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Burdens and outcomes of paediatric-onset inflammatory bowel disease in regional, national and pan-UK cohorts

Dr Victoria May-Wan Merrick

Doctorate (MD) thesis

University of Edinburgh

2022
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ABSTRACT

Background
Inflammatory bowel disease (IBD) comprising Crohn’s disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU) is a chronic condition affecting people globally; a significant proportion of patients present in childhood and adolescence and the incidence and prevalence of paediatric IBD (PIBD) is reported to be rising worldwide. It is a complex condition, multifactorial in origin, with genetics, environment, immunity and infection all contributing. Common genetic architecture is shared with other autoimmune diseases, which are known to cluster within families and individuals, and available treatment options also overlap; this includes the biological agents which inhibit TNF (anti-TNFα agents). Patients diagnosed in childhood and adolescence in most countries are cared for in paediatric services before moving to adult services at an appropriate time for lifelong care; this move is either by transfer of information only or as part of a transition process involving 1 or more joint clinic appointments involving the patient, their parents/carers, their current PIBD clinical team and the adult IBD team taking over their care.

Aims
This thesis aims to use cohort studies at different geographical levels to investigate the following:

1. The outcomes of a Scottish regional (South East Scotland) cohort of PIBD patients around the time of transition from paediatric to adults services
2. The prevalence of one or more additional autoimmune diseases (AIDs) in a Scotland-wide cohort of PIBD patients
3. The real-life experience of biological therapy (anti-TNF) use in a UK-wide cohort of PIBD patients

Methods
Transition cohort – data were collected locally of patients identified as having discharged from paediatric to adult services 2007-2013 via a database kept primarily for service development and delivery; comparing status at time of transfer and last adult follow-up (LAFU).
**Autoimmune diseases cohort** – data were collected from all 4 Scottish PIBD centres (Aberdeen, Dundee, Edinburgh, Glasgow) after identification from an incident and prevalent research cohort with previous recruitment via full informed consent.

**Biological therapy cohort** – data collected and held by the Royal College of Physicians as part of the IBD biological therapy audit, submitted by local clinicians, of PIBD patients newly commenced on biological therapy from 09/2011 to 02/2014.

**Results**

**Transition cohort** – Of 138 patients who transferred to adult services, pan-treatment exposure (to all commonly available therapies at the time of data collection) rose significantly from 12% at transfer to 27% at LAFU (p=0.006) and pan-treatment refractory disease from 4% at transfer to 19% at LAFU (p=0.001). 37% of all PIBD patients had one or more IBD related surgical procedure by LAFU, with 22% of CD patients requiring at least one procedure by time of transfer. Sixty percent of patients who miss ≥1 appointment in the year prior to transfer go on to miss appointments in the year post transfer compared to 21% (15/73) who had no missed appointments pre-transfer; this was statistically significant (p=0.00001). Thirty-one percent of those who missed appointments pre-transfer were lost to follow-up at the end of the study compared to 11% with no missed appointments (p=0.005). Fifteen percent of patients overall had significant psychological +/or social comorbidity during the study period, the commonest issues were depression, deliberate self-harm and anxiety.

**Autoimmune diseases cohort** – Of 809 patients in the cohort, 6.4% (52/809) had an additional diagnosis of an associated autoimmune disease; 3 patients had multiple co-morbid AIDs in addition to IBD. Autoimmune liver disease in 37% was the most frequently occurring co-morbid AID, followed by psoriasis (23%), then juvenile idiopathic arthritis (JIA 17%).

**Biological therapy cohort** – Of 524 patients newly started on biological therapy, the response to induction was recorded in just 17% (89/524); of those 75% had a positive response and 60% achieved remission. In 2287 infusions and 302 years of patient follow-up, acute infusion reactions were reported in just 2% of initial (and 1% of follow-up) infliximab infusions and with no adalimumab treatments. Patient reported outcome measures were poorly utilised.
Conclusions

PIBD patients have a significant clinical and therapeutic burden of disease within paediatric services which continues to progress in adulthood. A significant proportion of PIBD patients are lost to follow-up in adult services; patients who miss appointments prior to transfer appear to be more at risk for this and may benefit from a targeted approach. Clinicians should be vigilant to the possible co-existence of additional autoimmune diseases in PIBD patients and actively monitor liver function and extra-intestinal signs and symptoms. Biological therapy appears to be safe and effective in real-world practice but the response to induction is poorly documented and this risks inappropriate continuation of therapy or inadequate drug monitoring; the need for improvement is highlighted.
LAY SUMMARY

Background
Inflammatory bowel disease (IBD) is an umbrella term which includes the individual conditions Crohn’s disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU) – it is a lifelong condition which affects people all over the world and can start at any age, including in children and young people.

The immune system (which helps keep you well by preventing and fighting infection) can sometimes misbehave causing problems (autoimmune disease); IBD is one of the conditions where this happens. We know that other conditions where this happens sometimes cluster together so that either multiple people in one family are affected by different conditions, or one person has more than one type of autoimmune condition.

There are lots of different treatments available but there is no cure (yet), so people who have the disease are looked after by specialist IBD teams in children’s (paediatric) and adult services according to their age. Some of the treatments available (biological therapies) in the last 10-15 years have been very effective in getting and keeping people better, but because they are new we are still learning about how patients and their medical teams find them.

What is this study about?
This study aims to look at different groups (cohorts) of children and young people with IBD to answer 3 main questions.

1. What are they like around the time they move from paediatric to adult services and what happens to them?
2. How many of them have one or more other autoimmune conditions?
3. What is the ‘real-life’ experience of biological therapies in these patients?

What are some of the findings?
By the time they move to adult services, young people with IBD already have a significant impact of disease in terms of how much of their bowel is affected and how badly, as well as the number of treatments they have required, including operations; their disease intensity and need for treatment continues to progress after they move to adult services. Patients
who miss appointments before leaving paediatric services are more likely to miss them in adult services and ultimately no longer be in regular follow-up, as are patients who don’t have joint appointments with their paediatric and adult teams before they finally leave children’s services.

Roughly 1 in every 16 patients with paediatric IBD had one or more other (additional) autoimmune condition; liver disease was the most common, followed by psoriasis (a skin condition) and a particular type of arthritis (joint condition).

The majority of patients have a positive response (as determined by their medical team) to biological therapy and over half have their disease brought under control completely, but this was not formally documented in most cases. The medications are safe and well tolerated, but patient reported quality of life scores were not used often enough to interpret any results.

**Why does it matter?**

Understanding more about how IBD impacts children and young people should help us to provide better care and information for them. Findings from this study suggest that missing appointments may be a red flag for being lost from follow-up in adult services and offer an opportunity to intervene with these patients. They also support the use of clinics where both the paediatric and adult IBD teams see patients together in the run-up to formally moving over to adult services.

These findings allow us to confidently inform our patients about how well treatments like biological therapy work and how safe they are, but also highlight the need to use and choose treatments carefully so we get the best out of each one over a lifetime of disease. The study increases the awareness of the chance of having more than one autoimmune condition, reminding us to be vigilant in looking out for these and also shows that we can do better in using scoring systems (such as Quality of Life questionnaires) and other measures, to assess how patients feel their quality of life is affected by IBD and their treatments.
DECLARATION OF ORIGINALITY

I declare that the work presented in this thesis is my own, unless otherwise indicated, performed at the department of Child Life and Health at the University of Edinburgh from September 2014 until September of 2017. This work has not been submitted for any other professional degree or qualification.

The data collection was executed by Dr Victoria Merrick with the following exceptions:

- Data for the autoimmune diseases (PICTS) cohort (chapter 4) were historically collected and kept on the database managed by Hazel Drummond at the University of Edinburgh Institute of genetics and molecular medicine. Hazel interrogated the database to identify patients with an additional autoimmune disease diagnosis who then went on to have full record review by me in their local centre. Access to records was facilitated by Dr Sabari Loganathan in the North of Scotland and Professor Richard Russell in the West of Scotland.

- Data for the UK IBD biologics audit (chapter 5) was collected locally by individual clinicians and submitted to the Royal College of Physicians who retained the raw data. The data were managed and released by Kajal Mortier, UK IBD audit project coordinator.

Statistical analysis was performed by Dr Victoria Merrick with the following exception:

- Data for the UK IBD biologics audit was retained in complete form by the Royal College of Physicians; any statistical analysis beyond comparison of categorical data and Chi squared analysis was performed by the RCP project statistician Dr Linda Williams (medical statistician in the University of Edinburgh Centre for Population Health Sciences).

Authorship of the included publication in the appendix is as follows:

ACKNOWLEDGEMENTS

It is difficult to adequately thank my supervisor, Professor David Wilson, for getting me to the point of thesis submission. His encouragement to pursue a career in paediatric gastroenterology, enthusiasm and belief that I would be capable of clinical research, and his endless patience and wisdom have been the catalyst to see this project to completion. He has used his knowledge and skill to foster and develop independent thinking and a desire to learn. I must also thank Professor Jack Satsangi, who welcomed me into his lab meetings and exposed me to basic science in IBD and the exciting progress in this field. Professor Richard Russell opened access to the UK biologics audit, then guided and supported me through data handling and manuscript submission, with patient motivation. Having internationally renowned experts believe you are capable of making a contribution to their team is extremely humbling and I am so grateful for their advice and support.

The SSPGHAN network is a critical pathway in Scottish paediatric GI research and the collegiate nature of the three tertiary centres is always inspiring. In the North of Scotland I am particularly grateful to Dr Sabari Loganathan who facilitated data collection there. In the West of Scotland my clinical colleagues in the MDT were very supportive and a particular thank you to Michelle Brooks for her ongoing interest and motivational messages to finish! In South East Scotland the whole GI MDT have encouraged and supported me in my GI journey so far, but particular thanks must go to Dr Peter Gillett, who made time for an interested trainee, welcomed me into his own research and, along with David Wilson, supported and nurtured my clinical progress.

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Of course this research is only possible through the willingness of patients and their families to participate in studies and the clinical teams who record and submit data for audit, so a huge thanks to them.

Finally I must thank my parents, Lan and Doug (to whom it never even occurred I might not finish), for a lifetime of encouragement and many weeks of help with childcare; my husband Ali, for all the belief, support and sacrifice, as well as the formatting and overall IT knowledge; and to Isaac and Jonathan – the best kinds of interruption and joyful providers of perspective.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AA</td>
<td>Alopecia areata</td>
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<tr>
<td>AI</td>
<td>Artificial intelligence</td>
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<tr>
<td>AIDs</td>
<td>Autoimmune diseases</td>
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<tr>
<td>AIH</td>
<td>Autoimmune hepatitis</td>
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<tr>
<td>AILD</td>
<td>Autoimmune liver disease</td>
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<tr>
<td>AIP</td>
<td>Autoimmune pancreatitis</td>
</tr>
<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
</tr>
<tr>
<td>ASC</td>
<td>acute severe colitis</td>
</tr>
<tr>
<td>ASCA</td>
<td>anti-Saccharomyces cerevisiae antibody</td>
</tr>
<tr>
<td>ASC/Overlap</td>
<td>Autoimmune sclerosing cholangitis/overlap syndrome</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BSPGHAN</td>
<td>British Society for Paediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
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<tr>
<td>CLaH</td>
<td>Department of child life and health</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus disease 2019 – infection caused by SARS-CoV-2 virus</td>
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<tr>
<td>CPRD</td>
<td>Clinical practice research datalink</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CVID</td>
<td>Common variable immune deficiency</td>
</tr>
<tr>
<td>CYP</td>
<td>Children and young people</td>
</tr>
<tr>
<td>DMARDs</td>
<td>Disease modifying anti-rheumatic drugs</td>
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<tr>
<td>ECCO</td>
<td>European Crohn’s and colitis organisation</td>
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<tr>
<td>EIM</td>
<td>extra-intestinal manifestation</td>
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<tr>
<td>EpiCom cohort</td>
<td>ECCO epidemiological committee cohort study</td>
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<tr>
<td>ESPGHAN</td>
<td>European Society for Paediatric Gastroenterology, Hepatology and Nutrition</td>
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<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>EUA</td>
<td>examination under anaesthetic</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<tr>
<td>GWAS</td>
<td>genome wide association studies</td>
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<tr>
<td>HLH</td>
<td>haemophagocytic lymphohistiocytosis</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<td>HSTCL</td>
<td>hepatosplenic T-cell lymphoma</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
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<tr>
<td>IBDU</td>
<td>inflammatory bowel disease unclassified</td>
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<td>ICN</td>
<td>ImproveCareNow network</td>
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<td>IMID</td>
<td>Immune mediated inflammatory disease</td>
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<td>IQR</td>
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<td>intravenous</td>
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<td>International Society for Pediatric and Adolescent Diabetes</td>
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<tr>
<td>JIA</td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>MAP</td>
<td>Mycobacterium avium paratuberculosis</td>
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<tr>
<td>MDT</td>
<td>Multi-disciplinary team</td>
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<tr>
<td>miRNA</td>
<td>microRNA</td>
</tr>
<tr>
<td>MRE</td>
<td>magnetic resonance enterography</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NGT</td>
<td>nasogastric tube</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for health and Care Excellence</td>
</tr>
<tr>
<td>NOD2</td>
<td>nucleotide-binding oligomerization domain-containing 2</td>
</tr>
<tr>
<td>OFG</td>
<td>orofacial granulomatosis</td>
</tr>
<tr>
<td>pANCA</td>
<td>perinuclear anti-neutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>PBC</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>PEN</td>
<td>Partial enteral nutrition</td>
</tr>
<tr>
<td>PIBD</td>
<td>paediatric inflammatory bowel disease</td>
</tr>
<tr>
<td>PIBD-SETQuality</td>
<td>Paediatric Inflammatory Bowel Disease network – Safety, Efficacy, Treatment and Quality improvement of care project</td>
</tr>
<tr>
<td>PICR</td>
<td>Pediatric IBD collaborative research group registry</td>
</tr>
<tr>
<td>PGA</td>
<td>physician global assessment</td>
</tr>
<tr>
<td>PROMs</td>
<td>Patient reported outcome measures</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>PSOR</td>
<td>psoriasis</td>
</tr>
<tr>
<td>PUCAI</td>
<td>paediatric ulcerative colitis activity index</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCP</td>
<td>Royal College of Physicians</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>Rx</td>
<td>therapy</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>S1P</td>
<td>Sphingosine 1 phosphate</td>
</tr>
<tr>
<td>SAR</td>
<td>sarcoidosis</td>
</tr>
<tr>
<td>SECURE-IBD</td>
<td>Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion – IBD</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>SFR</td>
<td>steroid free remission</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>SPA</td>
<td>spondyloarthritis</td>
</tr>
<tr>
<td>SS</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>T1DM</td>
<td>type 1 diabetes mellitus</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TCS</td>
<td>Transition clinic - single</td>
</tr>
<tr>
<td>TDM</td>
<td>Therapeutic drug monitoring</td>
</tr>
<tr>
<td>TE</td>
<td>Transfer event</td>
</tr>
<tr>
<td>THY</td>
<td>Thyroid disease (including Grave’s disease and Hashimoto’s thyroiditis)</td>
</tr>
<tr>
<td>TP</td>
<td>Transition process</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>VAS</td>
<td>vasculitis</td>
</tr>
<tr>
<td>VDZ</td>
<td>vedolizumab</td>
</tr>
<tr>
<td>VEOIBD</td>
<td>very early onset inflammatory bowel disease</td>
</tr>
<tr>
<td>VIT</td>
<td>vitiligo</td>
</tr>
<tr>
<td>WCE</td>
<td>wireless capsule endoscopy</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>wPCDAI</td>
<td>weighted paediatric Crohn’s disease activity index</td>
</tr>
<tr>
<td>YAC</td>
<td>Young adult clinic</td>
</tr>
<tr>
<td>Yr</td>
<td>year</td>
</tr>
</tbody>
</table>
1 INTRODUCTION AND BACKGROUND

When we hear the terms ‘childhood and adolescence’, we typically think of things such as play, learning, wonder, excitement, exploration, socialisation, growth and development. Running to the toilet, tummy pain, being too tired to go to school or see friends, regular medications and visits to hospital on the other hand, don’t usually spring to mind. And yet for many children and young people, these are every day realities that shape their formative years.

1.1 Inflammatory Bowel Disease

The Inflammatory Bowel Diseases (IBD), comprising Crohn’s Disease (CD), Ulcerative Colitis (UC) and IBD Unclassified (IBDU) are estimated to affect 2.6 million people in Europe and are increasing in incidence and prevalence, notably in children. This is a global phenomenon, although much of the data is from Europe and North America, with the United Kingdom (UK) and Scotland in particular being no exception. UK data report a paediatric IBD (PIBD) incidence of 7.82/100,000/yr (4.75/100,000/yr CD, 2.06/100,000/yr UC) in Scotland and 9.37/100,000/yr (5.85/100,000/yr CD, 2.67/100,000/yr UC) in a South England population. The most recent Scottish data (published as an abstract) measuring PIBD incidence between 2015 and 2017, report an incidence of 12.0/100,000/yr. Recent local data from Lothian reveals that the point prevalence for IBD at any age is 1 in 125 (0.8%), and that 8% of those patients had onset and diagnosis of disease at <17 years of age. As a lifelong inflammatory condition, the burden both to the patient and the healthcare system is great, with expensive medical treatment, hospitalisation and high chances of needing surgery.

Molodecky et al in a systematic review of 260 epidemiological studies report highest incidence and prevalence rates of IBD in westernised nations, in particular Canada, Northern Europe and Australia and amongst those of Caucasian and Jewish ethnicity (trends which have long been reported), with an overall increasing incidence with time. What is more recently emerging however is that incidence and prevalence rates are increasing in developing countries, as they become more industrialised, and that people from traditionally low prevalent regions increase their risk on moving to high prevalent countries, especially first generation children. Alatab et al, on behalf of the Global Burden of Disease Study 2017 Inflammatory Bowel Disease Collaborators, report 6.8 million cases
of IBD globally in 2017, increased from 3.7 million in 1990, with the highest age standardised prevalence in high income North America and the UK, but rising rates in regions with formerly low rates including Asia, Oceania and sub-Saharan Africa.\textsuperscript{10} Ng et al in their systematic review of predominantly adult population data demonstrate that incidence is stabilising in Europe and North America (compared to accelerating incidence in newly industrialised regions in Africa, Asia and South America) whilst the prevalence globally continues to rise.\textsuperscript{11} A more recently published systematic review and meta-analysis of purely paediatric IBD incidence and prevalence data across all 51 European states since 1970 demonstrates much stronger evidence of a north-south gradient (highest in north) in incidence with less defined east-west gradient (highest in west) compared to adult data, with widespread increasing incidence across Europe. When limited to national studies only, there was some evidence of the highest increases in earlier years of study and a suggestion of levelling off in more recent years.\textsuperscript{12} A Canadian study of health administrative data examined over 5000 incident cases and over 6500 prevalent cases of PIBD, diagnosed 1999-2010. It showed geographical variations in incidence between Canadian provinces and a significant increase in prevalence over time. Whilst there was no significant rise in overall incidence, there was a rapid increase in the incidence of very early onset IBD (VEOIBD), in this study defined as diagnosis <5 years of age.\textsuperscript{9} Recently published registry data from Saxony in Germany also shows a downward trend in age at diagnosis as well as age-standardised incidence rising over a decade (2000-2009) from 4.6 to 10.5 per 100,000 person years.\textsuperscript{13} In contrast to this, Finnish nationwide registry data published in 2017 demonstrated a consistent year on year rise in PIBD incidence from 7/100,000 in 1987-1990 to 23/100,000 in 2011-2014, but the most prominent increase amongst adolescents, with a relative plateau in children presenting aged 0-9 years.\textsuperscript{14} Systematic review of global paediatric (age <21 years) data (131 studies) convincingly supports such local trends, with 100% of studies reporting increasing prevalence and 84% increasing incidence.\textsuperscript{15} There is a paucity of epidemiological PIBD data from Asia but studies to date show sharply rising incidence and a younger mean age of onset compared to European registry figures as well as disproportionately higher representation amongst Indian ethnicity patients in multi-ethnic Asian settings such as Singapore and Malaysia.\textsuperscript{16} Inflammatory bowel disease therefore, is becoming increasingly common globally, presents before adulthood in approximately 1 in 12 cases\textsuperscript{8,17}, and age at diagnosis seems to be getting younger; but how is it defined and what is the underlying pathophysiology?
1.1.1 IBD phenotypes

The umbrella term Inflammatory Bowel Diseases (IBD) refers to chronic (lifelong) conditions of inflammation of the gastrointestinal (GI) tract. Affected patients typically present with any combination of abdominal pain, loose stools with or without blood, weight loss, growth failure and fatigue.\textsuperscript{18,19} There is no single underlying cause and a complex combination of genetic, immune and environmental factors are implicated.\textsuperscript{20–22}

Typical clinical features for each IBD subtype are shown in Table 1 but patients may present with any or all of the findings listed, and a low threshold for considering IBD in the differential diagnosis of many clinical presentations should be maintained.

1.1.1.1 Crohn’s Disease

Traditionally separated into two major types, Crohn’s disease (CD) can affect the gut anywhere from the mouth to the anus and can also be associated with extra-intestinal manifestations involving the skin, eyes or joints. Hallmark histopathological features are focal transmural (full wall thickness) inflammation and identification of non-caseating granulomas, distant from any ruptured crypts. Involvement is often discontinuous, with areas of healthy gut lining interspersed with diseased segments of inflammation.\textsuperscript{18,21} Isolated granulomatous inflammation of the mouth is conventionally referred to as orofacial granulomatosis (OFG), whereas in patients who have intestinal luminal disease, involvement in the mouth is usually described as oral Crohn’s. Oral involvement may be more common in paediatric onset IBD than adult,\textsuperscript{23,24} and whilst the oral manifestations are often lost over time, luminal disease burden can be severe. Although oral involvement has been proposed as a marker for a more severe phenotype, this has not been proven.\textsuperscript{24,25}

1.1.1.2 Ulcerative Colitis

In contrast, the other major type, Ulcerative Colitis (UC), is typically defined by diffuse continuous inflammation only affecting the colon, usually progressing proximally from the rectum.\textsuperscript{18,21} There is usually disturbance of crypt architecture and basal plasmacytosis and the absence of epithelioid granulomas. However, there may be atypical features such as macroscopic rectal sparing or the presence of a caecal patch (inflammation in the caecum adjacent to normal segment of mucosa separating it from distal [left sided] inflammation). Extra-intestinal manifestations may also be present, as with Crohn’s.
<table>
<thead>
<tr>
<th>Clinical findings (commonest)</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
<th>Atypical UC</th>
<th>IBDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Diarrhoea</td>
<td>As UC</td>
<td>As UC</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Weight loss</td>
<td>Rectal bleeding</td>
<td>Short duration of symptoms</td>
<td>Positive ASCA with negative pANCA</td>
</tr>
<tr>
<td>Diarrhoea ± bleeding</td>
<td>Diarrhoea</td>
<td>Abdominal pain</td>
<td>Acute Severe Colitis</td>
<td>Non—bloody diarrhoea</td>
</tr>
<tr>
<td>Unexplained anaemia</td>
<td>Ulcerative Colitis</td>
<td>Inflammation may end in a transition zone in colon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>Erythema, Granularity, Friability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth failure</td>
<td></td>
<td>Purulence exudate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orofacial Granulomatosis</td>
<td></td>
<td>Superficial ulcers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Macroscopic findings | | |
|----------------------|---|
| Mucosal aphthous, linear or serpentine ulcers | Erythema, Granularity, Friability |
| Cobblestoning        | Purulence exudate |
| Strictureing or stenosis ± pre-stenotic dilatation | Inflammation
| Small bowel ulceration | may end in a transition zone in colon |
| Perianal inflammation or abscess | Distal colon most severely affected – proximal gradient of improvement (if any) |
| Large perianal skin tags | |
| Skip lesions         | Rectal sparing |

| Microscopic findings | | |
|----------------------|---|
| Non-caseating granulomas (distant from any ruptured crypts) | Continuous inflammation of the colon starting distally in rectum and extending proximally |
| Focal, transmural chronic inflammation | Distorted crypt architecture |
| Submucosal fibrosis | Cryptitis / crypt abscesses |
|                      | Focal or diffuse basal plasmacytosis |
|                      | Backwash ileitis (must have abnormal caecum) |
|                      | Signs of chronicity may be absent (esp if short duration) |
|                      | Normal crypt architecture |
|                      | Diffuse or focal gastritis (but no granulomas) |
|                      | Transmural inflammation in ASC |

| Microscopic findings | | |
|----------------------|---|
| Complete (macro+microscopic) rectal sparing | |
| Transmural inflammation (not ASC) | |
| Focal chronic duodenitis on multiple biopsies | |
| Focal active colitis on >1 biopsy | |
**Extraintestinal manifestations**

<table>
<thead>
<tr>
<th>Extraintestinal manifestations</th>
<th>Dermatological e.g. erythema nodosum, pyoderma gangrenosum, pyostomatitis vegetans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ophthalmological e.g. iritis, uveitis, papilloedema</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal e.g. arthritis (axial or peripheral), osteopenia/osteoporosis,</td>
</tr>
<tr>
<td></td>
<td>compression fracture</td>
</tr>
<tr>
<td></td>
<td>Hepatobiliary e.g. Primary Sclerosing Cholangitis, gallstones, autoimmune hepatitis</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Aphthous stomatitis</td>
</tr>
</tbody>
</table>

IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis; ASC, acute severe colitis; ASCA, anti-Saccharomyces cerevisiae antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody

### 1.1.3 IBD Unclassified

Evolving from the diagnosis ‘Indeterminate colitis’, essentially used when cases could not clearly be stratified into UC or CD, the term IBD unclassified (IBDU) has predominantly come to be used for patients with isolated colonic disease resembling UC but some non-diagnostic ‘soft’ features suggestive of CD.\(^{21,27}\) However there is a growing understanding that IBDU is most likely a distinct diagnostic subtype with genuine overlapping features of both CD and UC, and a move towards using robust criteria to consistently identify and label IBD subtypes; UC, atypical UC (phenotypic variants of rectal sparing, caecal patch, some upper GI changes, or patchy microscopic changes associated with short duration)\(^{18}\), IBDU and CD.\(^{27}\)

### 1.1.4 Classification of PIBD

Disease expression can further be described according to location and behaviour, amongst other features, allowing classification of an individual’s disease by phenotype. Agreed international IBD classification has evolved from the Vienna classification (1998) into the Montreal revision (2005)\(^{28,29}\) and then further modified for specific use in the paediatric population – the Paris classification (2011).\(^{30}\) Age at presentation and disease location and behaviour are more accurately defined, and the importance of growth delay is accounted for (Table 2). This is expanded upon further in Chapter 2 Methodology. These systems allow consistent description and accurate categorisation of disease type, allowing uniformity in PIBD research, which in turn facilitates appropriate interpretation of data and application in clinical practice, both for prognostication and management. As gene discovery evolves and expands our understanding of the relationship between phenotype and genotype, further modification of classification systems will likely be required and
indeed, since the Paris age categories of 0-<10yrs and 10-<17yrs were introduced, further delineation to 0-<6yrs as very early onset IBD (VEOIBD) has become commonplace.\textsuperscript{31,32}

<table>
<thead>
<tr>
<th>Table 2 - Paris classification of PIBD\textsuperscript{30}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn’s disease</strong></td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
</tr>
<tr>
<td>A1a: 0-&lt;10 years</td>
</tr>
<tr>
<td>A1b: 10-&lt;17 years</td>
</tr>
<tr>
<td>A2: 17-40 years</td>
</tr>
<tr>
<td>A3: &gt;40 years</td>
</tr>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td>L1: distal 1/3 ileum ± limited caecal disease</td>
</tr>
<tr>
<td>L2: colonic</td>
</tr>
<tr>
<td>L3: ileocolonic</td>
</tr>
<tr>
<td>L4a: upper disease proximal to Ligament of Treitz</td>
</tr>
<tr>
<td>L4b: upper disease distal to ligament of Treitz but proximal to distal 1/3 ileum</td>
</tr>
<tr>
<td><strong>Behaviour</strong></td>
</tr>
<tr>
<td>B1: non-stricturing and non-penetrating</td>
</tr>
<tr>
<td>B2: stricturing (constant luminal narrowing demonstrated by radiologic/endoscopic/surgical examination \textit{WITH} pre-stenotic dilatation \textit{+}or obstructive signs or symptoms)</td>
</tr>
<tr>
<td>B3: penetrating (occurrence of bowel perforation, \textit{intra-abdominal fistulas, inflammatory masses} \textit{+/or abscesses, at any time in disease course EXCLUDING} postoperative complications \textit{or} isolated perianal or rectovaginal fistulae)</td>
</tr>
<tr>
<td>B2B3: penetrating + structuring disease (either concurrently or at different times)</td>
</tr>
<tr>
<td>P: perianal disease modifier</td>
</tr>
<tr>
<td><strong>Growth</strong></td>
</tr>
<tr>
<td>G\textsubscript{0}: No evidence of growth delay \textit{(at diagnosis or subsequently)}</td>
</tr>
<tr>
<td>G\textsubscript{1}: Growth delay \textit{(impaired linear growth at diagnosis or subsequently; defined as either height score significantly less than expected height z-score} \textit{or current height z-score} \textit{significantly less than height z-score at diagnosis})</td>
</tr>
<tr>
<td>* Difference between observed and predicted height z-scores \textit{(using mid-parental height formula)} \textit{&gt;2.0 OR} difference between observed and pre-illness height z-scores \textit{&gt;1.0.}</td>
</tr>
<tr>
<td>^reduction in height z-score since diagnosis \textit{≥0.75}</td>
</tr>
<tr>
<td><strong>Ulcerative colitis</strong></td>
</tr>
<tr>
<td><strong>Extent</strong></td>
</tr>
<tr>
<td>E1: ulcerative proctitis</td>
</tr>
<tr>
<td>E2: left sided UC \textit{(distal to the splenic flexure)}</td>
</tr>
<tr>
<td>E3: extensive disease \textit{(hepatic flexure distally)}</td>
</tr>
<tr>
<td>E4: pancolitis \textit{(disease extends proximal to hepatic flexure)}</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
</tr>
<tr>
<td>S0: never severe</td>
</tr>
<tr>
<td>S1: ever severe</td>
</tr>
<tr>
<td>\textit{Severe disease defined according to Paediatric Ulcerative Colitis Activity Index (PUCAI) score ≥65}</td>
</tr>
</tbody>
</table>
1.1.2 IBD pathogenesis

1.1.2.1 Genetics

The global rise in incidence of IBD in recent decades tells us that simple genetics alone cannot determine the onset of disease, supported by the rapid advance of gene discovery through genome wide association studies (GWAS)\textsuperscript{33} and twin studies showing concordance of 16%-36% in monozygotic twins.\textsuperscript{2} Since the discovery of a loss of function gene variant in NOD2 associated with increased susceptibility to CD in 2001, >200 IBD susceptibility loci have been identified; some unique to UC, some to CD and the rest conferring risk to both subtypes.\textsuperscript{34–37} Most IBD genetics research has focused on European ancestry cohorts; a recent study by Gettler et al using genetic data to generate polygenic risk scores (a score usually calculated as a weighted sum of the number of risk alleles carried by an individual, with the aim of identifying subsets of higher risk individuals in a population) revealed poorer accuracy in prediction of IBD in populations of non-European ancestry, particularly in African-Americans, and highlighted the need for study of genetic data from increasingly diverse racial populations.\textsuperscript{38,39} Genetic architecture may have the most prominent role in VEOIBD, including the presence of monogenic defects rather than combinations of the IBD key genes, which may go some way to explaining the relatively distinct phenotype in this age group with higher prevalence of severe and extensive disease and an IBDU diagnosis.\textsuperscript{40}

1.1.2.2 Immunity

The immune response is the reaction of an organism to the presence of an external (and therefore potentially hostile) constituent for the purpose of defence and protection. In the human body it is a complex series of processes which is founded upon the ability to recognise host cells (self) from potential pathogens (non-self) and from there regulate the response, to balance the elimination of harmful microbes with the need to tolerate (and regulate) beneficial commensal microbes and avoid excessive damage of its own tissues.\textsuperscript{41,42} Innate immunity is the ‘first line of defence’ against a pathogen – non-specific, hard-wired responses that happen rapidly when molecular structures not normally present in the host (non-self) are identified, with no immunogenic memory. Adaptive immunity is the complementary, slower but more specific antigen-dependent response with the capacity for memory, allowing a faster more efficient response in the event of future exposure to the same pathogen (and antigen).\textsuperscript{41,43} Pro-inflammatory and anti-inflammatory molecules play a role in both arms of the immune response; aberrant expression of these
molecules is part of the puzzle leading to unwanted tissue destruction and chronic intestinal inflammation in IBD.  

Discovery of susceptibility loci and monogenetic defects shed light on possible functional mechanisms in the onset of IBD; defects at the epithelial barrier, including epithelial cell function, autophagy and endoplasmic reticulum stress; disordered immune regulation including defects in T and B cell activation and other defects in control of innate and adaptive immunity; defects in bacterial handling by neutrophil granulocytes; auto-inflammatory defects.  

Macrophages for example, have a critical role in homeostasis and protective immunity and are found throughout the GI tract; specific functions in different locations may be dependent on the localised environment around them.  

There is intense infiltration of monocytes and macrophages in active inflammatory bowel disease, and dysregulated monocyte-macrophage differentiation resulting in impaired bacterial clearance and increased cytokine secretion is implicated in failure to resolve inflammation.  

As technology advances and new analytical techniques become available (and established techniques more affordable), the expanding discovery of implicated pathways at a molecular level continues. MicroRNA (miRNA) research is an example of one of the latest evolving fields with the potential to shed more light on the exact mechanisms of immune dysregulation at a gene expression level.  

The gap between implicated genes, heritability and development of IBD is likely explained in part by epigenetics, that is modification of gene expression (rather than alteration of genetic code) leading to phenotypic change; how genes interact with one another, within pathways and with the environment.  

The effect of smoking on IBD for example is well documented but still not understood – it has a protective effect in UC but worsens CD activity, but whilst it is a consistently replicated risk factor, there are gender and ethnic variations which suggest gene-environment interactions have a role in these pathways.  

1.1.2.3 Environment  

The role of environmental factors in the onset of IBD has been widely studied and many have been implicated. Geographic variation has long been documented with the highest rates in Northern Europe, the United Kingdom and North America historically, but IBD is convincingly on the ascendance in Asia and Saudi Arabia, with evidence for rising incidence in Africa and Latin America too.  

Dietary factors have long been thought to have a role in IBD pathogenesis, borne out in epidemiological studies which suggest a protective
effect of a high fibre diet, particularly as regular fruit and vegetable consumption, and a negative effect of high sugar intake and regular fast food consumption.\textsuperscript{51,52,54} Appendectomy (particularly at a young age) appears to be inversely associated with the onset of UC but the relationship with CD is less clear.\textsuperscript{51,52,54} Vitamin D deficiency has also been proposed as a factor in IBD pathogenesis - it is common in patients with newly diagnosed IBD and studies in mice have shown association with colitis and a corresponding suppression of inflammation with administration of vitamin D (although a recent mouse model has challenged this, suggesting high dose vitamin D therapy may have a negative effect).\textsuperscript{55–59} Epidemiological data demonstrate variation in incidence of paediatric Crohn’s disease in relation to latitude and ambient UV light exposure, further supporting this theory.\textsuperscript{60,61} Medications including NSAIDs and the oral contraceptive pill have been associated with an increased risk of IBD (independently of smoking, which as mentioned above is broadly negatively associated with developing UC but positively associated with onset of CD), as has stress.\textsuperscript{49,52} Stress is thought to affect gut inflammation through changes in the hormonal axis and autonomic nervous system triggering pro-inflammatory pathways, as well as effects on the gut microbiota; major life stressors have been associated with anxiety, depression and increased risk of IBD.\textsuperscript{52}

Socioeconomic status is thought to have an impact on outcomes in IBD. A Canadian population based cohort study of 9298 IBD patients using health administrative database data, found that lower socioeconomic status (SES) is associated with worse outcomes in people with IBD, with increased rates of outpatient visits, intensive care admission, use of corticosteroids and death compared to patients who did not meet the criteria for lower socioeconomic status, more marked in CD than UC.\textsuperscript{62} A retrospective cohort study in the US of 944 CD patients also showed an association between lower SES and increased hospitalisation rates.\textsuperscript{63} The association is likely to be complex and linked to other risk factors and comorbidities that are also more prevalent in patients with lower SES, such as obesity, smoking, anxiety and depression. A link between lower SES and risk of IBD is less convincing with no clear associations between SES and disease incidence or prevalence in global studies, including from multiple studies of data from the same Canadian cohort in Manitoba.\textsuperscript{64}
Infection and the microbiome

If dysregulation of the immune system is a key part of IBD aetiology, it makes sense that things that trigger the immune system would be implicated as risk factors. Potential infectious pathogens have been of longstanding interest, with the strongest suspicion for *Mycobacterium avium paratuberculosis* (MAP) in the past, but mixed results from studies and no benefit from antimycobacterial treatment in an RCT.\(^{52}\) *Salmonella* and *Campylobacter* have also been implicated, as have viruses including measles and controversially the measles vaccine – robust data have subsequently shown no link between measles vaccination and IBD.\(^{52,65}\) Patients with an established diagnosis of IBD may find that infectious episodes, particularly with *Clostridium difficile* trigger relapse. The human gut is home to a plethora of microbes, commensal flora that are collectively described as the gut microbiome, and variations in the microbe population are increasingly proposed as a factor in IBD pathogenesis. Large scale studies of microbial genomes in human faecal specimens have demonstrated differences in the populations colonising the GI tract of healthy controls compared to patients with IBD, specifically a reduction in diversity of organisms in disease, and also variation in bacterial species abundance in those with Crohn’s disease compared to those with ulcerative colitis.\(^{66}\) This being said, there is marked diversity in the microbiome between healthy individuals as well; this is most notable in infancy. Colonization begins immediately following delivery, evolves over the first weeks and months of life, and has largely stabilised to an adult pattern of richness within the first few years.\(^{67-69}\) Mode of delivery (caesarean vs vaginal) and method of feeding (breast, bottle or mixed) are influential in this process; this is thought to play a part in explaining associations between these factors and immune mediated disorders such as atopy and diabetes.\(^{69-71}\) However, a recent Scottish retrospective data-linkage birth cohort study of over 2 million children born between 1981 and 2017, found no association with mode of delivery, prematurity or exclusive formula feeding at 6 weeks in 1721 patients with PIBD.\(^{72}\) Other external factors such as diet and exposure to antibiotics are thought to effect the microbiome throughout life, and potentially induce a state of dysbiosis (disruption to the normal balance and diversity of the microbial ecosystem) which may then be involved in the development of IBD.\(^{70,73,74}\) The function of many of the identified genetic susceptibility loci identified in IBD involves recognition and response to microbial antigens at the mucosal surface of the gut as part of the (aberrant) inflammatory process,
but it is not yet clear if changes in the microbiome are cause or consequence (or both) of host cell function.\textsuperscript{67,73}

1.1.3 IBD diagnosis

Diagnosis is confirmed based on history, bloods and faecal calprotectin (a stool marker of gut specific inflammation) and clinical suspicion leading to upper and lower endoscopy, with emphasis on both the macroscopic appearance and the histological findings from mucosal biopsies.\textsuperscript{18,75} Depending on the findings, further evaluation of the small bowel with the use of Magnetic Resonance Imaging (MRI) enterography (MRE) or wireless capsule endoscopy (WCE) may be necessary to differentiate between and classify disease type. IBD can also present with recognised extra-intestinal manifestations (EIMs) e.g. in the skin, eyes, joints or liver.\textsuperscript{26}

1.1.4 IBD treatment

The goal of treatment in IBD is first to achieve (induction) and then to maintain remission; to bring the inflammation under control and then prevent it from flaring up again. Some therapeutic agents do both of these tasks, others can either be used to induce remission but are not suitable for long-term use, or they act too slowly to be useful for induction but are good at preventing flares of disease activity over long periods. Remission can be defined in various ways but there has been a move in recent years to think beyond symptom resolution alone to the concept of mucosal healing (or deep remission) as the goal of treatment;\textsuperscript{76} endoscopic confirmation of mucosal healing would be the gold standard in a trial setting, but in clinical practice a combination of biochemical markers such as CRP and faecal calprotectin, in conjunction with disease activity scores (wPCDAI and PUCAI), are more commonly used.\textsuperscript{77–80}

The introduction of anti-TNF therapy to the treatment armoury of IBD has revolutionised management in paediatrics as well as adults and been shown to be safe and effective in PIBD.\textsuperscript{81–85} Other monoclonal antibodies (particularly anti-integrins and anti-IL-12/IL-23) and novel therapies have emerged since the established widespread use of anti-TNF, including the oral Janus Kinase inhibitor Tofacitinib, which offer further treatment options for those in whom conventional first and second line therapy has failed or is unsuitable.\textsuperscript{86–88} As a lifelong condition without cure at present, with an expanding but finite range of treatment options, the key to therapeutic management lies in judicious use of each medication (often in combination), to gain maximum efficacy and life-span from each therapy by tailoring
treatment decisions to the individual patient. Therapeutic drug monitoring of anti-TNF medications is increasingly used to identify patients at risk of treatment failure, then utilise a window of opportunity to optimise drug levels and minimise anti-drug antibody formation, with emerging evidence of improved outcome, as part of this careful drug management process.\textsuperscript{89–93} As experience of these medications grows, successive guidelines have become increasingly permissive to their use earlier in the disease course, particularly in CD.\textsuperscript{76,79} There has been an inexorable rise in the prescribing of biological therapies, which is undoubtedly aided by the availability of much cheaper biosimilar products.\textsuperscript{94}

Access to new medications is often delayed for paediatric IBD patients compared to their adult counterparts due to the challenges of drug trials in the paediatric population, not least unique age specific ethical considerations. The lag results in widespread use of medications off-label once efficacy in the adult population has been proven, but dosing by extrapolation from adult studies has often been too low and ultimately higher doses are recommended.\textsuperscript{95} Use of placebo in paediatric trials is controversial and generally use would only be appropriate in a narrow range of circumstances; eligibility criteria and endpoints should also be tailored for the paediatric population. Turner et al as part of a network of international PIBD experts have explored the pitfalls and challenges of drug trials in children and young people (CYP) with IBD with statements of recommendation to assist planning high quality RCTs in PIBD.\textsuperscript{96}

Decision making in therapeutic choices is informed by age, disease location and behaviour, exposure to other medications and diseases, co-occurrence of other conditions and family wishes and capability, amongst other factors. One question that remains unanswered in IBD management is whether early aggressive therapy with combined immunosuppression (the ‘top-down’ approach) is superior to monitored escalation of therapy (a ‘step-up’ approach) i.e. initial corticosteroids or EEN, progressing to immunomodulators +/- biologics as required. Whilst there is RCT evidence that a top down approach is associated with higher rates of steroid free remission (SFR),\textsuperscript{97,98} there is the risk of over-treating a group of patients who might never otherwise require immunosuppressive treatment to maintain disease remission (and thereby unnecessarily expose them to additional risks of side effects and adverse events). Tight monitoring of clinical symptoms and available biomarkers, with early escalation, may provide a lower risk alternative without compromising on long-term disease control.\textsuperscript{99,100} Multicentre paediatric studies such as TISKids and REDUCE-RISK are
ongoing to try and identify which specific patients will benefit most from more aggressive treatment strategies.\textsuperscript{101,102}

Surgery remains an important component of the management strategy in PIBD, particularly fistulising perianal Crohn’s disease and ulcerative colitis refractory to medical therapy.\textsuperscript{95,103}

There is also evidence to suggest that outcome after laparoscopic resection of limited (<40cm, predominantly inflammatory) terminal ileal disease is at least comparable to treatment with infliximab.\textsuperscript{104,105}

Table 3 gives a breakdown of current treatment options in PIBD as recommended in the current ECCO/ESPGHAN guidelines with a brief explanation of mechanism of action, main areas of use and major drawbacks.

| Table 3 - Treatment options in current PIBD guidelines\textsuperscript{76,79,95} |
|-------------------------------|-------------------------------|
| **TREATMENT (Disease)** | **MAIN MODE OF ACTION** | **MAIN ADVANTAGES** | **MAIN DISADVANTAGES/SIDE EFFECTS** |
| **Dietary therapies (CD)** | | | |
| Exclusive Enteral Nutrition\textsuperscript{106–111} | Modulation of the intestinal microflora Possible enhancement of intestinal mucosal barrier function Direct anti-inflammatory effect | Equivalent efficacy to steroids for induction of remission without side effect profile Mucosal healing Restorative weight gain Improvement in bone health Correction of micronutrient deficiencies Short term improvements in linear growth | Exclusive liquid diet: flavour fatigue; NGT often required; compliance can be poor; requires intensive support to maintain motivation Potential for refeeding syndrome |
| CD-TREAT\textsuperscript{112} CDED\textsuperscript{113} | As for EEN but allows ‘normal’ food to be eaten i.e. not a liquid diet – improved tolerance over EEN | CD-TREAT trial stage only; prescribed menu with delivery of individual meals CDED: Rigid adherence to dietary restrictions and requirement for fresh ‘homecooked’ food |
| Aminosalicylates (predominantly UC/IBDU)\textsuperscript{114} | Incompletely understood but probable effects on multiple pathways, including activation Suitable for induction and maintenance (mild-moderate disease) Can use oral and | Suitable for induction and maintenance (mild-moderate disease) Can use oral and | Only sulfasalazine available as liquid preparation Nausea/vomiting, headache, dyspepsia, malaise common side |
of PPAR-γ in colonic epithelial cells, to give anti-inflammatory action

| Corticosteroids (All PIBD) | PPAR-γ in colonic epithelial cells, to give anti-inflammatory action | topical therapy (Rx) for increased efficacy
5-ASA efficacy similar to sulfasalazine but with better side effect profile | effects of sulfasalazine |
|---------------------------|-------------------------------------------------|---------------------------------|-----------------------------|
| Prednisolone             | Interaction with the glucocorticoid receptor to down-regulate components of the pro-inflammatory cascade and increase production of anti-inflammatory molecules | Once daily dosing effective | Adrenal suppression
Growth retardation
Acne
Osteopenia
Glucoma; Cataracts
Increased appetite
Mood +/- or sleep disturbance | Suitable for induction but not maintenance Rx |
| Methylprednisolone       | Hydrocortisone                                  | Budesonide                      |                             |
| Corticosteroids (All PIBD) | Prednisolone                                    | Methylprednisolone              | Hydrocortisone              | Budesonide                   |
| Prednisolone             | Interaction with the glucocorticoid receptor to down-regulate components of the pro-inflammatory cascade and increase production of anti-inflammatory molecules | Once daily dosing effective | Adrenal suppression
Growth retardation
Acne
Osteopenia
Glucoma; Cataracts
Increased appetite
Mood +/- or sleep disturbance | Suitable for induction but not maintenance Rx |
| Methylprednisolone       | Hydrocortisone                                  | Budesonide                      |                             |
| Corticosteroids (All PIBD) | Prednisolone                                    | Methylprednisolone              | Hydrocortisone              | Budesonide                   |

| Immunomodulators (All PIBD) | Azathioprine/6-MP | 60-90% maintenance of remission rates in paediatric studies – allows steroid free remission
For hypermetabolisers, lower dosing in conjunction with allopurinol is an option
Oral once daily dosing | Suitable for maintenance but not induction Rx
Maximum efficacy requires 8-14 weeks of Rx
Requires regular monitoring of blood counts, liver enzymes and thiopurine metabolites to avoid toxicity
Risk of myelosuppression, hepatotoxicity and pancreatitis
Lifelong sun protection recommended
Increased risk of lymphoma and non-melanoma skin cancer |
| Azathioprine/6-MP | Incorporation into DNA leading to cell apoptosis; suppression of pro-inflammatory T-cell responses though blockade of Rac-1 signalling; inhibition of an enzyme involved in de novo purine synthesis | 60-90% maintenance of remission rates in paediatric studies – allows steroid free remission
For hypermetabolisers, lower dosing in conjunction with allopurinol is an option
Oral once daily dosing | Suitable for maintenance but not induction Rx
Maximum efficacy requires 8-14 weeks of Rx
Requires regular monitoring of blood counts, liver enzymes and thiopurine metabolites to avoid toxicity
Risk of myelosuppression, hepatotoxicity and pancreatitis
Lifelong sun protection recommended
Increased risk of lymphoma and non-melanoma skin cancer |
| Methotrexate | Induction of T-cell apoptosis; inhibition of pro-inflammatory cytokines and possible upregulation of some anti-inflammatory cytokines; alters adenosine levels, inhibiting pro-inflammatory cytokines including TNF-α | Once weekly dosing
Induction (slow) and maintenance suitable
Lower risk of cancer/lymphoma than thiopurines | Nausea, including anticipatory nausea
Folic acid supplementation required
Hepatotoxicity – monitoring of liver enzymes
Teratogenicity
Parenteral dosing more effective than oral
More evidence for efficacy in CD than UC
Rare risk of pulmonary toxicity |
<table>
<thead>
<tr>
<th>Tacrolimus (UC)</th>
<th>Calcineurin inhibition; inhibition of T-cell proliferation and adhesion molecule expression; suppression of NF-κB activation</th>
<th>Evidence for use in refractory UC to induce remission May be used as a bridge to establishing thiopurine or vedolizumab Rx Oral dosing</th>
<th>Monitoring of levels required Neurotoxicity (e.g. tremor, headache) Nephrotoxicity Metabolic disorders inc. hyperglycaemia GI disturbance Opportunistic infection (including pneumocystis pneumonia) Increased risk malignancy Long-term maintenance use not established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (CD)</td>
<td>Reduction of TNF-α, IL-6 and IL-1β production; may upregulate T-reg cell cytokines; may inhibit intestinal fibrosis (regulation of ECM protein expression)</td>
<td>Effective in refractory CD (non-response or loss of response to 1st line agents) Once daily oral doing</td>
<td>Teratogenicity – contraception mandatory where relevant Neuropathy – peripheral neuropathy common Depression/anxiety/mood changes</td>
</tr>
<tr>
<td>Antibiotics (All PIBD)</td>
<td>Alteration of composition of the gut microbiome; may shift microbial metabolism, reduce bacterial tissue invasion and translocation, treat microabscesses; may have immunomodulatory properties</td>
<td>Treatment of perianal fistulising CD Induction of remission in CD (and UC) and may offer bridge to maintenance Rx Effective for pouchitis (+/- probiotic) Limited course following surgical resection and re-anastamosis may be indicated</td>
<td>GI upset as common side effect Increased dysbiosis – may have negative effect Risk of antibiotic resistance Commonly limited by antibiotic allergy</td>
</tr>
<tr>
<td>Anti-TNF monoclonal antibodies (All PIBD)</td>
<td>Blockade of anti-TNF (key pathological cytokine in IBD); this may lead to multiple modes of action, including induction of lamina propria T-cell apoptosis and induction of M2-type wound healing macrophages (IFX+ADA)</td>
<td>1-8 weekly dosing schedule after induction phase (drug dependent) Effective for inducing and maintaining steroid free remission Mucosal healing Probable lower risk of cancer/lymphoma than thiopurines Opportunity for therapeutic drug</td>
<td>Pre-treatment screening for TB and Hepatitis B required Antibody mediated loss of response Risk of allergic reaction IV or S/C route of administration Routine blood monitoring required Hepatotoxicity Cancer risk Dermatological side effects Immunosuppression – increased risk of infection</td>
</tr>
</tbody>
</table>
## Other monoclonal antibodies (all PIBD)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Description</th>
<th>Indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vedolizumab</strong></td>
<td>Humanised monoclonal antibody against α4β7 integrin (a receptor expressed on lymphocytes to recognise MAdCAM1) to selectively block gut lymphocyte trafficking without affecting the brain or kidney</td>
<td>Suitable for induction and maintenance, effective in refractory disease. Provides ‘out of class’ option for patients with antibodies to anti-TNF. 4-8 weekly dosing schedule after induction phase.</td>
<td>Slightly superior effect in UC vs CD. Up to 14 weeks to see clinical effect – may require use of interim bridging agent. Pre-treatment screening for TB and Hepatitis B required. Risk of allergic reaction and potential for antibody mediated loss of response. IV route of administration.</td>
</tr>
<tr>
<td><strong>Ustekinumab</strong></td>
<td>Anti-interleukin monoclonal antibody (fully humanised) specifically blocking the shared p40 subunit of IL-12 and IL-23 which are involved in the inflammatory process in IBD</td>
<td>Suitable for induction and maintenance, 8-12 weekly dosing schedule. Effective treatment for psoriasis – may become first line agent for patients with UC and psoriasis. Treatment response may be seen as early as week 3. May be effective in perianal disease.</td>
<td>IV and then S/C route of administration. Optimal dosing regimen not yet determined in studies. Risk of allergic reaction and potential for immunogenicity. Immunosuppression – increased risk of infection. Pre-treatment screening for TB required. May not be suitable if latex allergy.</td>
</tr>
</tbody>
</table>

## Novel therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
<th>Indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tofacitinib</strong></td>
<td>Inhibits the Janus kinase (JAK) family of proteins (1,2 and 3) and the related tyrosine kinase 2 (TYK2) – blocks signal transduction pathways and downregulates variety of inflammatory mediators</td>
<td>Oral medication (conventional small molecule). Low risk of immunogenicity.</td>
<td>Potent immunosuppressive agent – risk of infection. Risk of anaemia. Risk of raised cholesterol levels. Potential risk of malignancy.</td>
</tr>
</tbody>
</table>

## Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
<th>Indications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perianal fistulising intervention</td>
<td>Insertion of Seton suture to provide drainage and prevent accumulation of pus and abscess formation. Diverting ileostomy.</td>
<td>Can provide definitive treatment. Can be used concurrently with medical therapy where response is suboptimal.</td>
<td>Need for general anaesthetic (GA). Some procedures irreversible. Scar formation. Risks of complications of individual procedures (e.g. scar formation).</td>
</tr>
<tr>
<td>Strictureplasty</td>
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<tr>
<td>Limited resection</td>
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<tr>
<td>Total colectomy +/- ileostomy or IPAA</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
or colostomy. Removal of diseased segment: small bowel, ileocaecal resection or whole colon.

May be only therapeutic option for strictureing +/or fistulising disease. May rescue reduction in growth velocity in cases where optimised medical and nutritional Rx has not worked.

B12 deficiency, bible acid malabsorption) and cumulative effect of multiple events (e.g. obstruction). Potential impact on fertility Poorer outcome in emergency surgery

CD, Crohn’s disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; NGT, nasogastric tube; PPAR-γ, peroxisome proliferator-activated receptors (γ-form); NF-κB, Nuclear Factor-κB; Rx, therapy; IL, interleukin; ECM, extracellular matrix; anti-TNF, anti-Tumour Necrosis Factor; IFX, infliximab; ADA, adalimumab; IPAA, ileal pouch anal anastomosis

1.2 Cohort studies

A cohort in the setting of epidemiological research is a defined group of people with a shared characteristic, followed over a period of time, with outcomes measured at one or more time points.148,149 The word is derived from the Latin ‘cohors’, which described 1/10th of a Roman legion (a military unit of 360 men) as a means of traceability during battle.149 Studies can be prospective – looking forward from the starting point when an outcome has not yet occurred, or retrospective – looking back from a starting point when the outcome has already occurred.148

When thinking of levels of evidence, traditionally randomised controlled trials (RCTs) were placed at the top of the pyramid as studies were ranked according to lowest risk of bias; systematic reviews and meta-analysis of multiple studies were then the icing on the cake.150,151 However, it became apparent that the type and level of evidence that is appropriate varies according to the question being asked. In more recent years there has been a call for recognition that RCTs and systematic review alone will not be able to uncover all evidence for causal relationships; multiple methods and sources of evidence, including studies of mechanisms of effect, will be required to accurately interpret research results and apply them appropriately to clinical practice.150,152,153

Prospective studies are ranked higher in the hierarchy of evidence than retrospective studies as there is greater control over co-variants and potential confounders, but retrospective studies still have a role to play.152 The availability of time and financial resources required are potentially major differences between prospective and
retrospective studies, driven by the need to wait for an outcome in a prospective design. The long wait for an outcome may also lead to a high rate of loss of follow-up which is a trade-off for accurately collected prospective data, in comparison to a retrospective study where the outcome has already occurred but data used may have been originally collected for another purpose; there is limited control over data collection therefore, bringing a potentially higher risk of inaccurate, incomplete or inconsistent data which increases the risk of bias. Retrospective cohorts can also provide valuable information to inform study design of future prospective observational studies or interventional studies, including RCTs.

One of the major advantages of a cohort study is the ability to study multiple outcomes +/or exposures simultaneously, as well as lending themselves to broader inclusion (+/or less strict exclusion) criteria than RCTs for example; findings from the study are therefore potentially more generalisable to the heterogeneous population that is found in day to day clinical practice. Guidelines are available to encourage and facilitate accurate data reporting in observational studies and are discussed further below, in section 1.2.3.

1.2.1 Inception cohorts
Inception cohorts are prospective cohorts which identify a group of patients at an early defined point in a disease process i.e. at or soon after diagnosis and then follow them longitudinally through the disease course for outcomes of interest. They require significant up-front planning and design to achieve the most accurate and relevant data collection, which can be costly with regards to both time and finance. Over time they can potentially identify patterns and associations which may highlight particular risk factors for poorer outcome; in turn this may guide areas for future research and enable development of prognostic markers to aid management decisions. Some examples are given in the following paragraphs.

The European Crohn's and colitis organisation (ECCO) initiated an epidemiological committee study (EpiCom) as a prospective population based cohort of unselected newly diagnosed IBD patients in the year 2010. 1560 incident patients were recruited from 31 centres across 22 countries in Eastern and Western Europe, representing the whole spectrum of disease severity and real-world outcomes with management according to local practice. Inclusion of centres in low resource settings without prior experience in epidemiological research was facilitated by a low-cost web based design to the study and
provision of education sessions on case ascertainment for robust methodology. Published data on patients aged 15 years or older at diagnosis has demonstrated an East-West gradient in incidence (highest known incidence in the world reported in the Faroe Islands in the West), as well as reporting on the association of environmental factors prior to diagnosis on disease extent and overall course, and regional variations in therapeutic regimens, particularly exposure to biologics.\textsuperscript{54,157,158}

The RISK study was a prospective inception cohort study of 913 paediatric patients in North America newly diagnosed with Crohn’s disease, collecting regular clinical and biologic data. Results were reported in the Lancet in 2017 showing that early use of anti-TNF therapy was associated with reduced rates of penetrating (B3) disease but did not impact stricturing complications.\textsuperscript{159} Genetic analysis also identified a novel gene signature associated with future stricturing complications and lack of benefit from early anti-TNF; these findings may in the future contribute to the evolution of risk stratification guiding personalised treatment decisions.

PROTECT is a North American prospective multicentre inception cohort study of early outcomes in 428 children with new-onset (treatment naïve) UC on standardised therapy. They found that corticosteroid free remission at week 12 was only seen in 48% of patients with mild disease initially treated with mesalazine, 33% of those with moderate disease initially treated with oral steroids, and 21% of those with severe disease initially treated with IV corticosteroids.\textsuperscript{160} By week 12, 12% of patients had started infliximab and 2% had required a colectomy for refractory disease. Predictors of corticosteroid free remission at week 12 were mild disease at baseline (PUCAI <35), higher albumin at baseline and clinical remission at week 4. Data from this cohort has also contributed to RNA sequencing studies (of rectal biopsies) identifying mitochondriopathy (suppression of mitochondrial genes and function) as a feature in active UC.\textsuperscript{161} This supports work from an Edinburgh adult IBD cohort demonstrating mitochondrial damage in mucosa of active UC patients and the release of mitochondrial DNA (mtDNA) and reactive oxygen species which have a pro-inflammatory effect, highlighting mtDNA as both a potential biomarker and therapeutic target.\textsuperscript{162} This in turn has led to the commencement of a phase 2b randomised placebo controlled trial (MARVEL) of an already existing oral drug, MitoQ (previously tested in other large trials for different diseases and shown to be relatively cheap and non-toxic), in patients with moderate UC; MARVEL is currently recruiting.\textsuperscript{163} Further collaboration has
now established a paediatric arm to the study (mini-MARVEL) aiming to recruit 120 paediatric UC patients to randomisation. This demonstrates clearly how robust cohort studies designed to assess clinical outcome can intertwine with basic science research to translate into clinical trials of new cost-effective treatments, potentially providing direct benefit to patients.

PINPOINT is a prospective incidence study of PIBD in the United Kingdom, currently in the recruitment phase. It aims to record each new diagnosis of IBD under 16 years of age in the UK over a 15 month period to accurately determine the current incidence rate and any areas of high or low prevalence. Such data informs understanding of current and projected disease burden which in turn assists in planning and optimising resource provision. Should additional funding become available, the aim is to follow-up the incident cohort long-term to identify predictors of disease outcome as well as better understand how patients use the NHS.

1.2.2 Data sources

There are a variety of data sources outwith the clinical trial setting, the most relevant of which, in the context of this research and cohort studies in general, are discussed below.

1.2.2.1 Administrative databases

Health administrative data is collected in healthcare systems as part of providing +/- paying for healthcare, with information generated at each encounter between the patient and the system. The primary purpose of data collection is for administrative or billing purposes, depending on the type of healthcare system, but is increasingly used to study health care delivery, usage, benefits, harms and costs, as well as to inform epidemiological studies.\(^5,164\) The data is usually readily available as it is collected routinely and cheaper to access, making it an attractive option for efficient research.\(^165,166\) It provides access to a large population of patients across a given setting with a relatively uniform method of gathering data. Data-linkage can be used to broaden a dataset by using multiple databases (e.g. birth registries, death registries, cancer and medication registries) to gather wider information on each patient, extending the potential even further.\(^72,167\) The major challenge with this type of data is the paucity of clinical information, since this is not the primary purpose of the databases, and the variability in accuracy of data input and coding, with regards to both correctness and completeness.\(^165\)
In North America these databases would primarily be claims databases linked to insurance providers, including universal government healthcare providers, which in isolation may have limited reliability but can be linked with other databases, such as pharmacy and laboratory databases, to broaden the clinical picture and collectively give more useful information. Accuracy in coding is impeded by ambiguity and multiplicity of the codes, and the impact, or lack thereof, of information on cost or reimbursement may also result in the recording of inaccurate or incomplete information. Detailed clinical information and data on outcomes are not typically recorded in these types of database.\textsuperscript{165} Loftus et al reported Crohn’s disease incidence, prevalence and survival rates from healthcare organisation data in Olmsted County, Minnesota, where all residents have healthcare provided by two organisations; to confirm accurate case ascertainment however they reviewed the medical record of all potential cases identified by the diagnostic index and excluded patients who did not meet all criteria.\textsuperscript{168}

In the UK the closest equivalent is public sector data, of which there are an abundance of sources, much of which is fed to the Office for National Statistics (ONS) and NHS Digital. In a drive to enable better access to data for researchers, in recent years the Economic and Social Research Council has created ADR UK (Administrative Data Research UK), a partnership to link together de-identified data from multiple government datasets, across the four nations, enabling pooled resources to facilitate longitudinal research with a large sample size.\textsuperscript{169,170}

\textbf{1.2.2.2 Health records}

Medical records in contrast, should be detailed, comprehensive and reliably accurate (for clinical and legal purposes), with the ability for cross-checking information. Historically, difficulty accessing paper records has been a stumbling block, compounded by illegible handwriting, missing or duplicate items, poorly maintained records, or disruption to chronological order providing major challenges for researchers in both time and expense.\textsuperscript{165} Travelling to multiple sites to view a small number of records in each location is costly, labour intensive and time consuming for example and requires the cooperation of local clinicians to obtain approval and facilitate access. The advent of the electronic patient record, which in primary care in the UK became commonplace in the 1990s and in the rest of the National Health Service (NHS) is an evolving process, has the potential to put paid to many of these barriers and offer previously unimaginable access to ‘big’ data.\textsuperscript{171} There has
been a political push for over a decade to not only advance the digitisation of the NHS for purposes of safer, more efficient patient care, but also to harness the power of a data pool at population level, for use by the research community.\(^{172}\) The COVID-19 global pandemic accelerated this process at a faster rate than might previously have been thought possible; linked health data from multiple sources was used to establish incidence, mortality and morbidity rates from COVID-19 in specific patient groups within whole population cohorts in the UK e.g. a cohort of 5.46 million people in a Scottish diabetes study and a cohort of 54.4 million people in England with acute cardiovascular disease and COVID-19.\(^{173,174}\) Data from such big population level cohorts is generalisable and can be used to inform policy and guidance at a national level. Beyond the global COVID-19 pandemic, it is hoped that ongoing appropriate and ethical access to large datasets will continue, to progress understanding of disease and develop better management.

**1.2.2.3 Disease registries**

Disease registries are another source of data for medical research. In comparison to an electronic (or paper) health record which stores all of a patient’s health information, registries are organised systems which collect standardised uniform health information over time, for a specific purpose.\(^{175-177}\) There are a number of PIBD registries around the world which have been reporting data from large numbers of young patients with IBD over many years. The DEVELOP registry is a multicentre prospective long-term observational registry of nearly 5000 participants with PIBD, of whom approximately half have been treated with infliximab and half have not. The study sponsor is Janssen Biotech (the makers of infliximab as Remicade\(^{®}\)) and will collect patient information every 6 months over 20 years in 63 different North American centres, to assess long-term outcome in this large cohort of patients with paediatric onset IBD; it has already reported on data from 5766 registered patients suggesting no evidence of increased risk of malignancy or haemophagocytic lymphohistiocytosis (HLH) in PIBD patients treated with infliximab.\(^{81,178}\)

The EPIMAD registry is a French population based registry (started in 1988) of inflammatory bowel disease patients of all ages, recording incident cases in a Northern region of France with a population of almost 6 million people.\(^{179}\) Data from this registry, with 2285 confirmed cases of IBD after a minimum of 2 years follow-up, has supported the trends described earlier of a rising incidence in inflammatory bowel disease and variation in phenotype between paediatric onset and adult onset IBD.\(^{179}\)
The Saxon Pediatric IBD registry recorded all IBD patients up to 15 years of age diagnosed and treated over a 10 year period (2000-2009) in the federal state of Saxony in eastern Germany. Incidence was shown to be rising as in other countries and this robust large scale data were confirmatory of earlier noted trends from single centre data within the region.\(^\text{13}\)

Their findings were also comparable to CEDATA data with regards to longer latency of diagnosis from symptom onset for newly presenting Crohn’s compared to UC. The Saxon registry reported a median of 4 months vs 3 months for Crohn’s and UC respectively, whilst CEDATA, a German language registry of PIBD patients in Germany and Austria founded in 2004, reported on data from 2463 patients in 2009 a median time to diagnosis of 5 months in Crohn’s and 3 months in UC, along with the presence of growth failure in 16% of patients with Crohn’s and 5% with UC.\(^\text{180}\)

In North America, the pediatric IBD collaborative research group registry (PICR) was initiated in 2002 as a prospective multi-centre observational study which has published a broad spectrum of data ranging from liver enzyme elevation within 3 months of diagnosis of IBD, to the use of methotrexate in Crohn’s disease, with 1786 patients registered in 2014.\(^\text{181,182}\)

Established in 2000, the Pediatric IBD Consortium is another PIBD registry recruiting from six regional IBD centres across the United States that has reported epidemiological characteristics of >1600 patients, including early recognition of the increasing presentation of VEOIBD.\(^\text{183}\)

EUROKIDS is a prospective ongoing registry, initiated in 2004, of newly diagnosed PIBD patients aged 0-18 years in Europe and Israel. Over 4000 patients are registered from 20 countries and data has been published on disease phenotype and quality of diagnostic workup.\(^\text{184,185}\)

Retrospective registries have estimated Spanish incidence rates at a national level from 1985-2009 (SPIRIT and EXPERIENCE registries) and reported a sixteen-fold increase over this 25 year period.\(^\text{186,187}\)

Other national PIBD registries in Europe include the prospective Hungarian nationwide PIBD registry (HUPIR, launched 2007), with over 1500 patients registered, and the Italian society of pediatric gastroenterology hepatology and nutrition (SIGENP) registry (1969 patients), both of which have recently published data; HUPIR on increasing adherence to Porto criteria for diagnostic workup and SIGENP showing a stabilisation from 2009-2018 of the previously increasing incidence rate and a continued low to medium incidence when compared with northern European countries.\(^\text{188,189}\)
The Nordic countries of northern Europe arguably have the strongest record in patient registries; Denmark, Finland, Iceland, Norway and Sweden have a combined population of approximately 27 million people and whilst they have individual health care systems, key common factors across all 5 countries are universally accessible publicly (tax) funded health care within a welfare state model, with limited private healthcare sectors and government maintained population based nationwide registries. All residents are assigned a unique personal identification number at birth which remains with them throughout their life, predominantly for administrative purposes and crucially links them to routinely collected data on a range of aspects of life and health, recorded in multiple databases such as total population registries, birth registries, cause of death registries, patient registries (hospital contact), cancer and prescription registries as well as disease specific registries and other databases. Cohort studies using these databases have yielded much published epidemiological PIBD data at a national level; combined registry data is also emerging but this remains an underutilised resource.

More recently registry data is emerging from Asia, which has typically been an underrepresented region in PIBD research. Arai et al published phenotypic data from a multicentre Japanese PIBD registry formed in 2012, with 243 included patients from across 20 centres. Although the cohort is small compared to European and North American reports, it is interesting to note that compared to EUROKIDS data, Japanese Crohn’s patients exhibit significantly less isolated colonic (L2) disease but more ileo-colonic (L3) and oesophago-gastro-duodenal (L4a) disease and perianal disease is significantly more prevalent. A single centre registry in Hyderabad, India has been prospectively recording data since 2004 on (all age) IBD patients and recently reported on 293 PIBD patients (<17 years of age); VEOIBD (<6 years) patients had a more severe phenotype and poorer outcomes when compared to later onset (6-17 years) patients, and compared to European data from the EPIMAD French registry, they found a higher incidence of strictureing and penetrating (B2B3) CD and pan-colitic (E3) UC as well as higher rates of isolated colonic (L2) and ileal (L1) disease, but less common upper GI involvement (L4).

The UK IBD registry is a not-for-profit national registry for IBD in the United Kingdom, collecting data from NHS hospitals to assess the state of IBD care, support research and help improve treatment and define standards to promote equity of access to high quality care. It now incorporates what was previously the Royal College of Physicians IBD Audit
which is discussed further in section 1.5.1. PIBDnet is an international network of PIBD experts with a particular focus on clinical research, collaborating to produce high quality research data. Under this umbrella, PIBD-SET Quality is an inception cohort and safety registry aiming to identify high and low risk predictors of disease outcome which has reported on rare and severe complications in PIBD after just 1 year of study, as a taste of future more robust data with ongoing international participation. Registries can take years to establish, but as with many areas of medical and scientific research, the current COVID-19 global pandemic has demonstrated how processes can be accelerated to facilitate the development of clinical research registries on an international scale. SECURE-IBD was a rapidly established international registry database for reporting outcomes, demographic and clinical characteristics of IBD patients with confirmed or suspected COVID-19. At the time of closing, over 7000 cases had been reported to the database in under 2 years, which allowed robust conclusions to be drawn in key areas of concern for IBD patients infected with COVID-19, for example safety of anti-TNF therapy, as the pandemic evolved, which had a direct impact on clinical practice and policy making. The authors emphasise that collegiality, generosity and transparency were essential to mobilise the international IBD community; a data entry form that could be completed in under 5 minutes and real-time updating of data on a weekly basis were key to maintaining momentum.

Increasingly registries include patient involvement, with representatives taking part in specification of development for registries, and are beginning to report patient reported outcome measures (PROMs) alongside clinical outcomes; some are even evolving into systems which partner with patients for interactive learning and disease management, such as the ImproveCareNow (ICN) network for PIBD which has expanded from the United States to some European centres. The ICN network is an international multicentre PIBD quality improvement collaborative established in 2007 which prospectively and longitudinally collects patient data on demographics, disease and treatment to a registry database; diagnosis and management are according to the usual practice of the primary gastroenterologist and includes prevalent and incident patients beyond 18 years of age. The network has published data on a range of PIBD questions including racial variation in disease phenotype and the prevalence and presentation of perianal Crohn’s disease.
1.2.3 Guidelines for use of routinely collected health data

Overall the benefits of using routinely collected health data are the relatively quick and cheap access to potentially large populations with longitudinal follow-up reflective of the real-world environment. However, weaknesses lie in the potential lack of clinical data (outwith health records), outside influences that cannot be accounted for, the accuracy of data coding, missing data and challenges with cohort definition. Data linkage across multiple datasets or at multiple time points within a dataset, further increases the risk of misclassification bias and error.\(^{205,206}\)

With the increasing use of routinely collected data from all of the aforementioned sources, gaps have been identified in existing guidelines for reporting research, such as the Strengthening of Reporting of Observational studies in Epidemiology (STROBE). The RECORD statement has therefore been developed as an extension to STROBE as part of an international collaborative process to address specific issues relating to reporting of research using routinely collected health data.\(^{206}\) The checklist emphasises accurate reporting of specific elements of methods (including data sources and search algorithms), participants and any linkage to ensure that misclassification bias, unmeasured confounding and missing data have all been considered in the process of interpreting findings.\(^{206}\)

Patient registries, administrative databases and electronic health records are not just of use in observational studies and have more recently been used for both recruitment of participants and assessment of outcomes in randomised controlled trials (RCTs) to reduce cost and increase efficiency. An extension to the CONSORT statement has been developed (CONSORT-ROUTINE) for RCTs embedded within cohorts or using routinely collected health data, to standardise reporting of methodology and transparency at the point of trial publication.\(^{205}\)

1.3 Transition

With approximately 1 in 12 incident cases of IBD being in the paediatric population, and a chronic disease with no cure but low mortality, CYP with paediatric onset IBD will spend most of their life cared for in adult services and are therefore of interest to the paediatric and adult gastroenterologist alike.\(^{8,17}\) The concerns of the paediatric gastroenterologist are slightly different to those of our adult counterparts; the goals of achieving and maintaining remission come packaged with the challenges of achieving adequate growth and puberty,
social and emotional development, educational attainment and navigating (often complex) family dynamics. In addition however, we know that patients will not remain under our care forever; as they progress through adolescence, patients must develop an understanding of their own disease, gain skills in self-care and evaluating and managing their treatment options and eventually move across to adult services. No small feat when adolescents are also discovering their own identity, often taking crucial exams or starting out in the workplace, and riding a rollercoaster of physical and emotional change! It is therefore our responsibility to guide them through this process and facilitate as smooth a transition as practically possible, all whilst striving for disease stability.

The natural history of paediatric onset IBD has generally been shown to be more extensive and aggressive than IBD diagnosed in adult life.\textsuperscript{23,207,208} The paediatric portion of the journey can be long and complex, before even reaching adult services (see Figure 1). There is an associated increased risk of cancer and overall mortality is higher.\textsuperscript{167,192,209} Patients with childhood onset IBD have been shown to be at higher risk of psychiatric disorders (particularly anxiety and depression) and attempted suicide, compared to both the general population and their siblings without IBD.\textsuperscript{210,211} A prospective study from the paediatric IBD Porto group of ESPGHAN of patients diagnosed with IBD before their 19\textsuperscript{th} birthday who went on to develop malignancy or die before the age of 26 years, found that suicide was the 3\textsuperscript{rd} leading cause of death (3 of 26 fatalities).\textsuperscript{212} Whilst those with higher disease activity show more anxiety, many children and young people with inactive disease report anxiety (general, school and separation anxiety) symptoms.\textsuperscript{213}
Figure 1 - Patient journey from diagnosis to point of transfer

Sx, symptoms; UC, ulcerative colitis; Dx, diagnosis; PO, per oral; IV, intravenous; AZA, azathioprine; IFX, infliximab; equiv. C. diff, equivocal *Clostridium difficile*; Abx, antibiotics; MTX, methotrexate; S/E, side effects; VDZ, vedolizumab; PR, per rectum; Steroid enema, steroid enemas; Pentasa supp, pentasa suppositories
Depression and anxiety not only negatively affect quality of life but can negatively impact illness-related attitudes and coping mechanisms, as well as manifest symptoms which are difficult to separate from active disease, and alter the perception of pain. Psychological morbidity is also associated with sleep dysfunction and reduced medication adherence and may have a direct effect on functional outcomes. Targeted interventions such as CBT have shown varying levels of effectiveness for improving symptoms in a clinical setting.

There has long been consensus amongst health care professionals working with adolescents that a structured transition process, which moves a patient (and their family) from paediatric to adult services in a gradual but purposeful manner, is desirable. The goal is to provide a continuum of care which not only manages disease activity but also prioritises social and emotional development, acquisition of life-skills for independent care and disease management, and addresses emerging issues including sexual and reproductive health, substance misuse and risk taking behaviour. In adolescence the brain continues in a state of active maturation which may be ongoing to as late as 24 years of age; executive functions controlled in the prefrontal cortex including strategic planning, balancing short-term rewards against long-term goals, processing multiple streams of information in complex decision making, and considering the future and making predictions, are taking place in a part of the brain still under construction. Functional MRI studies show that adolescent brains enlist different regions to fully mature adult brains when processing the same information, supporting the idea that this stage of development requires specific consideration and services to optimally manage chronic disease into adulthood.

Planned structured transition is highlighted as an area of importance in UK and North American guidelines for management of inflammatory bowel disease. It is also identified as an area of failing, in need of quality improvement. There is a wide variation in clinical practice both within nations and internationally, despite the existence of guidelines for transition. Transition in North America for example, where specific considerations related to healthcare insurance coverage apply, tends to happen at a later age (sometimes up to 25 years) than in the UK (usually before 19 years of age). Data from Germany also show a wide variation in age at transfer. Much has been written on potential models for transition but there is limited evidence in terms of outcome and no
clear data supporting one process over another. A survey of gastroenterologists in the UK found that structured transition is considered of more overall importance to paediatric gastroenterologists than their adult counterparts, and that the two groups differed in identification of key determinants of timing and readiness for transfer and indicators of suboptimal preparation. However, involvement in the transition process reduced the perception of inadequate preparation for both groups of gastroenterologists. Similar differences were evident in a study from Australia and New Zealand and a North American study of only adult gastroenterologists highlighted the same perceptions. A common theme across all of these surveys however was the need for flexibility in timing of transfer according to the individual patient, rather than a sole focus on reaching a particular age milestone. In contrast in Japan, where transition related healthcare is a relatively new concept compared to Europe and North America, separate surveys of adult and paediatric gastroenterologists revealed very clear but differing opinions on the optimal time for transfer – 16 years according to adult GI and 18-22 years according to paediatric GI.

Since the conception of this thesis in 2015 and subsequent collection of data, there has been a rapid increase in published research related to transition of adolescents with IBD. However, studies are often focussed on assessment of readiness for transfer e.g. with the use of the Transition Readiness Assessment Questionnaire (TRAQ) or IBD-Yourself, and adherence to treatment, but not on broad clinical outcome. Where disease outcome has been measured, it is often measured by health system utilisation, as contained within population based health administrative data. This data is important because it permits study of larger sample sizes, but whilst use of resources can be an effective proxy for disease activity, the quality of the data is reliant on clinical coding entries (which may be inaccurate) and it does not allow for more detailed assessment of clinical status, escalation of therapy or development of complications. There is a limited amount of data examining clinical outcome following transition and transfer of adolescents with IBD to adult services.

1.4 Autoimmune diseases (AIDs) and IBD

The underlying mechanism of recurrent chronic inflammation in IBD is thought to result from aberrant activity of pro-inflammatory and anti-inflammatory molecules, which when functioning correctly are part of the normal immune response. This is supported by the
effectiveness of anti-TNF therapy as a mainstay in the IBD treatment paradigm; TNF being one of the major increased pro-inflammatory cytokines in patients with IBD. But IBD is not the only disease where this is the case – there are a broad range of immune mediated inflammatory diseases (IMID) across organ systems, characterised by immune dysregulation and including classical autoimmune diseases, such as coeliac disease, where a self-antigen is identified and targeted, by the production of specific autoantibodies. 

Advancement in the understanding of the genetic landscape of complex disease has progressed rapidly in the last decade not only due to the advent of techniques such as GWAS and exploration of epigenetic processes, but also thanks to collaborative international consortia pooling data and resources to generate large cohorts and sample sets that are statistically powered to identify susceptibility loci even when the increased risk of disease is only modest; the international IBD genetics consortium is a good example of this. Clustering of different autoimmune diseases within families has been identified for some time, as well as high concordance rates in twin-twin studies and observation of sibling recurrence if the same disease. However polyautoimmunity i.e. the presence of two or more AIDs in a single individual is also recognised. Genome wide association (GWA) and Immunochip studies have identified common pathways with IBD associated genetic loci shared amongst a range of autoimmune conditions and overlapping heritability. As well as being implicated in IBD, IL10 for example is shared with systemic lupus erythematosus (SLE), Behçet’s and type 1 diabetes mellitus (T1DM); IL23R with ankylosing spondylitis (AS) and psoriasis. Whilst some loci may infer susceptibility for multiple diseases, others may be protective. As with IBD, the aetiology of other autoimmune diseases does not lie in genetic susceptibility alone and a variety of environmental factors also play their part, including at an epigenetic level and with influence from the gut microbiome/virome.

1.4.1 Burden of autoimmune diseases

Autoimmune disease prevalence may be as high as 9.4% in the general population (approximately 1 in 11) according to a 2009 analysis of international studies by Cooper et al, although a more commonly quoted prevalence is 3-5%. These chronic conditions usually require long-term input, may diminish quality of life and often incur significant healthcare costs. In some autoimmune conditions, autoantibodies can be detected serologically long before the onset of any clinical symptoms; this potentially gives
them predictive value and could potentially be useful, in conjunction with known susceptibility alleles and family history, for personalised medicine and targeted screening.\textsuperscript{254} The current BSPGHAN guideline for diagnosis of coeliac disease in asymptomatic children with associated conditions would be one example of this in practice, with the use of HLA-DQ2/DQ8 status as an indicator of the need for further testing.\textsuperscript{264}

Coeliac disease is a global disease; a systematic review and meta-analysis from 2018 found it to be reported worldwide and the pooled global prevalence to be 1.4% based on serological (antibody) testing and 0.7% on biopsy results, with a geographical variation from 0.4% prevalence in South America to 0.8% in Europe and Oceania.\textsuperscript{265} The study did however highlight a complete lack of data from 6 of the 10 most populous countries in the world and a paucity of data from Russia where the population is 143 million and wheat consumption is high, so there is still a vast potential burden of coeliac disease yet to be explored.\textsuperscript{265}

Type 1 diabetes (T1DM) is also a condition affecting children and young people worldwide and presents daily challenges for patients and their families, particularly in resource poor settings where access to medication and monitoring equipment is more limited. Poor glycaemic control has both short and long term consequences and ultimately may lead to premature death.\textsuperscript{266} The international diabetes federation diabetes atlas published estimates of worldwide incidence, prevalence and mortality rates of T1DM in children and adolescents in 2019; in Europe the annual incidence is 25.1 cases/1000 in the 0-14 year age group or 31.1/1000 in the 0-19 age group (prevalence 162.6/1000 or 296.5/1000 for the same age groups respectively).\textsuperscript{266} Patients with T1DM are regularly screened for coeliac disease and autoimmune thyroid disorders according to international (ISPAD) diabetes guidelines.\textsuperscript{267} A 9 year retrospective study of 493 newly diagnosed T1DM paediatric patients (0-18 years) from a single centre in Poland found 12.4% had a diagnosis of an additional AD (autoimmune thyroid disease or coeliac disease) during the study period and the prevalence doubled from 10.4% in 2010 to 20.8% in 2018.\textsuperscript{268}

Psoriasis is a common inflammatory skin disease which is chronic and associated with a high degree of morbidity, both from medication side effects and embarrassment about the appearance of the skin with associated impact on quality of life.\textsuperscript{269} There is a complex genetic inheritance with family history being a strong predictor of early onset disease and the estimated prevalence from a study of 1.3 million subjects via German health insurance data is 0.71% in children 0-18 years, with a roughly linear increase from 0.12% at 1 year to
A cross-sectional study from Danish health administrative data of all under 18s found significant associations between other autoimmune diseases and psoriasis and that there is a significantly higher risk of multiple concurrent autoimmune diseases in children with psoriasis compared to those without.\textsuperscript{271}

Juvenile idiopathic arthritis (JIA) is arthritis diagnosed before the age of 16 years, lasting a minimum of 6 weeks, with no known cause.\textsuperscript{272} It can be associated with long-term damage to joints and short-term and long-term disability, along with comorbidities like uveitis, and since the advent of biologic disease modifying anti-rheumatic drugs (DMARDs), treatment has been revolutionised – all of which adds up to a significant healthcare burden.\textsuperscript{273}

Recently published UK data from the Clinical Practice Research Datalink (CPRD) estimates the overall age-standardised incidence at 5.61/100,000 and the 2018 age-standardised prevalence at 43.5/100,000; rates were significantly higher in Scotland compared with the other nations.\textsuperscript{274} A retrospective cohort study of medical registry data from a single centre in the US found that 19% of patients with JIA had at least one autoimmune disease (from a pre-specified list of 26 conditions) compared with 5% of the general paediatric population.\textsuperscript{275}

Autoimmune thyroid disease is characterised by loss of tolerance to thyroid autoantigens and the presence of thyroid autoantibodies (of which there are several different types) circulating in the serum and targeting the thyroid gland resulting in dysfunction. It is more common in females and with onset in early to mid-puberty.\textsuperscript{276} Children are commonly referred for investigation following discovery of thyroid enlargement and at time of diagnosis may be euthyroid, overtly or sub-clinically hypothyroid or, less commonly in children, overtly or sub-clinically hyperthyroid.\textsuperscript{277} Thyroid peroxidase specific T-cells have also been shown to play a role, even in the absence of mature B cells and antibodies.\textsuperscript{278} A Scottish study published in 2000 used thyroxine prescriptions in a region-wide (Tayside) database to estimate a population prevalence of 0.135% for clinical hypothyroidism in people less than 22 years of age.\textsuperscript{279} There is a propensity for thyroid disease to run in families and higher (but incomplete) concordance between monozygotic than dizygotic twins, in keeping with complex heritability dependant on both genetic and environmental factors, as with the other AIDs discussed.\textsuperscript{276} In a Greek single centre retrospective study of 228 children with autoimmune thyroiditis over a 5 year period, 6.6% had another concomitant autoimmune disease.\textsuperscript{280}
Autoimmune liver disease (AILD) can be divided into three subtypes: autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Each has a broadly different pattern of inflammation and clinical phenotype but they are all progressive if untreated, eventually leading to liver failure. Autoimmune diseases in general are more prevalent in females than males to varying degrees (ankylosing spondylitis being one notable exception where the phenomenon is reversed), but this sex difference is particularly pronounced in PBC (4:1) and AIH (10:1). The explanation for this is likely to be multifactorial but genetic factors (including the sex chromosomes), hormonal profile, reproductive function, environmental exposures and variation in immune response have all been implicated.

Differentiating the diagnosis between the three conditions can be challenging as there is significant heterogeneity in clinical, biochemical, serological and histological findings. Whilst each condition can be defined by ‘classical’ features, the presence of overlapping features is not uncommon, particularly in children and young adults, leading to the concept of ‘overlap syndromes’ but without any standard definitions. This is further complicated by the possibility of drug induced liver injury as well as the relatively common finding of elevated liver enzymes early in paediatric IBD which often resolve spontaneously with time. There is a strong association between autoimmune liver disease and IBD, with PSC in the presence of UC being the most frequent occurrence. Unlike other extraintestinal manifestations of IBD, associated liver disease often follows an independent course, irrespective of the degree of intestinal inflammation. The incidence of autoimmune liver disease is estimated to be 1-2/100,000/year worldwide and a population based prospective study from New Zealand suggests the incidence of AIH is rising. A recent study of UK primary care data demonstrated a correlation between northerly latitude and increased incidence of PBC and AIH (but not PSC), with incidence ranging from 1.6-2/100,000/yr in the south of England, compared with 3.2/100,000/yr AIH and 4.5-4.9/100,000/yr PBC in the north of Scotland. Italian registry data has reported AILD prevalence of 6.8% in a PIBD cohort and review of US hospital system data in Utah reported a prevalence of 1.5/100,000 for PSC and 3.0/100,000 for AIH in the paediatric population. In the decade leading up to 2010, 11% of liver transplants in Europe were for autoimmune liver disease.

Understanding the prevalence of co-existing AIDs in a paediatric IBD population may contribute to the understanding of shared immune-pathogenesis and shape practice to be
vigilant to the evolution of concomitant disease, to tailor therapeutic options according to risk and even to consider preventative strategies.

1.5 Biologics

As already noted, IBD care has been revolutionised in the last decade by the advent of biological therapy, specifically anti-Tumour Necrosis Factor (anti-TNFα) therapy (including infliximab [IFX] and adalimumab [ADA]). The arena of targeted anti-inflammatory therapy continues to evolve with the availability of further monoclonal antibodies, such as ustekinumab (IL-12 + IL-23 binding antibody) and vedolizumab (α4β7 integrin binding antibody), the latter being particularly gut specific in mode of action. Anti-TNFα therapy can be used to both induce and maintain disease remission and has provided a steroid sparing treatment for many patients where previously there were limited options. Scottish data have shown that they are associated with improved linear growth, particularly when instituted in patients in the early stages of puberty; 18% of patients in a study by Cameron et al had demonstrable growth failure at the start of treatment. Data from Wessex have shown steady increased use of anti-TNF over a 10 year period with an associated fall in surgical resections rates in PIBD (predominantly Crohn’s), but comparable growth outcome over the study period. A Swedish nationwide study over a comparable time period however did not show a decrease in cumulative surgery risk, but findings may be limited by a lack of detailed clinical data.

These therapies of course carry their own risk and side effect profile, which can cause anxiety for patients and families, as well as clinicians alike; the risk of malignancy is usually the most perturbing. This must be balanced however against the well-recognised association between IBD and intestinal (small bowel adenocarcinoma, colorectal carcinoma, intestinal lymphoma) and extra-intestinal (leukaemia, lymphoma, skin cancer) malignancies as well as haemophagocytic lymphohistiocytosis (HLH), particularly in the context of chronic unbridled local and systemic inflammation. A Swedish population based study by Olén et al, of over 9000 patients diagnosed with childhood onset IBD over 50 years, found that they had a 3-fold increased relative risk of death (over childhood and later in life) compared with matched controls from the general population. The most common cause of death was malignancy, followed by digestive diseases (including IBD and liver disease). The greatest risk of death was in patients diagnosed with UC, in keeping with data published by the ESPGHAN Porto Paediatric IBD group in 2014, following a retrospective survey of
gastroenterologists in 20 European countries and Israel and with a systematic review of published literature by Aardoom et al in 2018. The Swedish study noted that there was no decline in hazard ratios since the use of immunomodulators and biological therapy has become commonplace, but it was not powered to assess their influence on patterns of mortality. The overall absolute mortality risk was low, due to the low risk of death in childhood in the general population, but PIBD patients warrant close follow-up to pro-actively manage disease activity and any warning signs of malignancy. Prospective multinational data from the Porto group in a 3 year cohort was published in 2018 reporting data collected via survey on cancer and mortality up to 26 years of age in IBD patients diagnosed below 19 years of age. 43 malignancies and 26 fatalities (9 due to cancer) were identified; haematopoietic tumours were the most frequently reported malignancy (21/23), of which 3 patients died, all with a diagnosis of hepatosplenic T-cell lymphoma (HSTCL). After this, colorectal cancer (12/43) and then cholangiocarcinoma (3/43) were the next most frequent malignancies; all patients with cholangiocarcinoma died. 5 out of 9 fatal cancer cases had a concomitant diagnosis of PSC, including all cholangiocarcinoma patients. Whilst causality between medication use and malignancy cannot be established by a study of this design, they did make some interesting observations. 95% patients who developed haematopoietic malignancy had been exposed to thiopurines at some point; in the 3 months prior to cancer diagnosis (i.e. current therapy), 57% had been on thiopurine monotherapy, 19% combination Rx and 19% biologic monotherapy. All 3 HSTCL patients were on current thiopurine therapy without biologic exposure. DEVELOP is an ongoing multinational prospective cohort study investigating long-term safety and clinical outcomes of PIBD patients treated with infliximab +/- other medical therapies. They published data from 5766 patients in 2017 which showed no associated increased risk of malignancy or HLH in PIBD patients with exposure to infliximab, but that exposure to combination therapy (infliximab + thiopurine) was associated with a significantly increased risk of malignancy, with a trend towards increased risk in thiopurine exposure irrespective of biologic use. The risk of serious infection is also a cause for concern for many families and clinical teams. A systematic review of available studies in 2014 by Dulai et al found the rates of serious infection from prospective studies were comparable between anti-TNF and the expected rate for immunomodulator therapy, but in fact lower than the expected rate with steroid use or in adult IBD patients treated with anti-TNF. The prospective data from the Porto group identified serious infection as the predominant cause of non-cancer related deaths.
(5/17) in whom 4 of 5 were receiving current immunosuppression (2 thiopurine, 2 biologic); 1 patient had disseminated TB on anti-TNF and all 5 had ever exposure to thiopurine. In a more recent systematic review by Aardoom et al infectious disease was the most common cause of non-cancer related death and most of the patients who died of sepsis were exposed to at least 2 immunosuppressants, one of which was commonly steroids.298

1.5.1 UK biologics audit
IFX and ADA have been licensed for use in PIBD in the UK since 2010 and 2013 respectively; UK survey data has demonstrated effectiveness in treating refractory disease whilst highlighting the potential for serious side effects.300,301 Scottish data on 132 PIBD patients treated with biologics over a decade show response rates of 87% with IFX (48% remission) and 76% with ADA (35% remission) replicating safety issues, especially serious infection.302

The UK IBD audit is a national gastrointestinal audit first commenced in 2006 (reporting in 2008) and run by the Royal College of Physicians; reports are available online at www.rcplondon.ac.uk/ibd. Data is collected from doctors, nursing staff and patients across the UK about the care that is provided and the services available, with the majority of hospitals providing IBD care included. It allows the quality of care to be assessed and compared against national standards to highlight good practice and where improvements are required.303 Data has previously been published on the outcomes of paediatric and adult patients with UC.304,305

The UK IBD audit has been collecting data on biological therapies, including in the paediatric population, since 2011 with the purpose of assessing efficacy, safety and appropriate use (according to national guidelines) in clinical practice. Unselected, large scale national data will help to quantify and categorise ‘real-world’ adverse events where data is lacking. The data presented in this thesis was collected in the third round of the audit, completed in 2014, and a report issued by the Royal College of Physicians.306 This however is only really available to people already aware of its existence and the data is reported without specific analysis to aid interpretation; it therefore has limited capacity to impact clinical practice. Further collation and analysis of the data with presentation in a format applicable to clinical practice would therefore reach a wider audience through publication in a peer reviewed journal and allow better utilisation to improve patient care.
1.6 This study

This thesis reflects all-ages IBD research from a paediatric perspective through a collection of cohort studies at regional, national (Scotland) and pan-UK levels.

Chapter 3 examines the outcomes of a regional cohort of PIBD patients around the time of transition from paediatric to adult services. As mentioned in section 1.3, this is an area of clinical importance where improvement is required but a relative paucity of evidence has been identified. Chapter 4 establishes the prevalence of concomitant autoimmune disease in a Scottish cohort of patients with PIBD and examines the frequency of individual AIDs. Chapter 5 focusses on the real-life experience of biological therapy in patients with PIBD from across the United Kingdom, analysing data from the national IBD audit in a format that is clinically relevant and can be used locally to improve practice.

The data presented in the remaining chapters aim to expand upon our understanding of the overall burden of paediatric inflammatory bowel disease and its treatment on young people, their families and the health service, and explore potential opportunities to improve care for PIBD patients.
2 METHODOLOGY AND METHODS

The cohorts included in this thesis incorporate common and individual methodology. The transition cohort is a regional study of patients in a single tertiary centre originating from three Scottish health boards primarily for the purpose of audit; all data collection, analysis and interpretation has been completed by me (see Figure 2). The autoimmune diseases study centres on the Paediatric-onset IBD cohort and treatment study (PICTS), a Scottish incident and prevalent cohort study recruiting from all 14 Scottish health boards. The PICTS database manager performed the initial database interrogation to identify cases with a potential concomitant autoimmune disease diagnosis. All subsequent record review and data collection was carried out independently except where specified. The biological therapy study is part of a national (UK) audit – data were held centrally by the Royal College of Physicians and entered by local clinicians. Statistical analysis was performed by an RCP appointed medical statistician and data released to me for interpretation under the guidance of Professor Richard Russell.

Figure 2 - Regional health boards of Scotland highlighting those incorporated within the South East Scotland PIBD service.
All data were collected whilst employed as a clinical research fellow by the University of Edinburgh under the supervision of Professor David Wilson in the department of Child Life and Health (CLaH); an honorary contract with NHS Lothian was held simultaneously. Methods for each study are outlined in detail below.

2.1 Phenotyping
The general term inflammatory bowel disease (IBD) is representative of several diseases and a range of clinical presentations. For both clinical clarity and to aid accurate and effective research, a collaboratively agreed classification system has been proposed since 1991 when an international working group met in Rome and issued a report on Crohn’s disease (CD) to describe disease location, behaviour, extent and operative history creating multiple subgroups. This was revised in 1998 by the working party at the World Congress of Gastroenterology meeting in Vienna to simplify for practical use and classify according to age at onset, disease location and clinical behaviour. In 2005 a working party met again at the world congress of gastroenterology in Montreal and issued a further report with modifications to the Vienna classification, acknowledging limitations that had become evident with their use and recognising that a classification system for ulcerative colitis was also required. Categories describing age at diagnosis were broadened to better represent the evolution of disease and the ability to add upper GI involvement and perianal disease as modifiers to disease elsewhere when occurring concomitantly.

The Montreal classification remains the standard to date for phenotyping in adult IBD (table 4). However as increasing data from paediatric IBD registries became available, the dynamic nature of paediatric IBD highlighted deficiencies in the Montreal system with regards to describing the paediatric IBD phenotype. An international group of paediatric IBD experts met at a PIBD symposium in Paris in 2009 and reviewed the available evidence to establish required modifications to adequately reflect the phenotypic spectrum in PIBD (table 2). The Paris classification published in 2011 delineated a further category for age at diagnosis by subdividing the A1 category into 0-<10 years and 10-<17 years. It also refined the definitions of disease location and behaviour/severity in Crohn’s disease and UC, as well as adding a paradigm to capture growth impairment.
### Table 4 - Montreal Classification of disease

<table>
<thead>
<tr>
<th>Crohn’s disease</th>
</tr>
</thead>
</table>
| **Age at diagnosis** | A1: ≤16 years  
A2: 17-40 years  
A3: >40 years |
| **Location** | L1: terminal ileal +/- limited caecal disease  
L2: colonic  
L3: ileocolonic  
L4: isolated upper disease  
*L4 disease can coexist with L1, L2 or L3* |
| **Behaviour** | B1: non-stricturing and non-penetrating  
B2: stricturing (*constant luminal narrowing demonstrated by radiologic/endoscopic/surgical examination WITH pre-stenotic dilatation +/- or obstructive signs or symptoms*)  
B3: penetrating (*occurrence of bowel perforation, intra-abdominal fistulas, inflammatory masses +/- or abscesses, at any time in disease course EXCLUDING postoperative complications or isolated perianal or rectovaginal fistulae*)  
p: perianal disease modifier (added to B1-B3 if concomitant perianal disease) |

#### Ulcerative colitis (UC)

| **Extent** | E1: ulcerative proctitis (*involvement distal to rectosigmoid junction*)  
E2: left sided UC (*distal to the splenic flexure*)  
E3: extensive disease (*involvement extends proximal to splenic flexure*) |
| **Severity** | S0: clinical remission (*asymptomatic*)  
S1: mild UC (*≤4 stools/day +/- blood, absence of systemic illness and normal ESR*)  
S2: moderate UC (*>4 stools/day but with minimal signs of systemic toxicity*)  
S3: severe UC (*≥6 bloody stools/day, heart rate ≥90 beats/minute, temperature ≥37.5°C, haemoglobin <10.5g/dL, ESR ≥30mm/hr*) |

ESR, erythrocyte sedimentation rate

Phenotyping in the South East Scotland (SES) transition cohort is according to Montreal classification – this allows phenotypic continuity for data collected in both paediatric and adult services and is in keeping with other published studies around transition.232,247,250

Phenotyping in the UK PIBD biologics cohort is also according to Montreal classification – this is the paediatric arm of a national audit run by adult gastroenterologists through the Royal College of Physicians. Phenotyping in the Scotland wide PICTS cohort examining the prevalence of other autoimmune diseases in PIBD is according to Paris classification – this is a paediatric only cohort. See table 2 for details of Paris classification and table 4 for Montreal classification.

Phenotyping in the transition and autoimmune diseases cohorts was independently undertaken by me at time of data collection and later verified with either Professor Wilson or Hazel Drummond (research associate and database manager) in the case of any
ambiguity. Phenotyping in the UK biologics audit is as per the local clinician entering the data.

2.2 South East Scotland (SES) Transition cohort

Diagnosis and management of inflammatory bowel disease below the age of 16 years has been provided centrally in South East Scotland since a dedicated tertiary paediatric gastroenterology service was established in 1997. Patients from three health boards (NHS Borders, NHS Fife and NHS Lothian) are cared for by the regional service until they transition to adult services (which are then provided within the local health board). The transition service first started in 1998 and quickly evolved to a version of the current service.

2.2.1 Case identification

A database of all PIBD patients in the South East Scotland regional service has been prospectively collected for audit purposes since 1997. The database was retrospectively interrogated for all patients discharged from the service by means of transition or transfer since 1st June 1998 (first patient discharged from the service) to 31st December 2013. Patients who transferred out of region prior to their 15th birthday (i.e. discharged prior to moving to adult services) were excluded. This provided basic information on age, gender, diagnosis and discharge destination. Case notes, laboratory records and results were then reviewed for all patients discharged on or after 1st January 2007 for more detailed information; hard copy notes were consulted when the electronic record was insufficient. This time point onwards marks the period when biological therapies were routinely available for use in standard clinical practice. Local clinicians in the two additional health boards within the region facilitated collection of adult data after local audit registration; no adult data were collected for patients who had transferred out of region. Data were initially collated on paper proformas designed by Professor Wilson and myself, stored securely within the department of Child Life and Health (CLaH); this was then anonymised and entered into a project specific database in Microsoft Access 2010 (stored on an encrypted computer) and each patient allocated a unique identifying number.

Data were collected as follows:

Demographic data; date of birth, gender, date of diagnosis and IBD subtype at diagnosis – histopathology and endoscopy details were checked to confirm phenotype.
Type and timing of transition; transition process (2 or more joint clinics), transition clinic (single joint clinic) or transfer event (letter or information sharing only) was documented. Mode of transition was documented according to clinical intention e.g. patients for whom a transition clinic was scheduled but who failed to attend or had surgery in adult services mid-process were still counted as transition rather than a transfer event. Transfer is defined as the point at which the patient is no longer under the care of paediatric services; usually taken as the date of the last booked paediatric or joint clinic (whether attended or not). Where the exact date of transfer was unknown and only the month and year available, the middle of the month was used e.g. 14th or 15th day of the month.

Medical therapy exposure in paediatric and adult services; use of enteral nutrition, steroids, immunomodulators and biological therapy, as well as reasons for discontinuation of therapy (including primary non-response or non-remission, intolerance or loss of response).

Surgery; IBD related surgery pre and post transition including type and timing of procedure. Surgical procedures were counted if considered to be IBD related, i.e. necessitated by the disease process; this included perianal abscess procedures where an intervention was performed (incision and drainage, laying open of fistula, Seton insertion) but not examination under anaesthetic (EUA).

Service use; number of admissions and booked appointments in the year pre and post transfer were documented; as a proxy for engagement with service in paediatric and adult settings, the number of missed appointments was documented for the same time periods.

Disease phenotype and activity; the primary time points for comparison of disease status were last paediatric follow-up (including joint transition clinics) and last adult follow-up to 28/02/17 or earlier, if the patient was lost to follow-up, left the region or died. At these time points disease activity was categorised using Physician Global Assessment (PGA, see table 5) and phenotype classified using Montreal classification for location and severity. Disease location according to Montreal classification was always recorded as maximum ever e.g. a patient who had previous stricturing ileo-colonic disease but post resection was in remission would still be recorded as stricturing i.e. L3 B2.
Table 5 - Physician Global Assessment (PGA) of disease activity

<table>
<thead>
<tr>
<th>SES transition cohort</th>
<th>PICTS Autoimmune diseases cohort</th>
<th>UK IBD biologics cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid free remission</td>
<td>Steroid free remission</td>
<td>Mild disease</td>
</tr>
<tr>
<td>Remission</td>
<td>Remission</td>
<td>Moderate disease</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Mild disease</td>
<td>Severe disease</td>
</tr>
<tr>
<td>Moderate – severe</td>
<td>Moderate – severe disease</td>
<td></td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Miscellaneous; Data were also collected on occurrence of psychosocial co-morbidity, cancer, mortality and pregnancy at any time. Psychosocial co-morbidity was defined as a formal psychiatric diagnosis, a period of regular psychology or psychiatry input (or intention for this if repeated family refusal), documented anxiety or depression, documented episodes of deliberate self-harm, or family/social issues necessitating professional involvement e.g. social work. This was broadly derived from World Health Organisation International Classification of Primary Care (ICPC-2-E) psychological and social chapters.\textsuperscript{308}

To minimise bias, adult data include all patients who left the service; where there is no follow-up due to transfer out of region, information is presented as the last observation carried forward. The only exclusion is when calculating loss to follow-up, where patients who transferred out of region (and therefore have no adult data) are excluded.

2.2.2 Statistical analysis

Data were stored and analysed using Microsoft Access (2013), Microsoft Excel (2013) and Minitab 18.1 (2017). Categorical data are expressed as proportions and compared using Chi-squared tests where appropriate; continuous variables are presented as median and interquartile range (IQR). A p value <0.05 was considered significant.

2.2.3 Ethical considerations

The local ethics committee have deemed the database is primarily for evaluation of service design and delivery and therefore does not require individual ethical approval for use. Local audit registration was obtained from peripheral health boards within the regional service, with the assistance of link clinicians (paediatricians with an interest in gastroenterology) – Dr Clare Irving in the Borders and Dr John Morrice in Fife.
2.3 Autoimmune diseases in PIBD (Scotland) cohort

The paediatric-onset IBD cohort and treatment study (PICTS) is an ongoing Scottish incident and prevalent cohort which collects phenotype, genotype, immunotype, environment and demographic data on recruited patients. Recruitment is carried out opportunistically across Scotland at either initial work-up or subsequent clinical follow-up in one of three tertiary regional referral centres (Aberdeen – North of Scotland, Edinburgh – South East Scotland, Glasgow – West of Scotland) overseeing all Scottish paediatric IBD (PIBD) care. Patients complete a questionnaire on enrolment to the study which includes details on past medical history and family history. Genotype data from this cohort was included in the Immunochip study, which has subsequently been included in wider meta-analysis and previously published.²⁵⁶,³⁰⁹

2.3.1 Case identification

The database was interrogated by database manager Hazel Drummond (HD) for all patients enrolled from 01/07/2002 up to 31/12/12 with at least one other autoimmune disease. Records for identified patients were then reviewed by me; follow-up was to 30/04/15 unless no longer in Scottish IBD services due to loss to follow up, emigration or death. This included follow-up into adult services where patients had graduated from paediatric care; electronic health record first followed by hard copy notes where electronic systems were not available or lacking adequate detail. Dr Sabarinathan Loganathan (Consultant Paediatric Gastroenterologist) kindly facilitated access to hard copy notes for confirmation and clarification of AID diagnosis in patients cared for in Dundee and Aberdeen, including any necessary local approval to review the notes. Professor Richard Russell coordinated an honorary contract with the Greater Glasgow and Clyde Health Board and requested hard copy notes to facilitate data access for the PICTS patients cared for in Glasgow. A pseudonymised proforma (designed by myself and Professor Wilson) was completed for each patient specific to this research question, namely the prevalence of co-existent autoimmune diseases in a PIBD population and clinical features in such cases. Pseudonymised paper proformas are stored securely within CLaH and anonymised data using Microsoft Excel.

2.3.2 Diagnosis and classification

Autoimmune diseases included were thyroid disease (THY), spondyloarthropathy (SPA), psoriasis (PSOR), coeliac disease (CEL), systemic lupus erythematosus (SLE), systemic
sclerosis (SS), sarcoidosis (SAR), vasculitis (VAS), type 1 diabetes mellitus (T1DM), juvenile idiopathic arthritis (JIA), common variable immunodeficiency (CVID), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary sclerosis (PBC), autoimmune sclerosing cholangitis (ASC), vitiligo (VIT), alopecia areata (AA). Symptoms clearly attributable to anti-TNFα use were excluded, cases where anti-TNF use may have been a contributing factor are clearly described. Atopic diseases (asthma, eczema, allergic rhinitis and food allergy) were also excluded due to their ubiquitous presence in the Scottish population.310

Disease classification was challenging since with many AID diagnoses, there isn’t a single agreed classification system and significant ambiguity exists. Additionally, multiple conditions rely on clinical diagnosis only, with no defining test for confirmation.

Where there are multiple classification systems, we adopted the following: Juvenile idiopathic arthritis (JIA) according to the International League of Associations for Rheumatology (ILAR) criteria311; Spondyloarthropathy according to Assessment in Spondyloarthritis international Society (ASAS) criteria312; Autoimmune liver disease according to the American Association for Study of Liver Disease (AASLD) Primary Sclerosing Cholangitis (PSC) practice guideline313 and the International Autoimmune Hepatitis Group overlap syndromes position statement284. To maximise diagnostic accuracy, coeliac disease required biopsy confirmation as well as positive serology for diagnosis; although the current BSPGHAN and ESPGHAN guidelines include criteria by which the diagnosis may be made without biopsy, these guidelines came into existence after all the patients were recruited into the PICTS cohort and would be not be reflective of standard clinical practice during the study period. Psoriasis, for which there are no established diagnostic criteria, was only considered as a definite diagnosis if confirmed by dermatology or a gastroenterology or paediatric consultant; unconfirmed self-reported cases were excluded.

IBD location and behaviour was documented according to Paris classification, as described at the start of the chapter and in table 2; any L4 disease i.e. proximal (L4a) or distal (L4b) to the ligament of Treitz was considered L4 disease.30 Severity in UC/IBDU by this classification is defined as never severe (S0) or ever severe (S1) according to a Paediatric Ulcerative Colitis Activity Index (PUCAI, see table 6 below) score ≥6S; where not explicitly provided in the notes (the majority of cases) this was calculated using the clinical information available.
Table 6 - Pediatric Ulcerative Colitis Activity Index (PUCAI)\textsuperscript{314,315}

<table>
<thead>
<tr>
<th>ITEM</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>0</td>
</tr>
<tr>
<td>Pain can be ignored</td>
<td>5</td>
</tr>
<tr>
<td>Pain cannot be ignored</td>
<td>10</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Small amount in &lt;50% stools</td>
<td>10</td>
</tr>
<tr>
<td>Small amount with most stools</td>
<td>20</td>
</tr>
<tr>
<td>Large amount (&gt;50% stool content)</td>
<td>30</td>
</tr>
<tr>
<td>Stool consistency (most stools)</td>
<td></td>
</tr>
<tr>
<td>Formed</td>
<td>0</td>
</tr>
<tr>
<td>Partially formed</td>
<td>5</td>
</tr>
<tr>
<td>Completely unformed</td>
<td>10</td>
</tr>
<tr>
<td>Number of stools/24 hours</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>3-5</td>
<td>5</td>
</tr>
<tr>
<td>6-8</td>
<td>10</td>
</tr>
<tr>
<td>&gt;8</td>
<td>15</td>
</tr>
<tr>
<td>Nocturnal stool (any episode causing wakening)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Activity level</td>
<td></td>
</tr>
<tr>
<td>No limitation</td>
<td>0</td>
</tr>
<tr>
<td>Occasional limitation</td>
<td>5</td>
</tr>
<tr>
<td>Severe restricted activity</td>
<td>10</td>
</tr>
<tr>
<td>SUM OF PUCAI (0-85)</td>
<td></td>
</tr>
<tr>
<td>Mild disease &lt;35</td>
<td></td>
</tr>
<tr>
<td>Moderate disease 35-60</td>
<td></td>
</tr>
<tr>
<td>Severe disease ≥65</td>
<td>______</td>
</tr>
</tbody>
</table>

2.3.3 Statistical analysis

Data were analysed using Microsoft Excel (2013) and GraphPad QuickCalcs Software (2015); differences in categorical data were analysed using Chi squared test, unless there were fewer than 5 observations in any cell in which case Fisher’s exact test was used.

2.3.4 Ethical considerations

All patients and/or their parents provided full written consent as part of the PICTS project – a Medical Research Council funded cohort study approved by local ethics committees in the 3 participating Scottish clinical networks: South-East Scotland (LREC/2002/6/18), West of Scotland (YREC/P12-03) and North of Scotland (GREC/03/0273).
2.4 Biologics in PIBD (UK) cohort

The IBD biological therapy audit is a project within the Royal College of Physicians (RCP) IBD programme, aiming to nationally assess the appropriate use and prescribing of Adalimumab (ADA) and Infliximab (IFX), their efficacy and safety and patients’ view of their own quality of life in the UK. An annual report was produced every year from 2013-2016 inclusive, with paediatric and adult data reported separately.

2.4.1 Data collection

Sites (either a single hospital or a represented health board or trust) were eligible to participate in the biological therapies audit if they prescribe and administer biological therapies to their patients with IBD, on a voluntary basis. There are 25 specialist paediatric IBD (PIBD) sites in the UK, of which 23 contributed data to this audit. Additionally there are another 14 paediatric sites providing biological therapy and submitting data, giving a total of 37 sites.

Children of all ages with a diagnosis of IBD who were newly started on biological therapy for treatment of their IBD from 12/09/11 were eligible for inclusion. Patients already on biological therapy prior to this date were not included. Data were collected prospectively and entered into a bespoke web based database, with security maintained through local site codes and the lead clinician for the site authorising local access. Data capture for the results included here ended on 28/02/14.

Table 7 - Paediatric Crohn’s Disease Activity Index (PCDAI)\textsuperscript{316,317}

<table>
<thead>
<tr>
<th>ITEM</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HISTORY (1 week recall)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild – brief, does not interfere with activities</td>
<td>5</td>
</tr>
<tr>
<td>Moderate/severe – daily, longer lasting affects activities, nocturnal</td>
<td>10</td>
</tr>
<tr>
<td>Stools (per day)</td>
<td></td>
</tr>
<tr>
<td>Formed stools or 0-1 liquid stools, no blood</td>
<td>0</td>
</tr>
<tr>
<td>0-2 semi-formed with small blood or 2-5 liquid stools</td>
<td>5</td>
</tr>
<tr>
<td>Gross bleeding or ≥6 liquid stools or nocturnal diarrhoea</td>
<td>10</td>
</tr>
<tr>
<td>Functioning - general wellbeing</td>
<td></td>
</tr>
<tr>
<td>No limitation of activities - well</td>
<td>0</td>
</tr>
<tr>
<td>Occasional difficulty maintaining age appropriate activities – below par</td>
<td>5</td>
</tr>
<tr>
<td>Frequent limitation of activity – very poor</td>
<td>10</td>
</tr>
</tbody>
</table>
### EXAMINATION

<table>
<thead>
<tr>
<th>Weight</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain or voluntary weight stable/loss</td>
<td>0</td>
</tr>
<tr>
<td>Involuntary weight stable or weight loss 1-9%</td>
<td>5</td>
</tr>
<tr>
<td>Weight loss ≥10%</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td>Height velocity ≥ -1SD</td>
</tr>
<tr>
<td>&lt;1 channel decrease</td>
<td>Height velocity &lt; -1SD but &gt; -2SD</td>
</tr>
<tr>
<td>≥1 but &lt;2 channel decrease</td>
<td>Height velocity ≤ -2SD</td>
</tr>
<tr>
<td>≥2 channel decrease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abdomen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No tenderness / no mass</td>
<td>0</td>
</tr>
<tr>
<td>Tenderness or mass without tenderness</td>
<td>5</td>
</tr>
<tr>
<td>Tenderness / involuntary guarding / definite mass</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perirectal disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None / asymptomatic tags</td>
<td>0</td>
</tr>
<tr>
<td>1-2 indolent fistulae / scant drainage / no tenderness</td>
<td>5</td>
</tr>
<tr>
<td>Active fistula / drainage / tenderness / abscess</td>
<td>10</td>
</tr>
</tbody>
</table>

**Extra-intestinal manifestations:** Fever ≥38.5 for 3 day in past week / definite arthritis / uveitis / erythema nodosum / pyoderma gangrenosum

<table>
<thead>
<tr>
<th>Extra-intestinal manifestations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>One</td>
<td>5</td>
</tr>
<tr>
<td>≥Two</td>
<td>10</td>
</tr>
</tbody>
</table>

### LABORATORY

<table>
<thead>
<tr>
<th>Haematocrit (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td></td>
</tr>
<tr>
<td>&gt;33</td>
<td>11-19 Female ≥34</td>
</tr>
<tr>
<td>28-32</td>
<td>11-14 Male ≥35</td>
</tr>
<tr>
<td>&lt;28</td>
<td>15-19 Male ≥37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR (mm/hr)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0</td>
</tr>
<tr>
<td>20-50</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;50</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin (g/dL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3.5</td>
<td>0</td>
</tr>
<tr>
<td>3.1-3.4</td>
<td>5</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score (0-95)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiescent disease ≤10</td>
<td></td>
</tr>
<tr>
<td>Mild disease 11-29</td>
<td></td>
</tr>
<tr>
<td>Moderate/severe disease ≥30</td>
<td></td>
</tr>
</tbody>
</table>

Demographic details were pseudo-anonymised at the point of data entry and identifiable only to the participating site. IBD disease details were phenotyped according to Montreal criteria for disease location and behaviour. Disease severity was assessed using Paediatric Crohn’s Disease Activity Index (PCDAI, table 7) or Paediatric Ulcerative Colitis Activity Index (PUCAI, table 6) scores and physician global assessment (PGA, table 5) of mild, moderate or
severe disease activity, collected at initial and follow-up treatments, along with details of comorbidities and any surgery.\textsuperscript{318,314,319} See table 8 for a summary of data collected. A full list of all data items collected is available on request from the RCP.

Table 8 - Biological therapy audit data collection details

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Pseudonymised at point of data entry and identifiable only to the participating site.</td>
</tr>
<tr>
<td>IBD disease details</td>
<td>Montreal classification and Physician Global Assessment (PGA) for disease location, behaviour and severity; any comorbidities and any surgery prior to initiation of therapy.</td>
</tr>
<tr>
<td>Initial anti-TNF(\alpha) treatment</td>
<td>Appropriate questions generated when either IFX or ADA chosen as treatment. Includes data on investigations and screening up to completion/abandonment, concomitant therapies and any adverse events.</td>
</tr>
<tr>
<td>Follow-up anti-TNF(\alpha) treatment</td>
<td>Each follow-up treatment relates to an initial submission. Outcome of treatment as intention to continue or stop is recorded. Response to treatment and remission recorded using PCDAI and HBI. Unlimited number of follow-up treatments permitted, adverse events recorded.</td>
</tr>
<tr>
<td>IBD related surgery</td>
<td>Details can be added at any time; a prompt to update flashes at any initial or follow-up treatment to identify any escalation of treatment.</td>
</tr>
<tr>
<td>Patient Reported Outcome Measures (PROMs)</td>
<td>Data collected using IMPACT III (health-related paediatric IBD specific) questionnaire at initial treatment, 3 months and 12 months.</td>
</tr>
</tbody>
</table>

PGA, Physician Global Assessment; IFX, Infliximab; ADA, Adalimumab; PCDAI, Paediatric Crohn’s Disease Activity Index; HBI, Harvey Bradshaw Index; IBD, Inflammatory Bowel Disease

Initial anti-TNF\(\alpha\) treatment: questions were generated depending on biologic selected i.e. IFX or ADA and included data on screening and investigations up to completion/abandonment, concomitant therapies and any adverse effects. Acute infusion reactions were as decided by the clinical team responsible for the patient; no specific timing was given. Each follow-up treatment relates to an initial submission and records outcome as intention to continue or stop; response with or without remission using reduction in PCDAI/PUCAI or Harvey Bradshaw Index (HBI), another commonly used disease activity scoring tool.\textsuperscript{320} Unlimited numbers of follow-up treatments are permitted and any
adverse events recorded. Poor response was used to describe those patients with no or limited response to anti-TNF treatment, which would include primary non-responders.

Details of IBD related surgery can be added at any time along with any escalation of treatment at each initial or follow-up treatment. Patient Reported Outcome Measures (PROM) data were collected using the IMPACT-III questionnaire (a validated tool to measure health related quality of life in PIBD, where scores range from 35-175 and a higher score indicates a better quality of life\textsuperscript{321-323}) at initiation and subsequently.

Some children received treatment with multiple biologics resulting in more initial treatments than patients. Since the number of submissions per patient is variable (e.g. multiple initial or follow-up treatments), the denominators vary considerably and results tables should be scrutinised carefully in conjunction with any explanatory notes for accurate data interpretation.

Guidance on the use of biological therapy in the UK comes via the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). NICE Technology Appraisals TA187 (CD) and TA329 (UC) recommend Infliximab within its licensed indication as an option for “the treatment of people aged 6-17 years with severe active disease who have not adequately responded to conventional therapy (including corticosteroids, immunomodulators and exclusive enteral nutrition [CD]), or who cannot tolerate or have contraindications to conventional therapy”. Data were collected on disease type and severity as well as previous therapies to assess prescribing against these criteria.

Selected data, including demographics, disease location and response to treatment were compared to data reported in the adult arm of the audit from the same time period, which can be seen at www.rcplondon.ac.uk/ibd.

Access to the data was facilitated by Kajal Mortier, IBD project manager in the clinical effectiveness and evaluation unit at the RCP. Data that was not included in the annual report was formally requested via completion of the Data Access Request Form (DARF) to the Healthcare Quality Improvement Partnership (HQIP); once approved it was released via Kajal Mortier to the project statistician (see below) who analysed the data and forwarded on results to me for interpretation.
2.4.2 Statistics

Data were analysed using SPSS version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Data manipulation was performed using SAS software v9.4 for Windows. Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. Chi-squared test and the kappa statistic were used to examine categorical data; the Mann-Whitney U test was used to examine continuous data; Kolmogorov-Smirnov (KS) test was used to analyse PROM data. Kappa statistic is expressed as per the boundaries described by Landis and Koch; range is from ‘poor/slight’ agreement (\( \kappa \leq 0.2 \)) through ‘fair’, ‘moderate’ and ‘substantial’, to ‘almost perfect’ agreement (\( \kappa 0.81-1.00 \)). A \( p \) value of <0.05 was considered statistically significant.

All raw data were retained by the Royal College of Physicians and statistical analysis beyond comparison of categorical data and Chi squared analysis performed by the RCP biological therapy audit statistician, Dr Linda Williams (medical statistician, Centre for Population Health Sciences, University of Edinburgh).

2.4.3 Ethical considerations

As an audit of clinical practice, with data anonymised at source, ethical permission was not applied for.
3 THE NATURAL HISTORY OF PAEDIATRIC INFLAMMATORY BOWEL DISEASE AROUND TRANSITION TO ADULT SERVICES: A SOUTH EAST SCOTLAND REGIONAL COHORT STUDY

3.1 Background

There are multiple definitions of transition but commonly quoted and helpfully concise is that of Blum et al as “the purposeful planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems”.

The Royal Hospital for Sick Children Edinburgh (RHSCE), now renamed Royal Hospital for Children and Young People (RHCYP), is the tertiary centre providing care to all paediatric patients with IBD in South East Scotland (SES). This is often through a shared care model with a paediatrician (with an interest in gastroenterology) from one of three local District General Hospitals (DGHs) in the region, if the patient lives outwith the city of Edinburgh. At transition, patients either move on to tertiary adult gastroenterology services (in Edinburgh) or an adult gastroenterologist in their local DGH with an interest in IBD. The transition service in SES was set up in 1998 and rapidly developed to the current structure of planned transition with 1 or more joint clinics with paediatric and adult gastroenterology whenever possible.

Transition describes the whole process of planning and moving from paediatric to adult services, including attendance at joint clinics where relevant – see figure 3. Transfer refers to the point at which the patient is no longer under the care of paediatric services and is solely under the care of an adult team.

3.2 Aim

As discussed in chapter 1, there is a paucity of data documenting outcome following transition to adult services in PIBD and limited consistency in practice between centres. This study aims to examine the natural history of disease in a regional cohort of young people pre and post transition to adult services, in order to understand areas of potential weakness and inform service development at a local and wider level.
Figure 3 - Outline of transition process in South East Scotland

Transition locally
- Joint visit (paediatric and adult IBD team) at RHCYP
- Joint visit (paediatric and adult IBD team) at adult hospital
- Last joint visit is point of transfer

Transition regionally
- Joint visit (paediatric and adult IBD team) at local DGH – usual point of transfer
- Subsequent paediatric visits only in exceptional circumstances

Transfer of information only
- Via tailored summary letter to appropriate adult physician
- May be within SES region to DGH or beyond

12-14 yrs
- Concept of transition and transfer to adult services broadly introduced including:
  - Knowing and understanding condition and treatment
  - Shared decision making
  - Working towards independent clinic visits

14-16 yrs
- Continuous assessment of skills and ongoing education
- Gradual aim to see patient alone for part of clinic visit
- Parent/carer kept fully involved

16-18 yrs
- Increased time alone in clinic working towards whole session independently
- Parent/carer remains involved
- Potential issues/concerns highlighted and addressed

Enhanced transition
- May be local or regional
- Bespoke process for patients requiring additional support such as extra joint visits
- May involve wider MDT e.g. psychology or other teams

RHCYP, Royal Hospital for Children and Young People; DGH, district general hospital; SES, South East Scotland; MDT, multi-disciplinary team
3.3 Methods

A prospectively collected database of patients in a regional PIBD service, held for audit and service development purposes, was retrospectively interrogated to identify patients who had transitioned to adult services; clinical outcome was established through subsequent review of case records for all patients discharged from 01.01.2007, with data capture ending 28.02.2017. Details are presented in chapter 2 section 2.2.

3.4 Results

3.4.1 Overview

1998-2013

209 patients with PIBD were discharged from the paediatric GI service on or after their 15th birthday in the 16 year study period (Figure 4); 54% male (112/209), 70% CD (146/209), 21% UC (43/209), 9% IBDU (20/209). 70% (146/209) were discharged via a transition process (one or more joint adult-paediatric clinics) and the remaining 30% (63/209) via a transfer event (referral letter or information sharing only). Median age (Interquartile range = IQR) at discharge was 17.7 years (16.9, 18.2), median (IQR) disease duration at discharge 4.9 years (3.4, 6.9). 20 patients transferred out of South East Scotland (this may have been to another paediatric IBD service or an adult service); 4 patients left the UK.

Figure 4 - Number of patients discharged from South East Scotland (SES) paediatric inflammatory bowel disease (PIBD) service by year 1998-2013
138 patients with PIBD were discharged ≥15 years of age between 1st January 2007 and 31st December 2013; 57% male (78/138). Median (IQR) age at time of transfer was 17.8 years (17.3, 18.3); median (IQR) disease duration at time of transfer (T/F) was 4.9 years (3.6, 6.9), (Table 9). 18 patients have no adult data; 6 failed to attend any adult follow-up after transfer and 12 transferred out of region. 73% (101/138) were discharged via a joint adult-paediatric transition clinic; 56% (77/138) via a full transition process i.e. 2 or more joint clinics and 17% (24/138) following a single joint transition clinic. The remaining 27% (37/138) were discharged via transfer of information only.

At time of transfer to adult services, breakdown by disease type was as follows; 69% CD (95/138), 20% UC (27/138), 12% IBDU (16/138). Three patients had their IBD diagnosis revised in adult services; one from CD to UC following colectomy, one from IBDU to UC following colectomy and one from UC to IBDU (Figure 5). Where data is presented by disease type, patients are categorised according to their final diagnosis. Median (IQR) length of follow-up post transfer from paediatric services was 5.1 years (3.8, 7.1), see table 9.
Table 9 - Characteristics of cohort by IBD subtype at transfer (T/F) and last adult follow-up (LAFU).

<table>
<thead>
<tr>
<th></th>
<th>CD n (%)</th>
<th>UC n (%)</th>
<th>IBDU n (%)</th>
<th>All PIBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T/F</td>
<td>LAFU</td>
<td>T/F</td>
<td>LAFU</td>
</tr>
<tr>
<td>No. patients</td>
<td>95 (69)</td>
<td>82 (68)</td>
<td>27 (20)</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>50</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Median age at diagnosis</td>
<td>12.55</td>
<td>12.62</td>
<td>13.45</td>
<td>13.69</td>
</tr>
<tr>
<td>Median age at T/F</td>
<td>17.85</td>
<td>17.86</td>
<td>17.75</td>
<td>17.75</td>
</tr>
<tr>
<td>Median age at LAFU</td>
<td>-</td>
<td>23.47</td>
<td>-</td>
<td>23.58</td>
</tr>
<tr>
<td>Median length of follow-up post T/F</td>
<td>-</td>
<td>5.21</td>
<td>-</td>
<td>5.04</td>
</tr>
<tr>
<td>Median length of follow-up at T/F</td>
<td>5.15</td>
<td>5.19</td>
<td>3.81</td>
<td>3.77</td>
</tr>
<tr>
<td>Median length of total follow-up (from diagnosis)</td>
<td>10.75</td>
<td>11.22</td>
<td>8.84</td>
<td>9.51</td>
</tr>
</tbody>
</table>

CD Crohn’s Disease; UC ulcerative colitis; IBDU Inflammatory Bowel Disease Unclassified; PIBD paediatric inflammatory bowel disease; age and length of follow-up in years.
CD, Crohn’s Disease; UC, Ulcerative Colitis; IBDU, Inflammatory Bowel Disease Unclassified; LTFU, Lost To Follow Up; OOA, Out of Area transfer; **---** > Revised diagnosis in adult service
3.4.2 Disease phenotype

77% (73/95) of CD patients had extensive disease distribution at time of transfer; ileocolonic (L3) 20% (19/95) or ileocolonic with upper disease (L3+L4) 57% (54/95), (Figure 6). Upper GI involvement increased proportionally in adult follow-up from 74% (70/95) to 82% (67/82); 5 patients with L4 disease had no adult follow-up and 2 patients had new UGI disease diagnosed post transfer. Whilst L3 rates fell to 13% (11/82), L3+L4 rates rose to 66% (54/82); overall extensive disease distribution was 79% (65/82) at last adult follow-up (LAFU), as shown in figure 6 and table 10. There was significant progression in disease severity; combined stricturing (B2+/-p) and penetrating (B3+/-p) disease rose from 20% (19/95) overall at transfer (16% [15/95] stricturing, 4% [4/95] penetrating), to 38% (31/82) overall at last adult follow-up (20% stricturing [16/82], 18% [15/82] penetrating, (p=0.009), see figure 7. Perianal disease rose from 21% (20/95) at transfer to 33% (27/82) at last adult follow-up (67% [18/27] male) but was not statistically significant (p=0.07).

Most UC/IBDU patients also had extensive and aggressive disease; 81% (35/43) had disease proximal to the splenic flexure (i.e. extensive) at transfer and this was static (82% [31/38]) at last adult follow-up. Disease severity was moderate or severe in 74% (32/43) at transfer and 76% (29/38) at LAFU as shown in figure 8 and table 10.
Figure 6 - Crohn’s disease phenotype at transfer (n=95) and last adult follow-up (n=82) expressed as % of patients.

T/F, transfer; LAFU, last adult follow-up; L1, terminal ileal ± limited caecal disease; L2, colonic; L3, ileocolonic; L4, isolated upper disease; B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating; p, perianal disease modifier
Table 10 - Disease phenotype at transfer (T/F) and last adult follow-up (LAFU) according to Montreal classification

<table>
<thead>
<tr>
<th></th>
<th>CD n (%)</th>
<th>UC n (%)</th>
<th>IBDU n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1</td>
<td>2 (7%)</td>
<td>2 (8%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>E2</td>
<td>3 (11%)</td>
<td>2 (8%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>E3</td>
<td>22 (82%)</td>
<td>21 (84%)</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>L1 (distal ileum)</td>
<td>1 (1%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L2 (colonic)</td>
<td>5 (5%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>L3 (ileo-colonic)</td>
<td>19 (20%)</td>
<td>11 (13%)</td>
<td></td>
</tr>
<tr>
<td>L4 (upper GI)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L1+L4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>L2+L4</td>
<td>16 (17%)</td>
<td>13 (16%)</td>
<td></td>
</tr>
<tr>
<td>L3+L4</td>
<td>54 (57%)</td>
<td>54 (66%)</td>
<td></td>
</tr>
<tr>
<td>Disease behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>59 (62%)</td>
<td>37 (45%)</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td>13 (14%)</td>
<td>11 (13%)</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>3 (3%)</td>
<td>7 (9%)</td>
<td></td>
</tr>
<tr>
<td>B1p</td>
<td>17 (18%)</td>
<td>14 (17%)</td>
<td></td>
</tr>
<tr>
<td>B2p</td>
<td>2 (2%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td>B3p</td>
<td>1 (1%)</td>
<td>8 (10%)</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>5 (19%)</td>
<td>4 (16%)</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>S2</td>
<td>13 (48%)</td>
<td>10 (40%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>S3</td>
<td>9 (33%)</td>
<td>11 (44%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>
Figure 7 - Crohn’s disease severity at T/F (n=95) and LAFU (n=82) expressed as % or patients.

Disease classification according to Montreal classification; B2 (15/95, 16/82) and B3 (4/95, 15/82) disease includes all patients with or without perianal disease modifier.
Figure 8 - UC/IBDU phenotype at transfer (n=44) and last adult follow-up (n=38) expressed as % of patients.

T/F, transfer; LAFU, last adult follow-up; E1, ulcerative proctitis; E2, left sided UC (distal to splenic flexure); E3, extensive (proximal to splenic flexure); S1, mild UC; S2, moderate UC; S3, severe UC
3.4.3 Clinical status at transfer and last adult follow-up

80% (111/138) of patients were in steroid free remission (SFR) at time of transfer and 8% (11/138) had moderate-severe disease, according to physician global assessment (PGA); 4% (5/138) were in remission on steroid therapy and 8% (11/138) had mild disease.

At last adult follow-up 75% (90/120) of patients were in SFR and just 13% (16/120) had moderate-severe disease; 1% (1/120) were in remission on steroids and 11% (13/120) had mild disease. There was no clear difference in clinical status at last adult follow-up between those who had a full transition process and those with a single transition clinic or transfer event; see table 11 and 12 A-D, and Figure 9. The overall trend is of higher rates of SFR and less disease activity in patients who underwent a full transition process but the difference was not statistically significant, except when comparing rates of SFR in patients with full transition to everyone else, 82% vs 64% respectively (p=0.03), and presence of any disease (mild or moderate-severe) in those with full transition compared to those with transfer event only, 14% vs 35% respectively (p=0.02). 26% (7/27) of patients who were not in SFR at transfer also had active disease or were on steroids at last adult follow-up, compared with 21% patients who were in SFR at transfer; this difference was not statistically significant (p=0.6).

<table>
<thead>
<tr>
<th>Status at LAFU</th>
<th>N(%) by transition type (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transition process  (n=76)</td>
</tr>
<tr>
<td>Steroid free remission</td>
<td>62 (82)</td>
</tr>
<tr>
<td>Remission</td>
<td>0</td>
</tr>
<tr>
<td>Mild disease</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Moderate-severe disease</td>
<td>9 (12)</td>
</tr>
</tbody>
</table>
Table 12 - A-D Clinical status at last adult follow-up (LAFU) comparing full transition with limited or no transition process

<table>
<thead>
<tr>
<th>A)</th>
<th>Status at LAFU</th>
<th>Full transition vs anything else</th>
<th>% by transition type (n=120)</th>
<th>Transition process (n=76)</th>
<th>Transition clinic (single) or transfer event (n=44)</th>
<th>P value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid free remission</td>
<td>82</td>
<td>64</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any disease</td>
<td>18</td>
<td>34</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate-severe disease</td>
<td>12</td>
<td>16</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B)</th>
<th>Status at LAFU</th>
<th>Any transition vs none</th>
<th>% by transition type (n=120)</th>
<th>Transition process or single transition clinic (n=97)</th>
<th>Transfer event (n=23)</th>
<th>P value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid free remission</td>
<td>77</td>
<td>65</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any disease</td>
<td>14</td>
<td>35</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate-severe disease</td>
<td>14</td>
<td>9</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C)</th>
<th>Status at LAFU</th>
<th>Full transition vs limited</th>
<th>% by transition type (n=120)</th>
<th>Transition process (n=76)</th>
<th>Transition clinic (single) (n=21)</th>
<th>P value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid free remission</td>
<td>82</td>
<td>62</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any disease</td>
<td>18</td>
<td>33</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate-severe disease</td>
<td>12</td>
<td>24</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D)</th>
<th>Status at LAFU</th>
<th>Full transition vs none</th>
<th>% by transition type (n=120)</th>
<th>Transition process (n=76)</th>
<th>Transfer event (n=23)</th>
<th>P value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid free remission</td>
<td>82</td>
<td>65</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any disease</td>
<td>18</td>
<td>35</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate-severe disease</td>
<td>12</td>
<td>9</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A) full transition vs single transition clinic or transfer event; B) Any degree of transition vs transfer event only; C) Full transition vs single transition clinic; D) Full transition vs transfer event only
Figure 9 - Disease status at last adult follow-up expressed as % by transition type (n=120).

Any disease, mild disease and moderate-severe disease combined
Two patients sadly died in adult services: one CD patient developed primary sclerosing cholangitis (PSC) and shortly afterwards was diagnosed with an aggressive cholangiocarcinoma which had already metastasised; the other patient had severe cerebral palsy and multiple co-morbidities in addition to UC and was palliated following recurrent aspiration pneumonias; death was unrelated to their IBD.

### 3.4.4 Medical therapy

79% (109/138) of the whole PIBD cohort have been treated with corticosteroids (prednisolone or hydrocortisone) by time of transfer to adult services; 81% (77/95) CD patients, 81% (22/27) UC patients and 63% (10/16) IBDU patients. Cumulative exposure (prednisolone, hydrocortisone or budesonide) increases to 86% (119/138) by the time of last adult follow-up; 89% (85/95) CD, 88% (24/27) UC, 63% (10/16) IBDU.

69% (66/95) CD patients have received at least one course of exclusive enteral nutrition (EEN) in paediatric services. 18% (15/82) CD patients received EEN post transition, 2% (2/82) in conjunction with steroids to induce remission, whilst a further 3 patients (4%) took supplemental Modulen as partial enteral nutrition (PEN).

By time of transfer to adult services, 78% (108/138) of all PIBD patients and 87% (83/95) CD patients have been exposed to one or more immunosuppressants; 76% (105/138) azathioprine (AZA) or mercaptopurine (MP), 41% (57/138) methotrexate (MTX). 24% (33/138) of PIBD patients [27% (26/95) CD patients] have been treated with at least one biological therapy and 9% (12/138) with both infliximab (IFX) and adalimumab (ADA). 12% (11/95) CD patients have had pan-treatment exposure; AZA or MP, MTX, IFX and ADA with 4% (4/95) refractory (primary non-response, loss of response or intolerance) to all of the above.

By time of last adult follow-up, 80% (111/138) patients have been exposed to AZA/MP, 44% (61/138) to MTX equating to 83% (114/138) exposure to at least one immunosuppressant. 38% (53/138) have had IFX and 28% (39/138) ADA equating to 46% (63/138) exposed to anti-TNF therapy which was a significant rise \(p=0.0001\), as shown in figure 10.

Pan-treatment exposure in CD increased significantly to 27% (26/95) \(p=0.006\) at last adult follow-up and pan-treatment refractory disease to 19% (18/95) \(p=0.001\), as shown in figures 11 and 12. 33% (46/138) patients had exhibited steroid dependency by time of transfer, increasing to 37% (51/138) by last adult follow-up; 75% (38/51) CD, 22% (11/51)
UC, 4% (2/51) IBDU. Of the total cohort therefore, 41% CD patients and 30% UC/IBDU patients had exhibited steroid dependency (no significant difference between the two groups p= 0.2) by LAFU. 79% (30/38) CD patients and 92% (12/32) UC/IBDU patients with steroid dependency had extensive disease (L3 or L3+L4 or E3).

Intolerance leading to cessation of therapy for thiopurines (AZA/MP) was 14% (15/105) at transfer and 22% (24/111) by last adult follow-up. 32% (18/57) patients on MTX had stopped therapy due to lack of tolerance by transfer and this increases significantly to 51% (31/61) at last adult follow-up (p=0.03).

7 patients (6% [7/120]) were treated with Vedolizumab (VDZ [6 CD, 1 UC]) and 2 patients (2% [2/120], both CD) received Ustekinumab (UST), all in adult services.

Pan-treatment exposure (PTE) rates were higher in patients who were discharged via a full transition process (20/77), compared to those who transitioned via single joint clinic (2/24) or transfer event (4/37); 26% vs 10% (p=0.02). 82% (9/11) patients with PTE prior to transfer had a full transition process. There was no significant difference in rates of pan-treatment refractory disease.
Figure 10 - Immunosuppressant exposure at transfer and last adult follow-up expressed as % (n=138).

AZA, azathioprine; MP, mercaptopurine; MTX, methotrexate; Anti-TNF, anti-tumour necrosis factor α (infliximab +/- adalimumab)
Figure 11 - Pan treatment exposure and refractory disease in Crohn’s Disease patients at transfer and last adult follow-up expressed as % (n=95).

Pan treatment exposure and refractory disease in Crohn’s Disease patients at transfer and last adult follow-up expressed as % (n=95).

Pan treatment = AZA/MP + MTX + IFX + ADA
3.4.5 Surgery

Overall 37% (51/138) of patients underwent at least one IBD related surgical procedure in either paediatric or adult services, as shown in figure 13. 18% (25/138) had their first procedure prior to formal transfer, 44% (11/25) of whom went on to have further surgery as adults; 26% (36/138) of the overall cohort had IBD surgery in adult services.

22% (21/95) of CD patients had required IBD related surgery by time of transfer with four patients having multiple procedures; recurrent perianal abscess/fistula surgery, multiple small bowel resections (including with ileostomy formation) and later stoma closure, defunctioning stoma followed by left colon resection and eventual completion colectomy with permanent stoma, right hemicolecetomy and later small bowel resection. Cumulative surgery rates in Crohn’s had risen to 51% (42/83) by time of last adult follow-up. Perianal abscess/fistula surgery was the commonest procedure both pre and post transfer, as shown in figure 14.
Figure 13 - Cumulative IBD surgery exposure expressed as a percentage of the total cohort (n=138).

Colectomy rates in UC rose from 15% (4/27) at time of transfer to 26% (7/27) at time of last adult follow-up; two patients had revised diagnoses after surgery, one from CD and one from IBDU, as shown in figure 5. A single IBDU patient (6%, 1/16) had colectomy in paediatric services and diagnosis remained unchanged at last adult follow-up.

Surgery rates post transfer were similar amongst those who underwent a full transition process and those via a single joint clinic or transfer event (32%, 14% and 30% respectively; \( p \geq 0.05 \) for any combination of comparison).
Figure 14 - IBD related surgical procedures in total cohort expressed as individual procedures (n=138)

- Defunctioning stoma
- Right hemicolectomy
- Left colon resection
- Colectomy + end ileostomy
- Small bowel resection
- Perianal abscess/fistula surgery
- Completion proctectomy +/- restoration
- Revision of stoma
- Reversal of stoma
- Laparotomy +/- adhesiolysis

Legend:
- Pre transfer (n=35)
- Post transfer (n=95)
3.4.6 Service use around transition

Service use is relatively heavy around the transition period. Median number of appointments in the year prior to transfer was 5 (IQR 3, 7) and in the year post transfer 3 (IQR 2, 6). Missed appointments were common; 42% (58/138) patients missed one or more appointments in the year prior to transfer and 36% (43/120) in the year post transfer (p=0.3); 23% (28/120) patients missed one or more appointments in the year both pre and post transfer. 60% (28/47) patients who missed one or more appointments in the year pre transfer went on to miss them post transfer compared to 21% (15/73) who had no missed appointments pre-transfer; this was statistically significant (p=0.00001). The ratio of missed appointments to booked appointments was calculated as a percentage for each individual; of those who missed at least one appointment, a median of 32% (IQR 18, 50) of appointments were missed in the year pre transfer and 50% (IQR 23, 90) in the year post transfer.

18% (25/138) of patients had one or more hospital admissions in the year prior to transfer (scheduled day-case endoscopy excluded) and 14% (17/120) in the year post transfer.

There were no significant differences in missed appointments pre or post transfer or hospital admissions post transfer according to type of transition. 42% (32/77) moving via transition process (TP), 46% (11/24) moving via single transition clinic (TCS) and 41% (15/37) moving via transfer event (TE) missed ≥1 planned appointment in the year prior to transfer; 38% (29/76) TP, 33% (7/21) TCS and 26% (6/23) TE missed ≥1 planned appointment in the year post-transfer; 18% (14/76) TP, 5% (1/21) TCS and 9% (2/23) TE had ≥1 hospital admission in the year post transfer.

3.4.7 Loss to follow-up

19% (24/126) of patients were lost to follow-up at the end of the study period (16 CD, 3 UC, 5 IBDU), of whom six (all CD, 50% male) have no follow-up since leaving paediatric services; four out of those six had a transition process of at least one joint clinic. For the remaining 18 patients, median time (IQR) from date of transfer to loss to follow-up (last adult follow-up attended) was 4.00 years (2.76, 5.31).

40% (10/25) of patients who had a transfer of information only (excluding out of area transfers) on moving to adult services were lost to follow-up compared to 14% (14/101) who had formal transition; 21% (5/24) a single transition clinic and 12% (9/77) with a full
transition process. The difference in loss to follow up in those with transfer of information only compared to those with full transition was significant (p=0.002); see figure 15. Significantly more patients who missed one or more appointments in the year pre-transfer were lost to follow-up at the end of the study compared to those who did not miss any appointments; 31% (16/52) vs 11% (8/74) p=0.005.

Of those lost to follow-up, 88% (21/24) were in steroid free remission when last seen; three patients (13%) had mild disease.

It should be noted that one of the patients counted as lost to follow-up with no adult follow-up for the purposes of analysis, did later represent to adult services. They failed to attend multiple appointments following transfer (at which point they were in steroid free remission on a thiopurine) and had no follow-up after leaving paediatric services for 8 years, before representing with active disease and progressing to adalimumab within a few months. Since the primary purpose of this study was to characterise disease around transition, I made the decision to consider as LTFU following discussion with Professor Wilson, and the adult data were not included in analysis.

3.4.8 Psychosocial co-morbidity
15% (20/138) of patients overall had significant psychological +/- or social co-morbidity at any point during follow-up (paediatric or adult); 55% (11/20) male, 65% (13/20) CD, 20% UC (4/20), 15% (3/20) IBDU. 60% (12/20) patients were affected pre-transition (9% [12/138] of the overall cohort), of whom 58% (7/12) had persistent problems post transfer. 12% (15/122) of patients post transition had psychosocial co-morbidity, including one out of area transfer for whom data were available. Depression was the commonest problem, affecting 55% (11/20) of those with psychosocial issues whilst 35% (7/20) had documented episodes of deliberate self-harm/overdose/suicidal ideation and 25% (5/20) had anxiety. Significant social issues affected 20% (4/20), with or without a mental health diagnosis. Multiple episodes of failing to attend appointments (DNA) was a common feature, documented in 40% (8/20) of patients with psychosocial comorbidity, see figure 16.
Figure 15 - Adverse outcomes expressed as % by type of transition (n=138 or n=120 for appointments missed post transfer).

Only significant difference between groups is shown – loss to follow-up in transition process compared to transfer event.
Figure 16 - Psychosocial comorbidity expressed as % (n=20).

- Depression
- Anxiety
- DSH
- Overdose/suicidal ideation
- Functional symptoms/IBS
- Chronic pain
- Social
- Multiple DNAs

DSH, deliberate self-harm; IBS, Irritable bowel syndrome; DNAs, “Did Not Attend” (i.e. missed) appointments
Rates of steroid free remission and moderate-severe disease at LAFU were comparable between patients with psychosocial comorbidity and those without; 68% (13/19) vs 76% (77/101) for SFR (p = 0.5) and 11% (2/19) vs 16% (16/101) respectively for MSD (p=0.6). Disease phenotype at LAFU was also comparable to the rest of the cohort; extensive (L3 or L3+L4) disease 85% (11/13) in Crohn’s patients with psychosocial comorbidity compared to 78% (54/69) in those without (p=0.6) and severe (B2 +/or B3) disease affecting 46% (6/13) compared to 36% (25/69) patients without psychosocial issues (p=0.5). This was also true for UC/IBDU patients; extensive (E3) disease affecting 80% (4/5) patients in the psychosocial morbidity group compared to 82% (27/33) in the rest of the cohort (p=0.9) and severe (S3) disease in 40% (2/5) compared to 33% (11/33) in patients without psychosocial comorbidity (p=0.77).

There was no obvious difference in type of transition or transfer amongst this subgroup of patients; 55% had a transition process, 5% a single joint transition clinic and 40% transfer of information only; figure 15. Rate of loss to follow-up was also comparable between those with psychosocial comorbidity and the rest of the cohort, 28% (5/18) and 18% (19/108) respectively (p=0.31).

3.4.9 Pregnancy

10 patients had 14 documented pregnancies during the follow-up period (17% of the female cohort). Two pregnancies were electively terminated. Three pregnancies in two patients ended in early miscarriage; the first patient subsequently became pregnant again and delivered a healthy live infant at 39 weeks gestation, the second patient was on infliximab during the first miscarriage and methotrexate during the second miscarriage but went on to deliver a healthy live infant at 31 weeks gestation, whilst on adalimumab. The remaining six women delivered seven live infants with no congenital abnormalities; three of these women were on biological therapy at conception of 4 pregnancies, two of whom delivered at 36 weeks gestation.

3.5 Discussion

This cohort study demonstrates that PIBD patients have a significant burden of disease by the time they transfer to adult services.
3.5.1 Disease activity and therapeutic exposure

78% of all PIBD patients and 87% of CD patients have required immunosuppressive treatment with a thiopurine or methotrexate by the time they leave paediatric services; over a quarter of CD patients have received treatment with biological therapy and almost a quarter of CD patients have required at least one IBD related surgical procedure. Use of biological therapy by transfer at 24% (all PIBD) is comparable with the adolescent IBD study of Goodhand et al.\(^232\) A more recent Italian observational study by Corsello et al, of consecutive IBD patients transitioning to adult services from 2014-2019 shows similar results with regards to exposure to immunosuppressive therapy (79% of patients) but much higher figures for biologic therapy (65% exposed to at least one biological therapy by time of transfer).\(^247\) This may reflect the increasing availability, affordability and use of these medications with the arrival of biosimilars and the move towards treating to a target of deep remission.\(^76,95\) Scotland-wide use of biologics rose inexorably in the period from 2015-2019, as demonstrated by Burgess et al and figures are in keeping with the Italian study.\(^94\) It should be noted however, that the mean age at transfer was 20.1 years in the Corsello et al study.\(^247\) This obviously means a longer disease duration and time/requirement for escalation of therapy prior to transfer, and may also explain the higher surgery rate before transition in this cohort of 40.2% patients, compared to 18% in our cohort. Interestingly, 21% of patients in this Italian cohort needed IBD related surgery within 2 years of transfer, but it is not stated if EUA is included in these procedures; they describe the ‘average length of follow-up to the end of data collection’ to be 18 months from transfer.\(^247\) By the time of last adult follow-up, almost half (46%) of the patients in our cohort had been exposed to biological therapy with infliximab +/- adalimumab.

Pan-treatment exposure (PTE) to the major therapies available during the study period rose from 12% at transfer to over a quarter (27%) of Crohn’s disease patients at LAFU, and pan-treatment refractory (PTR) disease increased from 4% to 19%. Whilst research activity is high and new therapies are emerging in IBD, for a chronic disease with a limited repertoire of therapeutic options, this rate of progression through therapies is concerning and highlights the need for judicious use of medications, to maximise their duration of efficacy over a lifetime of disease. To our knowledge, this is the first study to consider overall medication exposure at a patient level; since this is retrospective data from a relatively small observational cohort, further studies are needed to verify these figures. Additionally, the widening availability of new biologics such as vedolizumab and ustekinumab since the
period of data collection, and the emergence of novel therapies such as tofacitinib warrant further evaluation of this concept in the future.

In keeping with other published data, disease phenotype tends to be that of extensive involvement with aggressive behaviour in this cohort of early onset (Montreal A1) IBD patients.\textsuperscript{2,23} The prevalence of ileocolonic, stricturing and penetrating CD at transfer in this cohort is very similar to the adolescent group in the 2010 study by Goodhand et al.\textsuperscript{2,23} The prevalence of ileocolonic disease (79\% at LAFU) is also similar to EPIMAD data published by Fumery et al in 2019 (83\% at last follow-up) of 535 patients with Crohn’s disease diagnosed <17 years (from 1988-2004), but perianal disease is notably higher in our cohort at last follow-up (33\% vs 16\%).\textsuperscript{208} This is clinically significant as perianal disease is recognised as a predictor of poor outcome and disabling disease.\textsuperscript{76,79,324} Of note, some of the patients in this study will still have been in paediatric services at the time of last follow-up, but despite this (with longer median follow-up of 11.1 years) they report an overall increase of complicated disease behaviour (B2 +/- or B3) from 3\% at diagnosis to 58\% at last follow-up, indicating that the progression we describe in the short-term post transfer persists throughout adult follow-up.\textsuperscript{208} Another recent Italian study by Testa et al, of 106 patients transitioned through a structured programme (joint visits) from 2013-2018 and collecting data 12 months pre and post transition, shows similar rates of penetrating disease at baseline (4\%) but higher levels of stricturing disease (27\%) and lower levels of ileocolonic (53\%) and perianal (7\%) Crohn’s disease.\textsuperscript{250} The occurrence of extensive (E3) disease in ulcerative colitis was slightly lower (65-67\%) than in our cohort (82\%) in both studies.\textsuperscript{232,250} Testa et al did not report on actual age at transfer (or phenotype post transfer) but from the description of their clinical practice and transition process this would be around 18 years of age. Data from the Swiss IBD cohort indicate that progression from uncomplicated B1 disease to stricturing or penetrating disease increases with disease duration in adults and whilst early use of anti-TNF and immunosuppressants reduces the risk, earlier age at diagnosis (<17 years) is associated with increased risk.\textsuperscript{325} These findings are supported by those of Kugathasan et al in North American PIBD patients, although only the risk of penetrating and not stricturing disease was reduced with early anti-TNF.\textsuperscript{159}

Perianal Crohn’s disease is a particular problem in our cohort, affecting one third of CD patients by LA FU, and the need for surgery significant in our cohort; both of these findings match those of the adolescent cohort in the study by Goodhand et al.\textsuperscript{221} Perianal lesions are
reported to affect one quarter of Crohn’s patients globally and the burden to increase with duration of disease; approximately 30% of patients affected after 10 years and 43% patients after 20 years from diagnosis reported in a recent review.\textsuperscript{326}

It is interesting to consider the increased prevalence of upper GI (L4) disease at LAFU from 74\% (70/95) to 82\% (67/82). Upper GI endoscopy is not routinely performed in adult Crohn’s disease (in contrast to paediatric onset disease) and there is debate about whether its use should be extended beyond symptomatic patients to all CD patients.\textsuperscript{18,327–329} Some recent prospective studies have demonstrated much higher prevalence than the frequently quoted 0.5\%-5\%, up to 16\%-55\%, but the relevance of such findings for prognosis in asymptomatic patients is contested, so the role of routine oesophago-gastro-duodenoscopy (OGD) remains uncertain.\textsuperscript{329–331} This study did not assess rate of or indication for upper GI endoscopy in adult services, so it is unclear if the 2 patients newly identified with L4 disease post transition were symptomatic and therefore scoped, or had OGD due to paediatric onset of disease and the known higher reported rates of L4 involvement in this population compared to adult onset CD; this would be an interesting consideration for future research.\textsuperscript{327,328,331}

A key finding shown in our data is that disease progression and treatment burden continues after transition to adult services; 37\% of the cohort exhibited steroid dependency by the time of last adult follow-up and the number of CD patients requiring surgery increased to 51\%. Pan treatment exposure is an issue for 12\% by the time of transfer but in just a few short years of follow-up this has increased to 27\% of the cohort; this trend is mirrored by disease which is refractory to all medical treatment routinely available at time of data collection, rising from 4\% at transfer to 19\% in short-term adult follow-up. Previous studies have described the increasing prevalence of strictureing and penetrating disease over time from diagnosis (e.g. at 10 and 20 years post)\textsuperscript{332}; our data demonstrate the heavy burden of disease progression within adolescence and early adulthood. In a population based study of 536 patients using health administrative data, Zhao et al found increased rates of outpatient visits, emergency department use and laboratory tests (but not hospitalisation) following transfer to adult services for patients with IBD in Ontario, Canada; this may in part be due to a progressive burden of disease.\textsuperscript{164}

There is a significant increase in cessation of MTX therapy due to intolerance by LAFU; it is unclear if this reflects the length of time on therapy (only 4 additional patients on MTX
from T/F to LAFU), or if there is better tolerance in paediatrics compared to adults. Intolerance is well documented in adult and paediatric rheumatology populations – the phenomenon of anticipatory and associative symptoms playing a significant role.\textsuperscript{333,334} Limited long-term tolerance has been reported in adult IBD populations due to side effects, including nausea, bone marrow suppression and hepatotoxicity.\textsuperscript{335} Up to a third discontinue in the first year of treatment due to side effects.\textsuperscript{336,337} Early, or even baseline, intervention with prophylactic anti-emetics prior to dosing has been shown to be effective in reducing nausea, increasing tolerability for some.\textsuperscript{333,334,338} Perhaps there is earlier reporting of adverse effects by patients and parents in paediatrics and/or more intensive support in PIBD services to manage side effects and optimise tolerance? Various paediatric retrospective studies have reported effectiveness up to 55% (steroid and biologic free remission) with good tolerance.\textsuperscript{335,339}

3.5.2 Service use and loss to follow-up

Service use around the time of transition is fairly heavy with a median of 5 and 3 appointments/year in the year pre and post transfer respectively, however, a significant proportion of these appointments are missed. There is also a notable need for hospital admission (14-18\%) in the peri-transition period. No significant difference was found in missed appointments pre or post transfer between those who left paediatric services via full transition process, a single transition clinic or a transfer event. Hospital admissions in the year post transfer were higher in those moving via transition process than those moving by a single joint clinic or transfer event (18\% vs 7\% respectively), but this did not achieve statistical significance (p=0.08), and is in contrast to the findings of McCartney et al in their recent UK multicentre study which found fewer emergency visits leading to admission in those undergoing a structured transition process.\textsuperscript{340} A Dutch study of the value of an outpatient transition clinic for PIBD patients reported fewer missed consultations in the first 2 years after transfer for formally transitioned patients compared to controls (only statistically significant in year 2) and fewer emergency department admissions post transfer in transition clinic patients also, although this failed to achieve significance.\textsuperscript{341} Interestingly, in this study the transition clinics were not jointly held by paediatric and adult teams but over a 2 year period of 3 monthly visits, ¾ were paediatric and ¼ with adults; there was multidisciplinary communication in the interim but there was no use of a structured intervention such as Ready Steady Go and young people were not routinely seen independently.\textsuperscript{341}
19% of patients were lost to follow-up at the end of the study period despite some form of transition process in 58% of these cases; 5% had no adult follow-up at all. Patients who missed scheduled appointments in the year prior to transfer appear to be more likely to be lost to follow-up, as do those who transfer without a formal transition process; this is in keeping with other studies in IBD. A paediatric gastroenterology unit in New York has used the population management reports from the ImproveCareNow (ICN) network to identify their patients with a lack of documented visits, investigate possible reasons for non-attendance and then target them with a phone call and new appointment; they were able to demonstrate a significant increase in documented visits within a 12 month quality improvement cycle with this simple intervention. Identifying and targeting patients who are missing appointments in the lead up to transfer may be beneficial for their outcome in adult services. Socioeconomic status has been demonstrated to be associated with loss to follow-up in cohort studies of various populations including preterm infants, pregnancy cohorts, adults with ischaemic heart disease and also IBD. The lack of SES data in this study is a limiting factor when considering loss to follow-up and should be considered in future research.

### 3.5.3 Psychosocial issues

Psychosocial co-morbidity is a significant issue, affecting 15% of the overall cohort. This is likely a conservative estimate given the retrospective method of data capture from hospital records; it is possible that patients may have had issues which were fully dealt with in the community or are simply not documented or known about. The difficulty in defining such co-morbidity and the deliberate decision to include only those with documented diagnoses or professional involvement increases the likelihood that 15% is an underestimation of the prevalence of psychosocial issues. The relationship between IBD, anxiety and depression has been increasingly documented, particularly during times of active disease and potentially negatively affecting quality of life as well as adherence to medication, although some data suggests most patients do not experience ‘clinical levels’ of depressive symptoms. Adolescents are thought to be at increased risk compared to their healthy peers and screening for anxiety and depression is recommended in European adult guidelines for IBD, as noted in a recent systematic review by Brooks et al. It may be that anxiety is a particular problem; data from the 2012 Canadian Community Health Survey show a robust relationship between IBD and generalised anxiety disorder, even after controlling for a wide variety of potentially explanatory factors, including depression.
Anxiety symptoms have been shown to be associated with low satisfaction with healthcare in a cross-sectional survey study of adolescents with IBD in Austria and Germany, where they were more strongly associated than clinical measures of disease activity. A recent study from Ohio in the United States found both a mental health diagnosis and more than two cancelled appointments in the year prior to transfer to be potential predictors of unsuccessful transition, defined in their study as either a return to utilisation of paediatric care or escalation of care (ED visits, hospital admissions or increase in therapy) within one year of transfer. Psychosocial difficulties may be a barrier to successful transition as they can negatively impact on motivation and goal setting for disease management as well as impair communication and relationships with healthcare providers. Despite this, an Australian survey of adult IBD patients who were diagnosed <18 years of age, comparing those transitioned from paediatric to adult services with those who had all care in adult services (parental choice from 14 years in South Australia), found that whilst 35% of patients in the transition cohort reported mood disturbance (comparable to 46% in the non-transition cohort), only 5% were accessing specific care via psychological services, potentially representing a missed opportunity to identify and help these patients.

3.5.4 Strengths and limitations
The main limitations of our study are the retrospective nature of data collection and the relatively small number of patients from a single centre, with no control group for comparison, although it is worth noting that the cohort size is larger than other UK studies including that of Cole et al and the recent UK multicentre observational study (TRANSIT) of “real world” outcome by McCartney et al. With retrospective case note review it is possible that adult data in particular could be incomplete, especially regarding areas such as psychosocial co-morbidity and pregnancy, which may not be documented – missing data cannot readily be accounted for and is therefore an unknown. However, the cohort design means that data is representative of a defined geographical population and we are confident that all PIBD cases are included due to the tertiary nature of service provision in this region. We are also confident in the quality and accuracy of phenotyping due to the consistency of assessors and comprehensive access to macroscopic and histological data. Additionally, patient numbers are comparable to the other main previously published UK data in this area by Goodhand et al which compared 100 adolescents with IBD with 100 adults with IBD. A further strength of our study is the 5.1 year median length of follow-up post transfer to adult services which is longer than most other reported studies of
outcome following transition, typically reporting outcomes at 1-3 years. Additionally we have reported on disease activity (using PGA) as a direct measure of clinical outcome, making clear if remission is steroid free, rather than using healthcare utilisation alone as a proxy for disease activity. This is arguably the most relevant clinical outcome for the patient but is a potential source of error in retrospective data collection, mitigated as far as possible by use of the full clinical record (including endoscopy, histology and clinic documentation) to assess activity, as well as measuring resource use in the 12 months pre and post transition. The lack of patient recorded outcome measures (PROMs) is a limitation of the study, due to the retrospective audit design, but some of the major themes covered by PROM data are psychological symptoms and adherence, which we have conservatively assessed using strict criteria for psychological comorbidity and loss to follow-up.

As a retrospective observational cohort study it is not designed to assess the success of transition depending on the process, but the size does permit trends to be observed and indicate where future research or intervention may be targeted. Whilst the cohort is taken from a relatively small geographical area and population, the disease burden is likely to be representative of Scotland, and potentially the UK, in general. However, a significant weakness lies in the delay from data collection and last follow-up to reporting here. Therapeutic exposure described here was significant with high rates of biologic exposure and pan-treatment refractory disease to the available medications at the time, but this has been superseded by the widespread availability of biosimilar agents increasing affordability and the much more permissive use of biological therapies in current guidelines, in addition to new biologics, resulting in an unrelenting rise in biologic use.

We have not evaluated readiness for transition which has been a focus of other studies using validated assessment tools such as ‘IBD-yourself’ and ‘TRAQ; Transition Readiness Assessment Questionnaire’ to identify areas which can be addressed during the transition process to optimise independence prior to transfer. Interestingly however, despite broad recommendation to use such scoring systems as part of a structured transition process, scores have only been consistently associated with age and sex, and not with other measures of physical (disease activity indices or remission status), psychological (anxiety, depression, sleep disturbance) or social health (peer relationships, social satisfaction), in a recent Canadian study by Arvanitis et al. Similar to Cole et al in their
study, in our cohort readiness for transfer is globally assessed by the paediatric and adult care providers during the local transition process but a specific validated tool is not used. A recent survey of all UK paediatric IBD centres (including our own) revealed that all responding centres (20/21) had joint transition clinics at the paediatric centre but there was wide variation in other aspects of care including topics routinely discussed, use of patient held transition record and visits to adult services. Ready Steady Go is a transition programme developed in a large NHS teaching hospital in the UK which is generic and applicable across subspecialties, for use in CYP ≥11 years of age with a chronic health condition. There is heavy emphasis on equipping and empowering CYP over a prolonged period via a structured process, to ready them for independent care in adult services. Patients are introduced to the concept of transition via a leaflet and video at 11-12 years of age and then complete the first of 3 questionnaires assessing their skills and knowledge at 11-13 years (Ready), 14-16 years (Steady) and 16-18 years (Go) to assess progress and identify gaps in knowledge prior to transfer, at which point they complete the ‘Hello’ questionnaire (same as ‘Go’) to ensure any remaining issues can be identified and addressed. The developing centre surveyed their own CYP, caregivers and health care professionals using the programme and report excellent feedback, suggesting it helps address the key issues for good transition and improves clinical practice. It has not been compared to standard practice and the outcomes have not been objectively measured, but it has been widely adopted in many NHS hospitals across the UK; hopefully future data will demonstrate a positive impact on clinical outcome and resource utilisation. The broad concepts and timelines match the established PIBD transition process in South East Scotland but the specific documentation and materials are not used (see figure 3). More recently a German study implemented a patient education program in different health centres (as an addition to standard care) to adolescents with IBD or diabetes, delivered as a ‘transition workshop’ over two consecutive days (a weekend) covering relevant topics such as orientation in the health system, separation from parents, future planning (e.g. career) and communicating with peers and partners about health. It concentrated on a ‘low key approach’ in a group setting (minimum of 4 adolescents) aiming to offer practical knowledge and information as well as facilitate interaction amongst patients and was led by a paediatrician and psychologist. The intervention group demonstrated a significant increase in transition competence scores and Quality of Life (QoL) scores compared to controls in IBD patients and the authors speculated that the group element of the
Intervention may be particularly important for IBD patients, whose unpredictable disease course and episodes of pain may have interfered specifically with normal peer relations necessary for mastering the tasks of adolescence. Interestingly, recent data suggests that our expectations for independence in the adult setting may be too high – Fishman and colleagues surveyed 141 adult IBD patients aged 25-50 and found almost half delegated some self-management tasks to a relative (spouse/parent/significant other), with no difference between those with paediatric onset and adult onset disease. Additionally there was variable medication recall across the group and particularly poor knowledge of possible side effects. A recent North American study assessed age of acquisition of transition readiness skills in a PIBD population and found 50% of skills are mastered by 14 years of age but crucially some skills, including self-management were mastered after the age of 18. Studies of the adolescent brain, including functional MRI, show that several executive brain functions governed by the pre-frontal cortex remain in active maturation during adolescence with synaptic pruning and myelination continuing into the twenties; different brain areas for complex information processing are enlisted compared to older adults. One method that has been attempted in some specialties to address this is the development of jointly run adolescent clinics which patients transition through well into their early twenties (before moving completely to adult services), with a particular focus on mental health to improve clinical outcome. In Melbourne, Australia, a new Young Adult Clinic (YAC) has been introduced to care for IBD patients aged 16-25 years allowing coordinated care to be delivered by paediatric and adult specialist nurses and gastroenterologists, operating outside of business hours (5:30pm-8:30pm). Patients may be transitioned from paediatric services into this clinic or may be new presentations who previously would have gone straight into the adult service. A four year review of patients in the YAC demonstrated a significant reduction in ED attendance after enrolment into the YAC for those patients who were not previously under paediatric services (i.e. new diagnosis in this age group), and higher satisfaction scores with communication in the YAC and the clinic helping improve their IBD knowledge, compared to patients seen in adult clinics.

3.5.5 Lessons from other areas

Colleagues in other specialties have long reported on the increase in morbidity and mortality for CYP with chronic disease after moving from paediatric to adult services, including poor clinical and psychiatric outcomes in young adults with type 1 diabetes and
high levels of non-compliance with subsequent graft failure in renal transplant patients.\textsuperscript{367,368} The significance of gradual transition, with a process designed to prepare young people for eventual transfer is well established as a consequence and has been shown to improve outcome and be important to patients and their families.\textsuperscript{369–375} An open label randomised controlled trial of T1DM patients in Australia transitioning adult services via either standard care or an intervention group with targeted appointment management had no effect in the first 12 months after transfer but did have a positive effect on clinic attendance and engagement from 12-24 months post transfer; there was no effect on HbA1c.\textsuperscript{374} A Canadian multicentre RCT of an 18 month structured transition intervention vs standard care in T1DM patients demonstrated increased clinic attendance, improved patient satisfaction and reduced diabetes related distress during the process, but no difference in HbA1c and the results were not sustained at 12 month follow-up post completion.\textsuperscript{375} A Canadian randomised controlled trial of a nurse-led transition intervention (of 2 individualised sessions) for adolescents with congenital heart disease reduced the likelihood of a delay in obtaining adult follow-up, and resulted in greater disease knowledge and self-management skills which were retained for at least 18 months post intervention, compared to patients receiving usual care.\textsuperscript{376}

Despite the increasing volume of transition data published and the encouraging development of randomised controlled trials for direct comparison of defined programs or interventions vs standard care as described, there is currently no proven model for success and transition remains a high risk time for CYP with chronic health conditions.\textsuperscript{352,377} There is unlikely to be a perfect ‘one size fits all’ model, with variation in setting and resources, however, a recent systematic review of 15 reviews assessing adult outcomes in paediatric onset chronic health conditions, did find that older age at transfer was consistently associated with improved outcomes in all types of study, including clinical outcomes, service use and patient satisfaction.\textsuperscript{378}

\textbf{3.5.6 What this study adds}

To our knowledge this is novel data characterising a PIBD population around the time of transition to adult services and evaluating short-medium term outcomes post transition, with attention to disease phenotype and activity as well as psychosocial comorbidity and treatment burden to the individual patient. Previous studies have looked at medication adherence and use, and resource utilisation around this time in different settings with
comparable results. A small French study published in 2008 demonstrated that patients find joint clinic visits (with adult and paediatric teams present) beneficial for transmission of information and building confidence in a new team; subsequent studies have also reported improved outcome (measured in a variety of ways) and the recommendation for joint clinics in transitional care is now widespread. However, transition practice continues to vary widely and a survey of UK paediatric and adult gastroenterologists identified lack of funding, time and support services as the main barriers to successful transition. A recent retrospective Canadian study of health administrative data compared resource utilisation in 2,043 patients with PIBD in the 2 years immediately post transfer to adult care (primarily ED attendance), according to whether the adult provider was community based or in an academic centre. They found no significant difference between the two groups, but argue there may be selection bias with differing predominant phenotype transferring to each setting.

Since completion of data collection, the published UK guideline for transition of gastroenterology patients to adult care has made a series of recommendations which strongly support a structured process of care; our data adds to the weak but growing body of evidence for this, particularly by highlighting the extensive disease burden in this group of patients, therapeutic exposure around this period of transition and the potential for loss to follow-up and poor outcome.

### 3.6 Conclusions

We have shown in a regional PIBD cohort that by the time of transfer to adult services, patients already have a significant burden of disease and this continues to progress post transition. There was a lower incidence of loss to follow-up in those who had a formal transition process (including a joint clinic) compared with those who had transfer of information only. There may be a correlation between missing scheduled appointments in the year prior to transfer and later loss to follow-up; missed appointments could potentially be a useful red flag for patients at risk of disengaging with adult services. It will be essential for future research to evaluate newly implemented transition programmes by assessing both patient and practitioner experience, but also using objective measures of compliance, attendance and disease control and activity if we are to truly improve outcome for this important group of patients. A standardised multicentre approach with prospective data collection and evaluation, including patient reported outcome measures, would be
preferable, but may be difficult to achieve given the wide variation in service provision and availability of resources.
4 CONCOMITANT AUTOIMMUNE DISEASES IN THE PICTS COHORT: A NATIONWIDE STUDY IN SCOTLAND

4.1 Background

As discussed in chapter 1 (section 1.4), the global burden of autoimmune disease in the general population is significant at an individual, familial and societal level. Autoimmune conditions have a propensity to cluster within individuals and within families, magnifying the burden for those affected. These diseases may also be referred to as immune mediated inflammatory diseases (IMIDs) but generally the term autoimmune disease (AID) will be used throughout this chapter.

The paediatric-onset inflammatory bowel disease cohort and treatment study (PICTS) is a Scotland wide incident and prevalent cohort study of patients diagnosed with IBD before their 17th birthday (Montreal A1 disease), recruited opportunistically by their usual care teams, collecting a range of data as detailed in chapter 2 (section 2.3). PIBD care in Scotland is provided at a tertiary level (with strong links to secondary care) and there is excellent collaboration between the three main tertiary centres (which form an unfunded virtual network); the cohort can therefore be confidently considered representative of the Scottish PIBD population. As mentioned in chapter 2, genotype data from the PICTS cohort was included in the immunochip study and has previously been published.256,309 Phenotypic characteristics of this cohort have also been reported previously, at a time when 416 children had been recruited to the study.23

Health administrative data and population based registers have been used to assess the relationship between IBD and other autoimmune diseases but there is a paucity of paediatric data.251,255,258,379–383 It would be beneficial for patient care, and for family and MDT cognisance, to confidently estimate the prevalence of concomitant autoimmune disease in patients with PIBD.

4.2 Aim

This study aims to identify the prevalence of one or more additional autoimmune diagnoses in a paediatric inflammatory bowel disease cohort, with robust diagnostic criteria and the exclusion of atopic conditions which are ubiquitous in the Scottish population.
4.3 Methods
Original PICTS data were verified and handled by a dedicated database manager (HD) with particular expertise in disease phenotyping. HD interrogated the database to identify patients with at least one additional autoimmune disease; subsequent data collection for these patients was conducted by myself using local health records to confirm and detail the comorbidity. The process is outlined in detail in Chapter 2 section 2.3.

4.4 Results

4.4.1 Overview
There were 809 patients in the PICTS cohort at the time of database interrogation (basic characteristics are shown in table 13), of whom 56 were initially identified as having an additional AID diagnosis. 4 cases were subsequently excluded: 1 case of coeliac disease as on health record review, the diagnosis was not confirmed on biopsy findings; 3 cases of self-reported psoriasis for which there was no evidence of documentation in any medical records.

<table>
<thead>
<tr>
<th></th>
<th>Total IBD patients n=809 N (% of total cohort)</th>
<th>Concomitant AID n=52 N (% of IBD subtype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>533 (66%)</td>
<td>30 (5.6%)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>204 (25%)</td>
<td>20 (9.8%)</td>
</tr>
<tr>
<td>IBDU</td>
<td>72 (9%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>458 (57%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Median age at IBD diagnosis in years (IQR)</td>
<td>11.58 (9.08-13.33)</td>
<td>11.62 (8.48-13.72)</td>
</tr>
</tbody>
</table>

IBDU, inflammatory bowel disease unclassified; IQR, interquartile range

The prevalence of confirmed concomitant autoimmune disease in addition to a PIBD diagnosis was therefore 6.4% (52/809). 58% (30/52) of patients were male; 58% CD (30/52), 38% UC (20/52), 4% IBDU (2/52); median age (IQR) at PIBD diagnosis was 11.62 years (8.48-13.72), and at first AID diagnosis 13.0 years (8.57-15.47), but it was not possible to establish age at AID diagnosis in 9/52 (17%) of patients. This data is shown in table 14 along with disease phenotype according to Paris classification; phenotypic characteristics are also expressed in figure 17.
Table 14 - Characteristics of PICTS patients with concomitant autoimmune disease by IBD subtype.

<table>
<thead>
<tr>
<th></th>
<th>CD n=30</th>
<th>UC n=20</th>
<th>IBDU n=2</th>
<th>All PIBD n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>30 (58%)</td>
<td>20 (38%)</td>
<td>2 (4%)</td>
<td>52</td>
</tr>
<tr>
<td>Male</td>
<td>15 (50%)</td>
<td>14 (70%)</td>
<td>1 (50%)</td>
<td>30 (58%)</td>
</tr>
<tr>
<td>Median age at IBD diagnosis in years (IQR)</td>
<td>11.62</td>
<td>11.15</td>
<td>14.20</td>
<td>11.62 (8.48-13.72)</td>
</tr>
<tr>
<td>Median age at first AID diagnosis in years (IQR)</td>
<td>13.8</td>
<td>11.09</td>
<td>9.28</td>
<td>13.00 (8.57-15.47)</td>
</tr>
<tr>
<td>IBD diagnosis first</td>
<td>19 (63%)</td>
<td>8 (40%)</td>
<td>1 (50%)</td>
<td>28 (54%)</td>
</tr>
<tr>
<td>Concurrent IBD and AID diagnosis</td>
<td>2 (7%)</td>
<td>7 (35%)</td>
<td>0</td>
<td>9 (17%)</td>
</tr>
</tbody>
</table>

**Disease location**

<table>
<thead>
<tr>
<th>Location</th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
<th>All PIBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1+L4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2+L4</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3+L4</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>E3</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td></td>
<td>18</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Disease Behaviour**

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
<th>All PIBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1/B1p</td>
<td>17</td>
<td>2</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>B2/B2p</td>
<td>2</td>
<td>6</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>B3/B3p</td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>S0</td>
<td>13</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>S1</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; IBDU, IBD unclassified; PIBD, paediatric IBD; IQR, interquartile range; AID, autoimmune disease; Disease location and behaviour according to Paris classification, see table 2.
Figure 17 - Phenotypic characteristics of PICTS cohort patients with concomitant autoimmune disease.

CD, Crohn’s disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; L1, distal 1/3 ileum ± limited caecal disease; L2, colonic; L3, ileocolonic; L4, isolated upper disease; B1, non-stricturing, non-penetrating; B2, stricturing; B3, penetrating; p, perianal disease modifier; E2, left sided UC (distal to splenic flexure); E3, extensive (distal to hepatic flexure); E4, pancolitis; S0, never severe; S1, ever severe
Autoimmune liver disease (incorporating primary sclerosing cholangitis, autoimmune hepatitis and autoimmune sclerosing cholangitis/overlap syndrome) was the most frequently occurring concurrent AID, followed by psoriasis and juvenile idiopathic arthritis, as shown in figure 18. Three patients (0.4% of the whole cohort) had multiple co-morbid AIDs in addition to IBD; in all 3 cases this was a combination of psoriasis and joint disease in association with Crohn’s.

The prevalence of each autoimmune disease in the whole PICTS cohort by IBD subtype is shown in table 15. 5.6% CD patients had one or more concomitant AID diagnosis compared to 9.8% of UC patients and this difference was statistically significant (p=0.04).

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>CD n=533</th>
<th>UC n=204</th>
<th>IBDU n=72</th>
<th>All PIBD n=809</th>
<th>P value CD vs UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune liver disease</td>
<td>5 (0.9%)</td>
<td>13 (6.4%)</td>
<td>1 (1.4%)</td>
<td>19 (2.3%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>12 (2.3%)</td>
<td>0</td>
<td>0</td>
<td>12 (1.5%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>7 (1.3%)</td>
<td>1 (0.5%)</td>
<td>1 (1.4%)</td>
<td>9 (1.1%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Spondyloarthropathy</td>
<td>4 (0.8%)</td>
<td>2 (1.0%)</td>
<td>0</td>
<td>6 (0.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>4 (0.8%)</td>
<td>0</td>
<td>0</td>
<td>4 (0.5%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>0</td>
<td>3 (1.5%)</td>
<td>0</td>
<td>3 (0.4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>1 (0.2%)</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>2 (0.3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Multiple comorbid AIDs</td>
<td>3 (0.6%)</td>
<td>0</td>
<td>0</td>
<td>3 (0.4%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBDU inflammatory bowel disease unclassified; PIBD, paediatric IBD. *denotes statistical significance

4.4.2 Timing of diagnosis

IBD was the first diagnosis in 54% (28/52) of cases and diagnosed concurrently with the concomitant AID in 17% (9/52). Median (IQR) time to second diagnosis where PIBD was the first diagnosis was 3.39 years (1.03, 6.41). When IBD was the second diagnosis, median (IQR) time to diagnosis was 3.85 years (1.65, 6.51). 3 patients (6%), all of whom had Crohn’s disease, had multiple co-morbid AIDs; one with psoriasis and ankylosing spondylitis following an IBD diagnosis, and two with psoriasis and juvenile idiopathic arthritis preceding IBD, both of whom also had uveitis.
Figure 18 - Frequency of concomitant autoimmune disease by subtype

- Autoimmune Liver Disease: 37%
- Psoriasis: 23%
- Juvenile Idiopathic Arthritis: 17%
- Spondyloarthritis: 12%
- Coeliac disease: 8%
- Type 1 Diabetes: 6%
- Thyroid disease: 4%

CD, Crohn’s disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified.
4.4.3 IBD phenotype

There was a high prevalence of extensive disease on Paris classification in this group of patients. 77% (23/30) of CD patients had extensive disease i.e. ileo-colonic (L3) or greater, with 47% (14/30) having pan-enteric disease (L3+L4); perianal disease was present in 30% (9/30). 27% (8/30) had strictureting disease (B2) and 10% (3/30) penetrating disease (all also strictrutng, B2B3); of note this is documented as B3 only in table 14 for simplicity.

90% (18/20) of UC patients had pan-colonic disease (E4) and 50% (1/2) of IBDU patients; 35% (7/20) of UC patients had severe disease at some point in their course (i.e. S1) and 50% (1/2) of IBDU patients.

Where IBD was the primary diagnosis, 82% (23/28) of patients had extensive disease and 43% (12/28) severe disease; CD L3 32% (6/19), L3+L4 53% (10/19), B2 26% (5/19) and B2B3 11% (2/19); UC/IBDU E4 78% (7/9), S1 56% (5/9). Where IBD was the secondary diagnosis 67% (10/15) of patients had extensive disease and 33% (5/15) severe disease; CD L3 22% (2/9), L3+L4 33% (3/9), B2 22% (2/9), B2B3 11% (1/9); UC/IBDU E4 83% (5/6), S1 33% (2/6). Where both diseases were diagnosed concurrently, 100% (9/9) patients had extensive disease and 22% (2/9) severe disease; CD L3 50% (1/2), L3+L4 50% (1/2), B2 50% (1/2); UC E4 100% (7/7), S1 14% (1/7). There was no statistically significant difference in disease location or behaviour based on timing of IBD and AID diagnosis; all p values ≥ 0.1.

Autoimmune liver disease was significantly more common in UC patients than CD patients, 6.4% vs 0.9% respectively p<0.0001. Psoriasis only occurred in CD patients in this cohort with a prevalence of 2.3% vs 0% in UC and this difference was also significant (p=0.006). There were no other significant differences in individual AID prevalence by IBD subtype, as shown in table 15.

4.4.3 Family history

Family history was identifiable from documentation in 75% (39/52) cases; 54% (21/39) had no family history of IBD or AID; 18% (7/39) with a family history of IBD; 10% (4/39) with a family history of the same AID; 28% (11/39) with a family history of a different AID.

4.4.4 Autoimmune liver disease

37% (19/52) of patients with AID and 2.3% of the whole cohort had autoimmune liver disease (AILD); 53% (10/19) male, 68% (13/19) UC, 26% (5/19) CD, 5% (1/19) IBDU. 100% of
PSC-UC/IBDU patients had extensive (E4) disease phenotype. In 90% (17/19), the diagnosis of liver disease was made after (10/19) or concurrently with (7/19) the IBD diagnosis. 79% (15/19) of patients with AILD had a final diagnosis of primary sclerosing cholangitis (PSC); 4 with an initial diagnosis of overlap syndrome which progressed to PSC. 32% (6/19) of patients had an initial diagnosis of autoimmune sclerosing cholangitis/overlap syndrome, of which two thirds progressed to a final diagnosis of PSC, as shown in figure 19. One patient (5%) had small duct PSC and one patient maintained a non-specific diagnosis of ‘IBD associated immune liver disease’ as determined by the quaternary specialist paediatric liver team; the patient was SMA positive with equivocal histology and biochemistry completely normalised on immunosuppression, with disease remaining quiescent for over 5 years at the time of data collection.

![Figure 19 - Autoimmune liver disease (AILD) by subtype](image)

PSC, primary sclerosing cholangitis; ASC, autoimmune sclerosing cholangitis; IBD, inflammatory bowel disease

### 4.4.5 Autoimmune joint disease

29% (15/52) of patients with AILD and 1.8% of the whole cohort had autoimmune joint disease; 17% (9/52) juvenile idiopathic arthritis (JIA) and 12% (6/52) spondyloarthropathy; 53% (8/15) male, 73% (11/15) CD, 20% (3/15) UC, 7% (1/15) IBDU. The diagnosis of IBD preceded that of spondyloarthropathy in 100% cases, in contrast to JIA where IBD was the second diagnosis in 89% (8/9) cases. 44% (4/9) patients had polyarticular rheumatoid factor
(RF) negative arthritis, 22% (2/9) oligoarticular JIA, 22% (2/9) enthesitis related arthritis and 11% (1/9) psoriatic arthritis, shown in figure 20.

Figure 20 - Juvenile idiopathic arthritis (JIA) by subtype

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>45%</td>
<td></td>
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<tr>
<td>22%</td>
<td></td>
<td></td>
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<tr>
<td>22%</td>
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<td></td>
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</tr>
<tr>
<td>11%</td>
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</table>

RF, rheumatoid factor

4.4.6 Psoriasis

23% (12/52) of those with co-morbid AID and 1.5% of the whole cohort had psoriasis diagnosed by a dermatologist, paediatric gastroenterologist, gastroenterologist or paediatrician; 50% female (6/12), all with Crohn’s disease. IBD was diagnosed before psoriasis in two thirds of cases and in all cases was quiescent or controlled at last follow-up.

In two cases psoriasis was potentially precipitated by the use of biological therapy for IBD. One patient was previously treated with natalizumab (discontinued 2 years prior to developing psoriasis) and on IFX for 2 years prior to developing guttate psoriasis. The other patient was on natalizumab (as part of a trial) for over 2 years before developing mild psoriasis of the scalp, face and chest. Since neither the temporal relationship nor the location is typical of TNF-inhibitor induced psoriasis in IBD, we have included them in the analysis.\(^{384}\) If excluded the contribution of psoriasis would be as follows: 20% (10/50) of co-morbid AID, 1.9% (10/533) of CD patients, 1.2% (10/809) of total cohort, with an overall AID prevalence of 6.2% (50/809). Of note, in a third case an established diagnosis of mild
quiescent psoriasis flared whilst on IFX treatment. Where lesion site was documented (n=9), scalp was the most common location (affecting two thirds), followed by the ears.

4.4.7 Coeliac disease
8% (4/52) of co-morbid AID, affecting 0.5% of the total cohort was coeliac disease; there was an equal gender split but all four patients had Crohn’s disease, 50% were diagnosed after an established IBD diagnosis and 50% concurrently. None of the patients had a family history of IBD or coeliac disease and all had serological, histological and symptomatic resolution on a gluten free diet.

4.4.8 Type 1 Diabetes Mellitus
6% (3/52) of patients with co-morbid AID, and therefore 0.4% of the whole cohort, had type 1 diabetes; in all three cases the patients were male, had UC and were diagnosed several years before developing IBD, at which time they each presented with rectal bleeding. At last follow-up all three patients were in steroid free remission of their IBD (none have required colectomy), but two patients had relatively poor diabetic control requiring intermittent admission to hospital.

4.4.9 Autoimmune thyroid disease
4% (2/52) of AID patients (0.3% of the total cohort) had co-morbid hypothyroidism; both male, 1 CD and 1 UC and both diagnosed after an established IBD diagnosis. The patient with UC had a very strong family history of autoimmune disease with maternal coeliac disease and paternal hypothyroidism and type 1 diabetes, as well as two maternal aunts with thyroid disease; the patient with CD also had Trisomy 21. Both were in steroid free remission at last review and their thyroid disease was well controlled.

4.4.10 Biological therapy
48% (25/52) of patients were treated with at least one biological therapy. 40% (21/52) of patients were treated with infliximab (IFX); in 86% (18/21) of cases the indication for starting was IBD and in 14% (3/21) for AID – all cases of JIA. 14% (7/52) of patients were treated with adalimumab (ADA); 57% (4/7) were started for control of IBD, 29% (2/7) for both IBD and JIA and in 1 patient (14%) for SPA, after an established IBD diagnosis. 5 patients were started on etanercept for treatment of JIA, of whom 3 developed IBD whilst on treatment, potentially precipitated by the etanercept which was subsequently stopped. Other biological therapies used were vedolizumab (1 patient, for IBD), natalizumab (2
patients, 1 as part of an IBD trial) and tocolizumab (2 patients, for JIA). In two cases of biological therapy started for IBD, there was the possibility of this precipitating onset of another AID; both developed psoriasis, one on natalizumab and one on IFX as described above in section 4.4.6.

4.4.11 Disease activity at last follow-up

One patient sadly died of aggressive metastatic PSC-associated malignancy within 6 months of their PSC diagnosis. There were no other malignancies or deaths and nobody progressed to liver transplant. 75% (39/52) of patients were both in steroid free remission (SFR) from their IBD and had quiescent or controlled AID at last follow-up. 87% (45/52) of patients were in SFR overall and 87% (45/52) had quiescent or controlled autoimmune disease. 8% (4/52) had mild IBD activity and 4% (2/52) had moderate-severe disease; 10% (5/52) had active autoimmune disease and 2% (1/52) progressive disease. No patient had progressive or active disease in both IBD and AID at last follow-up.

4.5 Discussion

This large nationally representative paediatric IBD cohort of 809 patients in Scotland reveals a co-morbid autoimmune disease prevalence of 6.4%; overall prevalence was greater in UC than CD, 9.8% vs 5.6% respectively. Autoimmune liver disease is commonest, accounting for 37% of co-morbid AID, with a final diagnosis of PSC dominating. Autoimmune joint disease (juvenile idiopathic arthritis and spondyloarthritis) accounts for 29% of co-morbid AID and psoriasis for 23%. The predominant IBD phenotype in these patients is that of extensive disease; 77% of Crohn’s disease patients have ileo-colonic (or greater) disease (L3±L4) and 90% of UC patients pancolonic (E4) disease. Aggressive disease behaviour is demonstrated in 37% of patients overall; 37% of CD patients with strictureing or penetrating disease and 36% of UC/IBDU patients with severe disease. Previously published work from the PICTS cohort (then consisting of 416 patients) demonstrated that childhood onset IBD is characterised by extensive intestinal involvement (50.5% L3 ± L4, 74.7% E3 by Montreal classification) at diagnosis with rapid disease progression (60.2% L3 ± L4, 82.2% E3 at last follow-up), but in this subset of concomitant AID patients it is even more pronounced. It is worth noting however that the CD L3±L4 and B2/B3 phenotype prevalence are very similar to those at last adult follow-up in our transition cohort described in the previous chapter, raising the possibility that disease progression is faster in this subset with concomitant AID. The majority of patients (75%) were both in steroid free remission of their IBD and had
quiescent or controlled AID at last adult follow-up, but 48% of patients had been treated with at least one biological therapy.

### 4.5.1 Comparison with all ages IBD studies

Wilson et al used UK data from the Clinical Practice Research Datalink (CPRD) to compare the incidence of new autoimmune disease in 17428 IBD patients (all ages) with the incidence in 17428 IBD-free comparison subjects; they also compared IBD patients with and without additional AID to examine IBD treatment, severity and duration on AID risk. They only included patients where coding for an IBD diagnosis was followed by pharmacological treatment, except for patients <20 years of age who were included based on diagnostic code alone (in case they had received EEN only). 1069 IBD patients (including 112 diagnosed with IBD ≤19 years of age) developed an incident AID compared to 585 non-IBD patients, revealing a significantly increased incidence rate of 9.65 [95% CI 9.09-10.24] in the IBD group compared to 5.22 [95% CI 4.82-5.66] in IBD-free patients. They reported a marginally greater incidence in Crohn’s [IR 10.64, 95% CI 9.72-11.64] than in UC [IR 9.00, 95% CI 8.31-9.74] but noted the overlapping confidence interval suggesting little overall difference in risk. They included a broader range of AID diagnoses in this study than in our study, many of which are more relevant to an adult population, including neuropathies, polymyalgia rheumatica and fibromyalgia, and Goodpasture syndrome, but of note they did not include PSC. Using a higher number of IBD-related symptoms as a marker of increased disease severity, they reported an increased risk of AID in patients with more severe IBD. Whilst we cannot accurately compare prevalence with incidence and particularly note the difference in the two studies, with PSC not included by Wilson et al but the most frequently occurring co-morbid AID in our study, both studies demonstrate a predominance of diabetes mellitus in UC patients compared to CD, and psoriasis (or in the Wilson paper autoimmune dermatological conditions in general) highest in CD compared to UC.

Bar Yehuda et al utilised Israeli administrative database data to compare 12967 IBD patients (all ages) with an equal number of matched non-IBD controls and identify patients with at least one autoimmune disease diagnosis, including all the diseases in our study, except autoimmune hepatitis (PSC only) and joint disease. 1395 (11.1%) IBD patients had at least one AID compared to 740 (5.9%) controls OR 1.99 (95% CI 1.88-2.19), and the most frequent diseases in the IBD group were psoriasis (4.9%) followed by insulin dependent
diabetes mellitus (2.1%) and thyroiditis (1.5%) but the strongest association with IBD was for PSC, coeliac disease and psoriasis. \(^{380}\) Thyroiditis was the only AID not more frequently occurring in IBD patients than controls, in keeping with a Canadian administrative database study published in 2005 by Bernstein et al. \(^{385}\) The Israeli study found coeliac disease and psoriasis to be more prevalent in CD compared to UC (1.5% vs 0.7% and 5.5% vs 4.2% respectively), whilst diabetes and PSC were more common in UC, supporting the findings of Wilson et al. \(^{251,380}\) Our study echoes these findings, and whilst the numbers were too small to achieve statistical significance for coeliac disease and T1DM, it is notable that all coeliac patients had CD and all diabetic patients had UC in our cohort. The Israeli study reported a significantly higher rate of multiple co-morbid AIDs in IBD patients compared to controls, of 0.6% and 0.3% respectively and the rate in our paediatric IBD cohort is between these two figures at 0.4%. In contrast to the Israeli study, we found that the AID diagnosis is made before the PIBD diagnosis in just 29% (15/52) of cases, whereas they report this in 66% IBD cases, similar to the figure of 63% reported by Bernstein et al. \(^{380,385}\) This difference is most likely explained by the predominance of autoimmune liver disease in our cohort, specifically PSC which is well established as linked with IBD (concomitant IBD in 70-84% PSC) and typically develops after, or concurrently with, an IBD diagnosis rather than before. \(^{386-389}\) PSC as the most frequent AID is likely the significant contributor to higher rates of AID in UC compared to CD, since UC is the predominant phenotype in IBD with PSC. \(^{386,388-390}\)

Conway et al examined 2145 adult IBD patients enrolled in PRISM (the prospective registry for IBD study at Massachusetts General Hospital) and found 458 (21.4%) of the cohort had one or more immune mediated diseases, as reported by the patient at time of enrolment and confirmed via electronic medical record review where available. Asthma was the most commonly occurring comorbid disease, followed by psoriasis and rheumatoid arthritis. The prevalence of psoriasis was higher than in our cohort (6.1% vs 1.5%) but this may in part be accounted for by the higher prevalence of psoriasis in the adult population generally; in keeping with our findings this affected CD patients more than UC. \(^{269,270,391}\) Their reported 2% prevalence of rheumatoid arthritis is comparable with our autoimmune joint disease prevalence of 1.8% (JIA and SPA combined) and they also identified PSC prevalence to be significantly higher in UC than CD. They found no difference in disease extent and behaviour for CD patients with and without concomitant AID but found a significant trend towards pan-colonic disease in UC patients with concomitant AID compared to those without, in keeping with our findings. \(^{392}\) Supportive of our high rates of biological therapy
use, they also found IBD-AID patients significantly more likely to undergo IBD related surgery and need biological therapy, and these patients report general and disease specific lower quality of life when surveyed compared to IBD alone.\[492\]

4.5.2 Comparison with paediatric IBD studies

Andreoletti et al examined the Southampton PIBD cohort of 173 children and reported the prevalence of a second AID as 28.3%.\[258\] This is clearly much higher than in our study and that by Bar Yehuda et al in all age IBD patients, but 87% of the documented AID cases were the atopic diseases asthma and atopic dermatitis.\[258,380\] Although higher atopic disease prevalence in IBD patients has been noted in other studies, we chose to exclude these conditions due to their ubiquitous nature in the Scottish population, which has been documented in an earlier study by van Limbergen et al from this same PICTS cohort.\[379,385,393–395\] Other studies described below have also found no significant association between IBD and asthma.\[396,397\] The Southampton study found an identical prevalence to our study of 2.3% for autoimmune liver disease, and when the atopic diseases are excluded, the overall prevalence is 3.5%.\[258\]

Ghersin et al studied the medical records of 891 Jewish adolescents with IBD who attended for medical evaluation pre-enlistment to the Israeli Defence Force, with a median age of 17.1 years and a median age at diagnosis of 15 years. Only those with a comprehensive medical history supplied by their family physician were included as IBD cases and criteria for confirmation of IBD diagnosis were strict and included macroscopic and microscopic ileo-colonoscopy reports and small bowel imaging.\[396\] They compared the results in the IBD patients with the remainder of the 1,142,732 strong cohort of pre-enlistment medicals without IBD. They found an association between IBD and arthritis (any chronic inflammatory joint disease), autoimmune thyroid disease, uveitis and AIH as well as PSC, nephrolithiasis and pancreatitis, which they considered non-immune-mediated disorders. The findings are in keeping with ours, showing the strongest association with liver disease and joint disease.\[396\] They identified a male predominance (64%) in patients with comorbid AID; the male predominance was less marked in our study (58%). They found no association between IBD and coeliac disease, T1DM, asthma, atopic dermatitis and psoriasis, when compared to the control group. Interestingly this lack of association with psoriasis persisted in univariate and multivariate analysis of CD alone; this is in contrast to our higher prevalence of psoriasis in only Crohn’s patients. Clearly we do not have a control cohort
within our study for comparison, but our prevalence is higher than that reported for the
general paediatric population. This IBD cohort is of comparable size to ours but with an
older median age at IBD diagnosis. The methodology is robust for confirmation of IBD
diagnosis but the AID diagnostic criteria is not as strictly defined as in our study and an
overall prevalence of any comorbid AID is not reported. The strength of the study lies in the
large control group for comparison and the findings support our decision to exclude asthma
and atopic dermatitis from the associated AIDs we examined.

Kappelman et al performed a cross-sectional study of inpatient and outpatient insurance
claims from a database representing patients from 33 different states in the USA, including
all patients less than 20 years of age. They used a combination of disease codes on
multiple health contacts and prescriptions for IBD medication to identify 1242 IBD cases,
then compared the prevalence of the following 8 diseases (defined by ICD-9 diagnostic
codes) to 3353 non-IBD controls, taken from a source population of over 26 million
individuals less than 20 years of age; RA, lupus, hypothyroidism, diabetes, psoriasis,
asthma, eczema and allergic rhinitis. The three atopic disease were most prevalent in both
IBD patients and controls, with no difference between the groups, again supporting the
rationale for excluding these conditions from our study. They found CD to be significantly
associated with higher incidence of RA, SLE and hypothyroidism, whilst UC was associated
with a higher prevalence of diabetes. There were non-significant trends towards increased
prevalence of CD with diabetes, and UC with hypothyroidism, RA and SLE, but not psoriasis.
They also narrowed the study population, to meet Montreal classification criteria for
paediatric onset IBD, to individuals <17 years of age and found the associations with ‘any
immune-mediated disease’ largely unchanged for CD, UC and total IBD. The strongest
association for all IBD were the rheumatological conditions RA and SLE and they reported
that the associations in their paediatric study were in keeping with but much greater than
in adult studies, with OR for RA of 9.6 and for lupus OR 21.7. The main strength of the
study is the large number of IBD patients from a diverse population; the main weakness is
the dependence on disease coding for case ascertainment and the potential for
misdiagnosis, along with the lack of detailed clinical data, including phenotype.

Guinet-Charpentier et al followed 67 French children (<17 years) in a single centre for a
median of 4.8 years of follow-up; 22 with IBD and concomitant AID and 45 with what they
termed ‘classical’ UC. The majority of the patients had autoimmune liver disease, as with
our cohort, but they report more autoimmune hepatitis (13/22) than PSC (10/22) as well as 4/22 with autoimmune pancreatitis; they note however that 10 children had two or more of these diagnoses but do not give a break-down of which conditions. Presumably some of these children had what we have defined as ASC/overlap syndrome, so it is difficult to make any comparison. They also identified 3 cases of psoriasis and single cases of vitiligo, hyperthyroidism, polyarthritis and autoimmune anaemia; the lack of rheumatological disease in comparison to our cohort is interesting but according to the study methods, they were not specifically looking for joint disease and perhaps this may have affected the result. They found no significant differences in disease extent, severity or biologic use between those with and without concomitant AID, in contrast to the findings of Conway et al described above, and of Ordonez et al in their retrospective study of 28 paediatric patients with UC and one or more concomitant AID, compared with 27 age matched controls with ‘classical’ UC without associated AID. In this study, also from France, they found the AID patients had more extensive but less severe disease compared to those UC patients without AID, as defined by milder symptoms at diagnosis, fewer relapses and less dependence on steroids, immunosuppression and colectomy. The main weakness of both studies is relatively small numbers from a single centre but the data is interesting to consider nonetheless. The largest genotype-phenotype study of IBD to date using Immunochip data of over 29,000 IBD patients confirmed the evidence that extensive disease location was more common with diagnosis at younger age but that there is little variation in disease location over time, compared to disease behaviour which progresses over time and progresses faster in more extensive UC than left sided disease and faster in ileal than colonic disease. This suggests that disease location is a fundamental aspect of disease more dependent on genetic determination than disease behaviour, which is more of a marker of progression. If IBD with concomitant AID is associated with more extensive but less severe disease as found by Ordonez et al, this raises the possibility that genetic architecture may be a more prominent determinant of phenotype in IBD with concomitant AID than IBD alone. In contrast, we found both extensive and aggressive disease to be common in our cohort with 37% CD patients demonstrating B2/B3 disease and 37% UC/IBDU patients with S1 disease; whilst we do not have a control group for comparison, the earlier PICTS data (n=416) from van Limbergen et al reported a combined B2/B3 prevalence of 24% at 4 years follow-up, suggesting higher levels in this AID subset.
4.5.3 Comparison with other AID studies

Our cohort study did not have a control group for comparison but it is interesting to note how the prevalence of some individual AIDs in this PIBD population compare with the general population, and how the overall prevalence of AIDs compares to that in other single autoimmune disease cohorts. A recent Finnish nationwide register-based cohort study examined the frequency of T1DM, autoimmune thyroiditis, JIA and IBD in 11,407 children born between 2000 and 2005 and analysed the relationship with perinatal risk factors by linking to three national health registers. They reported a prevalence of 2.1% with at least one AID; this included T1DM in 0.89%, THY in 0.6% and JIA in 0.48%, with multiple AIDs present in 0.08% of the total cohort. Clearly our figures of 6.4% overall prevalence and 0.4% multiple AID prevalence are much higher in the PIBD cohort, and whilst comparison is hindered by the limited number of AIDs included, it is worth noting that our reported prevalence of T1DM in 1.5% UC patients and JIA in 1.1% all PIBD patients do appear to be higher.

JIA in our cohort has a prevalence of 1.1% in all PIBD and 1.3% in CD patients, compared to the 0.04% prevalence in the UK population reported by Costello et al. Both CD and UC (CD>UC) were reported to have higher prevalence in a JIA population compared to an ADHD (non-AID) population in the US healthcare claims database study by Simon et al. Psoriasis prevalence in our CD cohort is 2.3%, higher than the 0.71% documented in children <18 years by Augustin et al in their study of 1.3 million non-selected individuals in Germany by their health insurance data. A study of all patients <18 years of age on the Danish National Patient Register demonstrated a prevalence of 0.21% and 0.16% for CD and UC respectively in 1925 CYP with psoriasis, compared to a prevalence of 0.04% for each in the general population.

T1DM prevalence in our total PIBD cohort was 0.4%, comparable to the 0.3% estimate in the International Diabetes Federation Diabetes Atlas; but when considering UC in isolation (all three cases in our study had UC), the prevalence in our cohort is 1.5%. A recent meta-analysis by Lu et al found that when analysed by geographical region, patients in Northern Europe with CD and patients in Israel with UC had a higher risk of developing T1DM; when all 6 studies were analysed together, no clear association between T1DM and IBD could be identified.
Data from the East of Scotland estimates the prevalence of hypothyroidism in the paediatric population to be 0.14%. In our study the prevalence was 0.3% for all PIBD and 0.5% for UC patients. There is conflicting data on the association between IBD and autoimmune thyroid disorders; Ghersin et al found a significantly higher prevalence in all patients with Crohn’s and male patients with UC, whereas no clear association was demonstrated in various studies using health administrative database data. Comparable data for IBD prevalence in patients with autoimmune thyroid disease is also inconclusive, but some studies report nonsignificant trends toward increased prevalence, particularly of UC.

In a systematic review and meta-analysis, Singh et al report the global pooled prevalence of biopsy confirmed coeliac disease to be 0.7%, with variation dependent on sex, age and location; pooled prevalence in Europe was 0.8%. This is in keeping with our prevalence of 0.8% in CD patients but it is interesting to note that the prevalence of coeliac in the overall IBD cohort was lower than the reported global and European figures, more in keeping with the findings of Ghersin et al in adolescents than those of Bar Yehuda et al in all ages patients. Popp and Mäki in a recent article review paediatric coeliac disease prevalence rates by country; biopsy proven prevalence varies from as low as 0.04-0.08% in Denmark to as high as 2.9% in Sweden. Local estimated paediatric coeliac disease prevalence in South East Scotland up to 2009, is more similar to Denmark at 0.05-0.1%, lower than the pooled prevalence rates reported by Singh et al; the rates in this cohort of 0.5% (all PIBD) and 0.8% (CD) are increased by comparison, if this estimated prevalence is accurate.

A systematic review by Shah et al of 17 studies reporting the prevalence of coeliac disease in IBD found an overall prevalence of 1.1%, with the prevalence in the respective non-IBD population 0.6%, suggesting a two-fold increase. They evaluated 12 further studies of the prevalence of IBD in coeliac disease and demonstrated a much starker difference, with a prevalence of 2.1% in coeliac patients compared to 0.3% in the respective population. A recent retrospective observational case-control study by Bramuzzo et al using Italian IBD registry data reported coeliac disease in 1.75% of 2800 IBD patients aged 0-17 years; 76% of cases were diagnosed with coeliac before the IBD diagnosis and 10% concurrently, compared to 50% before and 50% concurrently in our cohort but clearly this is difficult to interpret with just four cases. Considering the prevalence in the reverse direction, an Irish adult coeliac disease cohort of 749 patients was retrospectively analysed for prevalence of various autoimmune diseases by Castro et al and reported 31.1%
prevalence of co-existent immune mediated conditions, with IBD prevalence 1.9% (0.8% CD, 1.1% UC). A cross sectional population based study of Jewish Israeli adolescents (median age 17.1 years) attending their recruitment medical examination (as with the Ghersin et al IBD study) analysed the prevalence of other autoimmune diseases in 7145 people with biopsy proven coeliac disease compared to >1.5 million controls, and found a prevalence of 0.36% vs 0.1% respectively; a significant difference (p≤0.001) with OR 3.8 (95%CI 2.5-5.6). It is intriguing to note that in the same geographical Israeli population, there is no significant difference in the coeliac disease prevalence between adolescents with IBD and controls, but there is a difference in prevalence of IBD between adolescents with coeliac disease and controls.

It is well documented that PSC is particularly associated with inflammatory bowel disease and that it can be part of an overlap syndrome with autoimmune hepatitis; an international multicentre retrospective study of 781 children with PSC reported associated IBD in 76% and AIH in 33%. Prevalence of 2.3% in our total AID cohort is notably higher than the 0.0015-0.003% reported by Deneau et al in the Utah general paediatric population or 0.014% reported in the all-ages study by Bambha et al. The higher prevalence of UC (68%) compared to CD (26%) or IBDU (5%) in patients with PSC-IBD is in keeping with other studies. A Canadian single centre retrospective study of 74 children (<18 years) with PSC-UC/IBDU reported concurrent presentation in 61% of patients, compared to 37% in our study, and IBD first in 21% compared to our 53%. Our figures are more comparable with those of Valentino et al who report 46% of 97 paediatric PSC-IBD patients (<21 years) were diagnosed concurrently and 44% after an IBD diagnosis. Of note however, the proportion of patients presenting with PSC before an IBD diagnosis is comparably small in all three studies (18% Ricciuto et al, 11% in our study, 9% Valentino et al); this minority trend for PSC as first diagnosis is even more marked in recently reported data from Leeds where just 4% (1/23) patients did not have IBD diagnosed prior or concurrently. The Canadian study reported significantly higher rate of extensive (E4) disease in PSC-IBD compared to UC/IBDU controls (80% vs 65% respectively p=0.023), which is in keeping with our findings of 100% PSC-UC/IBDU patients with pan-colonic (E4) disease. A smaller Finnish case-control study of 28 PSC-IBD patients found no difference in disease extent compared to controls (78% and 79% respectively). The majority of patients in our study had a final diagnosis of classical PSC (79%) rather than small-duct PSC (5%) or overlap (11%), a similar distribution trend to other studies. One patient in our cohort (5% PSC-IBD) died of
cholangiocarcinoma and there were no other malignancies; Deneau et al report cholangiocarcinoma in 1% of paediatric PSC patients compared to 8% reported in a large multicentre retrospective all ages study and no hepatobiliary malignancies in the paediatric study by Valentino et al. It is interesting to note that in the multicentre study by Deneau et al, 7% of PSC patients had an additional (non-IBD) comorbid immune-mediated disease; it is not reported what proportion of these also had IBD. In our cohort none of the PSC-IBD patients had an additional AID, but this may be explained simply by the comparatively small number of PSC patients, as 7% of our PSC-IBD cohort is equivalent to a single patient.

4.5.4 Strengths and weaknesses
The first major strength of this study is the large cohort size of 809 paediatric patients with clearly defined Montreal A1 disease, confirmed according to strict diagnostic criteria; only the study by Ghersin et al is of similar size in a paediatric population without dependence on administrative data. We are very confident in the accuracy of IBD diagnosis and lack of misclassification bias in this aspect of the data. The cohort size also allows us to consider the prevalence of relatively uncommon conditions in the paediatric population such as JIA, psoriasis and spondyloarthritis. The second major strength is that it can be reasonably considered nationally representative, as patients were recruited from all tertiary IBD centres, through which all Scottish PIBD patients are cared for, regardless of the severity of their disease; no other northern European studies of this design have been published to date. Timing and choice of diagnostic procedures may have changed over the included study period as services expanded and access to investigations improved; this may not have been perfectly uniform across the Scottish health boards but will be within the parameters of the National Health Service and the tertiary nature of service provision via 3 major centres, limiting the overall variation. A further strength lies in detailed records review and careful phenotyping, without any reliance on administrative or coding data for confirmation of diagnoses, as well as strict diagnostic criteria for AIDs. The reverse of this however is that our calculated AID prevalence of 6.4% may in fact be an underestimate due to the stringent requirements for diagnosis; for example it may be that the three patients who had self-reported psoriasis had mild disease diagnosed and managed by the GP that was never recorded by hospital teams.
There are several limitations of this study, the most obvious being the retrospective nature and associated risks of misclassification bias. Whilst this has confidently been accounted for with regards to IBD diagnosis, despite meticulous medical record review there remains the potential for missed AID diagnoses, particularly if mild and never disclosed on the initial health questionnaire on recruitment to the cohort or to their IBD care team; it is also possible that subsequent to their last data entry in the PICTS database, patients may have developed an AID unknown to the study. There also remains the possibility of inaccurate diagnosis of AID subtype e.g. type of autoimmune joint disease, as even with detailed record review it is not possible to eliminate this risk entirely when working retrospectively. The retrospective nature also limits the level of detail to which treatments can be examined due to the onerous nature of data collection; whilst we report the presence or absence of biological therapies and steroid free remission at last follow-up, to more thoroughly investigate therapeutic exposure retrospectively in a cohort of this size would be impossibly time consuming and prone to error. A second weakness is that unlike other large studies such as those by Gherin et al and Bar Yehuda et al, we do not have a matched population control group for direct comparison of disease prevalence and are therefore limited to comparisons with previously published studies, not necessarily from UK populations and potentially not representative of the equivalent non-IBD paediatric population in our setting. This is however mitigated in part by comparing to previously published from the same cohort at an earlier phase in its development, for example with regards to phenotype. A third weakness is the potential for selection bias – this is a research cohort which requires full informed consent for participation. It is possible that participants who agree to be part of such research may have more severe disease, may have closer follow-up and therefore be more likely to have an additional AID identified or may even be more likely to report symptoms and have those symptoms investigated. One further potential limitation is the lack of inclusion of autoimmune pancreatitis as a comorbid AID; recent international consensus guidelines have defined the relationship between IBD and, most commonly, type 2 autoimmune pancreatitis (AIP), and a dual centre adult cohort study revealed an IBD prevalence of 82.8% in 35 AIP type 2 patients. It is perhaps therefore a missed opportunity to have an estimated prevalence of another relatively rare autoimmune disease in a well defined paediatric IBD cohort.
4.5.5 Implications for future practice

The findings of this study highlight that comorbid autoimmune disease affects a significant proportion of children and young people with inflammatory bowel disease and more commonly presents at the same time as, or after an IBD diagnosis. Additionally it appears to be associated with a more severe disease phenotype, suggesting that whilst clinicians caring for CYP with IBD should be generally vigilant for development of new symptoms of potential AID, this should perhaps be particularly heightened in those patients with extensive and/or aggressive disease.

Better understanding of the relationship between IBD and other autoimmune diseases will aid diagnostic ability; one of the major challenges when faced with a known PIBD patient who has new or additional symptoms is to elucidate a new disease diagnosis from an extra-intestinal manifestation of IBD, or a secondary effect of one or more therapeutic agents. Joint pain for example may present as an extra-intestinal manifestation or a new presentation of an autoimmune arthritis; psoriasis may occur spontaneously or in response to anti-TNF treatment.26,417 As discussed in chapter 1, there are many common genetic pathways between IBD and individual autoimmune diseases, including T1DM, psoriasis and PSC, but shared genetics alone are not the whole story and shared environmental features and even gut microbiota are likely to play a role.33,392,418–420 Differentiating the underlying diagnosis may not always be possible and our findings support the need for effective cross-specialty multidisciplinary working. 29% of patients with PIBD-AID in our cohort had their AID diagnosed first, so vigilance of colleagues in other specialties such as rheumatology and endocrinology, along with open communication to IBD teams is essential for timely diagnostic work-up of potential shared patients. Over time, symptoms originally attributed to an extraintestinal manifestation or drug effect may evolve into a de novo presentation of additional AID.

MDT working continues to be essential longitudinally, particularly as the range of therapeutic options continues to broaden and choice of treatment can be increasingly personalised. Ideally therapeutic agents will be maximally effective against both conditions and commenced in agreement with all the relevant specialties involved with the patient. Complexities of shared mechanisms of inflammation guiding treatment choice are evident for example with the IL-23 action of Ustekinumab (an anti-IL-12/23 p40 monoclonal antibody) leading to efficacy both in IBD and psoriasis, but anti-TNF use being a risk factor
Another important example is anti-TNF therapy with infliximab and adalimumab being suitable for both IBD and autoimmune joint diseases including JIA and SPA, but etanercept treatment for AID in fact being a significant independent risk factor for subsequently developing inflammatory bowel disease. The advent of more selective agents and small molecule drugs increases the range of therapeutic choices for each patient; selective IL-23 blockers are licensed for use in psoriatic arthritis and in clinical trials phase for IBD, tofacitinib (an oral JAK inhibitor) is licensed for use in JIA and psoriatic arthritis as well as UC in adults and is increasingly being used off license in paediatric management of refractory UC. Collaborative inter-specialty working must be embraced to ensure effective and judicious use of medications for maximum benefit and minimum risk.

4.6 Conclusions

This study adds to the PIBD literature an overall prevalence rate of concomitant autoimmune disease in PIBD of 6.4%, from a large well defined cohort with robust data collection. It is more conservative than previous figures from other cohorts but does not include the atopic diseases asthma and eczema/atopic dermatitis which are widespread in the general Scottish paediatric population. The overall prevalence is greater in UC (9.8%) than CD (5.6%), likely accounted for by the predominance of autoimmune liver disease, specifically PSC, as the most common concomitant AID and already known to be most strongly associated with UC. We found high rates of extensive and severe IBD phenotype in both CD and UC patients with concomitant AID; almost half of the patients had required treatment with at least one biological therapy but most were in steroid free remission of their IBD and had quiescent or controlled AID at last follow. The majority of patients are diagnosed with IBD first or concurrently with the additional AID, highlighting that vigilance to new AID diagnoses should be a key part of IBD care. A prospective nationally representative cohort study with longitudinal follow-up would be the ideal way to verify our data and potentially capture other AIDs such as autoimmune pancreatitis, but would be both expensive and time consuming to establish.
5 BIOLOGICAL THERAPIES IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE: A UNITED KINGDOM NATIONWIDE AUDIT

5.1 Background

The landscape of PIBD treatment has changed dramatically in the last 20 years with the arrival of biological therapies, starting with the anti-TNFα drug infliximab (IFX) licensed for use in adults with Crohn’s in the UK in 2002 and for paediatric use here in 2010. This was later followed by the licensing of adalimumab (ADA) for paediatric CD use in 2013. Both medicines were increasingly used off license before these dates in paediatrics, on the basis of the robust body of evidence for their efficacy in adult IBD. Subsequently, there were paediatric trials to confirm the benefit in PIBD and use has steadily increased over the last decade. More recently new biological therapies such as vedolizumab and ustekinumab have become available and further expanded the biological treatment armoury.

Prior to the collection and publication of this data (see copy of publication in appendices), national UK data were limited. A retrospective Scottish study of 132 paediatric patients over the decade 2000-2010 who had biological therapy infliximab +/-adilimumab was methodologically robust with complete accrual in that time period, showing response rates of 87% with IFX (48% remission) and 76% with ADA (35% remission), but it only represents Scotland rather than the whole UK and has the same potential for missing or misinterpreted data that all retrospective studies have. A survey of BSPGHAN members published in 2011 summarised the experience of adalimumab use in a case series of 72 IBD patients <18 years old from 19 UK centres in the UK and Republic of Ireland. The authors highlighted the need for prospective study through national and international registries to accurately understand the risks and benefits of adalimumab use in paediatric IBD practice.

As already discussed in chapter 1.5.1 and chapter 2.4, the UK IBD audit is a national gastrointestinal audit through the Royal College of Physicians, of paediatric and adult patients, with a biologic arm. Data have previously been presented as annual reports on the College website, allowing individual centres to see their own figures tabulated against others, but this reaches a small audience and analysis is limited, curtailing the translatable relevance to clinical practice.
5.2 Aim
The aim of this study therefore is to analyse the prospectively collected existing data held by the RCP, to measure the effectiveness, safety and use of anti-TNF therapy in UK patients with PIBD and present it in a format that is accessible and useful to inform and improve clinical practice.

5.3 Methods
This was a prospective UK audit of PIBD patients newly starting anti-TNF therapy from 12.9.11 to 28.4.14. Data were submitted by local clinicians voluntarily and disease severity was assessed using Physician Global Assessment (PGA) +/- the Paediatric Crohn’s Disease Activity Index (PCDAI). As an audit of clinical practice, with data entry at a local level, not all fields were completed for every patient. The denominators vary considerably as a result, so are described in full in the text and tables below to allow accurate data interpretation. Detailed methods are described in chapter 2 section 2.4.

5.4 Results

5.4.1 Overview
By 28.02.14, demographic submissions were entered on 817 individual paediatric patients; 156 patients with no initial treatment details entered were excluded, leaving 661 patients with 746 initial treatments (as some patients were treated with more than one anti-TNF). Further exclusions of patients with initial treatments prior to 12.09.11 resulted in a final analysis on 524 patients (429 CD, 76 UC and 19 IBDU) with 562 initial treatments, as laid out in Figure 21. Details of patient demographics and disease location are shown in table 16. 30 CD, 4 UC and 4 IBDU patients were treated with both infliximab and adalimumab.
Figure 21 - Patient and treatment flow chart

N=817 patients (with demographic details)

N=746 initial treatments (561 patients)

N=576 initial treatments (529 patients)

N=562 initial treatments (524 patients)

N=156 patients excluded as no initial treatment

N=170 initial treatments before 12/09/11 excluded (132 patients)

N=9 initial treatments same treatment restarts excluded (0 patients)

N=5 initial treatments missing diagnosis and indication excluded (5 patients)

INFLIXIMAB ONLY
N=450 initial treatments
366 CD
69 UC
15 IBDU

ADALIMUMAB + INFLIXIMAB
N=76 initial treatments
30 CD
4 UC
15 IBDU

ADALIMUMAB ONLY
N=36 initial treatments
33 CD
3 UC

CD, Crohn’s Disease; UC, Ulcerative Colitis; IBDU Inflammatory Bowel Disease Unclassified
### Table 16 - Overview of demographics and disease details by IBD type

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>CD n=429</th>
<th>UC n=76</th>
<th>IBDU n=19</th>
<th>All IBD n=524</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male</td>
<td>62% (267/429)</td>
<td>58% (44/76)</td>
<td>53% (10/19)</td>
<td>61% (321/524)</td>
</tr>
<tr>
<td>Age at diagnosis, y, median (IQR)</td>
<td>n=411 12.0 (9.4, 13.8)</td>
<td>n=74 12.3 (9.5, 14.2)</td>
<td>n=17 11.7 (8.9, 12.8)</td>
<td>n=502 12.0 (9.4, 13.9)</td>
</tr>
<tr>
<td>Age at initial treatment, y, median (IQR)</td>
<td>n=427 14.2 (13.5, 15.7)</td>
<td>n=76 13.1 (11.7, 15.4)</td>
<td>n=19 13.5 (11.0, 14.8)</td>
<td>n=522 14.1 (12.3, 15.7)</td>
</tr>
<tr>
<td>Time from diagnosis to biologic, y, median (IQR)</td>
<td>n=411 1.43 (0.65, 3)</td>
<td>n=74 1.08 (0.3, 2.23)</td>
<td>n=17 0.82 (0.06, 3.5)</td>
<td>n=502 1.36 (0.61, 2.92)</td>
</tr>
</tbody>
</table>

#### Commonest disease distribution at decision to initiate treatment (by Montreal classification)

<table>
<thead>
<tr>
<th></th>
<th>CD (n=429)</th>
<th>UC (n=76)</th>
<th>IBDU (n=19)</th>
<th>All IBD (n=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic (L2)</td>
<td>40% (164/410)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ileocolonic (L3)</td>
<td>41% (166/410)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any gut proximal to TI (L4)</td>
<td>79% (288/364)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perianal involvement = Yes</td>
<td>54% (146/270)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extensive colitis (E3)</td>
<td>-</td>
<td>74% (54/73)</td>
<td>94% (16/17)</td>
<td>78% (70/90)</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IBDU, IBD unclassified; y, years; IQR, Inter Quartile Range
Infliximab was the commonest anti-TNF therapy representing 87% (488/562) of initial treatments. 79% (445/562) of patients were co-immunosuppressed; 79% (386/488) on IFX (91% thiopurines [351/386], 9% methotrexate [35/386]) and 80% (59/74) on ADA (80% thiopurines [47/59], 20% methotrexate [12/59]). Consent was taken in 99% (559/562), either verbally (46% [257/559]) or written (54% [302/559]). Verbal consent was significantly more common with ADA 51/74 (69%) compared with IFX 206/485 (42%), p=0.00002. In total 51% (223/437) of patients had failed on an immunosuppressant and/or steroids prior to treatment with anti-TNF. 5.2% patients (27/524) had no previous medication or concomitant therapies documented at time of anti-TNF initiation, suggesting a ‘top-down’ therapy approach.

5.4.2 Crohn’s Disease

40% (151/379) of patients starting IFX and 37% (22/60) starting ADA had extensive disease i.e. L3 (ileocolonic) at initiation and 80% (310/388) had upper GI involvement (proximal, L4). The commonest indication for starting therapy was active luminal CD in 78% (355/458); severe perianal CD accounted for 17% (77/458), as shown in table 17. 20% (79/396) IFX patients and 16% (10/63) ADA patients were receiving steroids at the time of initial anti-TNF treatment.

<table>
<thead>
<tr>
<th>Clinical indication for starting anti-TNFα therapy</th>
<th>Infliximab Frequency %</th>
<th>Adalimumab Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn’s disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe perianal CD</td>
<td>19% (74/395)</td>
<td>5% (3/63)</td>
</tr>
<tr>
<td>Active luminal CD</td>
<td>77% (304/395)</td>
<td>81% (51/63)</td>
</tr>
<tr>
<td>Fistulating CD</td>
<td>1% (4/395)</td>
<td>-</td>
</tr>
<tr>
<td>Other clinical indication</td>
<td>2% (6/395)</td>
<td>2% (1/63)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2% (7/395)</td>
<td>13% (6/63)</td>
</tr>
<tr>
<td><strong>Ulcerative colitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute severe UC</td>
<td>43% (31/72)</td>
<td>-</td>
</tr>
<tr>
<td>Chronic refractory UC</td>
<td>56% (40/72)</td>
<td>100% (7/7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1% (1/72)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Inflammatory Bowel Disease Unclassified</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute severe IBDU</td>
<td>47% (9/19)</td>
<td>50% (2/4)</td>
</tr>
<tr>
<td>Chronic refractory IBDU</td>
<td>53% (10/19)</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBDU, Inflammatory Bowel Disease Unclassified
Disease severity at initiation of anti-TNF was documented by PGA in 40% (171/429) and 51% (217/429) by PCDAI. Disease was moderate-severe in 91% (156/171 by PGA) and 41% (88/217 by PCDAI), as shown in table 18.

Cross-tabulation of PCDAI and PGA (grouping mild and remission together for comparison) reveals a Kappa statistic (K) of 0.28 (SE=0.055, p<0.001) indicating only ‘fair agreement’. PCDAI was less frequently recorded than PUCAI; 51% (217/429) PCDAI compared to 64% (53/76) PUCAI, p=0.02.

99% (347/349) of initial IFX was given at 5mg/kg i.e. standard dosing. 71% (45/63) of ADA was given at 80mg/40mg whilst 25% (16/63) was given at 160mg/80mg induction dose. Outcomes of treatment are shown in table 19; of note the overwhelming majority (97% IFX and 91% ADA) had a current plan of continuing treatment, and planned withdrawal following effective treatment occurred in just 21% (9/42) of IFX cessation and no cases with ADA.

5.4.3 Ulcerative Colitis

The majority of patients had extensive disease (E3) at initiation as shown in table 16. Chronic refractory UC was the commonest indication for treatment (59% [47/79] treatments) but 39% (31/79) were for acute severe UC, see table 17. 60% (44/73) patients starting IFX but none starting ADA were receiving steroids at the time of initial anti-TNF treatment. All IFX infusions were prescribed at 5mg/kg and 86% (6/7) of ADA given at 80mg/40mg induction dose.

Disease severity was moderate-severe in 92% (35/38, PGA) compared to 85% (45/53, PUCAI); the median PUCAI score at initiation was 55 (IQR 40, 70) and can be seen in more detail in table 18. Cross-tabulation had a Kappa statistic of 0.58 indicating ‘moderate’ agreement (0.41-0.60) between PGA and PUCAI.

There was 97% follow-up for ongoing IFX treatments (168/174), median 94 days (IQR 21, 215) and 83% (5/6) for ongoing ADA treatments, median 130 days (IQR 114, 304). 12% of treatments were stopped (21/173), with poor response or loss of response equally accounting for 76% (16/21), see table 20. Where PGA was documented, disease severity was mild in 53% patients (n=100) at follow-up compared to 8% at initial treatment (n=38), and severe in 13% at follow-up compared to 47% at initial treatment, as shown in table 18 and 20.
<table>
<thead>
<tr>
<th>Disease severity at initial treatment (per patient)</th>
<th>CD n=429</th>
<th>UC n=76</th>
<th>IBDU n=19</th>
<th>All IBD n=524</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9% (15/171)</td>
<td>8% (3/38)</td>
<td>-</td>
<td>8% (18/218)</td>
</tr>
<tr>
<td>Moderate</td>
<td>55% (94/171)</td>
<td>45% (17/38)</td>
<td>22% (2/9)</td>
<td>52% (113/218)</td>
</tr>
<tr>
<td>Severe</td>
<td>36% (62/171)</td>
<td>47% (18/38)</td>
<td>78% (7/9)</td>
<td>40% (87/218)</td>
</tr>
<tr>
<td>PCDAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>29 (20, 38)</td>
<td>-</td>
<td>-</td>
<td>29 (20, 38)</td>
</tr>
<tr>
<td>≤10 (remission)</td>
<td>12% (26/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11-30 (mild)</td>
<td>47% (103/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>31-37.5 (moderate)</td>
<td>17% (36/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥40</td>
<td>24% (52/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PUCAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>-</td>
<td>55 (40, 70)</td>
<td>43 (15, 58)</td>
<td>55 (39, 66)</td>
</tr>
<tr>
<td>&lt;10 (remission)</td>
<td>-</td>
<td>4% (2/53)</td>
<td>25% (2/8)</td>
<td>7% (4/61)</td>
</tr>
<tr>
<td>10-34 (mild)</td>
<td>-</td>
<td>11% (6/53)</td>
<td>13% (1/8)</td>
<td>11% (7/61)</td>
</tr>
<tr>
<td>35-64 (moderate)</td>
<td>-</td>
<td>42% (22/53)</td>
<td>38% (3/8)</td>
<td>41% (25/61)</td>
</tr>
<tr>
<td>65-85 (severe)</td>
<td>-</td>
<td>43% (23/53)</td>
<td>25% (2/8)</td>
<td>41% (25/61)</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IBDU, IBD unclassified; PGA, Physician Global Assessment; IQR, Inter Quartile Range; PCDAI, Paediatric Crohn’s Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index
Table 19 - Outcome at treatment follow-up in Crohn’s disease

<table>
<thead>
<tr>
<th>Crohn’s Disease follow-up anti-TNFα treatment</th>
<th>Infliximab (Frequency %)</th>
<th>Adalimumab (Frequency %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seen for follow-up</td>
<td>98% (1389/1414)</td>
<td>91% (88/97)</td>
</tr>
<tr>
<td>Transferred to another service</td>
<td>0.1% (2/1414)</td>
<td>1% (1/97)</td>
</tr>
<tr>
<td>Median days from initial dose to follow-up (IQR)</td>
<td>167 (46, 350)</td>
<td>81 (35, 232)</td>
</tr>
<tr>
<td>Current plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue treatment</td>
<td>97% (1346/1388)</td>
<td>91% (84/92)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>3% (42/1388)</td>
<td>9% (8/92)</td>
</tr>
<tr>
<td>Reason for stopping (if treatment stopped)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effective and discontinued</td>
<td>21% (9/42)</td>
<td>0% (0/8)</td>
</tr>
<tr>
<td>Loss of response</td>
<td>17% (7/42)</td>
<td>38% (3/8)</td>
</tr>
<tr>
<td>Poor response</td>
<td>29% (12/42)</td>
<td>50% (4/8)</td>
</tr>
<tr>
<td>Side effects / adverse events</td>
<td>14% (6/42)</td>
<td>0% (0/8)</td>
</tr>
<tr>
<td>Other</td>
<td>19% (8/42)</td>
<td>13% (1/8)</td>
</tr>
<tr>
<td>Disease severity (PGA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>69% (500/726)</td>
<td>26% (17/65)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26% (186/726)</td>
<td>51% (33/65)</td>
</tr>
<tr>
<td>Severe</td>
<td>6% (40/726)</td>
<td>23% (15/65)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; PGA, physician global assessment

Table 20 - Outcome at treatment follow-up in Ulcerative colitis

<table>
<thead>
<tr>
<th>UC follow-up anti-TNFα treatment</th>
<th>Infliximab (Frequency %)</th>
<th>Adalimumab (Frequency %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seen for follow-up</td>
<td>97% (168/174)</td>
<td>83% (5/6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>-</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>Transferred to adult care</td>
<td>2% (3/174)</td>
<td>-</td>
</tr>
<tr>
<td>Transferred to another service</td>
<td>2% (3/174)</td>
<td>-</td>
</tr>
<tr>
<td>Median days from initial dose to follow-up (IQR)</td>
<td>94 (21, 215)</td>
<td>130 (114, 304)</td>
</tr>
<tr>
<td>Current plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue treatment</td>
<td>88% (147/168)</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>13% (21/168)</td>
<td>-</td>
</tr>
<tr>
<td>Reason for stopping (if treatment stopped)</td>
<td>10% (2/21)</td>
<td>-</td>
</tr>
<tr>
<td>Treatment effective and discontinued</td>
<td>38% (8/21)</td>
<td>-</td>
</tr>
<tr>
<td>Loss of response</td>
<td>38% (8/21)</td>
<td>-</td>
</tr>
<tr>
<td>Poor response</td>
<td>38% (8/21)</td>
<td>-</td>
</tr>
<tr>
<td>Side effects / adverse events</td>
<td>10% (2/21)</td>
<td>-</td>
</tr>
<tr>
<td>Patient choice</td>
<td>5% (1/21)</td>
<td>-</td>
</tr>
<tr>
<td>Disease severity (PGA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>54% (51/95)</td>
<td>40% (2/5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>34% (32/95)</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td>Severe</td>
<td>13% (12/95)</td>
<td>-</td>
</tr>
</tbody>
</table>

UC, ulcerative colitis; IQR, interquartile range; PGA, physician global assessment
5.4.4 IBD Unclassified

94% (16/17) of IBDU patients had extensive disease (E3) at initiation. Acute severe and chronic refractory IBDU accounted for an equal proportion of treatments. 58% (11/19) patients starting IFX but none starting ADA were receiving steroids at the time of initial anti-TNF treatment. There was 97% (31/32) follow-up for ongoing anti-TNF at a median of 44 days (IQR 14, 98) for IFX. 16% of treatments were stopped (n=5); poor response (2/5), adverse effects (2/5), loss of response (1/5). Disease severity where recorded at follow-up was mild in 10%, moderate in 76% and severe in 14% (n=21), compared to 22% moderate and 78% severe at initiation (n=9), see table 21.

Table 21 - Outcome at treatment follow-up in Inflammatory bowel disease unclassified (IBDU)

<table>
<thead>
<tr>
<th>IBDU follow-up anti-TNFα treatment</th>
<th>Infliximab (Frequency %)</th>
<th>Adalimumab (Frequency %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=32</td>
<td>N=2</td>
</tr>
<tr>
<td>Follow-up outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seen for follow-up</td>
<td>97% (31/32)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td>Transferred to another service</td>
<td>3% (1/32)</td>
<td>-</td>
</tr>
<tr>
<td>Median days from initial dose to</td>
<td>44 (14, 98)</td>
<td>220 (75, 364)</td>
</tr>
<tr>
<td>follow-up (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue treatment</td>
<td>83% (25/30)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>17% (5/30)</td>
<td>-</td>
</tr>
<tr>
<td>Reason for stopping (if treatment stopped)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of response</td>
<td>20% (1/5)</td>
<td>-</td>
</tr>
<tr>
<td>Poor response</td>
<td>40% (2/5)</td>
<td>-</td>
</tr>
<tr>
<td>Side effects / adverse events</td>
<td>40% (2/5)</td>
<td>-</td>
</tr>
<tr>
<td>Disease severity (PGA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>11% (2/19)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>74% (14/19)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td>Severe</td>
<td>16% (3/19)</td>
<td>-</td>
</tr>
</tbody>
</table>

IQR, interquartile range; PGA, physician global assessment

Disease severity was moderate-severe in 100% (9/9) IBDU at initiation by PGA, where documented, compared with 62% (5/8) by PUCAI.

5.4.5 Response and remission

Response to induction was infrequently formally recorded; 17% (89/524) all IBD (CD 74/429, UC 12/76, IBDU 3/19). 75% (67/89) patients responded (defined as a fall in PCDAI ≥15, fall in PUCAI ≥20 or remission) at 10-14 week follow-up (CD 78% [58/74], UC/IBDU 60% [9/15]); 60% (56/93) achieved remission (CD 64% [50/78], PCDAI score ≤10 and UC/IBDU 40% [6/15], PUCAI <10).
5.4.6 Surgery

105 paediatric patients had surgery involving 166 individual surgical procedures at 156 surgeries (i.e. some operations involved more than one procedure). There was no significant difference between surgery in the 6 months pre and post initiating biologic; 7% (36/524) pre and 5% (27/524) post (p= 0.30). 87% (136/156) of surgeries were in CD patients, 8% (13/156) in UC patients and 5% (7/156) in patients with IBDU. The commonest surgical procedure in UC/IBDU was sub-total colectomy with ileostomy. The commonest procedures (by disease type) are detailed in table 5.7. The commonest procedure overall was examination under anaesthetic (EUA) of fistula, 24% (40/166) of all surgical procedures, 27% (39/144) of CD procedures. Drainage of perianal abscess was significantly less common in CD after anti-TNF than before 28% (27/96) vs. 8% (3/39) (p=0.01). However the time period of data collection was not equal pre and post anti-TNF and was variable from patient to patient. In total, 16% (12/74) of UC patients went on to have colectomy (see table 5.7).

Table 22 - IBD related surgical procedures

<table>
<thead>
<tr>
<th>IBD related surgery</th>
<th>Pre-biologic starting</th>
<th>Post-biologic starting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's disease 87% (144/166)</td>
<td>71% (102/144)</td>
<td>29% (42/144)</td>
</tr>
<tr>
<td>Right hemi-colectomy</td>
<td>6% (6/102)</td>
<td>17% (7/42)</td>
</tr>
<tr>
<td>Ileo-caecal resection</td>
<td>4% (4/102)</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>7% (7/102)</td>
<td>7% (3/42)</td>
</tr>
<tr>
<td>Colectomy + ileostomy (retained rectal stump)</td>
<td>6% (6/102)</td>
<td>7% (3/42)</td>
</tr>
<tr>
<td>Partial colectomy</td>
<td>4% (4/102)</td>
<td>2% (1/42)</td>
</tr>
<tr>
<td>Drainage of perianal sepsis</td>
<td>26% (27/102)</td>
<td>7% (3/42)</td>
</tr>
<tr>
<td>Insertion of Seton</td>
<td>9% (9/102)</td>
<td>5% (2/42)</td>
</tr>
<tr>
<td>EUA fistula procedure</td>
<td>26% (27/102)</td>
<td>29% (12/42)</td>
</tr>
<tr>
<td>Radiological drainage of abscess</td>
<td>2% (2/102)</td>
<td>10% (4/42)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IBD related surgery</th>
<th>Pre-biologic starting</th>
<th>Post-biologic starting</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC 8% (14/166)</td>
<td>UC 0% (0/14)</td>
<td>IBU 50% (4/8)</td>
</tr>
<tr>
<td>IBDU 5% (8/166)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colectomy + ileostomy (retained rectal stump)</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Colectomy + colostomy (retained rectal stump)</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Partial colectomy</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>Ileo-caecal resection</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td>EUA fistula procedure</td>
<td>-</td>
<td>25% (1/4)</td>
</tr>
</tbody>
</table>

N=105 patients, total no. individual procedures = 166, total no. surgeries = 156; EUA, examination under anaesthetic; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified
5.4.7 Safety data
There were 2287 infusions and 301.96 years of patient follow-up (n=385); median 0.65 (IQR 0.27-1.19).

2% (10/488) of all initial IFX infusions and 1% of all follow-up IFX infusions (23/1587) reported an acute reaction. There were no acute reactions with any ADA treatment (0/173). 3% (49/1587) of IFX and 2% (2/98) ADA infusions reported an adverse event, most commonly infection, although type and severity of infection was not specified, as shown in table 23. 10% of CD patients (32/316) experienced at least one adverse event over the course of their treatment. No malignancies or mortality were reported.

5.4.8 Pre-treatment Screening
Tuberculosis (TB) screening was carried out frequently with a combination of methods and 97% (478/493) had at least 1 test for TB; 88% (433/492) of patients had a chest x-ray, 47% (224/481) a gamma interferon TB test and 3% (15/469) a Mantoux test. 71% (343/485) of patients were screened for Varicella immunity; 46% (221/482) for Hepatitis B infection and 37% (176/480) for Hepatitis C; 12% (57/476) were screened for HIV infection. Details of tests by IBD subtype can be seen in table 24.

5.4.9 Comparison to adult data
Comparison was made to data from the adult biologic audit which ran over the same time period. There was a male preponderance in the paediatric cohort, with more extensive disease distribution and shorter time from diagnosis to anti-TNF initiation with median (IQR) of 1.3 years (0.61, 2.62) in the paediatric cohort compared to 4.55 years (1.31, 11.03) in the adult cohort over the same time period (p<0.001).

Response and remission rates were comparable but more children were co-immunosuppressed at the time of starting anti-TNF; 81% vs 55% paediatric and adult patients respectively on IFX and 76% vs 54% on ADA, p<0.001 for both biologics. Direct comparisons of a selected dataset are best viewed in table 25.
Table 23 - Safety data by disease subtype at initial and follow-up treatments

<table>
<thead>
<tr>
<th>Safety data frequency (%)</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
<th>IBD Unclassified</th>
<th>All IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFX n=396</td>
<td>ADA n=63</td>
<td>IFX n=73</td>
<td>ADA n=7</td>
</tr>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any acute reaction = yes</strong></td>
<td>1% (5/396)</td>
<td>0% (0/63)</td>
<td>4% (3/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Angioedema of upper airway</td>
<td>0.5% (2/396)</td>
<td>0% (0/63)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bronchospasm (cough/wheeze/SOB)</td>
<td>0.3% (1/396)</td>
<td>0% (0/63)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flushing</td>
<td>0.5% (2/396)</td>
<td>0% (0/63)</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.3% (1/396)</td>
<td>0% (0/63)</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3% (1/396)</td>
<td>0% (0/63)</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Rash</td>
<td>0.3% (1/396)</td>
<td>0% (0/63)</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>-</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>-</td>
<td>-</td>
<td>1% (1/73)</td>
<td>0% (0/7)</td>
</tr>
<tr>
<td>Itching</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>0.3% (1/396)</td>
<td>0% (0/63)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Follow-up treatment</strong></td>
<td>IFX n=1414</td>
<td>ADA n=97</td>
<td>IFX n=174</td>
<td>ADA n=6</td>
</tr>
<tr>
<td><strong>Acute Reactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any acute reaction = yes</strong></td>
<td>1% (16/1389)</td>
<td>0% (0/92)</td>
<td>2% (4/168)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any adverse event = yes</strong></td>
<td>3% (41/1389)</td>
<td>2% (2/91)</td>
<td>4% (7/168)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>-</td>
<td>-</td>
<td>0.6% (1/168)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Blood abnormality</td>
<td>0.1% (2/1389)</td>
<td>0% (0/91)</td>
<td>0.6% (1/168)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Infection</td>
<td>2% (30/1389)</td>
<td>2% (2/91)</td>
<td>2% (3/168)</td>
<td>0% (0/5)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0.1% (2/1389)</td>
<td>0% (0/91)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>0.1% (1/1389)</td>
<td>0% (0/91)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rash</td>
<td>0.1% (2/1389)</td>
<td>0% (0/91)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>0.3% (4/1389)</td>
<td>0% (0/91)</td>
<td>1% (2/168)</td>
<td>0% (0/5)</td>
</tr>
</tbody>
</table>

SOB, Shortness of Breath; IFX, infliximab; ADA, adalimumab
Table 24 - Pre-treatment screening tests by IBD subtype

<table>
<thead>
<tr>
<th>Pre-treatment screening test</th>
<th>Crohn’s disease N=429</th>
<th>Ulcerative colitis N=76</th>
<th>IBD unclassified N=19</th>
<th>All IBD N=524</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-Ray</td>
<td>87% (347/399)</td>
<td>96% (71/74)</td>
<td>79% (15/19)</td>
<td>88% (433/492)</td>
</tr>
<tr>
<td>Mantoux screen</td>
<td>3% (11/383)</td>
<td>5% (3/67)</td>
<td>5% (1/19)</td>
<td>3% (15/469)</td>
</tr>
<tr>
<td>Gamma interferon TB screen</td>
<td>48% (188/390)</td>
<td>34% (25/73)</td>
<td>61% (11/18)</td>
<td>47% (224/481)</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>45% (174/391)</td>
<td>56% (40/72)</td>
<td>37% (7/19)</td>
<td>46% (221/482)</td>
</tr>
<tr>
<td>Hepatitis C serology</td>
<td>35% (136/389)</td>
<td>47% (34/72)</td>
<td>32% (6/19)</td>
<td>37% (176/480)</td>
</tr>
<tr>
<td>HIV screen</td>
<td>11% (42/386)</td>
<td>18% (13/71)</td>
<td>11% (2/19)</td>
<td>12% (57/476)</td>
</tr>
<tr>
<td>Varicella screen</td>
<td>68% (268/393)</td>
<td>85% (62/73)</td>
<td>68% (13/19)</td>
<td>71% (343/485)</td>
</tr>
</tbody>
</table>

TB, tuberculosis; HIV, Human Immunodeficiency Virus
<table>
<thead>
<tr>
<th>Characteristic for paediatric/adult comparison</th>
<th>Paediatric % (n/n) or median (IQR)</th>
<th>Adult % (n/n) or median (IQR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>61% (321/524)</td>
<td>49% (1599/3272)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to diagnosis (years)</td>
<td>1.3 (0.61, 2.62)</td>
<td>4.55 (1.31, 11.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Extensive disease (L3 or E3)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD (L3 or greater)</td>
<td>41% (166/410)</td>
<td>32% (806/2553)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UC (E3)</td>
<td>74% (54/73)</td>
<td>47% (208/441)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IBDU (E3)</td>
<td>94% (16/17)</td>
<td>52% (45/87)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response (PCDAI fall ≥15 or HBI &gt;3)</td>
<td>77% (53/69)</td>
<td>87% (195/224)</td>
<td>0.04</td>
</tr>
<tr>
<td>Remission (at any 10-14 week f/u)</td>
<td>65% (46/71)</td>
<td>70% (170/224)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Co-immunosuppression in Crohn’s disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFX</td>
<td>81% (320/396)</td>
<td>55% (755/1363)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADA</td>
<td>76% (48/63)</td>
<td>54% (787/1450)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQR, Inter Quartile Range; CD, Crohn’s disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; L3, ileo-colonic disease; E3, disease proximal to splenic flexure; PCDAI, paediatric Crohn’s disease activity index; HBI, Harvey Bradshaw Index; IFX, infliximab; ADA, adalimumab
5.4.10 Patient Reported Outcome Measures (PROM)

19% (98/524) of patients had IMPACT-III scores recorded at baseline (see table 26), of whom only 33% (32/98) had a repeat at follow-up. The median (IQR) baseline score for overall IBD was 110.5 (91.0, 129.0) and at follow-up 113.5 (82.0, 141.0); for CD (n=78) 110.5 (92.0, 130.0) and 128.5 (85.0, 147.5) respectively. When considering patients with both baseline and follow-up scores (CD n=25, all IBD n=32) CD; 98.0 (87.0, 136.0) to 109.0 (72.0, 156.0), and ‘all IBD’; 103.5 (87.0, 131.5) to 101.0 (68.0, 147.5) (ns for both). It should be noted that a change of 10.8 or more is considered a significant change by the IMPACT-III design team.\textsuperscript{431}

Table 26 - Patient reported outcome measures (PROMs) using IMPACT III questionnaire

<table>
<thead>
<tr>
<th>At initial treatment</th>
<th>Crohn’s disease N=429</th>
<th>Ulcerative colitis N=76</th>
<th>IBD unclassified N=19</th>
<th>All IBD N=524</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>429</td>
<td>76</td>
<td>19</td>
<td>524</td>
</tr>
<tr>
<td>Completed IMPACT III</td>
<td>18% (78/429)</td>
<td>24% (18/76)</td>
<td>11% (2/19)</td>
<td>19% (98/524)</td>
</tr>
<tr>
<td>IMPACT Score, median (IQR)</td>
<td>111 (92, 130)</td>
<td>115 (86, 127)</td>
<td>-</td>
<td>111 (91, 129)</td>
</tr>
<tr>
<td>Patients with no follow-up PROM</td>
<td>68% (53/78)</td>
<td>72% (13/18)</td>
<td>-</td>
<td>67% (66/98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At follow-up</th>
<th>Number of treatments</th>
<th>Completed IMPACT III</th>
<th>IMPACT III score median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1511</td>
<td>4% (65/1511)</td>
<td>130 (96, 153)</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>4% (7/180)</td>
<td>110 (79, 114)</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>12% (4/34)</td>
<td>59 (56, 64)</td>
</tr>
<tr>
<td></td>
<td>1725</td>
<td>4% (76/1725)</td>
<td>123 (85, 147)</td>
</tr>
</tbody>
</table>

IMPACT III is a validated paediatric IBD health-related quality of life assessment tool; IQR, inter quartile range.

5.5 Discussion

5.5.1 Effectiveness

This large cohort of paediatric patients receiving anti-TNF therapy over a 2.46 year period gave a snapshot of use in real life clinical practice for PIBD across the UK from 2011-2014. The data represent the dosing schedules of that time period, when there was no routine therapeutic drug monitoring (TDM) via measurement of drug levels and anti-drug antibodies, and early use of anti-TNF in a ‘top-down’ approach was reserved for fistulising perianal CD or acute severe UC; the data were published online in the peer reviewed literature in 2017 (see appendix).\textsuperscript{300,306,412}
Overall response and remission rates are good (75% patients responding and 60% achieving remission), but one of the key outcomes is that formal documentation of this is infrequently done (17% patients). This is despite patients going on to receive maintenance therapy after their induction course. We would argue that formal post-induction assessment of response is essential to determine the need for on-going treatment and suggest a validated scoring system such as PCDAI or PUCAI as the best method. Failure to do this is highly concerning; patients may continue to receive treatment that is failing, thereby exposing them to the risks of biological therapy without the benefits, or alternatively, not have appropriate investigations performed, such as trough drug levels (if available), to ascertain if the therapeutic regimen can be optimised for maximum effect.

Complete accrual of all anti-TNF use, effectiveness and safety has been published in a nationwide Scottish PIBD registry study, but this only represents 8% of the UK paediatric population. Lower remission rates of 48% and 36% for IFX and ADA respectively were reported but the period studied was of longer duration and predominantly prior to paediatric licensing (2000 – 2010), perhaps therefore more reflective of early use of anti-TNF when current standard practice, such as maintenance (rather than episodic) treatment and dose optimisation, was not in place. The UK survey by Russell et al of adalimumab for paediatric CD reported an overall remission rate of 61% at follow-up and the RESEAT study a 65-71% clinical response rate at 3-12 months of ADA therapy in paediatric CD, which are comparable despite our low documentation rate.

There was a significant reduction in the need for drainage of perianal abscess after initiation with anti-TNF. We note that time periods pre and post initiation were not equal or defined, limiting the strength of any conclusions drawn from this, but we know that perianal disease is recognised as a debilitating CD phenotype and anti-TNFs have been shown to be the best available treatment in large studies. The rate of colectomy in UC patients at 16% is in keeping with adult studies, rate of colectomy post anti-TNF in IBDU patients is notable at 21% but numbers are small (4/19) and larger studies would be required to draw firmer conclusions.

5.5.2 Assessment of disease activity

There is a clear discrepancy between PGA and PCDAI scores; PGA is by definition subjective. The PCDAI is a validated activity index which uses clinical observations and laboratory data, taking growth into consideration, to form an objective assessment of Crohn’s disease.
activity, with low inter-observer variability.\textsuperscript{316,319,435} Documentation of PCDAI at follow-up was low, as in previous studies, and it has been proposed that this is potentially due in part to the inclusion of items that are less readily obtained such as height velocity, perianal examination and laboratory indices.\textsuperscript{78,314} Formal documentation of such data can be seen as a low priority in busy clinical practice. The PUCAI is also a validated scoring system shown to be highly reliable in providing an objective assessment of disease activity in ulcerative colitis.\textsuperscript{315} It contains just six scoring items, with no requirement for laboratory investigations; it is rapid to calculate and has been shown to be more readily collected than PCDAI.\textsuperscript{314,315} PCDAI was less frequently recorded than PUCAI in our study, which may support the theory that a simpler score is better used. Recently, the weighted PCDAI (wPCDAI) has been proposed as an alternative measure to the PCDAI and shown to have validity despite the exclusion of haematocrit, abdominal examination and height velocity as parameters.\textsuperscript{436} An app to allow easy calculation of wPCDAI and documentation was produced as a result of this study. Replacing PCDAI with wPCDAI in future audit or registry studies may encourage increased completion and documentation, thereby facilitating more objective clinical assessment to aid decision making. The PUCAI appeared to have better correlation with PGA than PCDAI, in keeping with other studies specifically designed to test this which show excellent agreement.\textsuperscript{314}

5.5.3 Safety and screening
Although the follow-up period is relatively short (max 2.46 years), the large number of patients allows us some confidence in the short term safety profile of the anti-TNF therapies, as 2287 infusions and 302 years of patient follow-up are represented. Infection was the commonest adverse event, in keeping with other published studies\textsuperscript{302,437,438} and whilst risks are minimised where possible, total prevention is not achievable. Cameron et al in their nationwide Scottish study of 132 PIBD patients on biologics reported IFX infusion reactions in 17% and serious infections in 3% IFX and 3% ADA cases, but no deaths or malignancy.\textsuperscript{302} The previously mentioned survey data from BSPGHAN members across the UK and Republic of Ireland reported adverse events in 21% of 72 patients on adalimumab, with serious adverse events in 6% including 2 sepsis related deaths (both of whom notably were receiving immunosuppression and parenteral nutrition in addition to ADA), equating to a mortality rate of 3%.\textsuperscript{301} The much lower rates of acute infusion reaction in our study may be linked to the later time period of observation, when anti-TNF is more routinely used for ongoing maintenance after the induction regimen, and administration protocols may be
more established, for example with increased use of hydrocortisone and antihistamine to reduce acute reactions. The lack of deaths or malignancy is in keeping with the Scottish study and is reassuring.

Despite safety concerns about the use of combination therapy and lymphoma risk, it is interesting to note that the majority of patients in this cohort were on combination therapy. Registry data from the DEVELOP study, a very large multicentre prospective cohort of paediatric patients (some from the UK) has shown no increased risk of malignancy during longer term follow up of patients exposed to IFX, or other biologics, compared to those never exposed to biologics, supporting the good safety profile of infliximab, as with previous anti-TNF safety data. They did however find a trend towards higher incidence rates and increased risk of both HLH and malignancy in patients who have been exposed to thiopurines, compared to those unexposed to thiopurines, regardless of biologic exposure; they advise careful consideration of the use of thiopurines in PIBD.

Concomitant immunomodulator use (with thiopurines or methotrexate), for at least 6 months after starting infliximab, is associated with reduction in the likelihood of developing anti-drug antibodies and increased longevity (i.e. durability) of infliximab therapy; it has been associated with superior efficacy compared to monotherapy with either agent in some trials, but less convincingly in other trials. The majority of lymphomas occur after >2 years of thiopurine exposure, so use of combination for a limited period of 9-12 months after anti-TNF administration may negate the risk. The risk-benefit ratio remains difficult to quantify and is patient specific; consequently the decision regarding combination therapy can be controversial but the benefit appears to be clearer for use with IFX compared to ADA; European guidelines for paediatric Crohn’s disease recommend combination immunomodulator therapy for all patients starting IFX and high risk patients starting ADA or those previously exposed to IFX.

Screening practice is variable; exclusion of TB infection is an obligatory part of guidelines so there remains room for improvement in the final unscreened 3%. The risk of hepatitis B reactivation is known (from adult IBD patients) but less than half of patients were screened, highlighting a need to improve on this.

5.5.4 Comparison to adults
The shortened time from diagnosis to starting anti-TNF in the paediatric population compared to adults is striking; it suggests aggressive progression of disease and rapid
cycling though medical therapeutic options. It may however also reflect the likelihood that the majority of PIBD patients commencing anti-TNF will be doing so in adolescence, when pubertal-led growth spurts and critically important school examinations must be factored into decision making around therapy. At the time of this data collection, top-down therapy was not yet really being explored in paediatric IBD, so early use of anti-TNF would be based on clinical factors and an escalation of therapy. Recent data from the TISKids study, of top-down vs step-up therapy in 100 paediatric patients with moderate-severe Crohn’s disease randomised to first-line infliximab (top-down) or conventional (step-up) therapy, suggests early combination therapy with a limited course of IFX and AZA maintenance is superior in achieving short term endoscopic and clinical remission and maintaining sustained clinical remission at 1 year, without further escalation of therapy. The authors argue that CYP with moderate-severe CD at diagnosis would benefit from first-line IFX therapy to reduce the risk of needing treatment escalation in the first year and optimise growth. This has not yet been adopted into routine practice by guidelines and the current approach favours tight monitoring and control of inflammation with ‘accelerated step-up’ when indicated. Other potential reasons for shorter time from diagnosis to anti-TNF in PIBD might be a reflection of poorer tolerance of standard treatments compared to adults, or the specific paediatric context of aiming for steroid free remission as quickly as possible, to minimise impact on growth, puberty and education, accelerating the progression to biological therapy.

A recent North American cohort study, derived from the electronic medical record of a health care system covering over 3.5 million patients, compared 2060 patients with CD diagnosed at <18 years of age with 4973 patients diagnosed with CD ≥18 years and found significantly higher rates of biologic use in the paediatric onset group compared with the adult onset patients – 63.6% vs 49.2% (p<0.001) respectively. Additionally they found that 10-year CD related surgery rates were higher in the adult-onset cohort compared to paediatric - 49.9% vs 37.7% (p<0.001) respectively as well as lower rates of surgery in patients treated with biologics ≥6 months, concluding that biologics are associated with lower surgery rates over time and potentially alter the natural history of the disease. Of note however, there is no assessment of disease phenotype so it is not known if higher surgery rates relate to more aggressive disease behaviour.
5.5.5 Quality of life

It is difficult to draw any meaningful conclusion regarding impact on quality of life (QoL) from this data due to the small numbers of documented PROMs. We recommended that completion in subsequent audit rounds should be promoted, as improvement in QoL is an important outcome and cannot be assumed from other markers of response. The UK IBD audit ended in 2016 and transitioned over to the new UK IBD Registry; the final annual report reveals a slight improvement in completion of PROMs to 30% at initial treatment.\(^4\)

Of note, significant improvement in QoL using IMPACT 3 in paediatric patients has been documented in a formal clinical study comparing anti-TNF with EEN and PEN; there were significant improvements in all 3 groups which correlated with clinical remission but not necessarily with mucosal healing and the largest effects were seen in the EEN group, despite the highly restrictive nature of the treatment.\(^5\)

5.5.6 Strengths and weaknesses

The main limitation of this study is the variability in completeness of data capture, reflected in the frequently changing denominator for different categories of data. This audit relies on clinical centres finding time to enter patient data and it is often only possible for them to supply the minimum data set. By comparison it is a major undertaking to capture all biological usage and outcomes in a PIBD population, as per personal communication of the senior author of the Scottish study by Cameron et al.\(^3\)

The lack of data in some fields makes interpretation challenging and in some cases impossible, such as with the QoL data, but identifying and acknowledging the difficulty in collecting this is an important observation in itself.

Another significant limitation of the study is the potential for variability in the quality of the data due to inter-observer variability and differences in clinical practice, particularly when the formal reporting of response and remission by validated scoring is so poor. As a national audit of routine clinical practice it is wholly dependent on the motivation of clinicians to submit data; there is a risk of bias with regards to patient selection, variation in follow-up and any changes to therapy, including dose escalation which is not captured here, at the discretion of the local clinician.

Follow-up post initiation of therapy is relatively short therefore the ongoing medical and surgical course of those who do not respond is unknown, again limiting the conclusions that can be drawn about impact on longer-term outcome and need for escalation of therapy.
Its strength however lies in the nationwide collaborative nature of the project and relatively large numbers represented, with over 90% of UK specialist PIBD centres participating and the ‘real-world’ clinical data; this should mean conclusions that can be drawn are broadly generalisable to the PIBD population. In day to day practice, clinicians looking after PIBD patients do not follow strict trial protocols to make decisions - they use guidelines as a framework but individual decisions are shaped by many influencing factors; understanding how therapies perform in this environment is important, but accuracy is compromised at data entry level compared to a prospective research cohort. Identifying the major issue of poor documentation of post induction response and highlighting it as an area of failing in need of improvement allows it to be addressed, which should result in a significant improvement in the clinical care PIBD patients.

5.6 Conclusions

The large number of treatments in routine clinical use support anti-TNF therapy as being both safe and effective in paediatric IBD with the majority of patients achieving response or remission and just 2% of initial infusions and 1% of follow-up infusions associated with acute adverse reactions. Documentation of response and remission using a validated scoring system was poorly recorded in this multi-centre study and is an area in need of significant improvement.

Biosimilar monoclonal antibodies were licensed towards the end of the data collection period for this study and have subsequently become frequently used; treatment with (or switch to) biosimilar anti-TNF in PIBD has had no impact on the efficacy, safety or immunogenicity in studies to date according to a recent review and has a much more favourable associated cost than originator IFX.446 Vedolizumab and ustekinumab are other biological therapies that have also now entered into routine clinical practice and ongoing national collaborative audit is recommended to evaluate their use and effectiveness going forwards.
6 CONCLUSIONS AND FUTURE DIRECTIONS

The data presented in the preceding chapters gives a snapshot of just some of the ways inflammatory bowel disease impacts children and young people in the UK. The common thread running through each cohort is the burden of disease on the patients and families at the centre of the story. In this final chapter I will summarise key findings of my data in the context of other relevant research, and consider the future directions of study in this arena which bring hope for the paediatric IBD community.

6.1 Burdens and outcomes in PIBD

6.1.1 Burden of progressive disease

The South East Scotland transition cohort (described in chapter 3) demonstrates that the majority (77%) of paediatric patients with IBD have extensive disease distribution by the time they transfer to adult gastroenterology services and that disease severity continues to progress, with rates of stricturing +/or penetrating disease increasing to affect over one third of patients by last adult follow-up (LAFU), compared to one fifth at point of transfer. This extensive disease with early progression is in keeping with previous Scottish paediatric IBD data. Perianal disease, shown to be associated with potentially devastating sequelae, including faecal incontinence, chronically draining wounds and infertility, affects one third of the cohort by LAFU and more than one third have had IBD related surgery. Larger paediatric or all ages studies have reported perianal disease affecting 14-24% of patients but rates have been slightly lower (6-11%) in the other main UK transition studies by Goodhand et al and McCartney et al. 15% of patients have documented psychosocial comorbidity but this is likely to be an underestimate given the conservative criteria used, however it is comparable to the 12% reported by Bollegala et al in their study of resource utilisation during transfer to adult care in 95 Canadian patients with IBD. Over a quarter of Crohn’s disease patients had pan-treatment exposure (to the key therapies available at the time of data collection i.e. AZA, MTX, IFX and ADA) by last adult follow-up and almost a fifth of CD patients had treatment failure (PTR) despite use of all four medications. To our knowledge other studies have not presented data on overall medication exposure within individual patients, but this may warrant further evaluation in future studies, particularly with the advent of newer therapies (new biologics with a
different mode of action and oral small molecule drugs). Describing the full landscape of treatment failure (i.e. primary non-response, primary non-remission [inadequate response without remission], loss of response or intolerance, to either the route of administration or to unacceptable side effects) as it characterises the therapeutic burden on the patient and the limitations of current treatment options and therapeutic models.

Transitioning to adult services is a time of increased vulnerability for IBD patients (and their families), not least because it often happens concurrently with other major life events such as significant school exams, commencement of further education or employment and leaving the family home. The transition process offers opportunities to have a positive impact on future outcome, but the optimal mode of transition is not yet understood and how best to measure transition success has not yet been decided. Globally there is a wide variation in the age at which transfer occurs, ranging from 14 years of age in some European countries to 21-22 years of age in the USA and Israel; most frequently it seems to be roughly when secondary education is complete at 17-18 years of age, but this is a source of confusion when reviewing the transition literature. Rosen et al evaluated transition readiness and disease outcome in the USA in 95 patients aged 18-25 years in either an adult or paediatric setting via 4 questionnaires, including the TRAQ transition readiness assessment tool, a mental health inventory and self-reported disease information. They concluded that patients who scored lower on medication management skills were more likely to be non-adherent (to medications +/- visits) and this could be used as a marker for readiness and risk of loss to follow-up, but found the strongest association between transition readiness scores and increasing age. It is noted that 37% of 46 patients in this adult setting in the USA had never been known to a paediatric service and of 49 patients in the paediatric setting (aged 18-25 years), only 51% said transition had been or was being discussed; this is obviously different to routine practice in our setting. Our data (where most patients are aged 17-18 years at transfer) suggest that missed hospital appointments in the lead-up to transfer are an indicator of missed appointments in adult services, and a potential predictor of future loss to follow-up. These patients may benefit from a targeted intervention to improve their engagement; simple measures such as calling patients to arrange the follow-up appointment and organising review on the same day as any treatment infusion have been shown to improve patient attendance. More patients were lost to follow-up after a transfer of information only, supporting the concept of a structured transition process and joint clinics with paediatric and adult services, as
proposed by Goodhand et al among others, and as recommended in current ECCO guidelines.229,232,244,245

6.1.2 Burden of other diseases
From the data presented in chapter 4, an estimated (potentially conservatively) 6.4% of PIBD patients will have the additional burden of developing a concomitant autoimmune disease (preceding, concurrently with, or following their PIBD diagnosis), before they graduate from adolescence; this brings both a symptom and therapeutic burden to the patients and their family as well as a diagnostic and cost burden to the IBD care team. Autoimmune liver disease (particularly PSC), autoimmune joint disease, and psoriasis are the most frequently occurring AIDs and usually present after or concurrently with IBD diagnosis, so awareness of the potential for evolving symptoms, with early investigation and appropriate diagnostic workup, should be a core part of IBD care. This subset of patients demonstrate high rates of extensive and severe disease, with almost half of patients exposed to at least one biological therapy, suggesting that we should be particularly vigilant for new AID developing in patients with that phenotype, and mindful of the fact that not all biologic therapies are effective in both diseases, with etanercept effective in inflammatory joint disease but not IBD.421

Our findings are in keeping with other studies from Israel, the UK, North America and France but to varying degrees. Prevalence of autoimmune liver disease in our study matched that of Andreoletti et al from Southampton and the overall prevalence, though lower, was comparable once atopic diseases were excluded.258 The association between CD and coeliac disease or diabetes and UC is supportive of findings from Wilson et al in UK data and Bar Yehuda et al with Israeli data.251,380 The strongest association with liver disease and joint disease is echoed by paediatric and adolescent data from Ghersin et al in Israel, Kappelman et al in North America and Guinet-Charpentier in France.381,396,397

The challenge of comparing any of these studies with any confidence is in the different methodology and the highly variable range of included autoimmune diseases. Many AIDs do not have equivalent rigorously developed evidence-based consensus criteria for diagnosis and phenotypic classification as we have with the revised Porto criteria for PIBD and Montreal (IBD) and Paris (PIBD) classification systems.18,28,30 What is clear from all of them however, is that concomitant AID must be a consideration for the IBD team caring for a patient when new symptoms or a change in symptoms arise, and we propose that close
working with MDT colleagues in other specialties will facilitate timely diagnosis and optimal management.

6.1.3 Burden of treatment
The data presented in chapter 5 are nationally representative of biological therapy use in the UK at the time of data collection (2011-2014), demonstrating through 2287 infusions in 524 patients with over 300 years of patient follow-up low rates of acute infusion reactions. Adverse events were also low; 3% with infliximab, 2% with adalimumab and infection the most frequently occurring adverse event with both biologics. 1 in 10 patients experienced an adverse event over the course of their treatment but there were no deaths or malignancies. Formal documentation of response to induction therapy using PGA, PCDAI or PUCAI was poorly recorded and this was appropriately identified as an area in need of significant improvement. When data were compared to the concurrently running adult IBD audit, paediatric patients treated with biological therapy had more extensive disease distribution and a shorter time from diagnosis to requirement for biological therapy.

Since the completion of this study there have been significant advances in biological therapy for IBD and the use of vedolizumab (VDZ, a gut selective antibody targeting the α4β7 integrin) and ustekinumab (UST, a monoclonal antibody targeting IL12 and IL23) has become part of current paediatric IBD guidelines; VDZ for both Crohn’s and UC (although likely more effective in UC) and UST for Crohn’s disease only (although increasingly used in UC ahead of guidelines). These drugs, with different modes of action, offer new therapeutic options beyond anti-TNF therapy for patients with intolerance, non-response or loss of response to first and second line therapies, albeit being used off license. This is hugely encouraging; at the time of data collection for the cohorts in the previous chapters there were no other standard therapies available.

As the incidence of PIBD rises in Scotland and around the world, the prevalence is also rising and with it the use of biological therapies, with guidelines increasingly permissive of their use at an earlier stage in disease course. Burgess et al in their recent Scottish population based longitudinal study of biologic use (anti-TNF, VDZ and UST) in PIBD from 2015-2019 demonstrate an increase from 20% to 43% for point prevalence biologic usage, with only a modest rise in the overall incidence rate from 6.9% to 8.1%, suggesting that once patients commence biologic therapy, the majority stay on a biologic pathway. They document a near-universal switch from originator to biosimilar anti-TNF use for PIBD
in Scotland, reflecting the much lower cost barrier to anti-TNF access with treatment almost 70% cheaper than when only the bio-originator product was available. This pathway should inevitably be replicated in due course as biosimilar products for the newer mode of action biologics and small molecule drugs eventually become available.

Other biologics are currently in the clinical trial phase in adults; risankizumab and mirikizumab are fully humanised monoclonal antibodies to different subunits of IL23 (IL-23A and IL-23p19 respectively), administered IV +/-SC for induction and maintenance, with evidence for efficacy in CD (Risankizumab) and both CD and UC (Mirikizumab). These bring further hope of an expanding armamentarium against refractory PIBD.

All of the aforementioned biological therapies require intravenous (IV) +/- subcutaneous (SC) administration; this equates to regular visits to hospital and for some patients difficulties with IV access (physically, emotionally or both) or regular injections at home, which for some is a source of tension within families and stress around injections, particularly with younger patients. This is in addition to prolonged periods on EEN or coping with the side effects of steroids, the anticipatory nausea of weekly methotrexate or the worry of cancer risk in long-term azathioprine use. The physical and psychological burden of medical therapy alone to maintain control of disease in CYP with IBD is heavy, and that is before considering any form of surgery, which the transition cohort in chapter 3 shows us will be required by 37% of patients within a few short years of adult follow-up, and which 18% of patients will already have required before leaving paediatric care. The biological therapy audit in chapter 5 supports a high requirement for IBD related surgery, with 20% of the cohort having at least one surgical procedure, though it is noted that 23% of procedures were EUA.

6.2 Cohort studies – challenges and opportunities

As discussed in chapter 1.2, observational cohort studies have an important role to play in understanding outcomes of disease, offering an opportunity to study multiple outcomes longitudinally, even with rarer exposures if studying large samples. In this thesis both retrospective and prospective data collection methods are presented and the comparative pitfalls discussed. The retrospective data collected in the transition and autoimmune disease cohorts (chapter 3 and 4 respectively) was time consuming and labour intensive to ascertain, but allowed confident confirmation of accuracy and maximised the...
reliability of the data. In contrast, the biological audit data (chapter 5) collected prospectively at a local level allowed a large number of patients to be studied across a wide geographical area, reflecting generally the state of clinical practice, but data were patchy and incomplete in many areas, limiting the conclusions that can be drawn for some key outcome measures.

It might be argued that Scotland is uniquely placed to produce high quality nationally representative PIBD cohort data; the population is well defined, has a unified health care service (the NHS) with universal access to the same medications and equivalent specialist services, through 3 tertiary paediatric gastroenterology centres providing a strong virtual national network for collaborative working. Use of this network as a resource has been most recently demonstrated by Burgess et al describing complete accrual of Scottish biological exposure and updated PIBD incidence and prevalence rates.6,94

Prospective inception cohorts are the ideal method of studying longitudinal trends and outcomes in large numbers of patients with chronic conditions such as IBD; data from the PROTECT, RISK and ECCO-Epicom cohorts have identified previously unknown epidemiological trends and genetic and phenotypic features associated with treatment response, which may have influence for future practice, as described in chapter 1.2.1.157–160 EUROKIDS, the DEVELOP registry and PIBD-SET Quality continue to recruit patients and offer the promise of further robust PIBD data in the future.81,178,184,198,456 The increasing use of routinely collected health administrative data in both observational studies and as a part of randomised controlled trials will benefit from the introduction of the RECORD and CONSORT-ROUTINE guidelines to maximise confidence in their findings.205,206

6.3 Future directions

Since data collection in the presented cohorts began, there have been advances in the research in all areas.

6.3.1 Transition

From their 2020 narrative review of 38 studies in the literature, Shapiro et al summarise the research in PIBD transition and identify gaps in knowledge around the US Government and American Academy of Pediatrics agreed ‘Six Core Elements’ approach for transitioning from paediatric to adult healthcare; transition policy, tracking and monitoring, transition readiness, transition planning, transfer of care and finally transition completion.241,457 They
highlight assessment of the association between transition readiness, adherence and hard clinical outcomes, as well as assessment of continuity and retention in care and the cost implications of any interventions as priority areas for further research.

Bollegala et al have published their protocol for a randomised controlled trial in 4 PIBD centres across Canada of a multimodal intervention to improve transition of PIBD patients; it will include individualised assessment, the role of a transition navigator, virtual patient skills building and a virtual structured education program, with the intention to recruit >100 patients for randomisation to either the intervention or standard care and a plan for final assessment 1-2 year after transfer. Disability and function (using the IBD Disability Index) will be the primary outcome and there will be multiple secondary outcomes including QoL, transition readiness scores, mental health, disease activity and health service utilisation. The results will be keenly awaited and hopefully will practically inform how transition care in PIBD can be improved.

Erős et al have also published their protocol for a randomised controlled trial to assess the effect of joint transition visits on quality of life in PIBD, with intention to randomise 80 participants to joint visits and 80 patients to standard care with the paediatric gastroenterologist until transfer at the age of 18 years, across 6 Hungarian tertiary IBD centres. Data will be collected in the 12 months pre and post transfer. Joint visits will be the only difference in patients care, to try and clearly establish if they are associated with superior outcome in Health related QoL, which will be measured using the IMPACT-III questionnaire (discussed in chapter 5). The results will be of great interest as joint visits are a core part of transition guidelines and robust data to demonstrate their efficacy would be beneficial.

Klosterman et al used semi-structured interviews and validated assessment tools to analyse what 20 patients identified as their needs for transition and having a variety of options for conveying information such as face to face discussion, written leaflets and websites to consult was felt to be important. Having a friend with IBD was identified as a helpful support in that study, and Gray et al, in their investigation into patient, parent and healthcare professional perspectives on transition, also reported that peer support and mentoring was also a common theme in patient and parent focus groups. Objective evaluation of interventions which offer the opportunity for interaction amongst adolescents with PIBD would be a valuable area of future research.
Carlsen et al have developed a personalised transition concept which they have integrated into an existing interactive internet based ehealth solution for adolescents with IBD, which will use exercises and PROMs to target key areas such as disease knowledge, medication and appointment self-management, and worries and stress, to run alongside face to face visits with the MDT. It will be assessed in an interventional case-control study in Denmark and it will be interesting to see if this paves the way for increasing use of e-learning, and other advances in technology, as part of transition medicine.

6.3.2 Autoimmune diseases

Genome-wide association studies have transformed the research landscape for understanding the shared polygenic architecture of autoimmune diseases and future research will no doubt focus on increasing understanding of the complex interaction between genotype, environment and phenotype, using big data such as the UK biobank. Concurrently, the emergence of the gut microbiome as a leading factor in health and disease has come to the fore, and understanding how this, the genotype and the environment intersect in immune mediated diseases will be important.

Reduction and enrichment of certain microbes has been demonstrated in IBD; for example the general increased abundance of bacteroidales and reduction in faecalibacterium, in particular *F. prausnitzii* (an anti-inflammatory commensal which produces SCA butyrate), is well documented. But gut bacteria as an autoimmune trigger in Rheumatoid arthritis has also long been known about, with research dating as far back as 1979. Recent studies have shown alterations in the gut microbiota of JIA patients compared to healthy subjects and proposed that early life antibiotic exposure may increase future risk of developing JIA. Di Paola et al also report a differentially abundant taxa which correlates with HLA-B27 allele positivity, a genetic marker strongly associated with sponyloarthropathy. Faecal microbiota transplant (FMT) has been trialled (RCTs) in UC, including recently in paediatric UC, as a treatment for active colitis with some success. A recent systematic review shows use of FMT in other AIDs, including T1DM and psoriatic arthritis which have been shown to be safe but are on too small a scale to give any clear indication of efficacy.

Finnish registry data have recently reported on the association between autoimmune diseases in children and perinatal risk factors, concluding that preterm birth was a shared risk factor for T1DM, THY, JIA and IBD, particularly when combined with postnatal antibiotic therapy. The same group has also reported from this cohort an association between
central obesity in school aged children and the same four AIDs, but interestingly no link to being overweight or dietary patterns.\textsuperscript{471} It is worth noting that follow-up body measurements were taken by parents at home and food consumption self-reported so a degree of inaccuracy in the data is possible, but these studies give a good flavour of the potential for large registries and databases to reveal environmental influences on immune mediated inflammatory disease (IMID) evolution, particularly when strengthened by data linkage.\textsuperscript{471}

Delineating the incident presentation of a subsequent immune mediated disease from extra-intestinal manifestations of IBD or therapeutic consequence (such as psoriaform eczema in IBD patients treated with anti-TNF) remains a challenge and will potentially continue to pose a problem for large scale studies of health databases dependent on the accuracy of coding.\textsuperscript{421,472–476} Artificial intelligence (AI) and in particular machine learning has emerged as a powerful tool for discovering patterns in complex high dimensional data with non-linear relationships so there is great interest in applying it to IMIDs and in particular data from electronic health records, with a view to biomarker discovery for diagnostic and prognostic advances in personalised medicine.\textsuperscript{477}

One controversial suggestion might be that rather than patients being looked after by multiple specialties e.g. endocrinology, gastroenterology, rheumatology, that immune mediated inflammatory diseases emerges as a specialty in its own right – the birth of the IMIDologist if you will. The upside would be holistic care – streamlined management by a single hospital MDT considering the patient as a whole and the patient able to focus on one team with whom to build a strong relationship. The practicalities though would surely be impossible – too many issues to address at a single visit would demand either the same frequency of visits as with multiple specialties or prolonged visits with the potential for loss of focus and dilution of problems. Tight control of diabetes would surely be compromised if managed by a team also responsible for joint injections and endoscopies? Maintaining skills and knowledge would be overwhelming, requiring interventions to be outsourced to other teams or services, thereby expanding the number of people involved again!

\textbf{6.3.3 Therapies}
As ustekinumab and vedolizumab move out of the trial phase into routine clinical use, and risankizumab and mirikizumab progress through clinical trials, patients can be encouraged
in the range of treatment options available but may still be troubled by the need for regular injections or infusions, particularly if they have difficult venous access or needle phobia.

The next generation of small molecule drugs which are administered orally provide alternative therapeutic pathways and are an exciting development. Janus kinase (JAK) inhibitors (jakinibs) target downstream signalling by a range of cytokines; tofacitinib has been shown to be effective and is used in paediatric UC but not yet part of routine guidelines.\textsuperscript{87,141,142,423} Selective JAK inhibitors are now in clinical trials phase having demonstrated effectiveness in other IMIDs; filgotinib is a selective JAK 1 inhibitor with efficacy in psoriatic arthritis and ankylosing spondylitis which has now been shown to be effective for induction and maintenance of moderately to severely active ulcerative colitis and approved for this indication in adults by NICE in June 2022.\textsuperscript{423,478–480} Additionally, phase 3 RCT data of upadacitinib (another oral selective JAK 1 inhibitor) for induction and maintenance in moderately to severely active UC was published earlier this year, demonstrating a positive efficacy and safety profile.\textsuperscript{481} Real world evidence of the effective use of upadacitinib in CD has already been published, prior to the conclusion of the phase 3 studies.\textsuperscript{482}

Sphingosine 1 phosphate (S1P) is a lipid mediator involved in the regulation of multiple cellular processes, including lymphocyte migration, by binding to specific receptors; S1P inhibitors bind to the receptor, preventing lymphocytes from leaving the lymphoid tissue and reducing the circulating effector T cell count and selectively suppressing the immune system. Ozanimod is a selective S1P receptor modulator demonstrated in a phase 3 multicentre, double-blind, randomised placebo controlled trial to be effective as induction and maintenance therapy for moderately to severely active UC and has very recently been approved by NICE for use in adults with moderately to severely active UC in whom conventional or biological therapies are not working or not tolerated.\textsuperscript{483,484}

The inherent issues around the lack of clinical trials of medications in PIBD, the average 7 year lag behind adult IBD medication approval to acceptance in PIBD and the difficulty in supporting paediatric ‘registration’ trials for the range of medications targeting IBD, is being addressed in a new initiative of multi-stakeholder meetings of interested North American and European individuals and organisations, with the aim of improving the development of new medicines for children; initial perspectives and strategic recommendations have recently been published.\textsuperscript{485}
In addition to new therapies, another major area of focus in IBD research is therapeutic drug monitoring and identification of biomarkers for diagnosis, prediction of treatment effect and prognostication of disease course, as we move into an era of personalised medicine.

The personalised anti-TNF therapy in Crohn’s disease study (PANTS) was a prospective multicentre cohort study of 1610 anti-TNF naïve patients ≥6 years of age initiated on IFX or ADA for active luminal CD. They identified that primary non-response is common (occurring in 23.8% of patients at week 14), that the only independently associated factor with non-response was low drug concentration at week 14, and that the optimum drug levels associated with remission are 7mg/L for IFX and 12mg/L for ADA. They also demonstrated that development of anti-drug antibodies is common (62.8% IFX, 28.5% ADA) and that suboptimal week 14 drug concentration predicts immunogenicity and vice versa; this is mitigated by the use of a combination immunomodulator (AZA or MTX), which reduces the risk of anti-drug antibody development and in IFX use is independently associated with remission at 1 year. The immunogenicity to second anti-TNF (IMSAT) study went on to look at patients who were treated with both ADA and IFX and demonstrated that immunogenicity to the first is associated with immunogenicity to the second, regardless of drug order, but commencing a combination immunomodulator with the second anti-TNF can improve drug persistence in patients with immunogenic treatment failure. This has directly guided clinical practice to ensure that anti-TNF treatments are optimised for the individual patient, discontinued appropriately if ineffective and that maximum longevity of therapeutic effect is preserved.

A recent Japanese study identified anti-integrin αvβ6 autoantibodies in 92% of 112 ulcerative colitis patients compared to 5.2% of 155 controls with high sensitivity (92%) and specificity (94.8%) for diagnosis of UC; additionally, the antibody titre correlated with UC disease activity (both extent and severity of mucosal damage). Further research is needed in other patients to assess the applicability in a wider patient group, but this is an exciting example of future less invasive markers to aid diagnosis and track disease activity.

6.3.4 General development

Holistic care in IBD is increasingly recognised as important and considerations for psychosocial support, optimising medication adherence and planning for transition are all part of PIBD guidelines. There have been many studies of the relationship between IBD
and health related quality of life (HRQoL), frequently demonstrating that increased disease activity is associated with worse HRQoL compared to remission/inactive disease.\textsuperscript{211,488} Anxiety, depression and stress are associated with lower HRQoL in IBD and lower adherence to provider recommendations.\textsuperscript{489,490} A recent systematic review and meta-analysis of childhood onset IMID found increased prevalence of psychiatric disorders, psychotropic medication and suicide attempt in PIBD compared to controls.\textsuperscript{491} A Canadian study of a UK primary care electronic medical records database assessed the impact of depression and antidepressants on development of IBD (in people 10-90 years of age), as whilst the association has been known the temporal relationship is not; patients with incident depression were more likely to develop IBD but this risk was mitigated to a degree by the use of antidepressants.\textsuperscript{492} Interestingly a recent randomised controlled trial of disease specific cognitive behavioural therapy (CBT) as an intervention in youth with IBD and subclinical anxiety or depression, measuring psychological symptoms, HRQoL, social functioning and illness perception as outcomes, found no difference between those with CBT (10 sessions over 3 months) compared to those receiving care as usual at 6 and 12 months, and both groups showed improvement. This is in keeping with findings of a previous Spanish study which found anxiety, depression and stress to be associated with lower HRQoL scores in patients with IBD, but no significant relationship between HRQoL and coping strategies.\textsuperscript{490} Clearly further research is needed to understand the psychological comorbidity in IBD and how best to manage and prevent it.

A final area of encouraging progress is the emergence of epidemiological and registry data from areas of the world which until recently have not been represented in the IBD literature. Phenotype data in PIBD from Japan and India as well as Japanese transition data, epidemiology and natural history data from Singapore, and a Korean health claims database study demonstrating an increased risk of inflammatory skin disease in IBD have all been published in recent years.\textsuperscript{16,195,235,493} Epidemiological data have also shown increasing trends in incidence in Argentina and across Latin America and limited data suggest rising incidence in Africa, with a Nigerian case series reporting on 5 children with PIBD and a protocol for a prospective registry of IBD patients in Zimbabwe recently published.\textsuperscript{494-498} Investing in understanding IBD in resource poor settings, where confounders such as intestinal TB and other enteric pathogens are highly prevalent, may lead research in directions not yet considered and advance improvement for the IBD community globally.
6.4 Concluding remarks

This thesis presents data from three UK cohorts exploring the burdens and outcomes of paediatric onset inflammatory bowel disease for children and young people. In particular it adds to our knowledge of clinical outcome following transition to adult services and describes the prevalence of concomitant autoimmune disease in a large well defined PIBD cohort. With Burgess et al recently reporting an ongoing rising incidence rate and the highest reported PIBD point prevalence worldwide in Scotland (46.3/100,000 in 2017), at the same time as identifying that PIBD patients account for <1.5% of all prevalent IBD cases, due to the compounding prevalence of a rising incidence in an ageing population with low mortality but no cure, there are significant implications for service provision and resource planning locally, nationally and globally.\textsuperscript{6–8} It is imperative that we continue to seek improvement in disease management and optimise outcomes to allow our patients to reach their full potential within a lifetime of chronic disease.
APPENDIX

Published paper relating to Chapter 5 (UK Biologics Audit)

Journal of Pediatric Gastroenterology and Nutrition Publish Ahead of Print

DOI: 10.1097/MPG.0000000000001679

Real-life anti-Tumour necrosis factor experience in > 500 paediatric

United Kingdom Inflammatory Bowel Disease patients

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ABSTRACT

Objectives: To measure the effectiveness, safety and use of anti-Tumour necrosis Factor (TNF) therapy in paediatric inflammatory bowel disease (PIBD) in the United Kingdom (UK).

Methods: Prospective UK audit of patients newly starting anti-TNF therapy. Disease severity was assessed using Physician Global Assessment (PGA) or the Paediatric Crohn’s Disease Activity Index (PCDAI).

Results: 37 centres participated (23 of 25 specialist PIBD sites). 524 patients were included; 429 Crohn’s disease (CD), 76 ulcerative colitis (UC), 19 IBD unclassified (IBDU). 87% (488/562) anti-TNF was infliximab; commonest indication was active luminal CD 77% (330/429) or chronic refractory UC/IBDU 56% (53/95); 79% (445/562) had concomitant co-immunosuppression. In CD (267/429 male), median time from diagnosis to treatment was 1.42 years (IQR 0.63-2.97). Disease (at initiation) was moderate or severe in 91% (156/171) by PGA compared to 41% (88/217) by PCDAI; Kappa (K) 0.28 = only “fair agreement” (p<0.001).

Where documented, 77% (53/69) of CD patients responded to induction; and 65% (46/71) entered remission. 2287 infusions and 301.96 years of patient follow-up (n=385) are represented; adverse events affected 3% (49/1587) infliximab and 2% (2/98) adalimumab infusions (no deaths or malignancies). Perianal abscess drainage was less common after anti-TNF initiation (CD): 26% (27/102) before, 7% (3/42) after (p<0.01); however pre and post anti-TNF data collection was not over equal time periods.
Conclusion: Anti-TNFs are effective treatments, usually given with thiopurine co-immunosuppression. This study highlights deficiencies in formal documentation of effect and disparity between disease severity scoring tools which need to be addressed to improve ongoing patient care.

Keywords: Paediatric gastroenterology, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, biologics (IBD)
What is known:

- Anti-Tumour necrosis Factor (TNF) therapy is a very effective treatment for refractory paediatric Inflammatory bowel disease.
- There are concerns about use of co-immunosuppression and potential increased lymphoma risk.
- Physician Global Assessment (PGA) and Paediatric Crohn’s disease activity index (PCDAI) are frequently used measures of disease activity.

What is new:

- Formal documentation of response/ remission rates to induction anti-TNF therapy is infrequent.
- The majority of patients in this large cohort are on combination therapy, usually with thiopurines.
- There was disparity between PGA and PCDAI scores; weighted PCDAI is suggested as an alternative.
INTRODUCTION

The Inflammatory Bowel Diseases (IBD), comprising Crohn’s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU) are increasing in incidence and prevalence, notably in the paediatric population.\(^1\) Paediatric care has been revolutionised in the last decade by the widespread introduction of anti-tumour necrosis factor (anti-TNF) therapy, both infliximab (IFX) and adalimumab (ADA); registration clinical trials have shown these agents to be effective where other therapies have failed.\(^2\) Paediatric onset IBD (PIBD) tends to be more extensive at diagnosis and aggressive in behaviour\(^3\) and use of anti-TNF therapy is proportionately greater in the paediatric population compared to adults (20% in adolescents vs 8% in adults in one case control study).\(^4\)

IFX and ADA have been licensed for use in PIBD in the UK since 2010 and 2013 respectively; UK survey data has demonstrated effectiveness in treating refractory disease whilst highlighting the potential for serious side effects.\(^5\) Scottish data on 132 PIBD patients treated with biologics over a decade show response rates of 87% with IFX (48% remission) and 76% with ADA (35% remission) replicating safety issues, especially serious infection.\(^6\)

The UK IBD audit is a national gastrointestinal audit first commenced in 2006 (reporting in 2008). Reports are available online at www.rcplondon.ac.uk/ibd. Data has previously been published on the outcomes of paediatric and adult patients with UC.\(^7\)\(^8\) We aimed to collect data on anti-TNF therapies in UK PIBD practice to assess effectiveness, safety and appropriate use (according to national guidelines) in clinical practice. Unselected, large scale national data will help quantify and categorise adverse events where real life clinical data is lacking.
MATERIALS AND METHODS

Sites (either a single hospital or a represented health board or trust) were eligible to participate in the audit if they prescribe and administer anti-TNF therapies to their patients with IBD, on a voluntary basis. A total of 37 sites participated, including 23 of 25 specialist PIBD sites, representing a broad subset of PIBD patients across the UK. Children with a diagnosis of IBD who were aged 18 years or younger when newly started on anti-TNF therapy for IBD from 12/09/11 were eligible for inclusion. Patients already on anti-TNF therapy prior to this date were excluded. Data was collected prospectively and entered into a bespoke web based database, with security maintained through local site codes and the lead clinician for the site authorising local access. All treatment decisions and data entry were at the discretion of the treating physician. Data capture for the results included here ended on 28/02/14.

Demographic details were pseudo-anonymised at the point of data entry and identifiable only to the participating site. IBD disease details were phenotyped according to Montreal criteria for disease location and behaviour.12 Physician Global Assessment (PGA), Paediatric Crohn’s Disease Activity Index (PCDAI) or Paediatric Ulcerative Colitis Activity Index (PUCAI) scores were collected at initial and follow-up treatments, along with details of comorbidities and any surgery.13,14,15 A full list of all data items collected is available on request.

Acute infusion reactions were as decided by the treating clinical team responsible for the patient; no specific guidance on specific timing was given to teams. Each follow-up treatment relates to an initial submission and records outcome as intention to continue or
stop; response with or without remission using reduction in PCDAI/PUCAI or Harvey Bradshaw Index (HBI).

Unlimited numbers of follow-up treatments are permitted and any adverse events recorded. Poor response was used to describe those patients with no or limited response to anti-TNF treatment, which included primary non-responders. Details of IBD related surgery can be added at any time, along with any escalation of treatment at each initial or follow-up treatment. Patient Reported Outcome Measures (PROM) data was collected using the IMPACT-III questionnaire \(^{13-16}\) at initiation and subsequently.

Some children received treatment with multiple biologics resulting in more initial treatments than patients. Since the number of submissions per patient is variable (e.g. multiple initial or follow-up treatments), the denominators presented vary considerably; results tables should therefore be scrutinised carefully in conjunction with any explanatory notes for accurate interpretation.

Guidance on the use of anti-TNF therapy in the UK comes via the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). NICE Technology Appraisals TA187 (CD) and TA329 (UC) recommend Infliximab [and adalimumab] within its licensed indication as an option for “the treatment of people aged 6-17 years with severe active disease who have not adequately responded to conventional therapy (including corticosteroids, immunomodulators and exclusive enteral nutrition [CD]), or who cannot tolerate or have contraindications to conventional therapy”. \(^{7,20}\) Data were collected on disease type and severity as well as previous therapies to assess prescribing against these criteria.

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Selected data, including demographics, disease location and response to treatment were compared to data reported in the adult arm of the audit from the same time period, which can be seen at www.replondon.ac.uk/ibd.21

Data were analysed using SPSS version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Data manipulation was performed using SAS software v9.4 for Windows. Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Chi-squared test and the kappa statistic were used to examine categorical data; the Mann-Whitney U test was used to examine continuous data; Kolmogorov-Smirnov (KS) test was used to analyse PROM data. Kappa statistic is expressed as per the boundaries described by Landis and Koch; range is from ‘poor/slight’ agreement (K ≤0.2) through ‘fair’, ‘moderate’ and ‘substantial’, to ‘almost perfect’ agreement (K 0.81-1.00). A p value of <0.05 was considered statistically significant.

ETHICAL CONSIDERATIONS

As an audit of clinical practice, ethical permission was not applied for.

RESULTS

Overview

By 28/02/14, demographic submissions were entered on 817 individual paediatric patients; 156 patients with no initial treatment details entered were excluded leaving 661 patients with 746 initial treatments (some patients were treated with more than one anti-
Further exclusions resulted in final analysis on 524 patients (429 CD, 76 UC and 19 IBDU) with 562 initial treatments (Figure 1). Patient demographics are shown in table 1. 30 CD, 4 UC and 4 IBDU patients were treated with both anti-TNFs. Infliximab was the commonest anti-TNF therapy representing 87% (488/562) of initial treatments. 79% (445/562) patients were co-immunosuppressed; 79% (386/488) on IFX (91% thiopurines [351/386], 9% methotrexate [35/386]) and 80% (59/74) on ADA (80% thiopurines [47/59], 20% methotrexate [12/59]). Consent was taken in 99% (559/562), either verbally (46% [257/559]) or written (54% [302/559]). Verbal consent was significantly more common with ADA 51/74 (69%) compared with IFX 206/485 (42%), p=0.00002. In total 51% (223/437) of patients had failed on an immunosuppressant and/or steroids prior to treatment with anti-TNF. 5.2% patients (27/524) had no previous medication or concomitant therapies documented at time of anti-TNF initiation, suggesting a ‘top-down’ therapy approach.

Crohn’s Disease

40% (151/379) of patients starting IFX and 37% (22/60) starting ADA had extensive disease i.e. I3 (ileocolonic) at initiation and 80% (310/388) had upper GI involvement (proximal = L4). The commonest indication for starting therapy was active luminal CD in 78% (355/458); severe perianal CD accounted for 17% (77/458) (Supplemental Digital Content, Table 1, http://links.lww.com/MPG/B43).

Disease severity at initiation of anti-TNF (where documented) was moderate-severe in 91% (156/171, PGA) and 41% (88/217, PCDAI) (table 2).

Cross-tabulation of PCDAI and PGA (grouping mild and remission together for comparison) reveals a Kappa statistic (K) of 0.28 (SE=0.055, p<0.001) indicating only.
‘fair agreement’. PCDAI was less frequently recorded than PUCAI; 51% (217/429)
PCDAI compared to 64% (53/76) PUCAI, p=0.02.
99% (347/349) of initial IFX was given at 5mg/kg i.e. standard dosing. 71% (45/63)
ADA was given at 80mg/40mg whilst 25% (16/63) was given at 160mg/80mg induction
dose. Outcomes of treatment are shown in table 3; of note, planned withdrawal following
effective treatment occurred in just 21% (9/42) of IFX cessation and no cases with ADA.

Ulcerative Colitis
The majority of patients had extensive disease (E3) at initiation (table 1). Chronic
refractory UC was the commonest indication (59%; [47/79] treatments) but 39% (31/79)
were for acute severe UC (Supplemental Digital Content, Table 1).
http://links.lww.com/MPG/B43). All IFX infusions were prescribed at 5mg/kg and 86%
(67/ of ADA given at 80mg/40mg induction dose.
Disease severity was moderate-severe in 92% (35/38, PGA) compared to 85% (45/53,
PUCAI). Median PUCAI score at initiation was 55 (IQR 40, 70), (table 2). Cross-
tabulation had a Kappa statistic of 0.58 indicating ‘moderate’ agreement (0.41-0.60)
between PGA and PUCAI.

There was 97% follow-up for ongoing IFX treatments (168/174), median 94 days (IQR
21, 215) and 83% (5/6) for ongoing ADA treatments, median 130 days (IQR 114, 304).
12% treatments were stopped (21/173), with poor response or loss of response equally
accounting for 76% (16/21). Where PGA was documented, disease severity (n=100)
 improved in most at follow-up (n=38) (table 2).

IBD Unclassified
95% (20/21) of IBDU patients had extensive disease (E3) at initiation. Acute severe and chronic refractory IBDU accounted for an equal proportion of treatments. There was 97% follow-up for ongoing anti-TNF at a median of 44 days (IQR 14, 98) for IFX. 16% treatments were stopped (n=5); poor response (2/5), adverse effects (2/5), loss of response (1/5). Disease severity where recorded at follow-up was mild in 10%, moderate in 76% and severe in 14% (n=21), compared to 0% mild, 22% moderate and 78% severe at initiation (n=9).

Disease severity was moderate-severe in 100% (9/9) IBDU at initiation by PGA, where documented, compared with 62% (5/8) by PUCAI.

Response and remission

Response to induction was infrequently formally recorded; 17% (89/524) all IBD (CD 74/429, UC 12/76, IBDU 3/19). 75% (67/89) patients responded (fall in PCDAI ≥15, fall in PUCAI ≥20 or remission) at 10-14 week follow-up (CD 78% [50/64], UC/IBDU 60% [9/15]); 60% (56/93) achieved remission (CD 64% [50/78], PCDAI score ≤10 and UC/IBDU 40% [6/15], PUCAI <10).

Surgery

105 pediatric patients had surgery involving 156 IBD-related surgical procedures. There was no significant difference between surgery in the 6 months pre and post initiating biologic; 7% (36/524) pre and 5% (27/524) post (p= 0.30). 87% (136/156) procedures were in CD patients, 8% (13/156) in UC patients and 5% (7/156) in patients with IBDU. The commonest surgical procedure in UC/ IBDU was sub-total colectomy with ileostomy. The commonest procedures (by disease type) are detailed in Supplemental Digital Content, Table 2, http://links.lww.com/MPG/B44. The commonest procedure
overall was examination under anaesthetic (EUA) of fistula, 24% (40/166) of all surgical procedures, 27% (39/144) CD procedures. Drainage of perianal abscess was significantly less common in CD after anti-TNF than before 28% (27/96) vs. 8% (3/39) (p=0.01).

However the time period of data collection was not equal pre and post anti-TNF and was variable from patient to patient. In total, 16% (12/74) of UC patients went on to have colectomy (Supplemental Digital Content, Table 2, http://links.lww.com/MPG/B44).

Safety data

There were 2287 infusions and 301.96 years of patient follow-up (n=385), median 0.65 (IQR 0.27-1.19).

2% (10/488) of all initial IFX infusions and 1% of all follow-up IFX infusions (23/1587) reported an acute reaction. There were no acute reactions with any ADA treatment (0/173). 3% (49/1587) of IFX and 2% (2/98) ADA infusions reported an adverse event, most commonly infection (Supplemental Digital Content, Table 3, http://links.lww.com/MPG/B45), although type and severity of infection was not specified. 10% of CD patients (32/316) experienced at least one adverse event over the course of their treatment. No malignancies or mortality were reported.

Pre-treatment Screening

Tuberculosis (TB) screening was carried out: 97% (478/493) had at least 1 test for TB; 88% (433/492) patients had a chest x-ray, 47% (224/481) a gamma interferon TB test and 3% (15/469) a Mantoux test. 71% (343/485) patients were screened for Varicella immunity, 46% (221/482) for Hepatitis B infection and 37% (176/480) for Hepatitis C; 12% (57/476) were screened for HIV infection.
Comparison to adult data

Comparison was made to data from the adult biologic audit which ran over the same time period. There was a male preponderance in the paediatric cohort, with more extensive disease distribution and shorter time from diagnosis to anti-TNF initiation. Response and remission rates were comparable but more children were co-immunosuppressed at the time of starting anti-TNF (Supplemental Digital Content, Table 4, http://links.lww.com/MPG/B46).

Patient Reported Outcome Measures (PROM)

19% (98/524) had IMPACT-III scores recorded at baseline with 33% (32/98) with a repeat at follow-up (Supplemental Digital Content, Table 5, http://links.lww.com/MPG/B47). The median (IQR) baseline score for IBD was 110.5 (91.0, 129.0) and at follow-up 113.5 (82.0, 141.0) and for CD (n=78) 110.5 (92.0, 130.0) and 128.5 (85.0, 147.5) respectively. When considering patients with both baseline and follow-up scores (CD n=25, all IBD n=32) CD: 98.0 (87.0, 136.0) to 109.0 (72.0, 156.0), and ‘all IBD’, 103.5 (87.0, 131.5) to 101.0 (68.0, 147.5) (ns for both). It should be noted that a change of 10.8 or more is considered a significant change by the IMPACT-III design team.23

DISCUSSION

This large cohort of paediatric patients receiving anti-TNF therapy over a 2.46 year period gives a snapshot of use in real life clinical practice for PIBD across the UK. Overall response and remission rates are good (75% patients responding and 60% achieving remission), but one of the key outcomes is that formal documentation of this is
infrequently done (17% patients). This is despite patients going on to receive maintenance therapy after their induction course. We highlight the need for formal post-induction assessment of response to determine the need for on-going treatment and suggest a validated scoring system as the best method. Failure to do this formally is highly concerning; patients may continue to receive treatment that is failing or not have appropriate investigations performed e.g. trough level determination.

Complete accrual of all anti-TNF use, effectiveness and safety has been published in a nationwide Scottish PIBD registry study, but this only represents 8% of the UK paediatric population.\(^5\) Lower remission rates of 48% and 36% for IFX and ADA respectively were reported here but the period studied was longer 2000 – 2010, perhaps reflecting early use of anti-TNF when current standard practice, such as maintenance rather than episodic treatment and dose optimisation, was not in place.\(^7\) A previous UK survey of adalimumab for paediatric CD reported a remission rate of 61% at follow-up\(^8\) and the RESEAT study a 65-71% clinical response rate at 3–12 months of ADA therapy in paediatric CD,\(^24\) which are comparable despite our low documentation rate.

There is a clear discrepancy between PGA and PCDAI scores. Documentation of PCDAI at follow-up was low, as in previous studies, thought potentially due in part to the inclusion of items that are less readily obtained such as height velocity, perianal examination and laboratory indices.\(^13,23\) Formal documentation of such data can be seen as a low priority in busy clinical practice. PCDAI was less frequently recorded than PUCAI here, which may support the theory that a simpler score is better used. Recently, the weighted PCDAI (wPCDAI) has been proposed as an alternative measure to the PCDAI and shown to have validity despite the exclusion of haematocrit, abdominal

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examination and height velocity as parameters. Replacing PCDAI with wPCDAI in
subsequent rounds of the audit may encourage increased completion and thereby
facilitate more objective clinical assessment and aid decision making. An app to allow
easy calculation of wPCDAI and documentation was produced as a result of this study.
The PUCAI appeared to have better correlation with PGA than PCDAI, in keeping with
other studies specifically designed to test this which show excellent agreement.15
There was a significant reduction in the need for drainage of perianal abscess after
initiation with anti-TNF. We note that time periods pre and post initiation were not equal
or defined, limiting the strength of any conclusions drawn from this, but we know that
perianal disease is recognised as a debilitating CD phenotype and anti-TNFs have been
shown to be an effective treatment in large studies.27 The rate of colectomy in UC
patients at 16% is in keeping with adult studies28,29, rate of colectomy post anti-TNF in
IBDU patients is notable at 21% but numbers are small (4/19).
Although the follow-up period is relatively short (max 2.46 years), the large number of
patients allows us some confidence in the short term safety profile of the anti-TNF
therapies, as 2287 infusions and 302 years of patient follow-up are represented. Infection
was the commonest adverse event, in keeping with other published studies30,9 and whilst
risks are minimised where possible, total prevention is not achievable. Despite safety
concerns about the use of combination therapy and lymphoma risk, it is interesting to
note that the majority of patients in this cohort were on combination therapy. Recently
published registry data from a very large cohort of paediatric patients (some from the
UK) have shown no increased risk of malignancy during longer term follow up,
supporting the good safety profile of infliximab, as with previous anti-TNF safety data. Screening practice is variable; exclusion of TB infection is an obligatory part of guidelines so there remains room for improvement in the final unscreened 3%. The risk of hepatitis B reactivation is well known but despite this less than half of patients were screened, highlighting a need to improve on this. The shortened time from diagnosis to starting anti-TNF in the paediatric population compared to adults is striking; it suggests aggressive progression of disease and rapid cycling though medical therapeutic options, although potentially reflects poorer tolerance of standard treatments and the context of aiming for steroid free remission as quickly as possible to minimise impact on growth, puberty and education. It is difficult to draw any meaningful conclusion regarding impact on quality of life (QoL) due to the small numbers of documented PROMs. Completion in subsequent audit rounds should be promoted as improvement in QoL is an important outcome and cannot be assumed from other markers of response. Of note, significant improvement in QoL using IMPACT 3 in paediatric patients has been recently documented in a formal clinical study. The main limitation of this study is the variability in completeness of data capture, reflected in the changing denominator for different categories of data. This audit relies on clinical centres finding time to enter patient data and it is often only possible for them to supply the minimum data set. By comparison it is a major undertaking to capture all biological usage and outcomes in a PIBD population. Follow-up is relatively short therefore the ongoing medical and surgical course of those who do not respond is
unknown. Its strength however lies in the nationwide collaborative nature of the project and relatively large numbers represented, with over 90% of specialist sites participating and the ‘real-world’ clinical data which should mean conclusions that can be drawn are broadly generalisable to the PIBD population. Addressing the major issue of poor documentation of post induction response is likely to result in a significant improvement in the clinical care PIBD patients. The large number of treatments in routine clinical use support anti-TNF therapy as safe and effective in paediatric IBD with the majority of patients achieving response or remission and just 2% of initial infusions and 1% of follow-up infusions associated with acute adverse reactions. Future audit is increasingly important with bio-similars now licensed for use in PIBD in the UK; generating comparative clinical data on their efficacy and safety profile is essential to evaluate their use, given the current lack of any published evidence in IBD. Ongoing national collaboration would be the best way to achieve this quickly and meaningfully.

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Fig 1. Patient flow chart. CD, Crohn’s Disease; UC, Ulcerative Colitis; IBDU, Inflammatory Bowel Disease Unclassified.
<table>
<thead>
<tr>
<th>Summary table</th>
<th>CD n=429</th>
<th>UC n=76</th>
<th>IBDU n=19</th>
<th>All IBD n=524</th>
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<tr>
<td><strong>General patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender: Male</td>
<td>62% (267/429)</td>
<td>58% (44/76)</td>
<td>53% (10/19)</td>
<td>61% (321/524)</td>
</tr>
<tr>
<td>Age at diagnosis, years, median (IQR)</td>
<td>n=411</td>
<td>n=74</td>
<td>n=17</td>
<td>n=502</td>
</tr>
<tr>
<td>Age at initial treatment, years, median (IQR)</td>
<td>n=427</td>
<td>n=76</td>
<td>n=19</td>
<td>n=522</td>
</tr>
<tr>
<td>Time from diagnosis to biologic, years, median (IQR)</td>
<td>n=411</td>
<td>n=74</td>
<td>n=17</td>
<td>n=502</td>
</tr>
</tbody>
</table>

| Commonest disease distribution at decision to initiate treatment (by Montreal classification) |          |
| Colonic (L2) | 40% (164/410) |
| Ileocolonic (L3) | 41% (166/410) |
| Any gut proximal to TI (L4) | 79% (288/364) |
| Perianal involvement = Yes | 54% (146/270) |
| Extensive colitis (E3) | 74% (54/73) |

Table 1: Overview of demographics and disease details by IBD type. IQR, Inter Quartile Range; PCDAI, Paediatric Crohn’s Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index

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<table>
<thead>
<tr>
<th>Disease severity at initial treatment (per patient)</th>
<th>CD n=429</th>
<th>UC n=76</th>
<th>IBDU n=19</th>
<th>All IBD n=524</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>n=171</td>
<td>n=38</td>
<td>n=9</td>
<td>n=218</td>
</tr>
<tr>
<td>Mild</td>
<td>9% (15/171)</td>
<td>8% (3/38)</td>
<td>0% (0/9)</td>
<td>8% (18/218)</td>
</tr>
<tr>
<td>Moderate</td>
<td>55% (94/171)</td>
<td>45% (17/38)</td>
<td>22% (2/9)</td>
<td>52% (113/218)</td>
</tr>
<tr>
<td>Severe</td>
<td>36% (62/171)</td>
<td>47% (18/38)</td>
<td>78% (7/9)</td>
<td>40% (87/218)</td>
</tr>
<tr>
<td>PDAI median (IQR)</td>
<td>n=217</td>
<td>-</td>
<td>-</td>
<td>n=217</td>
</tr>
<tr>
<td>≤10 (Remission)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11-30 (Mild)</td>
<td>12% (26/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>31-37.5 (Moderate)</td>
<td>47% (103/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥40 (Severe)</td>
<td>24% (52/217)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PUCAI median (IQR)</td>
<td>-</td>
<td>n=53</td>
<td>n=8</td>
<td>n=61</td>
</tr>
<tr>
<td>0-9 (Remission)</td>
<td>-</td>
<td>55 (40, 70)</td>
<td>43 (15, 58)</td>
<td>55 (39, 66)</td>
</tr>
<tr>
<td>10-34 (Mild)</td>
<td>-</td>
<td>4% (2/53)</td>
<td>25% (2/8)</td>
<td>7% (4/61)</td>
</tr>
<tr>
<td>35-64 (Moderate)</td>
<td>-</td>
<td>11% (6/53)</td>
<td>13% (1/8)</td>
<td>11% (7/61)</td>
</tr>
<tr>
<td>65-85 (Severe)</td>
<td>-</td>
<td>42% (22/53)</td>
<td>38% (3/8)</td>
<td>41% (25/61)</td>
</tr>
</tbody>
</table>

Table 2: Disease severity at initial treatment. PGA, Physician Global Assessment; IQR, Inter Quartile Range; PDAI, Paediatric Crohn's Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index.

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<table>
<thead>
<tr>
<th>Crohn's Disease Follow-up anti-TNFα treatment</th>
<th>Infliximab (Frequency %) n=1414</th>
<th>Adalimumab (Frequency %) n=97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seen for follow-up</td>
<td>98% (1389/1414)</td>
<td>91% (88/97)</td>
</tr>
<tr>
<td>Transitioned to adult care</td>
<td>2% (23/1414)</td>
<td>8% (8/97)</td>
</tr>
<tr>
<td>Transferred to another service</td>
<td>0.1% (2/1414)</td>
<td>1% (1/97)</td>
</tr>
<tr>
<td>Median days from initial dose to follow-up (IQR)</td>
<td>167 (46, 350)</td>
<td>81 (35, 232)</td>
</tr>
<tr>
<td>Current plan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continue treatment</td>
<td>97% (1346/1388)</td>
<td>91% (84/92)</td>
</tr>
<tr>
<td>Stop treatment</td>
<td>3% (42/1388)</td>
<td>9% (8/92)</td>
</tr>
<tr>
<td>Reason for stopping (if treatment stopped)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment effective and discontinued</td>
<td>21% (9/42)</td>
<td>0% (0/8)</td>
</tr>
<tr>
<td>Loss of response</td>
<td>17% (7/42)</td>
<td>38% (3/8)</td>
</tr>
<tr>
<td>Poor response</td>
<td>29% (12/42)</td>
<td>50% (4/8)</td>
</tr>
<tr>
<td>Side effects / adverse events</td>
<td>14% (6/42)</td>
<td>0% (0/8)</td>
</tr>
<tr>
<td>Other</td>
<td>19% (8/42)</td>
<td>13% (1/8)</td>
</tr>
<tr>
<td>Disease severity (PGA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>69% (500/726)</td>
<td>26% (17/65)</td>
</tr>
<tr>
<td>Moderate</td>
<td>26% (186/726)</td>
<td>51% (33/65)</td>
</tr>
<tr>
<td>Severe</td>
<td>6% (40/726)</td>
<td>23% (15/65)</td>
</tr>
</tbody>
</table>

Table 3: Outcome at follow-up in Crohn’s Disease; IQR, Inter Quartile Range; PGA, Physician Global Assessment

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