previously treated with IFX (77) which has been replicated in case series in PIBD(79).

Planned withdrawal

The STORI trial assessed response to planned drug withdrawal in adults with a multicentre prospective trial in those with stable CD/remission on eight weekly IFX AND stable doses of anti-metabolite medications (6 Mercaptopurine, Azathioprine and Methotrexate). 50% relapsed within two years of discontinuing therapy, most within the first year, although regained response when recommenced IFX but requiring dose intensification (265) . In this cohort, 43% of patients had a planned withdrawal, most in clinical remission at discontinuation of therapy and were males with CD. 15% restarted IFX after a median of 0.87 years similar to that seen by Molander(286).

The UK anti-TNF withdrawal study group reported a third of patients will have a moderate/severe relapse by 12 months after stopping therapy increasing to 54% by two years but, reassuringly 90% who restarted IFX did so successfully(287). In a prospective

study by Molander, 19% relapsed after a median of 6 months who had been in clinical and endoscopic remission prior to discontinuation and had received anti-TNF for a minimum of 12 months. 67% remained in remission at 12 months post planned withdrawal and 85% remained in endoscopic remission. Unfortunately, predictive factors for a sustained remission could not be elicited but re-introduction of anti-TNF therapy was successful(286). Due to transition, it is unclear how many patients had a relapse following planned drug withdrawal necessitating restarting anti-TNF, however, 4 patients (2 ADA and 2 IFX) had a second course having had a planned withdrawal on their first course.

Safety

No deaths or malignancy occurred in the anti-TNF cohort. IFX infusion reactions occurred in 18%, with 15% reported in multiple pooled studies (50). Serious infections occurred in 3%, similar to pooled studies at 3.3%(50). 14 (7%) required hospitalisation due to IFX toxicity. ADA was well tolerated with 5 (9%) hospitalised for toxicity but mostly minor side effects, although serious infections of 3% were noted in other studies(50).

Limitations of the study

As a 'real life' clinical experience from a nationwide managed clinical network from 3 different centres over a 13 year period there is significant heterogeneity in the data due to changing treatment practices as new evidence emerged and differing rates of uptake of change within these centres; example of these include episodic dosing with IFX in 2000-2007(134) and induction only moving to induction plus maintenance given improved outcomes in those that continued(55). No consensus guidelines existed on dosages, criteria for commencement of therapy or escalation/ de-escalation of treatment and PCDAI data was not routinely collected so PGA data was used instead which has a strong correlation

(144, 288). Only patients under 18 years treated in paediatric centres were included which may underrepresent the true numbers treated and could influence the efficacy and safety signals generated.

Growth results should be interpreted with caution as only those treated with anti-TNF therapy were reported which represents a more severe phenotype where a relatively higher rate of growth failure would be expected. Satisfactory growth data was available for only 49% and full pubertal status in 71% of these. Now treatment algorithms have changed considerably with IFX is given earlier in treatment course if a severe phenotype such as those with widespread colonic deep mucosal ulceration, growth failure or severe perianal disease with episodic treatment abandoned and long-term maintenance being the norm. Other studies have shown the benefit to early aggressive treatment in altering the disease progression(57), so it is possible that if IFX is given earlier the somewhat modest improvement in growth seen in this study will become more pronounced.

7.9. Conclusion

This Scottish national experience is the only UK population-based study on biological outcomes in a PIBD in real-life clinical setting, and the first nationwide study ever on IFX in either UC or IBDU, and on ADA in all PIBD subtypes. Biologicals are moderately effective in PIBD management, but many have limited duration of effect. Known safety signals were confirmed without any new types of adverse effect or deaths reported. Growth failure was relatively common, with 18% demonstrating severe growth failure at initiation of therapy. Infliximab and Adalimumab are both associated with improved linear growth after 12 months of treatment. Most improvement was seen in those who achieved remission, had disease for longer than 2 years, received combination therapy with azathioprine, received

maintenance therapy and were Tanner stages 1-3.for IFX. For Adalimumab, improvement in growth in those who were Tanner stages 2 and 3.

Dependency was commonly seen with IFX and ADA with 50% of ADA and 34% of IFX treated patients still on treatment at 12 months. MTX usage and remission post induction were associated with dependency but analysis is needed to examine these relationships more closely in a prospective trial. 35% of IFX treated patients had a planned drug withdrawal with only 15% restarted for disease relapse. Early identification of those in whom planned withdrawal will be successful has significant cost implications and needs to be more clearly defined.

Chapter 8

8. Mortality and cancer in paediatric inflammatory bowel disease in Scotland 2003-2013-a nationwide retrospective study

8.1 Background

Paediatric-onset inflammatory bowel disease (PIBD) has a more rapidly progressive phenotype which is often more extensive than adult-onset disease at diagnosis and has earlier use of immunosuppressant therapies including thiopurines and anti-TNF agents(16, 266). Short and long term complications of immunosuppression include the risk of malignancy and opportunistic infections which compound the already established increase risk of colonic cancer(289). The exact incidence of cancer and mortality in PIBD is unknown with a paucity of published literature, those that have been published have short term follow up only(120) often due to transition to adult services, or are retrospective, single or multi centre performed in a single country with few population-based cohorts. A systematic review on mortality in PIBD reported the most common cause of death was cancer in 76.2%, with other non-cancer deaths related to infection or gastrointestinal complications and those that died of sepsis, most 43.8%, were on dual immunosuppression (290).

8.2.1. Aims and hypothesis

The aim of this study was to characterise the risk of cancer and mortality in population-based cohort of PIBD patients within Scotland to provide relevant and appropriate information regarding risks of treatment for patients and their families.

8.3. Methods

8.3.1. Case identification

In Scotland, specialist paediatric gastroenterology, hepatology and nutrition (PGHAN) is provided through three tertiary funded Scottish regional networks covering all four academic centres (Glasgow, Edinburgh, Aberdeen and Dundee), and all district general hospitals having paediatric units thus forming a virtual Scottish national network as described previously(92, 134). Patients were identified through review of the national Paediatric Inflammatory Bowel Disease in Scotland Audit (PISA) and request for information from lead clinicians for each of the three main centres (Glasgow, Edinburgh and Aberdeen). All cases of mortality and cancer in PIBD patients cared for in paediatric services (<18 years) in Scotland were collected retrospectively from 01.01.2003 to 31.12.13. In 2011, Scotland had a population under 16 years of just under 1 million and the incidence of PIBD 2003-2013 was 9.4/100,000/year.

Diagnosis of IBD was based on clinical symptoms, laboratory results, endoscopic, radiological and histological assessment in-line with the revised Porto criteria(13) and Lennard Jones(135) by the local specialist PIBD team. Patients were diagnosed as either Crohn's disease (CD), Ulcerative Colitis (UC) or Inflammatory Bowel Disease Unclassified (IBDU).

8.2.2. Data collection

Further details were collected using standardised proformas on PIBD disease course, medications, cause of death/cancer and relation to IBD/IBD treatments (immunosuppressants, anti-TNF agents, corticosteroids) and outcome (death or outcome at

last follow up). Data was collected from date of diagnosis until date of death or last paediatric follow up, whichever came first.

8.2.3. Statistical methods

Continuous variables were expressed as median and interquartile ranges. Cancer and mortality rates were calculated using assumptions and methodology adapted from the Porto group's publication on mortality/cancer in PIBD (131). No Scottish prevalence data exists for this study periods, however, estimated PIBD prevalence rates were calculated based on the same assumptions as the Porto group of 30 per 100,000 (185, 291-293). The Porto group assumed a prevalence of 60 per 100,000 for 0-26 years but only ages 0-16 are covered in this study hence using 30 not 60 per 100,000. This assumption is supported by recent Scottish prevalence data from 2016 where prevalence was 58.9 per 100,000 at its highest in those 0-16 years(294). The incidence of PIBD increased from 7.82 per 100,000 in 2003-08 to 12 per 100,000 in 2015-2017 so assuming a similar increase in prevalence 38 per 100,000 would be the expected prevalence which is comparable with the Porto study. The total population covered was multiplied by the prevalence providing an estimation of the population at risk. then multiplied by 11 to calculate the exposure of the duration of the study. Incidence rates are reported based on the number of patient years.

8.4. Results

Four cases were identified within the study period, 2 males and 2 females. Three patients died, one male died of malignancy, one female died of IBD disease related complication and one female died of a non-disease related cause.

8.4.1. Mortality

One male with CD died of gamma delta non-Hodgkin 's lymphoma. The patient was diagnosed with panenteric CD at 14.6 years of age and treated initially with corticosteroids then commenced azathioprine after 3 months. He had a disease relapse and underwent a left hemicolectomy but continued azathioprine which was stopped at age 17.2 years then was diagnosed with gamma delta non-Hodgkin's lymphoma at aged 17.5 years. He underwent active treatment but unfortunately died aged 18 years, 3.4 years after his IBD diagnosis. He never received any anti-TNF agents and there was no family history of malignancy.

One female with UC died aged 12.2 years of a volvulus post restorative proctectomy. She has been diagnosed with UC aged 9.4 years and underwent a colectomy for active disease. Her duration of disease was 2 years and 9 months having never received any thiopurines or anti-TNF agents.

One female with IBDU died aged 11.7 years from a non-IBD related conditions. She had been diagnosed with IBDU aged 8.99 years and treated with corticosteroids only, never received thiopurines or anti-TNF agents. She had significant other underlying health issues and had chronic lung disease with home oxygen secondary to a left sided congenital diaphragmatic hernia. She died from a lower respiratory tract infection on the background of deteriorating lung function 2.7 years after her IBD diagnosis. Since the number of deaths was 3 in 3829 patient years, the incidence of mortality was 783 per 1,000,000 patient years.

8.4.2. Malignancy

Two cases of malignancy were diagnosed as mentioned above, one male with gamma delta non-Hodgkin's lymphoma and one acute myeloblastic leukaemia. The case of acute myeloblastic leukaemia was diagnosed in a male with CD aged 16.8 years. He was diagnosed with CD aged 15.5 years and treated with azathioprine for 13 months prior to his diagnosis of leukaemia. He was successfully treated and at last review with in remission from his CD on no active treatment. Since the number of cancers was 2 in 3829 patient years, the incidence of cancer was 522 per 1,000,000 patient years.

8.5. Discussion

Death and malignancy remain a rare occurrence in PIBD in Scotland with only 4 cases reported between 2003-2013 with 500 new cases diagnosed during this time was a mortality rate of 783 per 1,000,000 patient years and malignancy risk of 522 per 1,000,000 patient years. One death was non-IBD related with the remaining two cases linked, one died from treatment related complications who developed lymphoma and one from disease related complications post restorative proctectomy. The final case of cancer was leukaemia following thiopurine therapy in a male with CD. After data collection ended, a further malignancy was reported in a 10-year-old male diagnosed aged 4 years with CD who lost response to AZA so escalated to MTX then developed acute myeloblastic leukaemia which was treated initially with chemotherapy then bone marrow transplantation. Further case was reported post transition to adult care of a young man previously treated with thiopurines who developed a fatal lymphoma.

No serious infective complications were reported which could be related to the small numbers (4 versus 18) in ESPGHAN, or the levels of immunosuppression. Both fatal infections reported in UK/Irish audit of 72 children treated with ADA were on dual

immunosuppression and receiving parenteral nutrition (79), whilst 3/13 deaths due to sepsis in the ESPGHAN cohort had a central venous catheters(117).

The risk of malignancy in PIBD is unknown, however, the largest case series to date reported retrospectively on 2 cases of lymphoma (both males treated with thiopurines) amongst 1374 patients over a 4.8 year follow up in a North American cohort providing an incidence amongst those exposed to thiopurines of 4.5 per 10,000 patient years(44); although this is non-population-based. In the adult CESAME study examining 5867 patients were treated with thiopurines, the highest risk was associated with older age and longer disease duration(295) with a rate of 9 per 10,000 patient years. Population-based studies have reported 20 cancers in 9405 cases of childhood-onset IBD with colorectal, small bowel and liver cancers the most common with an increased risk of developing cancer of 3.3 per 1000 years with PIBD compared to 1.5 per 1000 years if no IBD(121). No increase in cancer was observed in those treated with anti-TNF agents and only 15 cases of cancer associate with thiopurines which is supported by a paediatric systematic review which with no increase in lymphoma risk in those treated with anti-TNF compared to other therapies(296).

The risk of lymphoma in PIBD appears to be treatment related with two key types, hepatosplenic T cell lymphoma and EBV driven lymphomas. Hepatosplenic T cell lymphomas were reported in relation to IBD in 2007 with a case series of 8 young patients, all of whom were treated with azathioprine and infliximab(119). This rare cancer was associated with a poor survival rate with 6 out of 8 cases dying. Reports of this cancer lead changes in practice on the use of concurrent use of immunomodulator with anti-TNF drugs, specifically azathioprine. Controversy still exists now within paediatric gastroenterology over single agent use of anti-TNF or use in combination with other immunosuppressant, particularly in EBV naive patients where it is thought to contribute to lymphoma(297). The

combination therapy has the advantage of reducing immunogenicity and potentially prolonging the response to the anti-TNF agent(298), however, it must be balanced against the potential increased risk of malignancy and now of infection. An adult systematic review was performed to examine the risk of malignancy associated with anti-TNF therapy which found no increased risk (299) but concluded that most studies had a relatively short follow up period of 1 year, that was potentially insufficient to detect an increased risk. The DEVELOP registry aimed to explore the risk in the paediatric population and reported that IFX was no associated with an increased risk, however, thiopurine use was(130). Importantly, in this study 3/15 cases of cancer occurred in patients over 18 years which in most UK centres would be managed by adult gastroenterologists.

Thiopurines have been implicated in the development of EBV driven lymphomas(300). In the CESAME study, 52% of lymphoproliferative disorders were EBV positive(295) with a reported incidence of 0.1 per 1000 patient years for primary EBV infection related lymphomas in EBV naive males under 35 years(301). EBV exposure often occurs in childhood/adolescence and with the increased risk of EBV driven lymphomas practice in many centres is to screen prior to commencement of AZA and considering alternative in those naive. In the ESPGHAN study, 3 out of 11 who developed lymphoma were EBV positive, all received thiopurines so were thought to be treatment related(117), this was also reported in a large Dutch study where 92% of IBD patients diagnosed with EBV positive lymphoma had received prior thiopurines compared to 19% of EBV negative lymphomas(302).

Cancer risk in PIBD may not become apparent until adult life, potentially related to the cumulative effects of disease severity, ongoing inflammation, medications including thiopurines and anti-TNF therapy, both in isolation or combination which may act synergistically. An adult nationwide study reported an increased risk of lymphoma in those

treated with AZA which became statistically significant after 4 years of use, , the risk then normalised after stopping for 4 years(303). Despite the more widespread use of anti-TNF agents, there is no decrease in malignancy with a suggestion that those diagnosed after 2002 have an increase in gastrointestinal and melanoma skin cancers(121), however, it was not powered to detect statistically significant differences which would require more participants and a longer duration of follow up. A systematic review on the natural history of paediatric-onset IBD reported cancer in 14 patients, 12 of whom were diagnosed over the age of 19 years(116) which in the UK would be in adult practice with 8/14 had UC and 7/14 had colonic adenocarcinoma suggesting the potential effects of uncontrolled inflammation on the risk of malignancy. An adult population-based study confirms this hypothesis having reported an excess mortality of 14% in IBD patients related to inflammation of the gut, for both UC and CD, which was highest in the first 3 years after diagnosis but remained significantly elevated in the long term(304).

Prospective European wide studies into mortality and morbidity are required with long duration of follow up which relies on prompt and full reporting from individual countries and clinicians within those countries for complete accrual. Transition age varies by country so cases may be seen and treated by adult gastroenterologists so not recorded in some countries for example, those over 16 years in Scotland are seen in adult practice whilst in France they would remain in paediatric practice until 19 years old. As is already known, environment has a role to play in the pathogenesis of IBD, it may also influence response to treatment, development of cancer and other adverse outcomes such as unusual infections (i.e. more likely in countries with a high prevalence of tuberculosis to have re-activation of this).

The strengths of this study lie with the robust nature of the nationwide data collection across Scotland and the managed network of care that exists ensuring that all new cases of PIBD and adverse events are recorded. All patients were treated in paediatric centres, so data collection was complete allowing appropriate information on treatments and risk factors to be identified over a 10-year period. The limitations of this study are that the numbers involved are low in comparison to other similar studies with only cases included who were treated within the paediatric service, potentially excluding those diagnosed and treated in adult services. Furthermore, the relatively short follow up period means that long term sequelae remain unknown as patients transitioned to numerous different adult hospitals so future collaboration with adult gastroenterologists is crucial. The use of anti-TNF agents has increased since the study ended so it is possible that more adverse events will be have occurred.

8.6. Conclusions

Cancer and mortality remain a rare occurrence in PIBD which is confirmed in this population-based nationwide cohort study with only three deaths, two related to IBD and two cases of malignancy, both related to azathioprine, one of whom died. The results of this study reassure clinicians as to the rarity of these devastating consequences which can be used when counselling families about commencing immunosuppression. Further prospective collection of data is required due to the relatively short follow up period of 10 years, particularly as the use of immunosuppressant and anti-TNF agents are increasing in Scotland to more fully understand the risks involved with these agents

Chapter 9

9. Discussion

9.1 Challenges of epidemiological research

Epidemiological research can provide information on the natural history of diseases and environmental associations that may be involved in pathogenesis. However, good epidemiological data is challenging to produce, firstly patients with the condition of interest must be identified. For PIBD, diagnostic approach varies between countries and, even within centres in the same country with not patients having endoscopic evaluation as per current guidelines(10) as exemplified within Scotland, where IBDU patients underwent differing procedures. Furthermore, historically studies have divided into "probable" and "possible" IBD(187, 190, 193) with Scottish data prior to 1995 having no cases of IBDU, with 2 being reclassified as UC before IBDU was a recognised IBD subtype. The varying classifications makes relating data from these studies difficult to correlate with the current literature and other historical data.

Secondly, epidemiological databases collect information through coding from hospital/government/insurance databases which is dependent upon correct insertion by coders and is fraught with misclassification bias(305). Approximately 10-20% of patients classified via ICD coding algorithms with IBD using administrative databases do not actually have IBD(305). Scottish incident data was validated from 1981-1995 to confirm the diagnosis, however, the most recent cohorts have not which is planned for future work. A challenge for the Scottish PGHAN network is the different practices of the units, both retro and prospective data collections were done, as well as database managers in some but not all centres. Practice varied on reviewing diagnosis for reclassification and inclusion of prevalent cases which may occur, particularly if the patient relocates to a new area. Certain studies have performed validation techniques to ensure the robust nature of data collected through administrative databases (111, 113), however, not all(183). Therefore, it is

plausible that rates of rise observed is over-estimations given the intrinsic difficulties collecting the data.

Thirdly, there is a challenge of ensuring all eligible patients are captured, particularly cases which may have been treated and diagnosed in adult centres, a challenge for older adolescents or stand-alone children's hospitals. Close collaboration with adult colleagues will ensure all relevant patients are included as well as well-established referral pathways. A further challenge is missing patients with a milder phenotype who may not require hospital admission, this is less problematic in paediatric practice in Scotland where children either undergo endoscopic assessment either under sedation or a general anaesthetic but may affect teenagers diagnosed in adult services.

Fourthly, when comparing incidence rates of PIBD between countries, age range used which varies between countries and even within individual countries. North American centres will include patients up to 19 years so incidence studies present data from 14 to 19 years(180, 189), which drives up incidence rates. In Scotland, patients under 16 years are managed in paediatric services, however, it is possible that patients on the cusp are seen in adult services dependent upon geographical location or mode of presentation (acute admission verses outpatient referral).

Finally, epidemiological research can suggest environmental factors associated with the development of PIBD but cannot prove causation. Often studies are limited by recall bias and confounders as many are retrospective with a complex interaction of factors making clear causal factors difficult to extrapolate. Population-based research reduces variability of data collection allowing improved generalisability.

9.2 Incidence and prevalence of paediatric-onset inflammatory bowel disease

The incidence and prevalence systematic reviews (**Chapters 3 and 4**) both demonstrate an increase in PIBD, CD and UC. Temporal trends on incidence demonstrated a significant increase in PIBD in 11/12 studies, 11/14 for CD and 10/15 for UC which were predominately from Western Europe and North America. The lack of data from Africa, Asia and Eastern Europe provides challenges in determining the global impact of PIBD, however, inferences can be drawn from adult studies which suggest an increase in South America (Brazil, Uruguay and Barbados)(306) and Asia(101). Prevalence in adult-onset IBD in Asian countries such as Japan, South Korea and Hong Kong has increased so it can be hypothesised that PIBD may be rising in these countries (2, 87). However, caution should be used when interpreting the results of systematic review due to the wide variation in methodologies used, variety of age range used for cut off of paediatric patients from 14 years or use of “possible” and probable” IBD diagnoses (2). Studies were not all population-based including those gathered from insurance databases so may not be a true reflection of the incident cases within that geographical area (307). Four studies were identified (2 from the UK, 1 each from Denmark and Bosnia(154, 155)) (93, 132)which were not included within this previous review which would have provided a more global representation of PIBD.

Potential environmental clues involved in PIBD aetiology may be revealed by exploring the incidence in developing countries which have not previously reported incidence data or those who have become “westernisation”(87). China reports higher incidences of IBD in areas with increased urbanisation(209, 308) supporting this hypothesis. Furthermore, incidence and prevalence rates from newly industrialised countries are similar to rates reported in Western Europe in the 1970s and 1980s(87). Recent inception

cohorts from areas with a paucity of data will aid understanding of the increase such as the Asia-Pacific Crohn's and Colitis Epidemiological study(308) and the ECCO-EpiCom study(108). The EpiCom study although based in countries in both Eastern and Western Europe (14 Western and 8 Eastern European countries) provides information on the incidence of IBD among migrants to 6 of these countries suggesting similar incidence between those born within the country and those who migrate there(309).

There is a paucity of data on prevalence of PIBD (**Chapter 4**) with only 27 studies reporting from 12 countries compared to 174 studies on incidence from 35 countries included in the previous and current incidence systematic reviews. The practicalities of collecting prevalent data contribute to this as patient can migrate into and out of the area. A prospective registry would capture patients at diagnosis but requires regular monitoring to ensure it remains accurate and that non-IBD cases and those who have emigrated/transitioned are removed.

Scottish incidence (**Chapter 5**) continues to increase over the last 45 years with the rise driven by paediatric-onset CD with an incidence of 10.6 per 100,000 for IBD, 6.6 per 100,000 for CD, 2.7 per 100,000 for UC and 1.3 per 100,000 for IBDU. The only other country reporting higher incidence was Finland with 13 per 100,000(173). Finland provides a good comparator for population-based incidence having similar population sizes, another is Ireland who reported an incidence of 5.6 per 100,000(153). Data collection differed between these studies with Ireland collecting data retrospectively through case note review and Finland gathering via a national health insurance scheme where physicians register a medical certificate for the patient with the condition according to diagnostic guidelines, families then are reimbursed for medications. This national data collection system may explain the increased incidence in Finland as new cases are captured

irrespective if diagnosed in paediatric or adult centres. Once validation work has been performed in Scotland, the incidence may increase more in line with Finland.

Previous assertions that the increase was related to a milder phenotype being diagnosed seems unlikely given the same diagnostic approach used in the centres for the previous study by Henderson(92) here. Others have hypothesised the increase is due to more young people aged 14-16 years being seen and diagnosed in paediatric centres now who would have previously been seen in adult services however, referral patterns have remained stable from the previous cohort to this so it is unlikely to sufficiently explain the observed rise and may even suggest an underestimate.

As PIBD increases, more attention focuses on potential causes and triggers. Genetics was initially thought to play a key role with the discovery of the NOD2/CARD15 gene which led to further exploration of the genome and the discovery of 163 loci thought to be involved in IBD(310).However, most risk alleles only increase the chance of developing IBD by a small magnitude supporting the role of environment in pathogenesis(186). Furthermore, genetics evolve over thousands of years so would not have had enough time to sufficiently change in the last 30 years to fully explain the increase. The current hypothesis is that in genetically susceptible hosts there is a dysregulated immune response to intestinal flora leading to the development of IBD. Disruption to the microbiome is associated with the development of IBD(311) and within IBD there are particular bacteria which are associated with IBD subtypes such as *Escherichia coli* in ileal CD(312) as well as reduced microbial diversity(229). Abnormalities in both the innate and adaptive immune responses are thought to contribute to abnormal intestinal responses in IBD. The results of GWAS studies has focused on mucosal innate immune responses such as defects in the epithelial barrier integrity, autophagy, innate microbial sensing and unfolded protein responses as leading to the development of IBD.

In countries with increased industrialisation and “westernisation” reporting increasing incidence of PIBD(2, 87), exploring the “exposome” or environmental triggers are crucial to understanding the pathogenesis. Several risk factors have been identified including air pollution, smoking, rural living, pets at home and larger family size(201, 217, 221). Environmental factors have been shown to cause epigenetic changes (233) which are then affect interaction with the intestinal microbiome(234) and immune response(235) potentially leading to the development of IBD. Epigenetic changes may explain the early onset of disease in childhood in certain patients given the significant overlap in susceptibility genes shared by both adults and children with IBD(313). Antibiotic usage may also contribute to PIBD with an increased risk in those treated with antibiotics in the first year of life developing PIBD(218), this assertion is further supported by a recent case control study which reported an increased risk of developing IBD in those who had received antibiotics between 3 months to 5 years prior to diagnosis of IBD, with the risk was highest in those under 18 years(314).

Diet has been implicated in PIBD with a recent systematic review reporting the only a consistent association between high dietary fibre and intake of fruit with a decreased rate of CD(227). Other studies have reported that a Mediterranean diet is protective(315) yet others report an association with lower intake of fruit and vegetables(228). Diet affects the microbiome as has been shown in PIBD patients treated with EEN(316) and in healthy children(317) which may then affect the risk of developing IBD.

The current trend of ever-increasing incidence and prevalence of PIBD continues in countries which have reported data, however, understanding of the pathogenesis leaves more questions unanswered than information provided. It is likely a complex and difficult relationship between genetics, environment, immune function and microbiota which leads to the development of PIBD.

9.3. Inflammatory bowel disease unclassified

Much about IBDU is contentious and in evolution having been first formally classified in 2005(9). Significant work is now underway to understand the natural history, disease reclassification, diagnostic algorithms and treatment options of this least common subtype of IBD(138, 239, 245). IBDU as a distinct subtype of PIBD is supported by the results of this study; 41% remained IBDU despite endoscopic reassessment with a median follow-up of 2.8 years. 23% did change diagnosis after endoscopic re-evaluation, most commonly to CD, with a small number requiring four endoscopic reassessments before changing diagnosis. The high rate of reassessment in IBDU patients is likely to reflect the clinician's discomfort with the diagnosis and keenness to reclassify as either CD/UC, yet despite these efforts, often patients remain IBDU reinforcing the assertion of a distinct subtype with its own disease course. However, treatment effects can complicate the interpretation of histology during reassessment so is likely to explain in part why some patients remain IBDU.

An interesting comparator for our data is the Eurokids registry, a prospective study across Europe, North America and Israel where at diagnosis, 7.7% of cases were IBDU which fell to 5.6% at the end of 5 year follow up as children underwent re-evaluation, most changed to UC (23/117) but 67% remained IBDU (138). However, Eurokids has methodological challenges that limit the generalisability of the findings including, lack of standardised diagnostic work up and histological review as both were clinician dependent at the individual centre. 42/265 reported cases of IBDU in Eurokids had features incompatible with the diagnosis such as granulomas or radiological evidence of small bowel disease(138). Another comparator is an Israeli population-based cohort of IBDU patients collected over 27 years with at least one year follow up, 45% changed to CD and 9% to

UC(318) in this cohort. However, the authors do not report on when cases were diagnosed or what investigations were performed, although the terminal ileum was not seen in 7% of cases who then had small bowel imaging (318). The high number of patients reclassified poses the question as to the validity of the initial diagnosis which the authors do not validate as IBDU. Potentially cases were labelled as IBDU where there was initial doubt but with modern classification would be diagnosed as CD/UC.

Current hypotheses are that IBDU affects younger patients with a more aggressive phenotype which contradicts our findings of a milder phenotype in older children with the commonest age group 11-15 years (**Chapter 6**). The incidence in Scotland increased over 13 years unlike other studies that have shown a steady rate(138), this could relate to a more robust diagnostic evaluation in this cohort compared to historical cases and that performed in other centres. A more rigorous diagnostic assessment may explain why IBDU is commoner in children than adults(140) who do not routinely undergo a upper gastrointestinal endoscopy and colonoscopy. Serology has been used in discerning IBD subtype but a recent study found no clear associations for IBDU(319), however, genetics have shown that it is different subtype differing from both UC, colonic and ileal CD suggesting a genetic continuum from ileal CD to UC(244).

In this cohort, most patients received UC treatment (5-ASAs/corticosteroids) at induction with 87% achieving remission, however, one patient who was treated with EEN entered remission and remained IBDU which suggests a more complex phenotype. Greater understanding will come from population-based studies of patients diagnosed using standard algorithms and regular monitoring via databases.

9.4. Anti-TNF therapy in Scotland

In **chapter 7**, anti-TNF drugs infliximab and adalimumab were shown to be safe and effective with 59% of CD and 54% of UC patients achieving remission post induction with IFX and 68% achieving remission with ADA. 13% had an infusion reaction to IFX and 7% had an adverse reaction requiring hospitalisation with no deaths. ADA was also well tolerated with only 9% had an adverse event requiring hospitalisation with 26% having milder events including infections. A significant number of patients went on to develop dependency requiring extended courses occurring in 40% for IFX and 60% for ADA. Risk factors for dependency was lack of steroid use at baseline. IFX had improvement in linear growth for those who achieved clinical remission post induction, were in the early stages of puberty (Tanner 2 and 3) and those who had disease for under 2 years. Improvement was seen with adalimumab at 12 months in Tanner stages 2-3.

Modern use of anti-TNF therapy in children has changed significantly from an episodic or “as needed” basis initially to maintenance therapy (53, 55) with dosing based on weight alone initially but now adjusted according to therapeutic drug levels (61). Current evidence supports a more personalised approach or “treat to target”, by proactively adjusting infliximab levels to a therapeutic range even when patients are well, which, results in reduced rates of treatment failure including the need for surgery, IBD related hospitalisation or serious infusion event(61). Additional benefits will come from cost savings related to decreased adverse events which may negate the higher costs incurred from increasing anti-TNF usage and doses. A key strategy going forward is to identify early in the disease course those patients who would benefit from anti-TNF therapy and commence early which may alter disease course.

9.5 Cancer and mortality in PIBD

As demonstrated in **Chapter 8**, cancer and death remain an infrequent but devastating consequence in PIBD with a quoted risk of 5.3 per 10,000 patient years in a recent systematic review of children treated with infliximab(296). While not all deaths in this cohort were directly related to IBD and none to the use of infliximab, two cases of cancer were observed, both of which were treated with thiopurines, including a case of gamma delta non-Hodgkin's lymphoma which proved fatal.

It is challenging to quote the exact risk of malignancy or death given the lack of accurate prevalence data to use as a denominator and paucity of population-based studies although this is now improving(120, 304). Population-based studies have reported an increased mortality for both CD and UC in PIBD patients(122, 304), including an recent Danish study where CD mortality was 62% higher for those diagnosed under 19 years when compared to those diagnosed aged 60-79 years with a two-fold increase for UC patients diagnosed in childhood(122). Other nationwide cohort studies have not observed this increase, potentially related to the limited follow-up of 11 years(120). Swedish registry data reported an increase in cancer in PIBD occurring under 18 years and in adulthood, quoting a relative risk of 3.2 of UC and for 1.8 CD(320). They suggested no increased risk for thiopurines contrary to other published evidence, however, these results must be interpreted with caution, data is from 1964-2014, during which time significant advances have been made in the treatment of PIBD improving disease control as uncontrolled inflammation is a significant risk factor for development of gastrointestinal malignancy (321) the most common type of cancer reported. EPIMAD also reported a three-fold increase risk of malignancy with 2/9 cancers colonic in origin. ESPGHAN reports 6/25 deaths related to infection and 8 to cancer. suggesting that immunosuppression is a key risk factor in these deaths. However, the increased risk of cancer precedes the widespread

use of anti-TNF drugs and azathioprine(120). A recent systematic review on the natural history of PIBD reported in 12/14 patients who developed cancer had either small bowel or colonic adenocarcinoma, after 19 years when most paediatric patients would be followed up in adult practice(116).

In adult-onset IBD, routine screening is advised for cancer surveillance which begins 8 years post diagnosis and is repeated every 2-3 years(322). Recent colonoscopy was associated with a reduced incidence of colorectal cancer and in those diagnosed a reduced mortality(323). Screening for colorectal cancers is not routine in paediatric practice, however, given the increased risk and evidence of improved outcomes, a potential strategy would be routine colonoscopy prior to transition in those who had not undergone in the last 3 years.

Cancers may be classed as disease related and secondary to chronic inflammation such as colonic or cholangiocarcinoma or treatment related such as lymphomas. The increased risk of colonic cancer associated with IBD is well established(324, 325) with cancers such as EBV positive lymphomas thought to be treatment related(117, 302).

Studies in adults with UC have shown a 4-fold increase in risk of lymphoma in those being treated with thiopurines which increases each year it is given reaching statistical significance after 4 years before reverting to baseline once the drug has been discontinued(303). This increased risk is supported by a multicentre prospective registry which reported no increased risk of malignancy with anti-TNF agents compared to those not treated with a biological yet an increased risk of malignancy in those treated with thiopurines with or without a biologic(130). Based on these result, deeper consideration to discontinuation of therapy should be discussed with patients and families, however, many paediatric gastroenterologists would be cautious about stopping treatment while potential adverse effects on growth, pubertal development and schooling exists(326). Therefore, a

balance is needed between treatment to control IBD symptoms affecting quality of life versus the risks of uncontrolled inflammation leading to colonic dysplasia and immune dysregulation leading to impaired tumour surveillance(118). Newer drugs being developed need to reduce bowel inflammation with no increased risk of infection and sepsis. Prospective national registries recording cancer and mortality in both adult and paediatric-onset IBD would aid clinicians in counselling patients and families. France and Finland have such databases to follow patients from diagnosis in childhood to adulthood so not lost to follow up, a key limitation in many studies on mortality.

9.6. Future directions and research agenda

Incidence in Scotland of PIBD has been collected for 45 years with validation of the cohort until 1995 ensuring the robust nature of the data obtained with non-IBD cases removed. A key success for PIBD in Scotland has been the introduction of managed clinical networks and strong relationships between tertiary and secondary care allowing patients to access high quality care close to home. Once the validation has been performed and relevant ethical permissions obtained, further temporal trend analysis can be performed on the North-South divide which has been demonstrated already.

A prevalent database is needed to ensure adequate provision of services for children and their families for this is a chronic lifelong condition which impacts upon growth, nutrition, psychological wellbeing and educational attainment. Financially this will allow the Scottish government to accurately understand the disease burden and cost involved to ensure high standards of care as per UK IBD standards. Once the validation work has been performed, this can be used to create a prevalent database for each of the lead centres. After the prevalent database is established, a database manager or researcher, would visit each centre on a regular basis to add in prospectively new incident cases, review changes

of diagnosis with the clinical team, remove those who have either transitioned or moved out of the area and add in those who have relocated.

The increase in mortality in adults who were diagnosed in childhood in other population-based cohorts is concerning, particularly given the increasing number of young people with IBD making it is critical to follow these children into adulthood. Once a prevalent database is established, it would allow cohort studies to be performed and explore in more depth mortality and morbidity of PIBD using data linkage via Information Services Division Scotland. Data linkage of patients with PIBD diagnosed from 1981-2014 (once validation work completed) could be matched (age, deprivation, geographical location and gender) to controls using a case control study design then access data on admissions (SMR01- covers inpatient admissions and morbidity), cancer registry (SMR06) and death (National Records for Scotland) using existing Scottish government held records. Similar methodology could be used to gather information on cardiovascular disease and thromboembolic events and to explore environmental risk factors including rural/urban location and latitude. However, an easier process would be the electronic transfer of information to adult hospitals where data could then be captured differentiating these cases from prevalent adult cases, consequently outcomes for these patients could be more easily identified.

The Scottish biologicals registry has now been established and by continuing to input data for all patients nationwide, long term data n the effects of these drugs including malignancy and mortality can be captured. Anti-TNF drugs have only been widely used in the last 10 years in paediatric practice and 15 years in adult practice so further longitudinal data will enhance knowledge and expertise in optimal management. The registry could be expanded to collect data on drug levels, co-immunosuppression and drug escalation and de-escalation pathways. An additional benefit will be the ability to capture data on newer

drugs including vedolizumab, ustekinumab and tofacitinib to gain further insight into efficacy/side effects to support or refute their use in PIBD using “real life” clinical data given the current delay of 6-8 years between obtaining a licence for use in adult-onset IBD and PIBD

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