

Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease: the third IBD?

Sreedhar Subramanian,¹ Anders Ekblom,² Jonathan M Rhodes¹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/gutjnl-2016-312673>).

¹Institute of Translational Medicine, University of Liverpool, The Henry Wellcome Laboratory, Liverpool, UK
²Department of Medicine, Karolinska Institute, Stockholm, Sweden

Correspondence to Professor Jonathan M Rhodes, Institute of Translational Medicine, University of Liverpool, The Henry Wellcome Laboratory, Nuffield Building, Crown St., Liverpool L69 3GE, UK; rhodesjm@liverpool.ac.uk

Received 18 July 2016
Revised 5 September 2016
Accepted 6 September 2016
Published Online First
6 October 2016

ABSTRACT

The genetics of isolated colonic Crohn's disease place it approximately midway between Crohn's disease with small intestinal involvement and UC, making a case for considering it as a separate condition. We have therefore systematically reviewed its epidemiology, pathophysiology and treatment. Key findings include a higher incidence in females (65%) and older average age at presentation than Crohn's disease at other sites, a mucosa-associated microbiota between that found in ileal Crohn's disease and UC, no response to mesalazine, but possibly better response to antitumour necrosis factor than Crohn's disease at other sites. Diagnostic distinction from UC is often difficult and also needs to exclude other conditions including ischaemic colitis, segmental colitis associated with diverticular disease and tuberculosis. Future studies, particularly clinical trials, but also historical cohorts, should assess isolated colonic Crohn's disease separately.

INTRODUCTION

Diagnosis of Crohn's disease is often contentious when ileal involvement is lacking. This has a long history. Colitis with skip lesions and rectal sparing was considered in 1930¹ as 'regional migratory ulcerative colitis'. Crohn's classic 1932 paper did not include cases with colonic involvement,² although non-tuberculous granulomatous involvement of ileum and colon had been reported in 1923³ and later by others.^{4 5} From the 1930s to the 1950s, colitis without rectal or terminal ileal involvement was usually designated 'regional' or 'segmental' colitis.⁶

The British surgeon Wells first used 'Crohn's disease of the colon' when describing cases of granulomatous regional colitis in 1952.⁷ Initially, this was not widely accepted and Kirsner (1960) continued to refer to cases with submucosal granulomata and skip lesions as UC.⁸ Identification of Crohn's disease of the colon separately from UC was strongly reinforced by Lockhart-Mummery and Morson,⁹ who described 25 cases with features including non-bloody diarrhoea, anal fistulae, rectal sparing, skip lesions and strictures. Histopathology showed submucosal giant cell granulomata, fibrous thickening and regional lymph node enlargement. This paper caused a 'paradigm shift' that has led practice since. It was reinforced the following year when Cornes and Stecher¹⁰ reported 45 patients with isolated colonic Crohn's disease, with fistulation in nearly two-thirds, and skip lesions in 20%.

Later evidence that colonic Crohn's disease, unlike UC, might be improved by faecal diversion,^{11 12} treatable by segmental resection¹³ and

associated with poor outcomes after ileal pouch-anal anastomosis,¹⁴ seemed to confirm even more securely its position as a form of Crohn's disease and distinct from UC.

Distinction of colonic Crohn's disease from UC may be difficult though. The term 'indeterminate colitis' was introduced to describe cases, '10%–20%', where, after colectomy and examination of the resected colon, a clear diagnosis is not possible.¹⁵ The term was often incorrectly applied to patients without colectomy until 'IBD unclassified' (IBD-U) was recommended for such cases.¹⁶

The scene is now changing again—extensive data show that isolated colonic Crohn's disease is genetically separable from Crohn's disease involving the small intestine.¹⁷ When the ratio of Crohn's disease-associated to UC-associated genes is compared with disease phenotype, isolated colonic Crohn's disease lies approximately midway between ileal Crohn's and UC. IBD-U, although statistically separable from UC overlaps it considerably and ileocolonic Crohn's disease similarly overlaps ileal Crohn's disease (figure 1). This finding led to recommendation that Crohn's disease with ileal involvement (ileal and ileocolonic), isolated colonic Crohn's disease and UC should be considered as three separate conditions.

It is therefore time to review the epidemiology, genetics, serology, microbiology, and response to treatment of isolated colonic Crohn's disease and to reconsider whether this 'evidence' favours isolated colonic Crohn's disease as a variant of Crohn's disease, as a variant of UC or as a separate condition.

METHODS

The medical literature was searched using National Library of Medicine/PubMed on 1 December 2015 using the terms 'colonic and Crohn's', 'Crohn's and colitis', 'epidemiology and Crohn's'. We conducted additional searches for 'smoking and Crohn's disease' and 'oral contraception and Crohn's'. Later (1 June 2016), additional searches for 'Crohn's' and each of the therapies covered were performed. After removal of duplicates and screening of abstracts for relevance, 840 were selected for further review (see online supplementary figures 1 and 2). While the literature search was fully systematic, the subject of this review is necessarily much broader than that of a conventional systematic review. We have only included full publications in English language and have not attempted to judge quality of the data. For epidemiological studies, we included all reports that (a) contained data on at



To cite: Subramanian S, Ekblom A, Rhodes JM. *Gut* 2017;**66**:362–381.

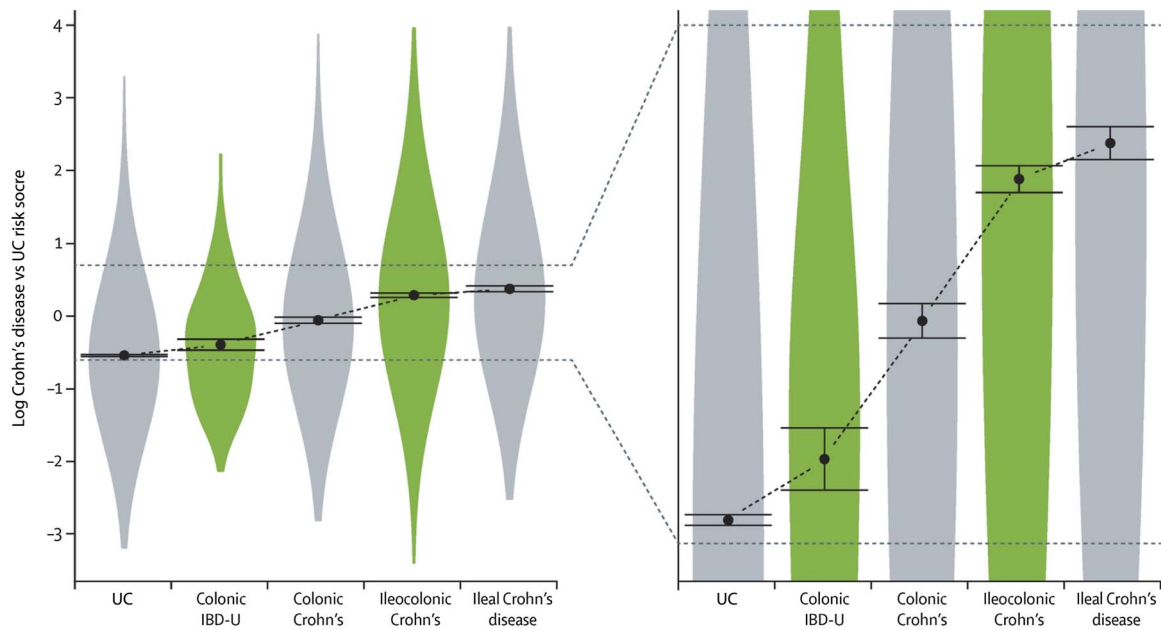


Figure 1 Comparison between Crohn's disease genetic risk score and UC genetic risk score for different locations of Crohn's disease, UC and IBD unclassified (from Cleyen *et al.*¹⁷ with permission). This shows that isolated colonic Crohn's lies approximately equidistant genetically between ileal Crohn's disease and UC. IBD-U, IBD unclassified.

least 100 patients with Crohn's disease and (b) included separate data for isolated colonic Crohn's disease (Montreal classification L2). Where published studies had overlapping patient base and time period, we used only the more completely described data set to avoid duplication. For other aspects of the review (genetics, serological testing, response to therapies and association with environmental factors), we included all studies that identified isolated colonic Crohn's disease separately. For therapeutic studies, we have separately identified data that have been obtained from randomised clinical trials and those that have been obtained from cohort studies. It should be noted that whereas pure ileal Crohn's and pure colonic Crohn's should be readily distinguished by a comprehensive diagnostic assessment including ileal intubation, incomplete assessment could mislabel ileocolonic as colonic. This should be taken into account particularly with respect to older studies, but we have taken care to ensure that all data included here regarding isolated colonic disease relate to patients thought at the time of publication not to have ileal disease. Statistical analysis was performed using StatsDirect V.3.0.171 (StatsDirect, UK).

PATHOLOGY, DIFFERENTIAL DIAGNOSIS AND DISEASE COURSE: DEFINING THE CONDITION

The histological features of isolated colonic Crohn's disease were first defined by Lockhart-Mummery and Morson.⁹ They labelled patients with this diagnosis because "they had the same characteristic pathology in the large intestinal lesions as that described by Hadfield¹⁸ for the disease as it affects the small intestine". Gross appearances of the colon following colectomy include less sharp demarcation of ulceration than typically seen in UC and with areas of intact intervening mucosa. In some cases, very marked fibrous thickening with associated stricturing was present. Fibrosis and oedema sometimes extended into the pericolonic fat and enlargement of regional lymph nodes was marked. Warren later split the macroscopic features into three patterns: isolated rectal disease; stricturing colonic disease and diffuse colitis—usually with rectal sparing, and noted that

approximately 75% develop perianal pathology during their disease course.¹⁹

Microscopic features described by Morson included discontinuous inflammation and ulceration, which could extend into the submucosa or deeper into the wall as the basis of fistula formation, plus focal crypt irregularity. Non-caseating epithelioid granulomas were present in the majority, distributed through all layers of the bowel wall as well as regional lymph nodes. Other features included submucosal lymphangiectasia and neuromatous hyperplasia.²⁰ It has subsequently been noted that the earliest lesions—aphthous ulcers—which usually overlie lymphoid follicles, are preceded by a 'red ring' sign on colonoscopy, biopsy of which reveals a lymphoid follicle surrounded by reactive hypervascularisation.²¹

Histopathology alone is diagnostic only in the minority—in a series of 103 cases of Crohn's colitis, diagnosis was determined by microscopy alone in 28%, by distribution (rectal sparing and/or discontinuity) alone in 22% and by combination of the two in 50%.²² Particularly discriminatory features suggesting Crohn's colitis rather than UC include granulomata, submucosal inflammation and relative preservation of goblet cells.^{23 24} At an international workshop, expert pathologists 'correctly' identified only 64% of cases with Crohn's colitis and 74% with UC²⁵ leading the European consensus on histopathology of IBD (2013) to note that "accurate discrimination between the two diseases (Crohn's colitis and ulcerative colitis) is not yet optimal among expert gastrointestinal pathologists". Given that inflammatory disease pathogenesis is multifactorial, an alternative interpretation would be that there is a continuous phenotypic spectrum that runs through from 'typical' UC, through IBD-U to 'typical' Crohn's colitis.

Early studies reported an additional incidence peak of Crohn's disease in the elderly resulting from cases particularly affecting the sigmoid colon.²⁶ Following the later clarification of segmental colitis associated with diverticular disease (SCAD), this seems probably attributable to SCAD. SCAD can be indistinguishable histologically from IBD and includes a

'Crohn's-like' variant with granulomata.²⁷ This reflects emphasis often placed on the diagnostic specificity of the granuloma. However, granulomas are only found in colonoscopic biopsies at diagnosis in about 66% of adults with colonic Crohn's disease, falling to 18% at follow-up.²⁸ Moreover, granulomas, particularly in association with crypts, can be found in UC.²⁹ Other forms of colitis that may need to be considered in the differential diagnosis include ischaemic colitis (see earlier) and infections including amoebiasis and tuberculosis, but it is beyond the scope of this review to consider these further.

Localisation of disease to the colon remains fairly constant over time. The largest published data set by far is the 16 902 Crohn's disease cohort, including 2933 with isolated colonic disease, in the recent genotype/phenotype association study.¹⁷ This confirmed previous reports of low rates of progression to ileocolonic disease (5%–14% over 7–10 years).^{30–32} Although luminal narrowing is common, stricturing (B2 disease) as defined in the Vienna/Montreal classifications requires the presence of prestenotic dilatation or obstructive signs or symptoms and this very rarely occurs, for example, 0/45 cases in a Belgian series,³³ whereas penetrating disease (B3) as defined by the Vienna classification (ie, including peri-anal fistulae) occurred in 23% in the same series, less frequently than in patients with ileal disease (46%; $p=0.0003$) or ileocolonic (28.6%; not significant (NS)). The much larger genotype/phenotype association study confirmed that cumulative probability of progression to B2 and B3 combined over 10 years was substantially lower in colonic disease—23%, than in ileocolonic disease—62%, or ileal disease—68%.¹⁷ The risk of surgery (discussed later) was also much lower at 10 years (22%) than for ileocolonic (42%) or ileal disease (62%). A recent meta-analysis showed that colon cancer risk in isolated colonic Crohn's disease is similar to UC of equivalent extent with a pooled standardised incidence ratio (SIR) of 1.7; 95% CI 0.9 to 2.6 (population-based data) compared with SIR 1.8; 95% CI 1.2 to 2.4 for UC but rising to SIR 18.2; 95% CI 7.8 to 35.8 for extensive colonic Crohn's disease in a referral centre population compared with SIR 21.6; 95% CI 15.0 to 31.0 for extensive UC.³⁴

EPIDEMIOLOGY

Changes over time

Studies reporting sequential data from a single centre or region show interesting time trends. Studies from the UK^{35–36} and Sweden³⁷ reported a marked increase in isolated colonic Crohn's as a proportion of total Crohn's from 1970 to 1990 (figure 2A), whereas later studies, particularly from France³⁸ have shown a downward trend since 1990. When looked at across all geographical areas (table 1), although there is no obvious difference in proportion of isolated colonic disease between countries or regions, there is a similar time trend with increase in isolated colonic disease between 1960 and 1990, peaking at an average of about one-third of all Crohn's disease cases, and decreasing since ($p=0.02$ by polynomial regression, figure 2B).

Sex variation

We found eight studies that stated the sex distribution of patients with isolated colonic Crohn's disease. In all but one, the female preponderance was equal or greater to that reported from the same study for total Crohn's disease (table 1)—isolated colonic Crohn's disease averaging 65.1% female, compared with Crohn's disease excluding isolated colonic 55.3% female ($p=0.027$ by paired t-test).

Age at diagnosis

Age at diagnosis of isolated colonic Crohn's disease (in seven studies; table 1), has a median between 28 and 45, around 10 years older than generally reported for all Crohn's—for example, median 25 years in the 16 902 patients studied by Cleynen *et al.*¹⁷ Older age of isolated colonic versus other sites of Crohn's disease was also confirmed by the IBDchip European Project.⁷² The preponderance of isolated colonic disease among children with very early onset Crohn's disease is discussed later.

Smoking

Cigarette smoking is associated with increased risk for development and progression of Crohn's disease but reduced risk for UC. Smoking is more strongly associated with risk for ileal and ileocolonic Crohn's disease than for isolated colonic disease (table 2). Only one study (of nine)⁷⁹ reported a higher rate of smoking among patients with isolated colonic Crohn's disease. If the South African data⁸³ that reported exceptionally high rates (73%) across all groups are excluded, the other studies report rates for smoking among patients with isolated colonic disease that averaged 37.8% compared with 49.8% ($p=0.008$ by paired t-test) for other Crohn's disease sites. This smoking rate is probably slightly higher than for the general population—approximately 30% European adults were smokers in 2008 (WHO).⁸⁴

Smoking worsens prognosis of Crohn's disease overall and cessation of smoking improves it.^{85–86} This has been studied less in isolated colonic disease but the conclusion is similar. The largest study⁸⁰ included 688 patients with Crohn's colitis, 978 with UC and 118 with 'indeterminate' colitis. Sixty-one per cent of patients with UC or indeterminate colitis had stopped smoking before disease onset compared with only 12% in isolated colonic Crohn's disease. In women but not men with isolated colonic disease, the risk of needing immunosuppression was increased among smokers (10-year cumulative risk 48% in non-smokers vs 58% in smokers, $p<0.01$). An earlier study⁷⁴ showed that smokers with Crohn's colitis relapsed approximately 50% more often ($p=0.028$) and with more pain ($p<0.007$) than non-smokers.

Thus, smoking at best has a neutral effect on isolated colonic Crohn's disease but more likely is harmful.

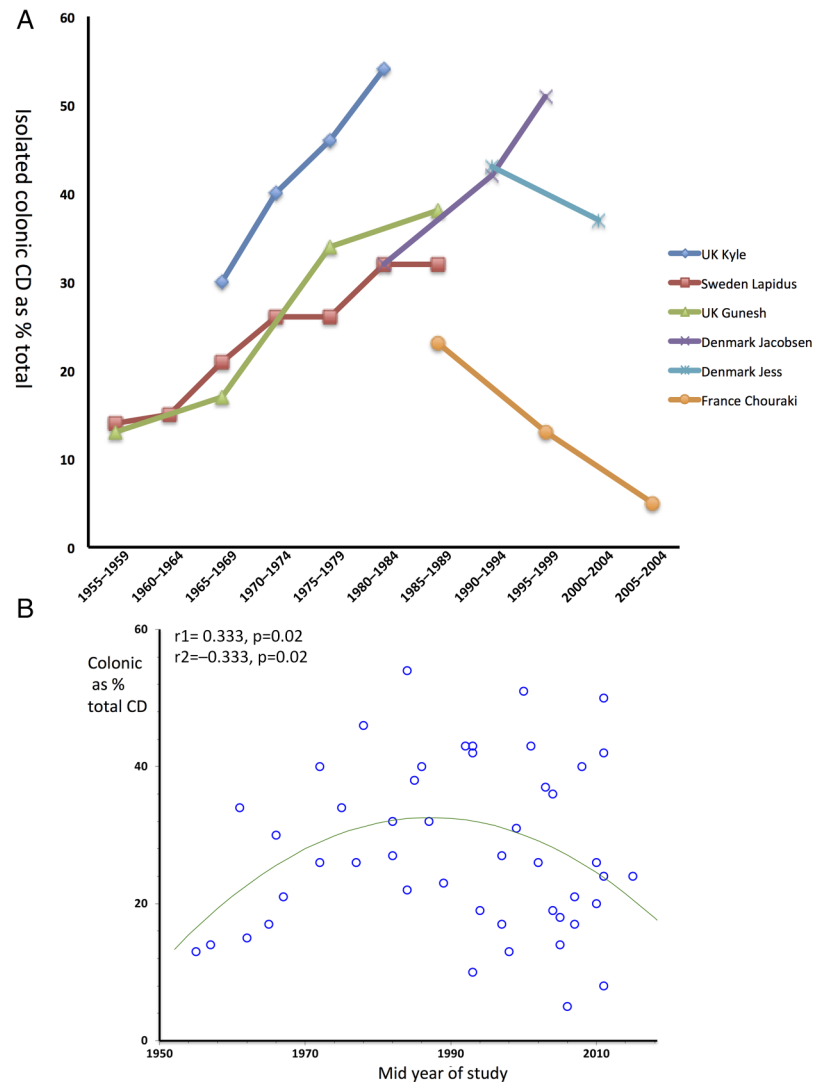
Oral contraception

Meta-analysis of 14 studies, with adjustment for smoking, showed a relative risk of 1.51 (95% CI 1.17 to 1.96, $p=0.002$) for Crohn's disease among women currently taking oral contraception.⁸⁷ The relative risk for UC was also increased at 1.53 (95% CI 1.21–1.94, $p=0.001$). Six of the seven studies that reported risk associated with oral contraception separately for isolated colonic disease found a significant association (table 3) with relatively high OR (2.63), risk ratios (3.6 and 3.23) or HR (4.13). The sole exception⁸⁹ only included eight cases with isolated colonic Crohn's disease and showed no overall association between oral contraception and risk for Crohn's disease. Excluding the latter study,⁸⁹ five of the other six studies show higher risks among oral contraceptive users for isolated colonic Crohn's than for other sites.

Oestrogen-associated ischaemic colitis as a confounder

An early study from Birmingham⁵⁰ reported patients with apparent oral contraceptive-associated colonic Crohn's disease who had non-granulomatous colitis with rectal sparing.

Figure 2 (A) Isolated colonic Crohn's disease (CD) as percentage of all CD by year in studies reporting sequential data from the same centres or geographical areas. (B) Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all studies.



Ischaemic colitis is a rare but recognised complication of oral contraception that might cause diagnostic confusion.⁹⁵⁻⁹⁷ Most cases have a short duration with typical features of ischaemic colitis including abdominal pain, and rectal bleeding. Colonoscopy shows mucosal friability but no linear ulceration and the proximal colon and rectum are typically normal. Such cases should be readily distinguishable from colonic Crohn's disease, but Tedesco *et al*⁹⁸ reported five cases of oral contraceptive-associated colitis with features that overlapped more with colonic Crohn's disease than with ischaemic colitis. Moreover, colonic 'thumbprinting', a characteristic feature of ischaemic colitis has been reported in Crohn's disease.⁹⁹ It is unclear whether diagnostic overlap with milder cases of oral contraceptive-associated ischaemic colitis contributes to the female preponderance of isolated colonic Crohn's disease. If it does then the change to lower oestrogen dosing in later versions of the contraceptive pill might be a plausible explanation for the apparent fall off in cases in recent decades.¹⁰⁰ Clinicians should be aware of the possible associations between oral contraception and IBD or ischaemic colitis and advise patients accordingly—such advice should usually include at least a temporary cessation of oral contraception to assess impact on the colitis.

GENETICS

The strongest genetic association with IBD is the link between NOD2/CARD15 and Crohn's disease. Meta-analysis of 42 studies showed that this association was stronger for Crohn's disease with small bowel involvement than for those without (OR 2.53; 95% CI 2.01 to 3.16).¹⁰¹ Subsequent study of 1528 patients with Crohn's disease from 8 centres (in 7 European countries) (IBDchip) confirmed the association of NOD2/CARD15 with ileal involvement and also showed that interleukin-23 receptor polymorphisms were more strongly associated with isolated colonic Crohn's (OR 2.20; 95% CI 1.17 to 4.57).⁷²

The most consistent genetic link with UC is with the rare major histocompatibility complex/human leucocyte antigen (HLA) class II allele HLA-DRB*0103. This occurs in <2% in European and white North American populations and is absent in the Japanese. It is strongly associated with colonic Crohn's disease, where it is present at up to 32% frequency with ORs for isolated colonic disease of 5.1 to 18.5 compared with Crohn's disease at other sites.¹⁰²

The largest study to compare genetic associations with Crohn's disease phenotype included 19 713 patients from 49 centres across 16 countries in Europe, North America and

Table 1 Studies of CD age and sex distribution and proportion of total, where isolated colonic CD separately identified (in approximate median date order)

Authors/ref	Country	Years analysed	Number of cases all CD	All CD % female	Isolated colonic CD as % of total CD	Isolated colonic CD % female	CD excluding Isolated colonic % female (calculated)	Median age at presentation (colonic CD)	Unspecified or indeterminate as ratio to colonic CD in same series
Cornes and Stecher ¹⁰	UK	1961	131	46	34	60	38	41–50	–
Gollop <i>et al</i> ³⁹	USA	1943–1982	103	64	36	68	62	25–34	–
Loftus <i>et al</i> ⁴⁰	USA	1940–1993	225	54	32	–	–	–	–
Humphreys <i>et al</i> ⁴¹	UK	1966–1981	440	58	40	–	–	–	–
Ekbom <i>et al</i> ⁴²	Sweden	1965–1983	1469	53	25	–	–	33 (mean)	–
Kyle ³⁵	UK	1955–1988	856	63	41	63	63	40–49	–
Kyle ³⁵	UK	1964–1969	122	–	30	–	–	–	–
Kyle ³⁵	UK	1970–1975	167	–	40	–	–	–	–
Kyle ³⁵	UK	1976–1981	204	–	46	–	–	–	–
Kyle ³⁵	UK	1982–1987	263	–	54	–	–	–	–
Lapidus <i>et al</i> ³⁷	Sweden	1955–1959	83	61	14	–	–	–	–
		1960–1964	145	48	15	–	–	–	–
		1965–1969	270	51	21	–	–	–	–
		1970–1974	364	53	26	–	–	–	–
		1975–1979	331	54	26	–	–	–	–
		1980–1984	348	58	32	–	–	–	–
		1985–1989	395	49	32	–	–	–	–
Gunesh <i>et al</i> ³⁶	UK (Cardiff)	1950–1960	40	–	13	–	–	–	–
Gunesh <i>et al</i> ³⁶	UK (Cardiff)	1960–1970	89	–	17	–	–	–	–
Gunesh <i>et al</i> ³⁶	UK (Cardiff)	1970–1980	148	–	34	–	–	–	–
Gunesh <i>et al</i> ³⁶	UK (Cardiff)	1980–1990	217	–	38	–	–	–	–
Yapp <i>et al</i> ⁴³	UK (Cardiff)	1991–1995	84	68	43	–	–	–	–
Gunesh <i>et al</i> ³⁶	UK (Cardiff)	1996–2005	212	61	43	68	55	–	–
Jayanthi <i>et al</i> ⁴⁴	UK	1972–1989	235	50	25 (increase from 1972 to 89)	–	–	–	–
Cottone <i>et al</i> ⁴⁵	Italy	1975–1995	882	–	18	–	–	–	–
Jacobsen <i>et al</i> ⁴⁶	Denmark	1978–1987	196	67 (1978–87)	32	–	–	–	–
Jacobsen <i>et al</i> ⁴⁶	Denmark	1988–1997	354	67 (1978–87)	42	–	–	–	–
Jacobsen <i>et al</i> ⁴⁶	Denmark	1998–2002	230	67 (1978–87)	51	–	–	–	–
Wright <i>et al</i> ⁴⁷	South Africa	1980–1984	134	69	27	–	–	–	0.44
Manninen <i>et al</i> ⁴⁸	Finland	1986–1999	470	50	40% 1986 31% 1999	–	–	–	0.56
Economou <i>et al</i> ⁴⁹	Greece	1983–2005	105	37	40	–	–	–	0.40
Rhodes <i>et al</i> ⁵⁰	UK	1984	395	55	22	72	50	28 (subset)	–
Gower-Rousseau <i>et al</i> ⁵¹	France	1994	674	57	19	–	–	28	1.15

Continued

Table 1 Continued

Authors/ref	Country	Years analysed	Number of cases all CD	All CD % female	Isolated colonic CD as % of total CD	Isolated colonic CD % female	CD excluding Isolated colonic % female (calculated)	Median age at presentation (colonic CD)	Unspecified or indeterminate as ratio to colonic CD in same series
Auvin <i>et al</i> ⁵²	France	1988–1999	367 (<17 years)	47	10	–	–	–	0.54
Spanish Epidemiological and Economic Study Group on CD ⁵³	Spain	1997	635	52	17	–	–	–	–
Jess <i>et al</i> ⁵⁴	Denmark	1962–1987	374	58	30	–	–	–	–
Jess <i>et al</i> ⁵⁴	Denmark	1991–1993	58	66	43	–	–	–	–
Jess <i>et al</i> ⁵⁴	Denmark	2003–2004	209	54	37	–	–	–	–
Chow <i>et al</i> ³¹	China	1987–2005	109	29	35	–	–	–	–
Chouraki <i>et al</i> ³⁸	France	1988–2007	7409	56	11	–	–	–	0.90
Chouraki <i>et al</i> ³⁸	France	1988–1990	544	–	23	–	–	–	–
Chouraki <i>et al</i> ³⁸	France	1997–1999	1044	–	13	–	–	–	–
Chouraki <i>et al</i> ³⁸	France	2006–2007	533	–	5	–	–	–	–
Romberg-Camps <i>et al</i> ⁵⁵	The Netherlands	1991–2003	476	61	27	66	59	34 (mean)	0.63
Bjornsson <i>et al</i> ⁵⁶	Iceland	1995–2009	279	54	55	–	–	–	0.08
Tozun <i>et al</i> ⁵⁷	Turkey	2001–2003	216	44	26	–	–	–	–
Lakatos <i>et al</i> ⁵⁸	Hungary	2002–2006	163	48	36	–	–	–	–
Nguyen <i>et al</i> ⁵⁹	USA/Canada	2003–2005	579	–	19	–	–	–	0.30
Ott <i>et al</i> ⁶⁰	Germany	2004–2006	168	55	18	–	–	–	0.43
Siddique <i>et al</i> ⁶¹	Kuwait	2005–2006	206	52	14	–	–	–	–
Chen <i>et al</i> ⁶²	USA	2005–2010	628	55	21	50	56	–	–
Lucendo <i>et al</i> ⁶³	Spain	2000–2012	599	49	24	–	–	–	0.10
Henckaerts <i>et al</i> ⁶⁴	Belgium	2007	874	–	17	–	–	–	0.03
Herrinton <i>et al</i> ⁶⁵	USA	2008	948	55	40	–	–	–	0.10
Hancock <i>et al</i> ⁶⁶	UK	2008	675	62	20 ('enriched')	74	59	31 (mean)	–
Aloi <i>et al</i> ⁶⁷	Italy	2009–2013	10 (<5 years)	–	50	–	–	–	–
Aloi <i>et al</i> ⁶⁷	Italy	2009–2013	215 (6–18 years)	–	15	–	–	–	1.00
Aljebreen <i>et al</i> ⁶⁸	Saudi	2009–2013	497	41	8	–	–	–	–
Burisch <i>et al</i> ⁶⁹	Western Europe	2010	345	48	26	–	–	–	1.19
Burisch <i>et al</i> ⁶⁹	Eastern Europe	2010	99	41	20	–	–	–	0.30
Eglinton <i>et al</i> ⁷⁰	New Zealand	2011	507	63	42	–	–	–	–
Ng <i>et al</i> ⁷¹	Asia-Pacific	2011–2012	166	Asia 39% Australia 52%	24	–	–	–	0.53
Cleynen <i>et al</i> ¹⁷	16 countries	2015	16 902	56	24	–	–	–	0.06

CD, Crohn's disease.

Table 2 Studies of smoking in CD where isolated colonic disease was separately identified

Author/ref	Year	Country	Number of cases CD	Nature of study	Current smoking OR/RR for CD phenotype	Current smoking* isolated colonic CD %	Current smoking all CD%	Current smoking CD excluding isolated colonic %	Current smoking healthy controls %	Current smoking UC %
Somerville <i>et al</i> ⁷³	1984	UK	82	Case-control	RR for smoking and CD: Small bowel only 3.5 (0.8–14.6) Colon only 4.7 (1.4–16.1) Small and large bowel 4.5 (1.8–11.5)	–	56	–	26	–
Holdstock <i>et al</i> ⁷⁴	1984	UK	150	Consecutive outpatients	–	25 (smokers with isolated colon CD had more relapses $p=0.028$)	35	52	–	8
Tobin <i>et al</i> ⁷⁵	1987	UK	137	Case-control	RR for smoking at onset and CD: Small bowel only 1.4 (0.5–4.0) Ileum and ascending colon 6.0 (2.1–17.2) Small bowel and rest of colon 3.9 (1.5–10.2) Colon only 2.5 (0.8–7.3)	–	47	–	33 (controls for UC 40%)	11
Lindberg <i>et al</i> ⁷⁶	1992	Sweden	231	Postal questionnaire (95% response)	–	42	51	53	–	–
Breuer-Katschinski <i>et al</i> ⁷⁷	1995	Germany	346	Postal questionnaire (82% response)	–	49	50	49	–	–
Russel <i>et al</i> ⁷⁸	1998	Europe (20 centres, 13 countries)	457	Prospective consecutive cases	–	35	47	59	–	16
Cosnes <i>et al</i> ⁷⁹	1999	France	622	Consecutive outpatients	–	54	49	49	–	–
Cosnes <i>et al</i> ⁸⁰	2004	France	688 all colonic	Consecutive outpatients	–	61	–	–	–	42
Aldhous <i>et al</i> ⁸¹	2007	UK (Scotland)	408	Retrospective outpatients	–	33	43	50	–	–
Hancock <i>et al</i> ⁶⁶	2008	UK	675	Database	OR 1.64 (1.09–2.45) for never smokers with isolated colonic CD vs ileal or ileocolonic	51 (ever)	61 (ever)	63	–	–
Chen <i>et al</i> ⁶²	2011	USA	628	University database	OR 1.69 (1.07–2.66) for any ileal involvement (L1+L3) vs colon only (L2)	25	37	38	–	–
Nunes <i>et al</i> ⁸²	2013	Spain	3224	National registry	–	26	34	35	–	–
Chivese <i>et al</i> ⁸³	2015	South Africa	194	Prospective consecutive cases	RR 3.63 (1.32–9.98) for ileocolonic vs colonic; RR 3.54 (1.06–11.83) for ileal vs colonic	62	73	79	–	–

*‘Current smoking’ variably either smoking at time of diagnosis or at time of sampling but excluding ‘ex-smoking’.
CD, Crohn’s disease; RR, relative risk.

Table 3 Studies of oral contraceptive usage in CD where isolated colonic disease was separately identified

Author/ref	Study design	N (total CD)	n/% isolated colonic CD taking OC at onset	n/% all other CD taking OC at onset	OR/RR (95% CI) for OC use compared with healthy controls (when documented by disease location)	OC use in isolated colonic vs all other CD
Rhodes <i>et al</i> ⁵⁰	Case-control matched for age and year of onset	37	9/12 75%	11/25 44%	–	NS increased p=0.09
Vessey <i>et al</i> ⁸⁸	Cohort study in patients attending family planning clinics	18	4/7 57%	4/11 36%	–	NS increased 0.63
Lashner <i>et al</i> ⁸⁹	Case-control	51 (including 8 isolated colonic)	–	–	Isolated colonic OR 0.50 (0.05–5.26) Small bowel only 1.25 (0.34–4.64) Ileocolonic 0.56 (0.20–1.52)	NS reduced (and no significant association in this study between OC use and any CD)
Sandler <i>et al</i> ⁹⁰	Case-control Age-matched and excluding onset before menarche	184 (including 26 isolated colonic)	–	–	Isolated colonic OR 2.63 (1.00–7.11) Small bowel only 1.33 (0.70–2.53) Ileocolonic 1.52 (0.82–2.83)	NS increased
Persson <i>et al</i> ⁹¹	Case-control age-matched and sex-matched	152	–	–	Isolated colonic RR 3.6 (1.1–12.2) Small bowel only 0.8 (0.3–2.4) Ileocolonic 1.7 (0.8–4.0)	NS increased
Katschinski <i>et al</i> ⁹²	Case-control premenopausal	90 (including 30 isolated colonic)	–	–	Isolated colonic RR 3.2 (1.1–15.3) Small bowel only RR 4.7 (1.6–17.8) Ileocolonic RR 3.8 (1.3–17.0)	NS reduced
Khalili <i>et al</i> ⁹³ Khalili and Chan ⁹⁴	Cohort—nurses' health	315 (including 141 isolated colonic)	–	–	Isolated colonic HR 4.13 (1.77–9.68) Ileal only HR 2.99 (1.06–8.49)	NS increased

CD, Crohn's disease; NS, not significant; OC, oral contraceptive; RR, relative risk.

Australasia.¹⁷ This confirmed that the strongest association with isolated colonic Crohn's disease was HLA-DRB1*01:03 ($p=1.47 \times 10^{-23}$, ileal vs colonic OR 0.32, 95% CI 0.29 to 0.41; ileocolonic vs colonic OR 0.47, 95% CI 0.39 to 0.57). The only other loci that were significant across all analyses in this study were NOD2 (16q12), again associated with increased risk for ileal involvement (OR ileocolonic vs colonic 1.61 to 1.59, and 1.89 for the three NOD2 polymorphisms tested) and also macrophage stimulating 1 that encodes a protein which induces macrophage phagocytosis polymorphisms which were more weakly associated with ileal involvement (OR 1.07 to 1.10 according to polymorphism and whether comparing ileal or ileocolonic with colonic disease). When overall genetic risk scores for Crohn's disease and UC were computed as a ratio and compared with phenotype, isolated colonic Crohn's disease was found to be approximately 'balanced' in respect of Crohn's disease versus UC genetic risk factors (figure 1). It was found though that even the combination of smoking status with the strongest genetic predictors could only explain 6.8% of the variance for disease location.

ISOLATED COLONIC CROHN'S DISEASE IN CHILDHOOD AND SINGLE GENE DISORDERS

Among children with very early onset Crohn's disease, there is a marked preponderance of cases with isolated colonic disease, for example, 76.5% before age 5¹⁰³ and 42% before age 8.¹⁰⁴ Among younger cases, there is a strong male preponderance, for example, 1.6:1 across all Crohn's disease presenting <5¹⁰³ and some of this is accounted for by X linked single gene disorders. The first such condition to be identified was X linked chronic granulomatous disease. Chronic granulomatous disease is associated with defects in neutrophil function leading to skin lesions and in around 40% with a form of IBD that is indistinguishable from Crohn's disease, typically with predominant colorectal and perianal involvement.¹⁰⁵ It is due to mutations in one of four nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex component genes of which the most common (CYBB) located on the X chromosome accounts for about 65% cases.

Rapid developments in DNA sequencing have allowed identification of over 50 further single gene disorders that present as IBD, typically as colonic disease and with presentation before age 6, defined as very early onset IBD (VEO-IBD).¹⁰⁶ VEO-IBD cases account for 4%–10% of paediatric IBD.¹⁰⁷ One of the most common single gene variants is in the coding region of X linked inhibitor of apoptosis protein that accounts for about 4% of male patients with paediatric onset Crohn's disease.¹⁰⁸

SEROLOGY INCLUDING ANTIMICROBIAL AND ANTINEUTROPHIL ANTIBODIES

Antimicrobial antibodies such as anti-*Saccharomyces cerevisiae* (ASCA) and antibodies to outer membrane protein (ompC) are found less often and/or at lower titre in isolated colonic Crohn's than in other Crohn's phenotypes.¹⁰⁹ Meta-analyses confirm this particularly for ASCA.^{110–112} Average sensitivity of ASCA for isolated colonic Crohn's disease diagnosis is 31% but with a wide range (8%–59%) and an average 14% positivity rate in UC (table 4). The clinical utility of ompC antibodies has been less studied, but reported positivity/sensitivity in isolated colonic Crohn's disease is substantially lower than that for ASCA.

Antineutrophil antibodies, particularly an atypical perinuclear antibody (pANCA), are present in around 55% of patients with UC¹¹² and 23% of patients with isolated colonic Crohn's disease (table 4). This compares with pANCA positivity of

around 11% in Crohn's disease overall and 3% in non-IBD controls.¹¹²

A combination of positive ASCA and negative pANCA is more discriminatory, for example, positivity rate in isolated colonic Crohn's disease of 52% compared with 9% in UC,¹²⁰ but is still insufficiently predictive for routine clinical use.¹²³

Thus, the frequency in isolated colonic Crohn's disease of both ASCA and pANCA antibodies lies somewhere in between that found in Crohn's disease with ileal involvement (more likely ASCA+, and pANCA–) and that found in UC (more likely ASCA– and pANCA+).

MICROBIOTA

The faecal microbiota in active IBD is commonly dysbiotic with reduced bacterial diversity.^{124–125} This could be secondary to inflammation yet still significant in maintaining chronicity. The large study of pretreatment Crohn's disease by Gevers *et al* showed only a mild dysbiosis in the faecal microbiota and much greater separation of Crohn's disease from healthy controls when the mucosa-associated microbiota was studied.¹²⁶ Ileal and rectal mucosal samples typically showed a reduction in Firmicutes such as *Faecalibacterium prausnitzii* and an increase in Proteobacteria such as *Escherichia coli* as well as in *Veillonella*, *Haemophilus* and *Fusibacteria*. This confirmed many previous studies showing an increase in mucosa-associated *E. coli* in Crohn's disease as well as several showing a reduction in *F. prausnitzii*.^{127–130}

The faecal and mucosa-associated microbiota in isolated colonic Crohn's disease is generally closer to that of healthy controls than is found in patients with ileal or ileocolonic Crohn's disease (table 5). Thus, Baumgart *et al*¹²⁷ found that an increase in ileal mucosa-associated *E. coli* and reduction in ileal *F. prausnitzii* was only present in patients with Crohn's disease who had ileal involvement and not in those with isolated colonic disease. Similarly, a study of twins with/without Crohn's disease showed that faecal microbial diversity was only reduced and Proteobacteria increased in patients with ileal involvement and not in patients with isolated colonic disease.¹²⁸ A previous report by the same group also showed a reduction in *F. prausnitzii* in patients with Crohn's disease with ileal involvement but not in isolated colonic disease.¹²⁹ Both the twin study by Willing *et al*¹²⁹ and the large study in children¹²⁶ and adolescents¹³² did however show differences between the mucosa-associated microbiota in isolated colonic Crohn's disease and UC. 16sRNA pyrosequencing of mucosal samples¹³¹ confirms the increase in *E. coli* and reduced *F. prausnitzii* in Crohn's disease with ileal involvement with milder changes in isolated colonic disease, although the latter did show some reduction in *F. prausnitzii* compared with healthy controls. This study also confirmed that the mucosa-associated microbiota is consistent at different sites from ileum to rectum in the same individual.

In conclusion, mucosa-associated microbiota changes in Crohn's disease are more marked than faecal changes. The microbiota in isolated colonic Crohn's disease shows changes that tend to be less marked and less consistent than those found in Crohn's disease with ileal involvement.

RESPONSE TO TREATMENT

Mesalazine

Systematic reviews show no convincing benefit of oral mesalazine (5-aminosalicylic acid) over placebo either in induction of remission or in maintenance of medically induced remission in Crohn's disease as a whole,^{133–137} although it may have a

Table 4 Serological test results in isolated colonic CD and UC

Author/ref	Year	Study design	N (isolated colonic CD)	ASCA IgA (n/%)	ASCA IgG (n/%)	ASCA (IgG or IgA) (n/%)	pANCA (n/%)	ompC (n/%)	GP2	UC results in same study	Comments
Duerr <i>et al</i> ¹¹³	1991	Prospective	18	–	–	–	5/18 (28%)	–	–	pANCA 34/40 (85%)	pANCA+ in isolated colonic CD not significant commoner than diarrhoea, predominantly IBS (4/27 15%)
Cambridge <i>et al</i> ¹¹⁴	1992	Stored sera IBD and healthy controls	18	–	–	–	1/18 (6%)	–	–	pANCA 27/50 (54%)	pANCA+ in 4/32 CD with small bowel involvement
Joossens <i>et al</i> ¹¹⁵	2002	Prospective follow-up of 97 patients with initial diagnosis of indeterminate colitis	17	NA	NA	10/17 (59%)	6/17 (35%)	–	–	ASCA+ in 3/14 (21%) pANCA+ in 8/14 (57%)	All patients initially indeterminate
Lawrance <i>et al</i> ¹¹⁶	2004	Prospective Caucasian and Chinese	35	6/35 (18%)	9/35 (26%)	NA	NA	–	–	ASCA IgA 6/100 ASCA IgG 11/100	ASCA less likely positive in isolated colonic CD than CD with ileal involvement
Annese <i>et al</i> ¹¹⁷	2004	Prospective	61	NA	NA	25/61 (41%)	–	–	–	ASCA 32/197 (16%)	ASCA in CD overall 51%
Ferrante <i>et al</i> ¹¹⁸	2007	Prospective study IBD plus non-IBD and healthy controls	70	NA	6%	NA	21%	3.5%	–	ASCA IgG 9.6% pANCA 37%	All antimicrobial abs lower titre in isolated colonic CD than other CD
Vind <i>et al</i> ¹¹⁹	2008	Prospective cohort	60	NA	NA	5/60 (8%)	15/60 (25%)	–	–	ASCA 14% pANCA 55%	ASCA CD overall 22%
Lakatos <i>et al</i> ¹²⁰	2009	Cohort	143	NA	NA	NA	NA	–	–	ASCA (either IgA or IgG)+/pANCA– combination in 9% UC	ASCA (either IgA or IgG) +/pANCA– combination in 52% isolated colonic CD
Bogdanos <i>et al</i> ¹²¹	2012	Prospective paediatric	32	NA	NA	5/32 (16%)	–	–	2/32 (6.2%)	GP2 9/102 (8.8%) ASCA 7/102 (7%)	GP2 ab (IgG or IgA) in 49/137 (35.8%) other (non-L2) CD ASCA 55/137 (40.1%) other (non-L2) CD
Bertin <i>et al</i> ¹²²	2013	Prospective recruited at colonoscopy	67	NA	NA	21/67 (31%)	–	15/67 (22%)	–	ompC 2/35 (6%) ASCA 5/35 (14%)	Colon mucosal culture supernatant ab measures discriminated better between L2 CD and UC
Elkadri <i>et al</i> ¹⁰⁹	2013	Prospective cohort adults and children	55	NA	NA	NA but OR 0.25 (0.12–0.51; p=0.0002) for association with isolated colonic disease vs other sites	NA but OR 2.27 (1.50–4.92; p<0.03 for association with isolated colonic disease	42.7% all CD, isolated CD NA	–	ASCA (either IgA or IgG) in 12.1% UC; 62.9% CD; pANCA in 55.6% UC, 14.3% CD; anti-ompC in 28.0% UC, 42.7% CD	ASCA positivity less common in isolated colonic CD than other sites

CD, Crohn's disease; ASCA, anti-*Saccharomyces cerevisiae*; NA, not applicable; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

Table 5 Studies of mucosal microbiota in CD where isolated colonic disease was separately identified

Author/ref	Year	Specimen type	Number of cases CD	Ileal CD	Ileocolonic CD	Isolated colonic CD	UC	Healthy controls	Conclusions
Naftali <i>et al</i> ¹³¹	2016	Ileum and colon	31	15 Increased abundance of <i>Escherichia</i> and reduced <i>Faecalibacterium</i> ; disease activity correlated with abundance of <i>Fusobacterium</i>	8* Similar to colonic CD apart from <i>Faecalibacterium</i> abundance 2.7-fold lower than in isolated colonic CD (not significant)	8* Higher levels of <i>Faecalibacterium</i> and 2 unidentified genera of the Clostridiales and Ruminococceae; lower levels of Enterobacteriaceae compared with ileal	NA	NA	Ileal CD and colonic CD microbiomes distinct
Haberman <i>et al</i> ¹³²	2015	Ileal biopsy	243 (Paediatric)	180 Persistent reduction in Lachnospiraceae, Bifidobacteriaceae, Clostridiales and Erysipelotrichaceae in all forms of CD, with expansion of Veillonellaceae, Pasteurellaceae, Neisseriaceae, Gemellaceae, Fusobacteriaceae and Enterobacteriaceae		63 Persistent reduction in Lachnospiraceae, Bifidobacteriaceae, Clostridiales and Erysipelotrichaceae in all forms of CD, with expansion of Veillonellaceae, Pasteurellaceae, Neisseriaceae, Gemellaceae, Fusobacteriaceae and Enterobacteriaceae	73 Increased abundance of Firmicutes phyla	43	No difference between ileal/ileocolonic CD and colonic CD microbiome
Lopez-Siles <i>et al</i> ¹³⁰	2014	Ileum and colon	45	19 Reduction in <i>Faecalibacterium prausnitzii</i> , <i>Escherichia coli</i> moderately increased.	13 Reduction in <i>F. prausnitzii</i>	13 <i>F. prausnitzii</i> comparable to UC; <i>E. coli</i> commoner than UC particularly in ulcerated zones	28 <i>F. prausnitzii</i> abundance intermediate between CD and HC	28	<i>F. prausnitzii</i> / <i>E. coli</i> (FE index)† allowed differentiation between ileal CD and other CD phenotypes. Microbiota changes in colonic CD intermediate between ileal CD and UC
Willing <i>et al</i> ^{128, 129, †}	2009, 2010	Ileum and colon	14	6 Increased Enterobacteriaceae and <i>Ruminococcus gnavus</i> ; decreased <i>Faecalibacterium</i> and <i>Roseburia</i> and compared with healthy controls. Increased <i>E. coli</i>		8 No reduction in <i>Faecalibacterium</i> or <i>Roseburia</i> . Some increase in <i>E. coli</i> but less marked than ileocolonic		6	Colonic CD microbiome intermediate between ileal CD and healthy controls
Baumgart <i>et al</i> ¹²⁷	2007	Ileum	29	13 Increased abundance of Enterobacteriaceae, (<i>E. coli</i> , <i>Shigella</i>) reduction in Lachnospiraceae, (<i>Ruminococci</i> , <i>Roseburia</i> and <i>Coprococci</i>) and Clostridiales (<i>Faecalibacterium</i> and <i>Subdoligranula</i>)	8 Results not presented separately	8 Enterobacteriaceae not increased and <i>Faecalibacterium</i> not reduced	NA	7	Ileal CD and colonic CD microbiome were distinct. Colonic CD more closely resembled healthy controls

*Although the study included patients with isolated colonic CD, results were pooled for patients with colonic involvement.

†Willing *et al*¹²⁸, similar patient cohort to Willing *et al*¹²⁹, but sequencing methodology compared with terminal-restriction fragment length polymorphism in Willing *et al*¹²⁹.

‡FE index was calculated as: $\log_{10} (F/HC) - \log_{10} (E/HC)/\log_{10} (TB/HC)$, F being the 16S rRNA gene copies of *F. prausnitzii*, E the 16S rRNA gene copies of *E. coli*, HC a million of human cells and TB a million of 16S rRNA gene copies of total bacteria. CD, Crohn's disease.

Table 6 Trials of 5-ASA preparations where data presented separately for isolated colonic CD

Author/ref	N (isolated colonic CD)	5-ASA	Placebo	p Value	Conclusions
Singleton <i>et al</i> ¹³⁸	64	CDAI mean change: –77 (±27) at 2 g/day –81 (±31) at 4 g/day	CDAI mean change –52 (±31)	Overall <0.01 for mesalazine vs placebo in all CD, p=0.42 for difference in ileal vs ileocolonic vs colonic	High placebo response rate in isolated colonic CD so NS if this group taken alone; better response in ileal only disease
(a) Placebo-controlled trials of oral 5-ASA in isolated colonic CD (i) induction					
Author/ref	N (isolated colonic CD)	5-ASA relapse rate 12 months	Placebo relapse rate 12 months	p Value	Conclusions
International Mesalazine Study Group ¹³⁹	56	32.1% (9/28)	38.9% (11/28)	0.49	5-ASA only showed benefit in ileal disease
Prantera <i>et al</i> ¹⁴⁰	18	40% (2/5)	55% (6/11) extrapolated from table	NS	5-ASA only showed benefit in ileal disease
Gendre <i>et al</i> ¹⁴¹	48	–	–	–	5-ASA better (p<0.003) than placebo in all patients with CD in remission <3 months at onset, no significant difference according to disease location
de Franchis <i>et al</i> ¹⁴²	36	45% (8/17) (extrapolated from figure)	45% (9/19)	1.0	5-ASA ineffective in ileal, colonic or ileocolonic
(a) Placebo-controlled trials of oral 5-ASA in isolated colonic CD (ii) maintenance					
Author/ref	N (isolated colonic CD)	Sulfasalazine remission	Placebo remission	p Value	Conclusions
Singleton <i>et al</i> ¹⁴³	20	–	–	NS	Both groups also received tapering prednisolone. Placebo better than sulfasalazine in patients with ileal disease
Summers <i>et al</i> ¹⁴⁴	17	–	–	0.006 (comparison of outcome ranks)	Sulfasalazine better than placebo in colonic CD (also effective in ileocolonic but not ileal only)
Malchow <i>et al</i> ¹⁴⁵	27	31% (4/13)	14% (2/14)	0.4	NS for remission but p<0.01 for effect when judged by 'failure and relapse'
(b) Placebo-controlled trials of oral sulfasalazine in isolated colonic CD (i) induction					
Author/ref	N (isolated colonic CD)	Sulfasalazine relapse rate 12 months	Placebo relapse rate 12 months	p Value	Conclusions
Singleton <i>et al</i> ¹⁴³	20	–	–	NS	Sulfasalazine not significantly different from placebo in CD overall and no relation to disease location
Summers <i>et al</i> ¹⁴⁴	19	–	–	NS	No significant effect (judged by outcome rank based on CDAI)
(b) Placebo-controlled trials of oral sulfasalazine in isolated colonic CD (ii) maintenance					
Author/ref	N (isolated colonic CD)	Olsalazine relapse /failure rate 12 months	Placebo relapse /failure rate 12 months	p Value	Comments
Mahmud <i>et al</i> ¹⁴⁶	145	65.4%	53.6%	0.035 (olsalazine worse)	Olsalazine induces diarrhoea, no evidence of efficacy
(c) Placebo-controlled trial of olsalazine in isolated colonic Crohn's maintenance					
5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; NS, not significant.					

modest benefit in maintaining surgically induced remission.¹³⁷ Sulfasalazine (sulfapyridine linked via azo bond to 5-aminosalicylate) has possible modest efficacy in induction of remission.^{133 134}

Among trials that have reported data separately for isolated colonic Crohn's disease, only one trial studied the effect of oral mesalazine in remission induction¹³⁸ and four studied its effect in maintenance of medically induced remission^{139–142} (table 6). In none of these was mesalazine significantly more effective than placebo but in two studies,^{139 140} there was a weak signal suggesting a better response in ileal disease. A single trial of olsalazine showed worse results than for placebo, probably because of drug-related diarrhoea.¹⁴⁶ Sulfasalazine was no better than placebo in two trials of maintenance,^{143 144} but there was a weak signal of efficacy in remission induction in two trials^{144 145} and these only studied 17 and 27 patients with isolated colonic disease, respectively (including placebo). Apart from case reports, there have been no published studies of rectal mesalazine in isolated colonic Crohn's disease.

It can be reasonably concluded that mesalazine and olsalazine do not have efficacy in isolated colonic Crohn's disease. Sulfasalazine possibly has some efficacy in remission induction.

Antibiotics

Systematic reviews suggest a beneficial effect for antibiotics in the induction of remission for Crohn's disease, although these have included diverse antibiotics and small trials.^{147–149} The largest study to date is for rifaximin.¹⁵⁰ Three doses were tested: 400, 800, 1200 mg or placebo twice daily for 12 weeks with good efficacy overall but no dose response. Among patients with isolated colonic disease, higher remission rates (51%) were found for rifaximin (pooled doses) than for placebo (37%) and efficacy was better in this group than for other disease sites (table 7).

Metronidazole has also shown better efficacy in isolated colonic Crohn's disease but based on very small numbers (Blichfeldt *et al.*¹⁵¹ n=6 crossover; Sutherland *et al.*¹⁵² 8 active and 4 placebo). In a study of 134 patients randomly assigned to ciprofloxacin and metronidazole, both 500 mg twice daily, or placebo in combination with budesonide 9 mg daily,¹⁵³ a trend was seen towards benefit in patients with colonic involvement compared with those without, but separate data were not reported for patients with isolated colonic disease. A large randomised trial of long duration (up to 2 years) antibiotic therapy (clarithromycin, rifabutin and clofazimine) targeted against *Mycobacterium avium paratuberculosis* in patients also receiving tapered prednisolone showed short-term efficacy with 66% active in remission at 16 weeks compared with 50% placebo (p=0.02) and 39% relapsed by 12 months compared with 56% placebo (p=0.054).¹⁵⁴ No differential response was seen according to disease location, but data were not presented separately for patients with isolated colonic disease.

Thus, rifaximin and metronidazole show some evidence of efficacy in patients with isolated colonic Crohn's disease and antibiotics tend to perform better in this group of patients than in Crohn's disease at other sites but based on very small data sets. Further trials are clearly needed.

Corticosteroids

Given the widespread use of corticosteroids in Crohn's disease, the quality of evidence for their efficacy is surprisingly poor. There have only been two placebo-controlled trials of standard glucocorticosteroids.^{144 145} Each of these included only eight steroid-treated patients with isolated colonic disease (table 8)

Table 7 Trials of antibiotics where data provided separately for patients with isolated colonic CD

Author/ref	N (isolated colonic CD)	Comparator	Primary end point	Rifaximin remission rate	Placebo remission rate	p Value	Conclusions
Prantera <i>et al.</i> ¹⁵⁰	190 active; 76 placebo (from online supplementary table S2)	Placebo	Week 12 remission (CDAI <150)	3 doses: 400 mg twice daily; 800 mg twice daily; 1200 mg twice daily; no dose-response overall; pooled doses remission in 96/190 (51%)	28/76 (37%)	0.04	Rifaximin more effective for colonic than ileal disease
(a) Controlled trial of oral rifaximin							
Author/ref	N (isolated colonic CD)	Comparator	Primary end point	Metronidazole response rate	Placebo response rate	p Value	Conclusions
Blichfeldt <i>et al.</i> ¹⁵¹	6	Placebo (crossover)	Week 8 response	100%	2/6 (33%)	NS overall	Metronidazole 1 g daily improved symptoms and lab values in all six with colonic disease
Sutherland <i>et al.</i> ¹⁵²	12 (4 received 10 mg/kg; 4 received 20 mg/kg; placebo)	Placebo	Week 16 response	Mean CDAI drop 145, 95% CI 26 to 265, n=8	CDAI increased by mean of 61, n=4	0.05	Metronidazole more effective than placebo in colonic and ileocolonic disease but not small bowel disease
(b) Controlled trials of oral metronidazole							
CD, Crohn's disease; NS, not significant							

with one trial¹⁴⁴ showing no benefit and the other¹⁴⁵ showing efficacy. There has never been a trial to assess dose-responsiveness to conventional corticosteroids in Crohn's disease, so optimal dosage is unknown. More data are available for budesonide but trials have focused predominantly on patients with ileal or ileocolonic disease, so data in isolated colonic disease are again very sparse. The data from one comparison with mesalazine¹⁵⁵ support efficacy in isolated colonic Crohn's disease, possibly with a weaker effect than conventional corticosteroids,¹⁵⁶ but reduced corticosteroid side effects.

Antitumour necrosis factor

None of the randomised trials of infliximab^{157 158} or adalimumab¹⁵⁹⁻¹⁶² reported subgroup analyses of outcomes based on disease location. In a randomised, placebo controlled trial of certolizumab pegol, patients with colonic (OR 2.39, 95% CI 0.99 to 5.75, $p=0.052$) and ileocolonic disease (OR 2.07, 95% CI 1.01 to 4.28, $p=0.048$) were more likely to achieve remission at week 6 compared with ileal disease (OR 0.42, 95% CI 0.18 to 0.99, $p=0.048$)¹⁶³ (table 9).

Several cohort studies have assessed colonic disease location as a predictor of response to antitumour necrosis factor (TNF) agents, four with infliximab and one with adalimumab. Three cohort studies assessing induction therapy with infliximab¹⁶⁴⁻¹⁶⁶ all showed better response rates in isolated colonic disease than for disease at other sites. Paradoxically, cohort studies of infliximab maintenance in children¹⁶⁷ and of adalimumab maintenance in adults¹⁶⁸ both showed higher risk of lost response or dose escalation in isolated colonic disease. Overall, the evidence supports good efficacy for anti-TNF therapy in induction of remission in isolated colonic Crohn's disease, but possibly with a higher subsequent rate of loss of response.

Vedolizumab

In the combined induction and maintenance study of vedolizumab, there was no significant difference in efficacy in isolated colonic disease compared with other locations¹⁶⁹ (table 9).

Enteral nutrition

Exclusive enteral nutrition is effective as primary therapy in patients with active Crohn's disease^{170 171} and partial enteral nutrition has shown efficacy in maintenance of remission.¹⁷² In UC, total parenteral nutrition and bowel rest are ineffective¹⁷³ and comparison of enteral with parenteral nutrition showed no difference in efficacy,¹⁷⁴ implying no efficacy for enteral nutrition either. Whether enteral nutrition is effective as primary therapy in isolated colonic Crohn's disease is controversial. Relatively few studies provide separate data on patients with isolated colonic Crohn's disease (table 10). Five of the six studies are in children. Two studies^{176 177} report poorer results in children with isolated colonic disease compared with those with small intestinal involvement. Numbers are small though (19 cases of isolated colonic disease across the 2 trials) and the other studies (including 72 cases of isolated colonic disease across 4 trials) found no significant difference in remission rates for those with isolated colonic disease compared with other sites. Further trials of exclusive enteral nutrition are needed in patients with isolated colonic disease.

Surgery

Faecal diversion

Colonic Crohn's disease commonly responds to 'bowel rest' induced by a defunctioning ileostomy, whereas UC does not.^{11 12} Instillation of unfiltered ileostomy contents into the

Table 8 Trials of oral corticosteroids where data provided separately for isolated colonic CD

Author/ref	N (isolated colonic CD)	Budesonide/comparator	Primary end point	Budesonide remission rate	Comparator remission rate	p Value	Steroid-related adverse events	Conclusions
Tromm <i>et al</i> ¹⁵⁵	50 (distal colon excluding rectum) of 307 in trial	Budesonide 9 mg once daily vs 3 mg three times daily vs mesalazine 1.5 g three times daily	Week 8 remission, CDAI ≤ 150	23/30 (76.7%)	10/20 (50%)	0.051	Only 1 budesonide patient with acne, no other steroid-related events	Budesonide borderline significance better than mesalazine
Bar-Meir <i>et al</i> ¹⁵⁶	27 of 201 in trial	Budesonide 9 mg once daily vs prednisone 40 mg once daily 2 weeks then taper	Week 8 remission, CDAI ≤ 150	2/10 (20%)	10/17 (58.8%)	0.1	67% Prednisone vs 44% budesonide	Trend towards better efficacy in colonic disease with prednisone, similar efficacy if small bowel involved
(a) Controlled trials of pH-modified release oral budesonide								
Author/ref	N (isolated colonic CD)	Prednisone/comparator	Primary end point	Prednis(ol)one remission rate	Comparator remission rate	p Value		Conclusions
Summers <i>et al</i> ¹⁴³	34 of 295 in trial (Pt 1)	Prednisone up to 60 mg/day (n=8) vs azathioprine 2.5 mg/kg (n=9) vs Sulfasalazine 1 g/15 kg (n=8) vs placebo (n=9)	Week 17 remission	Data presented as rank outcome	6/8 (75%)	0.465	Data presented as rank outcome	Prednisone not effective in colon only disease (but only n=8 treated)
Malchow <i>et al</i> ¹⁴⁴	49 of 215 in trial (induction data from table 11)	Sulfasalazine or combination of sulfasalazine and 6-methyl prednisolone	Remission by week 18	Remission by week 18	4/13 (31%)	<0.01 for Sulfasalazine and 6-methylprednisolone and <0.001 for combination	Placebo 2/14 (14%) Sulfasalazine 4/13 (31%) Combination 13/14 (93%)	All active treatments better than placebo but combination superior to either agent alone
(b) Controlled trials of oral prednis(ol)one								
CD, Crohn's disease; Pt 1, Part 1.								

Table 9 Randomised controlled trials (RCTs) and cohort studies of biological therapy in Crohn's disease where data were provided separately for patients with isolated colonic disease

Author	Year	Type of study	Study agent	Total number of patients	Number with colonic CD	End point	Main findings	p Value (for colonic vs other sites unless stated)	Conclusion
Sandborn <i>et al</i> ¹⁶³	2011	RCT	Certolizumab pegol (CZP)	338	120	Week 6 remission (CDAI \leq 150)	23/63 (36.5%) CZP vs 10/57 (17.5%) placebo	0.052 (colon vs other locations); 0.034 (active vs placebo)	Probable efficacy in colonic disease
Arnett <i>et al</i> ¹⁶⁴	2003	Cohort	Infliximab	74	26	Week 4 response (fall in HBI by >3)	23/26 (88%) response in colonic vs 6/11 (54%) in ileal	0.042	Better efficacy in colonic than ileal
Laharie <i>et al</i> ¹⁶⁵	2005	Cohort	Infliximab	44	18	Week 8 response (fall in CDAI by \geq 100)	83.3% colonic CD vs 50% ileal/ileocolonic	0.03	Better efficacy in colonic than combined ileal/ileocolonic
Vermeire <i>et al</i> ¹⁶⁶	2002	Cohort	Infliximab	240	89	Week 4 (luminal) or week 10 (fistulising) response (fall in CDAI by \geq 70 or 50% decrease in draining fistulae)	81% response colonic CD vs 55% ileal CD vs 74% ileocolonic OR 1.905, 95% CI 1.010 to 3.597	0.046	Better efficacy in colonic than combined ileal/ileocolonic. Remission also more likely in isolated colonic (p=0.019)
Dupont-Lucas <i>et al</i> ¹⁶⁷	2016	Cohort	Infliximab	248 (children)	63	Loss of response to maintenance therapy (moderate or severe global assessment requiring cessation of therapy)	Colonic 25/54 (46%) responders or remitters vs ileal/ileocolonic 148/185 (80%). HR 2.72 (95% CI 1.30 to 5.71) for loss of response in isolated colonic CD vs other sites	0.008	Isolated colonic disease more likely to lose response
Cohen <i>et al</i> ¹⁶⁸	2012	Cohort	Adalimumab	75	15	Time to dose escalation	13.2 weeks for colonic vs 34.6 weeks for other sites	0.0062	Isolated colonic disease required earlier dose escalation
Sandborn <i>et al</i> ¹⁶⁹	2013	RCT	Vedolizumab	1115	316 (273 active, 43 placebo) Subgroup analysis based on 62 active and 43 placebo	Remission (CDAI \leq 150) at week 6 over placebo, response (CDAI fall \geq 100) week 6	Remission difference from placebo: 5.9% for colonic vs 6.7% for ileal vs 8.9% for ileocolonic Response: 10.6% for colonic vs minus 10.4% for ileal vs 7.1% for ileocolonic	0.30 remission 0.23 response	No difference between isolated colonic and other Crohn's for induction with vedolizumab
Sandborn <i>et al</i> ¹⁶⁹	2013	RCT	Vedolizumab	461	117	Remission at week 52 over placebo	Remission 8 weekly vedolizumab: 18.9% difference from placebo for colonic vs 11.8% for ileal vs 19.9% for ileocolonic Remission 4 weekly vedolizumab: 12.7% for colonic vs 25.4% for ileal vs 12% for ileocolonic	0.11 0.19	No difference between isolated colonic and other Crohn's for maintenance with vedolizumab

CD, Crohn's disease; HBI, Harvey Brshaw Index.

Table 10 Results of exclusive enteral nutrition as primary therapy in CD where data provided separately for isolated colonic CD

Author/ref	Year	Nature of study	Adults/children	n=	Intervention	Duration	Primary end point	Results in patients with ileal involvement	Results in isolated colonic CD	p Value
Lochs <i>et al</i> ¹⁷⁵	1991	RCT	Adults	55 (enteral nutrition; 9 colon only); 52 drug treatment	Exclusive Peptisorb (oligopeptide diet)	4–6 weeks	Remission (CDAI reduced by 40% or 100 points)	Mean time until remission 26 days	Mean time until remission 31 days	NS
Wilchanski <i>et al</i> ¹⁷⁶	1996	Retrospective cohort	Children 7–17	65 (5 colon only)	Exclusive amino acid or peptide	4 weeks or more	Remission PCDAI ≤ 20	Remission 47/60 (78%)	Remission 1/5 (20%)	0.02
Alfari <i>et al</i> ¹⁷⁷	2005	Prospective cohort	Children 8–17	65 (14 colon only)	Exclusive polymeric	8 weeks	Remission PCDAI ≤ 20	Remission 43/51 (84%)	Remission 7/14 (50%)	0.01
Buchanan <i>et al</i> ¹⁷⁸	2009	Prospective cohort	ChildrenMedian age 12	110 (19 colon only)	Exclusive polymeric (Modulen) in 105, elemental in 5	8 weeks	Remission (improvement in all domains of global assessment)	Remission 73/91 (80.2%)	Remission 15/19 (78.9%)	NS
Rubio <i>et al</i> ¹⁷⁹	2011	Retrospective cohort	Children Mean age 11	106 (26 colon only)	Exclusive polymeric (Modulen)	8 weeks	Remission PCDAI ≤ 10	Remission 86/106 (81%) overall, colonic data not presented separately but site not correlated with outcome	Remission 8/15 (53%)	NS
de Bie <i>et al</i> ¹⁸⁰	2013	Retrospective cohort	Children Median age 14	76 (18 colon only)	Exclusive polymeric or semi-polymeric	6 weeks	Remission defined as no diarrhoea, pain or weight loss	Remission 32/51 (63%)	Remission 8/15 (53%)	NS

CD, Crohn's disease; NS, not significant; PCDAI, Paediatric Crohn's disease activity index; RCT, randomised controlled trial.

defunctioned colon induced relapse, whereas instillation of content that had passed through a 0.22 micron pore diameter filter did not, implying a role for bacteria in pathogenesis.¹⁸¹ Defunctioning ileostomy is less commonly performed for the treatment of uncomplicated colonic Crohn's disease since it was shown that at least 50% relapsed after continuity was restored.¹⁸²

Resection

The cumulative risk of surgery for isolated colonic Crohn's disease is reported to be 22%–33% 10 years after diagnosis compared with around 75%–90% for ileal disease.^{17 66} Partial resection, either right hemicolectomy for proximal disease or a segmental resection for more distal disease has been shown to be successful therapy for colonic Crohn's disease^{13 183} as is colectomy with ileorectal anastomosis for more extensive disease if the rectum is uninvolved.^{184 185} Approximately 75% of patients with ileorectal anastomosis will still have a functioning anastomosis after 10 years and about two-thirds of those treated by segmental resection will not have required a further resection.¹⁸⁵ Recurrence rates are similar after either procedure.¹⁸⁶ This contrasts with left-sided UC, where the tempting option of left hemicolectomy with right-sided colo-anal anastomosis consistently fails, usually with rapid recurrence of colitis in the retained colon.¹⁸⁷ It should be noted though that segmental resection for colon cancer complicating colonic Crohn's disease has been associated with high (39%) risk for metachronous colon cancer¹⁸⁸ suggesting that panproctocolectomy might be a safer option for such patients.

Ileo-anal pouch reconstruction

Crohn's disease has generally been considered a contraindication for restorative ileo-anal pouch surgery and even in selected patients pouch failure of 57% has been reported from the UK.¹⁸⁹ Others have suggested that it may be successful in very carefully selected patients. Thus, a series of 3707 patients with ileal-pouch anal anastomosis from the Cleveland Clinic included 150 with Crohn's disease, of whom 32 had a preoperative diagnosis, the remainder diagnosed by postoperative histopathology or on follow-up. Among 59 patients with Crohn's disease reaching 10-year follow-up, pouch survival was 80%.¹⁹⁰ Forty-nine of 132 patients (37%) needing pouch excision had a histological diagnosis of Crohn's disease. Considering that a preoperative diagnosis of Crohn's disease was only present in <1% of patients receiving pouch-anal anastomosis, these data do not make a strong case for this procedure in patients with a definite diagnosis of colonic Crohn's disease.

CONCLUSION

Current data suggest that the genetics, microbiota, serology and smoking association of isolated colonic Crohn's disease lie between those of ileo/ileocolonic Crohn's disease and UC and make a strong case for this phenotype being considered separately (table 11). Genetic data in particular show good separation from ileal/ileocolonic Crohn's disease and the low rate of progression from isolated colonic to ileocolonic disease helps to justify this distinction. There is a disappointing paucity of good quality therapeutic data but the lack of response to mesalazine, whose target cell is the surface epithelium, suggests a different pathophysiology to UC and there are important differences from UC in surgical outcomes, including a good response to segmental resection in selected cases and a generally poor response to pouch reconstruction. Taken together, this implies a compelling need for isolated colonic Crohn's disease to be

Table 11 A summary of the distinguishing features of the three IBDs: ileal/ileocolonic CD, isolated colonic CD, UC

	Ileal/ileocolonic CD	Isolated colonic CD	UC
Sex	Slightly commoner in females (55%)	Commoner in females (65%)	Equal or slight male predominance
Genetics	Crohn's-associated genotype including NOD2/CARD15	Genotype midway between CD and UC Associated with HLA-DRB1*01:03 but not NOD2/CARD15	UC-associated genotype including HLA-DRB1*01:03
Smoking	Marked association Worsens prognosis	Weak association Possibly worsens prognosis	Marked negative association
Oral contraception	Positively associated	Positively associated	Positively associated (mainly in smokers)
Serology	ASCA commonly positive pANCA usually negative	ASCA less commonly positive than ileal/ileocolonic CD pANCA positive in minority	ASCA usually negative pANCA commonly positive
Mucosa-associated microbiota	Marked changes commonly including increased Proteobacteria (eg, <i>Escherichia coli</i>) and Fusobacteria, reduced Firmicutes (eg, <i>F. prausnitzii</i>)	Intermediate changes similar to ileal/ileocolonic CD but less consistent	Modest changes, including slight increase in <i>E. coli</i> but no reduction in <i>F. prausnitzii</i>
Response to mesalazine	No efficacy	No efficacy	Good efficacy
Response to anti-TNF	Good efficacy	Good efficacy—probably better than for ileal/ileocolonic	Good efficacy
Response to exclusive enteral nutrition	Good efficacy	Probably good efficacy but mixed reports	No efficacy
Surgery rate and type	Required in majority	Required in minority Segmental colectomy effective High failure for pouch-anal reconstruction	Required in minority Segmental colectomy not effective Low failure for pouch-anal reconstruction

CD, Crohn's disease; ASCA, anti-*Saccharomyces cerevisiae*; HLA, human leucocyte antigen; pANCA, perinuclear antineutrophil cytoplasmic antibodies; TNF, tumour necrosis factor.

identified separately from ileal/ileocolonic disease and from UC. This is particularly important when future therapeutic trials are designed and when cohort studies are reported.

Contributors JMR initiated the review. JMR and SS performed the literature searches and together wrote the first draft. AE advised on the analysis and presentation of epidemiology data. All authors contributed to the writing of the manuscript and approved the final version of the manuscript.

Competing interests SS has received speaker fee from MSD, Actavis, AbbVie, Dr Falk Pharmaceuticals, Shire and received educational grant from MSD, AbbVie, Actavis and is an advisory board member for AbbVie, Dr Falk Pharmaceuticals, Janssen and Vifor Pharmaceuticals. JMR is or has been a member of advisory boards for Atlantic, Pharmacosmos, Procter and Gamble, Vifor and Dr Falk Pharmaceuticals, has received speaking honoraria from Abbott, Dr Falk Pharmaceuticals, Ferring, GlaxoSmithKline, Merck, Procter and Gamble, Schering Plough, Shire and Wyeth and with the University of Liverpool and Proxevix UK, holds a patent for use of a soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent pending for its use in antibiotic-associated diarrhoea.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All relevant data are included in the article.

REFERENCES

- Bargen JA, Weber HM. Regional migratory chronic ulcerative colitis. *Surg Gynecol Obstet* 1930;1:964–72.
- Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathologic and clinical entity. *J Amer Med Assoc* 1932;99:1323–9.
- Moschowitz E, Wilensky AO. Non-specific granulomata of the intestine. *Am J Med Sci* 1923;166:48–66.
- Colp R. A case of nonspecific granuloma of the terminal ileum and caecum. *Surg Clin N America* 1934;14:443–9.
- Crohn BB, Rosenak BD. A combined form of ileitis and colitis. *J Amer Med Assoc* 1936;106:1–7.
- Neuman HW, Bargen JA, Judd ES Jr. A clinical study of two hundred and one cases of regional (segmental) colitis. *Surg Gynecol Obstet* 1954;99:563–71.
- Wells C. Ulcerative colitis and Crohn's disease. *Ann Roy Coll Surg Engl* 1952;11:105–20.
- Goldgraber MB, Kirsner JB, Palmer WL. The histopathology of chronic ulcerative colitis and its pathogenic implications. *Gastroenterology* 1960;38:596–604.
- Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) of the large intestine and its distinction from ulcerative colitis. *Gut* 1960;1:87–105.
- Cornes JS, Stecher M. Primary Crohn's disease of the colon and rectum. *Gut* 1961;2:189–201.
- Truelove SC, Ellis H, Webster CU. The place of a double-barrelled ileostomy in ulcerative colitis and Crohn's disease of the colon: a preliminary report. *Br Med J* 1965;1:150–3.
- Burman JH, Thompson H, Cooke WT, et al. The effects of diversion of intestinal contents on the progress of Crohn's disease of the large bowel. *Gut* 1971;12:11–15.
- Allan A, Andrews H, Hilton CJ, et al. Segmental colonic resection is an appropriate operation for short skip lesions due to Crohn's disease in the colon. *World J Surg* 1989;13:611–14.
- Reese GE, Lovegrove RE, Tilney HS, et al. The effect of Crohn's disease on outcomes after restorative proctocolectomy. *Dis Colon Rectum* 2007;50:239–50.
- Price AB. Overlap in the spectrum on non-specific inflammatory bowel disease—"colitis indeterminate". *J Clin Pathol* 1978;31:567–77.
- Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus and implications. *Gut* 2006;55:749–53.
- Cleynen I, Boucher G, Jostins L, et al. Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study. *Lancet* 2016;387:156–67.
- Hadfield G. The primary histological lesion of regional ileitis. *Lancet* 1939;2:773–5.
- Warren BF. Classic pathology of ulcerative and Crohn's colitis. *J Clin Gastroenterol* 2004;38:S33–5.
- Morson BC. Crohn's disease. *Proc R Soc Med* 1968;61:79–81.
- Krauss E, Agaimy A, Neumann H, et al. Characterization of lymphoid follicles with red ring signs as first manifestation of early Crohn's disease by conventional histopathology and confocal laser endomicroscopy. *Int J Clin Exp Pathol* 2012;5:411–21.
- Bull DM. Crohn's disease of the colon. *Gastroenterology* 1979;76:607–21.
- Cook MG, Dixon MF. An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis. *Gut* 1973;14:255–62.
- Jones JH, Lennard-Jones JE, Morson BC, et al. Numerical taxonomy and discriminant analysis applied to non-specific colitis. *Q J Med* 1973;42:715–32.
- Bentley E, Jenkins D, Campbell F, et al. How could pathologists improve the initial diagnosis of colitis? Evidence from an international workshop. *J Clin Pathol* 2002;55:955–60.
- Fabricius PJ, Gyde SN, Shouler P, et al. Crohn's disease in the elderly. *Gut* 1985;26:461–5.

- 27 Harpaz N, Sachar DB. Segmental colitis associate with diverticular disease and other IBD look-alikes. *J Clin Gastro* 2006;40(S132–5).
- 28 Rubio CA, Orrego A, Nesi G, et al. Frequency of epithelioid granulomas in colonoscopic biopsy specimens from paediatric and adult patients with Crohn's colitis. *J Clin Pathol* 2007;60:1268–72.
- 29 Mahadeva U, Martin JP, Patel NK, et al. Granulomatous ulcerative colitis: a re-appraisal of the mucosal granuloma in the distinction of Crohn's disease from ulcerative colitis. *Histopathology* 2002;41:50–5.
- 30 Louis E, Collard A, Oger AF, et al. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;49:777–82.
- 31 Chow DK, Leong RW, Lai LH, et al. Changes in Crohn's disease phenotype over time in the Chinese population: validation of the Montreal classification system. *Inflamm Bowel Dis* 2008;14:536–41.
- 32 Vester-Andersen MK, Prosser MV, Jess T, et al. Disease course and surgery rates in inflammatory bowel disease: a population-based, 7-year follow-up study in the era of immunomodulating therapy. *Am J Gastroenterol* 2014;109:705–14.
- 33 Louis E, Michel V, Hugot JP, et al. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. *Gut* 2003;52:552–7.
- 34 Lutgens MWMD, van Oijen MGH, van der Heijden GJMG et al. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;19:789–99.
- 35 Kyle J. Crohn's disease in the Northeastern and Northern Isles of Scotland: an epidemiological review. *Gastroenterology* 1992;103:392–9.
- 36 Gunesh S, Thomas GA, Williams GT, et al. The incidence of Crohn's disease in Cardiff over the last 75 years: an update for 1996–2005. *Aliment Pharmacol Ther* 2008;27:211–19.
- 37 Lapidus A, Bernell O, Hellers G, et al. Incidence of Crohn's disease in Stockholm County 1955–1989. *Gut* 1997;41:480–6.
- 38 Chouraki V, Savoye G, Dauchet L, et al. The changing pattern of Crohn's disease incidence in northern France: a continuing increase in the 10- to 19-year-old age bracket (1988–2007). *Aliment Pharmacol Ther* 2011;33:1133–42.
- 39 Gollop JH, Phillips SF, Melton LJ III, et al. Epidemiologic aspects of Crohn's disease: a population based study in Olmsted County, Minnesota, 1943–1982. *Gut* 1988;29:49–56.
- 40 Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Crohn's disease in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gastroenterology* 1998;114:1161–8. Erratum in: *Gastroenterology* 1999;116:1507.
- 41 Humphreys WG, Brown JS, Parks TG. Crohn's disease in Northern Ireland: a retrospective study of 440 cases. *Ulster Med J* 1990;59:30–5.
- 42 Ekborn A, Helmick C, Zack M, et al. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterology* 1991;100:350–8.
- 43 Yapp TR, Stenson R, Thomas GA, et al. Crohn's disease incidence in Cardiff from 1930: an update for 1991–1995. *Eur J Gastroenterol Hepatol* 2000;12:907–11.
- 44 Jayanthi V, Probert CS, Pinder D, et al. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. *Q J Med* 1992;82:125–38.
- 45 Cottone M, Brignola C, Rosselli M, et al. Relationship between site of disease and familial occurrence in Crohn's disease. *Dig Dis Sci* 1997;42:129–32.
- 46 Jacobsen BA, Fallingborg J, Rasmussen HH, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978–2002. *Eur J Gastroenterol Hepatol* 2006;18:601–6.
- 47 Wright JP, Froggatt J, O'Keefe EA, et al. The epidemiology of inflammatory bowel disease in Cape Town 1980–1984. *S Afr Med J* 1986;70:10–15.
- 48 Manninen P, Karvonen AL, Huhtala H, et al. The epidemiology of inflammatory bowel diseases in Finland. *Scand J Gastroenterol* 2010;45:1063–7.
- 49 Economou M, Filis G, Tsianou Z, et al. Crohn's disease incidence evolution in North-western Greece is not associated with alteration of NOD2/CARD15 variants. *World J Gastroenterol* 2007;13:5116–20.
- 50 Rhodes JM, Cockell R, Allan RN, et al. Colonic Crohn's disease and the contraceptive pill. *Br Med J (Clin Res Ed)* 1984;288:595–6.
- 51 Gower-Rousseau C, Salomez JL, Dupas JL, et al. Incidence of inflammatory bowel disease in northern France (1988–1990). *Gut* 1994;35:1433–8.
- 52 Auvin S, Molinié F, Gower-Rousseau C, et al. Incidence, clinical presentation and location at diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in northern France (1988–1999). *J Pediatr Gastroenterol Nutr* 2005;41:49–55.
- 53 Spanish Epidemiological and Economic Study Group on Crohn's disease. Epidemiological and clinical features of Spanish patients with Crohn's disease. *Eur J Gastroenterol Hepatol* 1999;11:1121–7.
- 54 Jess T, Riis L, Vind I, et al. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007;13:481–9.
- 55 Romberg-Camps MJL, Dagnelle PC, Kester ADM, et al. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. *Am J Gastroenterol* 2009;104:371–83.
- 56 Björnsson S, Tryggvason FB, Jónasson JG, et al. Incidence of inflammatory bowel disease in Iceland 1995–2009. A nationwide population-based study. *Scand J Gastroenterol* 2015;50:1368–75.
- 57 Tozun N, Atug O, Imeriyuz N, et al. Members of the Turkish IBD Study Group. Clinical characteristics of inflammatory bowel disease in Turkey: a multicenter epidemiologic survey. *J Clin Gastroenterol* 2009;43:51–7.
- 58 Lakatos L, Kiss LS, David G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002–2006. *Inflamm Bowel Dis* 2011;17:2558–65.
- 59 Nguyen GC, Torres EA, Regueiro M, et al. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol* 2006;101:1012–23.
- 60 Ott C, Obermeier F, Thiel S, et al. The incidence of inflammatory bowel disease in a rural region of Southern Germany: a prospective population-based study. *Eur J Gastroenterol Hepatol* 2008;20:917–23.
- 61 Siddique I, Alazmi W, Al-Ali J, et al. Clinical epidemiology of Crohn's disease in Arabs based on the Montreal Classification. *Inflamm Bowel Dis* 2012;18:1689–97.
- 62 Chen H, Lee A, Bowcock A, et al. Influence of Crohn's disease risk alleles and smoking on disease location. *Dis Colon Rectum* 2011;54:1020–5.
- 63 Lucendo AJ, Hervias D, Roncero O, et al. Epidemiology and temporal trends (2000–2012) of inflammatory bowel disease in adult patients in a central region of Spain. *Eur J Gastroenterol Hepatol* 2014;26:1399–407.
- 64 Henckaerts L, Pierik M, Joossens M, et al. Mutations in pattern recognition receptor genes modulate seroreactivity to microbial antigens in patients with inflammatory bowel disease. *Gut* 2007;56:1536–42.
- 65 Herrinton LJ, Liu L, Lewis JD, et al. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996–2002. *Am J Gastroenterol* 2008;103:1998–2006.
- 66 Hancock L, Beckly J, Geremia A, et al. Clinical and molecular characteristics of isolated colonic Crohn's disease. *Inflamm Bowel Dis* 2008;14:1667–77.
- 67 Aloï M, Lionetti P, Barabino A, et al., SIGENP IBD Group. Phenotype and disease course of early-onset pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2014;20:597–605.
- 68 Aljebreen AM, Alharbi OR, Azzam NA, et al. Clinical epidemiology and phenotypic characteristics of Crohn's disease in the central region of Saudi Arabia. *Saudi J Gastroenterol* 2014;20:162–9.
- 69 Burisch J, Pedersen N, Cukovic-Cavka S, et al. Environmental factors in a population-based inception cohort of inflammatory bowel disease patients in Europe: an ECCO-EpiCom study. *J Crohns Colitis* 2014;8:607–16.
- 70 Eglinton TW, Roberts R, Pearson J, et al. Clinical and genetic risk factors for perianal Crohn's disease in a population-based cohort. *Am J Gastroenterol* 2012;107:589–96.
- 71 Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013;145:158–65.
- 72 Cleyne I, Gonzalez JR, Figueroa A, et al. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut* 2013;62:1556–65.
- 73 Somerville KW, Logan RFA, Edmond M, et al. Smoking and Crohn's disease. *Brit Med J* 1984;289:954–6.
- 74 Holdstock G, Savage D, Harman M, et al. Should patients with inflammatory bowel disease smoke? *Brit Med J* 1984;288:362.
- 75 Tobin MV, Logan RFA, Langman MJS, et al. Cigarette smoking and inflammatory bowel disease. *Gastroenterology* 1987;93:316–21.
- 76 Lindberg E, Järnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and clinical course. *Gut* 1992;33:779–82.
- 77 Breuer-Katschinski B, Hollander N, Goebell H. Effect of cigarette smoking on the course of Crohn's disease. *Eur J Gastroenterol Hepatol* 1996;8:225–8.
- 78 Russel MG, Volovics A, Schoon EJ, et al. Inflammatory bowel disease: is there any relation between smoking status and disease presentation? European Collaborative IBD Study Group. *Inflamm Bowel Dis* 1998;4:182–6.
- 79 Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former smoking on the clinical course of Crohn's disease. *Aliment Pharmacol Ther* 1999;13:1403–11.
- 80 Cosnes J, Nion-Larmurier I, Afchain P, et al. Gender differences in the response of colitis to smoking. *Clin Gastroenterol Hepatol* 2004;2:41–8.
- 81 Aldhous MC, Drummond HE, Anderson N, et al. Does cigarette smoking influence the phenotype of Crohn's disease? Analysis using the Montreal classification. *Am J Gastroenterol* 2007;102:577–88.
- 82 Nunes T, Etchevers MJ, Domènech E, et al. Smoking does influence disease behaviour and impacts the need for therapy in Crohn's disease in the biologic era. *Aliment Pharmacol Ther* 2013;38:752–60.

- 83 Chiveste T, Esterhuizen TM, Basson AR. The influence of second-hand cigarette smoke exposure during childhood and active cigarette smoking on Crohn's disease phenotype defined by the Montreal classification scheme in a western cape population, South Africa. *PLoS ONE* 2015;10:e0139597.
- 84 World Health Organisation. WHO Report on the global tobacco epidemic 2008: The MPOWER package. <http://www.who.int/tobacco/mpower/2008/en/>
- 85 Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;110:424–31.
- 86 To N, Gracie DJ, Ford AC. Systematic review with meta-analysis: the adverse effects of tobacco smoking on the natural history of Crohn's disease. *Aliment Pharmacol Ther* 2016;43:549–61.
- 87 Cornish JA, Tan E, Simillis C, et al. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol* 2008;103:2394–400.
- 88 Vessey M, Jewell D, Smith A, et al. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *Br Med J* 1986;292:1101–3.
- 89 Lashner BA, Kane SV, Hanauer SB. Lack of association between oral contraceptive use and Crohn's disease: a community-based matched case-control study. *Gastroenterology* 1989;97:1442–7.
- 90 Sandler RS, Wurzelmann JI, Lyles CM. Oral contraceptive use and the risk of inflammatory bowel disease. *Epidemiology* 1992;3:374–8.
- 91 Persson PG, Leijonmark CE, Bernell O, et al. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;22:268–72.
- 92 Katschinski B, Fingerle D, Scherbaum B, et al. Oral contraceptive use and cigarette smoking in Crohn's disease. *Dig Dis Sci* 1993;38:1596–600.
- 93 Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut* 2013;62:1153–9.
- 94 Khalili H, Chan AT. Author response: oral contraceptives and Crohn's disease. *Gut* 2015;64:854.
- 95 Kilpatrick ZM, Silverman JF, Betancourt E, et al. Vascular occlusion of the colon and oral contraceptives. Possible relation. *N Engl J Med* 1968;278:438–40.
- 96 Rasmussen DK, Segars LW. Case of ischemic colitis in a young adolescent associated with triphasic hormonal contraceptive therapy: a case report and review of the literature. *W V Med J* 2011;107:22–5.
- 97 Deana DG, Dean PJ. Reversible ischemic colitis in young women. Association with oral contraceptive use. *Am J Surg Pathol* 1995;19:454–62.
- 98 Tedesco FJ, Volpicelli NA, Moore FS. Estrogen- and progesterone-associated colitis: a disorder with clinical and endoscopic features mimicking Crohn's colitis. *Gastrointest Endosc* 1982;28:247–9.
- 99 Tsai HH, Howden CW, Thomson TJ. Probable Crohn's colitis mimicking ischaemic colitis in a young adult. *Scott Med J* 1989;34:406–7.
- 100 Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease. *Gut* 2000;46:140.
- 101 Economou M, Trikalinos TA, Loizou KT, et al. Differential effects of NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a meta-analysis. *Am J Gastroenterol* 2004;99:2393–404.
- 102 Ahmad T, Marshall SE, Jewell D. Genetics of inflammatory bowel disease: the role of the HLA complex. *World J Gastroenterol* 2006;12:3628–35.
- 103 Paul T, Birnbaum A, Pal DK, et al. Distinct phenotype of early childhood inflammatory bowel disease. *J Clin Gastroenterol* 2006;40:583–6.
- 104 Maisawa S, Sasaki M, Ida S, et al. Characteristics of inflammatory bowel disease with an onset before eight years of age: a multicenter epidemiological survey in Japan. *J Gastroenterol Hepatol* 2013;28:499–504.
- 105 Marks DJ, Miyagi K, Rahman FZ, et al. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. *Am J Gastroenterol* 2009;104:117–24.
- 106 Uhlig HH, Schwerdt T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology* 2014;147:990–1007.
- 107 Moran CJ, Klein C, Muise AM, et al. Very early-onset inflammatory bowel disease: gaining insight through focused discovery. *Inflamm Bowel Dis* 2015;21:1166–75.
- 108 Zeissig Y, Petersen BS, Milutinovic S, et al. XIAP variants in male Crohn's disease. *Gut* 2015;64:66–76.
- 109 Elkadri AA, Stempak JM, Walters TD, et al. Serum antibodies associated with complex inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1499–505.
- 110 Zhang Z, Li C, Zhao X, et al. Anti-Saccharomyces cerevisiae antibodies associate with phenotypes and higher risk for surgery in Crohn's disease: a meta-analysis. *Dig Dis Sci* 2012;57:2944–54.
- 111 Kaul A, Hutfless S, Liu L, et al. Serum anti-glycan antibody biomarkers for inflammatory bowel disease diagnosis and progression: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2012;18:1872–84.
- 112 Reese GE, Constantinides VA, Simillis C, et al. Diagnostic precision of anti-Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006;101:2410–22.
- 113 Duerr RH, Targan SR, Landers CJ, et al. Anti-neutrophil cytoplasmic antibodies in ulcerative colitis. Comparison with other colitides/diarrheal illnesses. *Gastroenterology* 1991;100:1590–6.
- 114 Cambridge G, Rampton DS, Stevens TR, et al. Anti-neutrophil antibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1992;33:668–74.
- 115 Joossens S, Reinisch W, Vermeire S, et al. The value of serologic markers in indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002;122:1242–7.
- 116 Lawrance IC, Murray K, Hall A, et al. A prospective comparative study of ASCA and pANCA in Chinese and Caucasian IBD patients. *Am J Gastroenterol* 2004;99:2186–94.
- 117 Annesse V, Piepoli A, Perri F, et al. Anti-Saccharomyces cerevisiae mannan antibodies in inflammatory bowel disease: comparison of different assays and correlation with clinical features. *Aliment Pharmacol Ther* 2004;20:1143–52.
- 118 Ferrante M, Henckaerts L, Joossens M, et al. New serological markers in inflammatory bowel disease are associated with complicated disease behaviour. *Gut* 2007;56:1394–403.
- 119 Vind I, Riis L, Jespersgaard C, et al. Genetic and environmental factors as predictors of disease severity and extent at time of diagnosis in an inception cohort of inflammatory bowel disease, Copenhagen County and City 2003–2005. *J Crohns Colitis* 2008;2:162–9.
- 120 Lakatos PL, Altorjay I, Szamosi T, et al. Pancreatic autoantibodies are associated with reactivity to microbial antibodies, penetrating disease behavior, perianal disease, and extraintestinal manifestations, but not with NOD2/CARD15 or TLR4 genotype in a Hungarian IBD cohort. *Inflamm Bowel Dis* 2009;15:365–74.
- 121 Bogdanos DP, Roggenbuck D, Reinhold D, et al. Pancreatic-specific autoantibodies to glycoprotein 2 mirror disease location and behaviour in younger patients with Crohn's disease. *BMC Gastroenterol* 2012;12:102.
- 122 Bertin D, Grimaud JC, Lesavre N, et al. Targeting tissular immune response improves diagnostic performance of anti-Saccharomyces cerevisiae antibodies (ASCA) in Crohn's disease. *PLoS ONE* 2013;8:e80433.
- 123 Pridaux L, De Cruz P, Ng SC, et al. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2012;18:1340–55.
- 124 Hold G, Smith M, Grange C, et al. Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? *World J Gastro* 2014;20:1192–210.
- 125 Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014;146:1489–99.
- 126 Gevers D, Kugathasan S, Denson LA, et al. The treatment-naïve microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014;15:382–92.
- 127 Baumgart M, Dogan B, Rishniw M, et al. Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum. *ISME J* 2007;1:403–18.
- 128 Willing BP, Dicksved J, Halfvarson J, et al. A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. *Gastroenterology* 2010;139:1844–54.
- 129 Willing BP, Halfvarson J, Dicksved J, et al. Twin studies reveal specific imbalances in the mucosa-associated microbiota of patients with ileal Crohn's disease. *Inflamm Bowel Dis* 2009;15:653–60.
- 130 Lopez-Siles M, Martinez-Medina M, Busquets D, et al. Mucosa-associated Faecalibacterium prausnitzii and Escherichia coli co-abundance can distinguish irritable bowel syndrome and inflammatory bowel disease phenotypes. *Int J Med Microbiol* 2014;304:464–75.
- 131 Naftali T, Reshef L, Kovacs A, et al. Distinct microbiotas are associated with ileum-restricted and colon-involving Crohn's disease. *Inflamm Bowel Dis* 2016;22:293–302.
- 132 Haberman Y, Tickle TL, Dexheimer PJ, et al. Pediatric Crohn's disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 2014;124:3617–33. Erratum in: *J Clin Invest* 2015;125:1363.
- 133 Ford AC, Kane SV, Khan KJ, et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:617–29.
- 134 Lim WC, Hanauer S. Aminosaliclates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010(12):CD008870.
- 135 Moja L, Danese S, Fiorino G, et al. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. *Aliment Pharmacol Ther* 2015;41:1055–65.
- 136 Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2005(1):CD003715.
- 137 Ford AC, Khan KJ, Talley NJ, et al. 5-Aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:413–20.
- 138 Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;104:1293–301.

- 139 International Mesalazine Study Group. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. *Aliment Pharmacol Ther* 1990;4:55–64.
- 140 Prantera C, Pallone F, Brunetti G, et al. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. The Italian IBD Study Group. *Gastroenterology* 1992;103:363–8.
- 141 Gendre JP, Mary JY, Florent C, et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID). *Gastroenterology* 1993;104:435–9.
- 142 de Franchis R, Omodei P, Ranzi T, et al. Controlled trial of oral 5-aminosalicylic acid for the prevention of early relapse in Crohn's disease. *Aliment Pharmacol Ther* 1997;11:845–52.
- 143 Singleton JW, Summers RW, Kern F Jr, et al. A trial of sulfasalazine as adjunctive therapy in Crohn's disease. *Gastroenterology* 1979;77:887–97.
- 144 Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847–69.
- 145 Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;86:249–66.
- 146 Mahmud N, Kamm MA, Dupas JL, et al. Olsalazine is not superior to placebo in maintaining remission of inactive Crohn's colitis and ileocolitis: a double blind, parallel, randomised, multicentre study. *Gut* 2001;49:552–6.
- 147 Khan, KJ, Ullman TA, Ford AC et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:661–73.
- 148 Nitzan, O., Elias M, Peretz A et al. Role of antibiotics for treatment of inflammatory bowel disease. *World J Gastroenterol* 2016;22:1078–87.
- 149 Su JW, Ma JJ, Zhang HJ. Use of antibiotics in patients with Crohn's disease: a systematic review and meta-analysis. *J Dig Dis* 2015;16:58–66.
- 150 Prantera C, Lochs H, Grimaldi M, et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. *Gastroenterology* 2012;142:473–81.
- 151 Blichfeldt P, Blomhoff JP, Myhre E, et al. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand J Gastroenterol* 1978;13:123–7.
- 152 Sutherland L, Singleton J, Sessions J, et al. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991;32:1071–5.
- 153 Steinhart AH, Feagan BG, Wong CJ, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology* 2002;123:33–40.
- 154 Selby W, Pavli P, Crotty B, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and cefazolin for Crohn's disease. *Gastroenterology* 2007;132:2313–19.
- 155 Tromm A, Bunganic I, Tomsava E, et al. Budesonide 9 mg is at least as effective as mesalazine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;140:425–34.
- 156 Bar-Meir S, Chowers Y, Lavy A, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology* 1998;115:835–40.
- 157 Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029–35.
- 158 Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541–9.
- 159 Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;130:323–33.
- 160 Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;56:1232–9.
- 161 Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;146:829–38.
- 162 Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52–65.
- 163 Sandborn WJ, Schreiber S, Feagan BG, et al. Certolizumab pegol for active Crohn's disease: a placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol* 2011;9:670–8.
- 164 Arnett ID, McNeill G, Satsangi J. An analysis of factors influencing short-term and sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther* 2003;17:1451–7.
- 165 Laharie D, Salzmann M, Boubekeur H, et al. Predictors of response to infliximab in luminal Crohn's disease. *Gastroenterol Clin Biol* 2005;29:145–9.
- 166 Vermeire S, Louis E, Carbonez A, et al. Demographic and clinical parameters influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment in Crohn's disease. *Am J Gastroenterol* 2002;97:2357–63.
- 167 Dupont-Lucas C, Sternszus R, Ezri J, et al. Identifying patients at high risk of loss of response to infliximab maintenance therapy in paediatric Crohn's disease. *J Crohns Colitis* 2016;10:795–804.
- 168 Cohen RD, Lewis JR, Turner H, et al. Predictors of adalimumab dose escalation in patients with Crohn's disease at a tertiary referral center. *Inflamm Bowel Dis* 2012;18:10–16.
- 169 Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711–21.
- 170 Kansal S, Wagner J, Kirkwood CD, et al. Enteral nutrition in Crohn's disease: an underused therapy. *Gastroenterol Res Pract* 2013;2013:482108.
- 171 Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 2015;148:1087–106.
- 172 El-Matary W, Otley A, Critch J, et al. Enteral feeding therapy for maintaining remission in Crohn's disease: a systematic review. *J Parenter Enteral Nutr* 2015; Dec 8. pii: 0148607115621051.
- 173 Dickinson RJ, Ashton MG, Axon AT, et al. Controlled trial of intravenous hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute colitis. *Gastroenterology* 1980;79:1199–204.
- 174 González-Huix F, Fernández-Bañares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;88:227–32.
- 175 Lochs H, Steinhardt HJ, Klaus-Wentz B, et al. Comparison of enteral nutrition and drug treatment in active Crohn's disease. Results of the European Cooperative Crohn's Disease Study. IV. *Gastroenterology* 1991;101:881–8.
- 176 Wilschanski M, Sherman P, Pencharz P, et al. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996;38:543–8.
- 177 Afzal NA, Davies S, Paintin M, et al. Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci* 2005;50:1471–5.
- 178 Buchanan E, Gaunt WW, Cardigan T, et al. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009;30:501–7.
- 179 Rubio A, Pigneur B, Garnier-Lengliné H, et al. The efficacy of exclusive nutritional therapy in paediatric Crohn's disease, comparing fractionated oral vs. continuous enteral feeding. *Aliment Pharmacol Ther* 2011;33:1332–9.
- 180 de Bie C, Kindermann A, Escher J. Use of exclusive enteral nutrition in paediatric Crohn's disease in the Netherlands. *J Crohn's Colitis* 2013;7:263–70.
- 181 Harper PH, Lee EC, Kettlewell MG, et al. Role of the faecal stream in the maintenance of Crohn's colitis. *Gut* 1985;26:279–84.
- 182 Harper PH, Truelove SC, Lee EC, et al. Split ileostomy and ileocolostomy for Crohn's disease of the colon and ulcerative colitis: a 20 year survey. *Gut* 1983;24:106–13.
- 183 Andersson P, Olaison G, Hallböök O, et al. Segmental resection or subtotal colectomy in Crohn's colitis? *Dis Colon Rectum* 2002;45:47–53.
- 184 Bernell O, Lapidus A, Hellers G. Recurrence after colectomy in Crohn's colitis. *Dis Colon Rectum* 2001;44:647–54.
- 185 Martin ST, Vogel JD. Restorative procedures in colonic Crohn's disease. *Clin Colon Rectal Surg* 2013;26:100–5.
- 186 Kiran RP, Nisar PJ, Church JM, et al. The role of primary surgical procedure in maintaining intestinal continuity for patients with Crohn's colitis. *Ann Surg* 2011;253:1130–5.
- 187 Schwarz RJ, Pezim ME. Failure of right-sided coloanal anastomosis for treatment of left-sided ulcerative colitis. Report of a case. *Dis Colon Rectum* 1991;34:618–21.
- 188 Maser EA, Sachar DB, Kruse D, et al. High rates of metachronous colon cancer or dysplasia after segmental resection or subtotal colectomy in Crohn's colitis. *Inflamm Bowel Dis* 2013;19:1827–32.
- 189 Tekkis PP, Heriot AG, Smith O, et al. Long-term outcomes of restorative proctocolectomy for Crohn's disease and indeterminate colitis. *Colorectal Dis* 2005;7:218–23.
- 190 Fazio VW, Kiran RP, Remzi FH, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg* 2013;257:679–85.