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

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3 **Recent advances in clinical practice: a systematic review of isolated colonic Crohn's**
4 **disease – the third inflammatory bowel disease?**
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ABSTRACT

The genetics of isolated colonic Crohn's disease place it approximately midway between Crohn's disease with small intestinal involvement and ulcerative colitis, 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 ulcerative colitis, no response to mesalazine, but possibly better response to anti-TNF than Crohn's disease at other sites. Diagnostic distinction from ulcerative colitis 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 involvement² although non-tuberculous granulomatous involvement of ileum and colon had been reported in 1923³ and later by others.^{4,5} From the 1930's to the 1950's, 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 ulcerative colitis.⁸ Identification of Crohn's disease of the colon separately from ulcerative colitis was strongly reinforced by Lockhart-Mummery and Morson, (1960) who described 25 cases with features including non-bloody diarrhoea, anal fistulae, rectal sparing, skip lesions and strictures.⁹ 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 Stecher reported 45 patients with isolated colonic Crohn's disease, with fistulation in nearly two thirds, and skip lesions in 20%.¹⁰

Later evidence that colonic Crohn's disease, unlike ulcerative colitis, 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 ulcerative colitis.

Distinction of colonic Crohn's disease from ulcerative colitis 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 "inflammatory bowel disease unclassified" (IBD-U) was recommended for such cases.¹⁶

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3 The scene is now changing again – extensive data show that isolated colonic Crohn’s disease
4 is genetically separable from Crohn’s disease involving the small intestine.¹⁷ When the ratio
5 of Crohn’s-associated genes to ulcerative colitis-associated is compared with disease
6 phenotype isolated colonic Crohn’s disease lies approximately midway between ileal
7 Crohn’s and ulcerative colitis. IBD-U, although statistically separable from ulcerative colitis
8 overlaps it considerably and ileo-colonic Crohn’s disease similarly overlaps ileal Crohn’s
9 disease (Figure 1). This finding led to recommendation that Crohn’s disease with ileal
10 involvement (ileal and ileocolonic), isolated colonic Crohn’s disease and ulcerative colitis
11 should be considered as three separate conditions.
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15 It is therefore timely to review the epidemiology, genetics, serology, microbiology, and
16 response to treatment of isolated colonic Crohn’s disease and to reconsider whether this
17 “evidence” favours isolated colonic Crohn’s disease as a variant of Crohn’s disease, as a
18 variant of ulcerative colitis, or as a separate condition.
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20 21 **METHODS**

22 The medical literature was searched using National Library of Medicine/Pubmed to 1st
23 December 2015 using the terms “colonic and Crohn’s” “Crohn’s and colitis” “epidemiology
24 and Crohn’s”. We conducted additional searches for “smoking and Crohn’s disease” and
25 “oral contraception and Crohn’s”. Later (to 1st June 2016) additional searches for “Crohn’s”
26 and each of the therapies covered were performed. After removal of duplicates and
27 screening of abstracts for relevance, 840 were selected for further review (Supplementary
28 Figures 1 & 2). Whilst the literature search was fully systematic, the subject of this review is
29 necessarily much broader than that of a conventional systematic review. We have only
30 included full publications in English language and have not attempted to judge quality of the
31 data. For epidemiological studies we included all reports that (a) contained data on at least
32 100 patients with Crohn’s disease and (b) included separate data for isolated colonic
33 Crohn’s disease (Montreal classification L2). Where published studies had overlapping
34 patient base and time period we used only the more completely described data set to avoid
35 duplication. For other aspects of the review (genetics, serological testing, response to
36 therapies and association with environmental factors) we included all studies that identified
37 isolated colonic Crohn’s disease separately. For therapeutic studies we have separately
38 identified data that have been obtained from randomized clinical trials and those that have
39 been obtained from cohort studies. It should be noted that, whereas pure ileal Crohn’s and
40 pure colonic Crohn’s should be readily distinguished by a comprehensive diagnostic
41 assessment including ileal intubation, incomplete assessment could mislabel ileocolonic as
42 colonic. This should be taken into account particularly in respect of older studies but we
43 have taken care to ensure that all data included here regarding isolated colonic disease
44 relate to patients thought at the time of publication not to have ileal disease. Statistical
45 analysis was performed using StatsDirect3 v 3.0.171 StatsDirect Ltd, UK.
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51 **PATHOLOGY, DIFFERENTIAL DIAGNOSIS, AND DISEASE COURSE – DEFINING THE** 52 **CONDITION**

53 The histological features of isolated colonic Crohn’s disease were first defined by Lockhart-
54 Mummery and Morson.⁹ They labeled patients with this diagnosis because “they had the
55 same characteristic pathology in the large intestinal lesions as that described by Hadfield¹⁸
56 for the disease as it affects the small intestine”. Gross appearances of the colon following
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3 colectomy include less sharp demarcation of ulceration than typically seen in ulcerative
4 colitis and with areas of intact intervening mucosa. In some cases, very marked fibrous
5 thickening with associated stricturing was present. Fibrosis and oedema sometimes
6 extended into the pericolic fat and enlargement of regional lymph nodes was marked.
7 Warren later split the macroscopic features into three patterns: isolated rectal disease;
8 stricturing colonic disease; diffuse colitis – usually with rectal sparing, and noted that
9 approximately 75% develop perianal pathology during their disease course.¹⁹
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12 Microscopic features described by Morson included discontinuous inflammation and
13 ulceration which could extend into the submucosa or deeper into the wall as the basis of
14 fistula formation, plus focal crypt irregularity. Non-caseating epithelioid granulomas were
15 present in the majority, distributed through all layers of the bowel wall as well as regional
16 lymph nodes. Other features included submucosal lymphangiectasia and neuromatous
17 hyperplasia.²⁰ It has subsequently been noted that the earliest lesions – aphthous ulcers –
18 which usually overlie lymphoid follicles, are preceded by a “red ring” sign on colonoscopy,
19 biopsy of which reveals a lymphoid follicle surrounded by reactive hypervascularisation.²¹
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23 Histopathology alone is diagnostic only in the minority – in a series of 103 cases of Crohn’s
24 colitis, diagnosis was determined by microscopy alone in 28%, by distribution (rectal sparing
25 and/or discontinuity) alone in 22% and by combination of the two in 50%.²² Particularly
26 discriminatory features suggesting Crohn’s colitis rather than ulcerative colitis include
27 granulomata, submucosal inflammation, and relative preservation of goblet cells.^{23,24} At an
28 international workshop expert pathologists “correctly” identified only 64% of cases with
29 Crohn’s colitis and 74% with ulcerative colitis²⁵ leading the European consensus on
30 histopathology of inflammatory bowel disease (2013) to note that “accurate discrimination
31 between the two diseases (Crohn’s colitis and ulcerative colitis) is not yet optimal amongst
32 expert gastrointestinal pathologists”. Given that inflammatory disease pathogenesis is
33 multifactorial an alternative interpretation would be that there is a continuous phenotypic
34 spectrum that runs through from “typical” ulcerative colitis, through IBD-unclassified to
35 “typical” Crohn’s colitis.
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39 Early studies reported an additional incidence peak of Crohn’s disease in the elderly
40 resulting from cases particularly affecting the sigmoid colon.²⁶ Following the later
41 clarification of segmental colitis associated with diverticular disease (SCAD) this seems
42 probably attributable to SCAD. SCAD can be indistinguishable histologically from
43 inflammatory bowel disease and includes a “Crohn’s-like” variant with granulomata.²⁷ This
44 reflects emphasis often placed on the diagnostic specificity of the granuloma. However,
45 granulomas are only found in colonoscopic biopsies at diagnosis in about 66% of adults with
46 colonic Crohn’s disease, falling to 18% at follow-up.²⁸ Moreover granulomas, particularly in
47 association with crypts, can be found in ulcerative colitis.²⁹ Other forms of colitis that may
48 need to be considered in the differential include ischemic colitis (see earlier) and infections
49 including amoebiasis and tuberculosis but it is beyond the scope of this review to consider
50 these further.
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55 Localisation of disease to the colon remains fairly constant over time. The largest published
56 data set by far is the 16,902 Crohn’s disease cohort, including 2,933 with isolated colonic
57 disease, in the recent genotype/phenotype association study.¹⁷ This confirmed previous
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reports of low rates of progression to ileo-colonic 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, eg 0/45 cases in a Belgian series³³ whereas penetrating disease (B3) as defined by the Vienna classification (ie including perianal fistulae) occurred in 23% in the same series, less frequently than in patients with ileal disease (46%; $P=0.0003$) or ileocolonic (28.6%; NS). The much larger genotype/phenotype association study confirmed that cumulative probability of progression to B2 and B3 combined over ten 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 ten years (22%) than for ileo-colonic (42%) or ileal disease (62%). A recent meta-analysis showed that colon cancer risk in isolated colonic Crohn's disease is similar to ulcerative colitis of equivalent extent with a pooled standardized incidence ratio (SIR) of 1.7; 0.9-2.6 95%CI (population based data) compared with SIR 1.8; 1.2-2.4 for ulcerative colitis but rising to SIR 18.2; 7.8-35.8 for extensive colonic Crohn's disease in a referral centre population compared with SIR 21.6; 15.0-31.0 for extensive ulcerative colitis.³⁴

EPIDEMIOLOGY

Changes over time

Studies reporting sequential data from a single centre or region show interesting time trends. Studies from 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 which 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 – eg median 25 years in the 16,902 patients studied by Cleynen et al¹⁷. Older age of isolated colonic versus other sites of Crohn's disease was also confirmed by the IBDchip European Project.⁸⁵ The preponderance of isolated colonic disease amongst children with very early onset Crohn's disease is discussed later.

Smoking

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3 Cigarette smoking is associated with increased risk for development and progression of
4 Crohn's disease but reduced risk for ulcerative colitis. Smoking is more strongly associated
5 with risk for ileal and ileo-colonic Crohn's disease than for isolated colonic disease (Table 2).
6 Only one study (of nine)⁷⁹ reported a higher rate of smoking amongst patients with isolated
7 colonic Crohn's disease. If the South African data⁸⁴ which reported exceptionally high rates
8 (73%) across all groups are excluded, the other studies report rates for smoking amongst
9 patients with isolated colonic disease that averaged 37.8% compared with 49.8% (P=0.008
10 by paired t test) for other Crohn's disease sites. This smoking rate is probably slightly higher
11 than for the general population – approximately 30% European adults were smokers in 2008
12 (WHO).⁸⁶

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16 Smoking worsens prognosis of Crohn's disease overall and cessation of smoking improves
17 it.^{87,88} This has been studied less in isolated colonic disease but the conclusion is similar. The
18 largest study⁸⁰ included 688 patients with Crohn's colitis, 978 with ulcerative colitis and 118
19 with "indeterminate" colitis. Sixty-one per cent of patients with ulcerative colitis or
20 indeterminate colitis had stopped smoking before disease onset compared with only 12% in
21 isolated colonic Crohn's disease. In women but not men with isolated colonic disease the
22 risk of needing immunosuppression was increased amongst smokers (10-yr cumulative risk
23 48% in non-smokers vs 58% in smokers, P<0.01). An earlier study⁷⁴ showed that smokers
24 with Crohn's colitis relapsed approximately 50% more often (P=0.028) and with more pain
25 (P<0.007) than non-smokers.

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

31 32 33 **Oral contraception**

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35 Meta-analysis of 14 studies, with adjustment for smoking, showed a relative risk of 1.51
36 (95%CI 1.17-1.96, P=0.002) for Crohn's disease amongst women currently taking oral
37 contraception⁸⁹. The relative risk for ulcerative colitis was also increased at 1.53 (1.21-1.94,
38 P=0.001). Six of the seven studies that reported risk associated with oral contraception
39 separately for isolated colonic disease found a significant association (Table 3) with
40 relatively high odds ratio (2.63), risk ratios (3.6 and 3.23) or hazard ratio (4.13). The sole
41 exception⁹¹ only included 8 cases with isolated colonic Crohn's disease and showed no
42 overall association between oral contraception and risk for Crohn's disease. Excluding the
43 latter study⁹¹, five of the other six show higher risks amongst oral contraceptive users for
44 isolated colonic Crohn's than for other sites.

45 46 47 *Oestrogen-associated ischaemic colitis as a confounder*

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50 An early study from Birmingham⁵⁰ reported patients with apparent oral contraceptive-
51 associated colonic Crohn's disease who had non-granulomatous colitis with rectal sparing.
52 Ischaemic colitis is a rare but recognized complication of oral contraception that might
53 cause diagnostic confusion.^{97,98,99} Most cases have a short duration with typical features of
54 ischaemic colitis including abdominal pain, and rectal bleeding. Colonoscopy shows mucosal
55 friability but no linear ulceration and the proximal colon and rectum are typically normal.
56 Such cases should be readily distinguishable from colonic Crohn's disease but Tedesco¹⁰⁰

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3 reported five cases of oral contraceptive-associated colitis with features that overlapped
4 more with colonic Crohn's disease than ischaemic colitis. Moreover, colonic
5 "thumbprinting", a characteristic feature of ischaemic colitis, has been reported in Crohn's
6 disease.¹⁰¹ It is unclear whether diagnostic overlap with milder cases of oral contraceptive-
7 associated ischaemic colitis contributes to the female preponderance of isolated colonic
8 Crohn's disease. If it does then the change to lower oestrogen dosing in later versions of the
9 contraceptive pill might be a plausible explanation for the apparent fall off in cases in recent
10 decades.¹⁰² Clinicians should be aware of the possible associations between oral
11 contraception and inflammatory bowel disease or ischaemic colitis and advise patients
12 accordingly – such advice should usually include at least a temporary cessation of oral
13 contraception to assess impact on the colitis.
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16 17 18 **GENETICS**

19 The strongest genetic association with IBD is the link between NOD2/CARD15 and Crohn's
20 disease. Meta-analysis of 42 studies showed that this association was stronger for Crohn's
21 disease with small bowel involvement than for those without (OR 2.53; 95%CI 2.01-3.16).¹⁰³
22 Subsequent study of 1528 patients with Crohn's disease from 8 centres (in 7 European
23 countries) (IBDchip) confirmed the association of NOD2/CARD15 with ileal involvement and
24 also showed that Interleukin23 receptor polymorphisms were more strongly associated with
25 isolated colonic Crohn's (OR 2.20; 95%CI 1.17-4.57).⁸⁵
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28 The most consistent genetic link with ulcerative colitis is with the rare Major
29 histocompatibility Complex (MHC) / Human Leucocyte Antigen (HLA) Class II allele HLA-
30 DRB*0103. This occurs in less than 2% in European and white North American populations
31 and is absent in the Japanese. It is strongly associated with colonic Crohn's disease where it
32 is present at up to 32% frequency with Odds Ratios for isolated colonic disease of 5.1-18.5
33 compared with Crohn's disease at other sites.¹⁰⁴
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36 The largest study to compare genetic associations with Crohn's disease phenotype included
37 19713 patients from 49 centres across 16 countries in Europe, North American and
38 Australasia.¹⁷ This confirmed that the strongest association with isolated colonic Crohn's
39 disease was HLA-DRB1*01:03 ($p=1.47 \times 10^{-23}$, ileal vs colonic OR 0.32, 95%CI 0.29-0.41;
40 ileocolonic vs colonic OR 0.47, 95%CI 0.39-0.57). The only other loci that were significant
41 across all analyses in this study were NOD2 (16q12), again associated with increased risk for
42 ileal involvement (OR ileocolonic vs colonic 1.61, 1.59, and 1.89 for the three NOD2
43 polymorphisms tested) and also MST1 (macrophage stimulating -1 that encodes a protein
44 which induces macrophage phagocytosis) polymorphisms which were more weakly
45 associated with ileal involvement (OR 1.07 -1.10 according to polymorphism and whether
46 comparing ileal or ileocolonic with colonic disease). When overall genetic risk scores for
47 Crohn's disease and ulcerative colitis were computed as a ratio and compared with
48 phenotype, isolated colonic Crohn's disease was found to be approximately "balanced" in
49 respect of Crohn's disease versus ulcerative colitis genetic risk factors (Figure 1). It was
50 found though that even the combination of smoking status with the strongest genetic
51 predictors could only explain 6.8% of the variance for disease location.
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56 **ISOLATED COLONIC CROHN'S DISEASE IN CHILDHOOD AND SINGLE GENE DISORDERS**

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3 Amongst children with very early onset Crohn's disease there is a marked preponderance of
4 cases with isolated colonic disease eg 76.5% before age 5¹⁰⁵ and 42% before age 8.¹⁰⁶
5 Amongst younger cases there is a strong male preponderance – eg 1.6:1 across all Crohn's
6 disease presenting <5¹⁰⁵ and some of this is accounted for by X-linked single gene disorders.
7 The first such condition to be identified was X-linked Chronic Granulomatous Disease.
8 Chronic Granulomatous Disease is associated with defects in neutrophil function leading to
9 skin lesions and in around 40% with a form of inflammatory bowel disease that is
10 indistinguishable from Crohn's disease, typically with predominant colorectal and perianal
11 involvement.¹⁰⁷ It is due to mutations in one of four NADPH oxidase complex component
12 genes of which the commonest (CYBB) located on the X chromosome accounts for about
13 65% cases.
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17 Rapid developments in DNA sequencing have allowed identification of over 50 further single
18 gene disorders that present as inflammatory bowel disease, typically as colonic disease and
19 with presentation before age 6, defined as Very Early Onset IBD or VEO-IBD.¹⁰⁸ VEO-IBD
20 cases account for 4-10% of paediatric inflammatory bowel disease.¹⁰⁹ One of the commoner
21 single gene variants is in the coding region of X-linked inhibitor of apoptosis protein (XIAP)
22 that accounts for about 4% of male patients with paediatric onset Crohn's disease.¹¹⁰
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27 **SEROLOGY INCLUDING ANTI-MICROBIAL AND ANTI-NEUTROPHIL ANTIBODIES**

28 Anti-microbial antibodies such as Anti-Saccharomyces cerevesiae (ASCA) and antibodies to
29 outer membrane protein (ompC) are found less often and/or at lower titre in isolated
30 colonic Crohn's than in other Crohn's phenotypes.¹¹¹ Meta-analyses confirm this particularly
31 for ASCA.¹¹²⁻¹¹⁴ Average sensitivity of ASCA for isolated colonic Crohn's disease diagnosis is
32 31% but with a wide range (8-59%) and an average 14% positivity rate in ulcerative colitis
33 (Table 4). The clinical utility of ompC antibodies has been less studied but reported
34 positivity/sensitivity in isolated colonic Crohn's disease is substantially lower than that for
35 ASCA.
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38 Anti-neutrophil antibodies, particularly an atypical peri-nuclear antibody (pANCA), are
39 present in around 55% of patients with ulcerative colitis¹¹⁴ and 23% of patients with isolated
40 colonic Crohn's disease (Table 4). This compares with pANCA positivity of around 11% in
41 Crohn's disease overall and 3% in non-IBD controls.¹¹⁴
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44 A combination of positive ASCA and negative pANCA is more discriminatory eg positivity
45 rate in isolated colonic Crohn's disease of 52% compared with 9% in ulcerative colitis¹²² but
46 is still insufficiently predictive for routine clinical use.¹²⁵
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49 Thus the frequency in isolated colonic Crohn's disease of both ASCA and pANCA antibodies
50 lies somewhere in between that found in Crohn's disease with ileal involvement (more likely
51 ASCA+, and pANCA-) and that found in ulcerative colitis (more likely ASCA- and pANCA+).
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54 **MICROBIOTA**

55 The faecal microbiota in active inflammatory bowel disease is commonly dysbiotic with
56 reduced bacterial diversity.^{126,127} This could be secondary to inflammation yet still significant
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3 in maintaining chronicity. The large study of pre-treatment Crohn's disease by Gevers
4 showed only a mild dysbiosis in the faecal microbiota and much greater separation of
5 Crohn's disease from healthy controls when the mucosa-associated microbiota was
6 studied.¹²⁸ Ileal and rectal mucosal samples typically showed a reduction in *Firmicutes* such
7 as *Faecalibacterium prausnitzii* and an increase in *Proteobacteria* such as *Escherichia coli* as
8 well as in *Veillonella*, *Haemophilus* and *Fusibacteria*. This confirmed many previous studies
9 showing an increase in mucosa-associated *E. coli* in Crohn's disease as well as several
10 showing a reduction in *F. prausnitzii*¹²⁹⁻¹³².

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13 The faecal and mucosa-associated microbiota in isolated colonic Crohn's disease are
14 generally closer to that of healthy controls than is found in patients with ileal or ileocolonic
15 Crohn's disease (Table 5). Thus Baumgart *et al*¹²⁹ found that an increase in ileal mucosa-
16 associated *E. coli* and reduction in ileal *F. prausnitzii* was only present in patients with
17 Crohn's disease who had ileal involvement and not in those with isolated colonic disease.
18 Similarly, a study of twins with/without Crohn's disease showed that faecal microbial
19 diversity was only reduced and *Proteobacteria* increased in patients with ileal involvement
20 and not in patients with isolated colonic disease.¹³⁰ A previous report by the same group
21 also showed a reduction in *F. prausnitzii* in Crohn's patients with ileal involvement but not in
22 isolated colonic disease.¹³¹ Both the twin study by Willing¹³¹ and the large study in
23 children¹²⁸ and adolescents¹³⁴ did however show differences between the mucosa-
24 associated microbiota in isolated colonic Crohn's disease and ulcerative colitis. 16sRNA
25 pyrosequencing of mucosal samples¹³³ confirms the increase in *E. coli* and reduced *F.*
26 *prausnitzii* in Crohn's disease with ileal involvement with milder changes in isolated colonic
27 disease, although the latter did show some reduction in *F. prausnitzii* compared with
28 healthy controls. This study also confirmed that the mucosa-associated microbiota are
29 consistent at different sites from ileum to rectum in the same individual.

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

36 37 38 39 40 41 42 43 **RESPONSE TO TREATMENT**

44 45 **Mesalazine**

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47 Systematic reviews show no convincing benefit of oral mesalazine (5-aminosalicylic acid)
48 over placebo either in induction of remission or in maintenance of medically induced
49 remission in Crohn's disease as a whole^{134,138} although they may have a modest benefit in
50 maintaining surgically-induced remission.¹³⁹ Sulphasalazine (sulphapyridine linked via azo
51 bond to 5-aminosalicylate) has possible modest efficacy in induction of remission.^{134, 136}

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55 Amongst trials that have reported data separately for isolated colonic Crohn's disease, only
56 one trial studied the effect of oral mesalazine in remission induction¹⁴⁰ and four studied its
57 effect in maintenance of medically-induced remission¹⁴¹⁻¹⁴⁴ (Table 6). In none of these was
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mesalazine significantly more effective than placebo but in two studies^{141,142} 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 diarrhea.¹⁴⁵ Sulphasalazine was no better than placebo in two trials of maintenance^{146,147} but there was a weak signal of efficacy in remission induction in two trials^{147,148} but 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. Sulphasalazine 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 though these have included diverse antibiotics and small trials.¹⁴⁹⁻¹⁵¹ The largest study to date is for rifaximin.¹⁵² Three doses were tested: 400, 800, 1200mg or placebo twice daily for 12 weeks with good efficacy overall but no dose response. Amongst 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 (Blichfeldt¹⁵³: n=6 crossover; Sutherland¹⁵⁴: 8 active and 4 placebo). In a study of 134 patients randomly assigned to ciprofloxacin and metronidazole, both 500mg twice daily, or placebo in combination with budesonide 9mg daily¹⁵⁵ 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 randomized 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).¹⁵⁶ No differential response was seen according to disease location but data were not presented separately for patients with isolated colonic disease.

Rifaximin and metronidazole thus show some evidence of efficacy in patient 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.^{147,148} Each of these included only 8 steroid-treated patients with isolated colonic disease (Table 8) with one trial¹⁴⁷ showing no benefit and the other¹⁴⁸ showing efficacy. There has never been a trial to assess dose-responsiveness to

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3 conventional corticosteroids in Crohn's disease so optimal dosage is unknown. More data
4 are available for budesonide but trials have focused predominantly on patients with ileal or
5 ileo-colonic disease so data in isolated colonic disease are again very sparse. The data from
6 one comparison with mesalazine¹⁵⁷, support efficacy in isolated colonic Crohn's disease,
7 possibly with a weaker effect than conventional corticosteroids¹⁵⁸, but reduced
8 corticosteroid side-effects.
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10 11 12 13 **Anti-TNF**

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17 None of the randomised trials of infliximab^{159,160} or adalimumab¹⁶¹⁻¹⁶⁴ reported subgroup
18 analyses of outcomes based on disease location. In a randomised, placebo controlled trial of
19 certolizumab pegol, patients with colonic (OR 2.39, 95% CI 0.99-5.75, P=0.052) and
20 ileocolonic disease (OR 2.07, 95% CI 1.01-4.28, P=0.048) were more likely to achieve
21 remission at week 6 compared to ileal disease (OR 0.42, 95% CI=0.18-0.99, P=0.048)¹⁶⁵ (Table
22 9)
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25 Several cohort studies have assessed colonic disease location as a predictor of response to
26 anti-TNF agents, four with infliximab and one with adalimumab. Three cohort studies
27 assessing induction therapy with infliximab¹⁶⁶⁻¹⁶⁸ all showed better response rates in
28 isolated colonic disease than for disease at other sites. Paradoxically, cohort studies of
29 infliximab maintenance in children¹⁶⁹ and of adalimumab maintenance in adults¹⁷⁰ both
30 showed higher risk of lost response or dose escalation in isolated colonic disease. Overall,
31 the evidence supports good efficacy for anti-TNF therapy in induction of remission in
32 isolated colonic Crohn's disease but possibly with a higher subsequent rate of loss of
33 response.
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36 37 **Vedolizumab**

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39 In the combined induction and maintenance study of vedolizumab there was no significant
40 difference in efficacy in isolated colonic disease compared with other locations.¹⁷¹ (Table 9)
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42 43 **Enteral nutrition**

44 Exclusive enteral nutrition is effective as primary therapy in patients with active Crohn's
45 disease^{172,173} and partial enteral nutrition has shown efficacy in maintenance of remission.¹⁷⁴
46 In ulcerative colitis total parenteral nutrition and bowel rest are ineffective¹⁷⁵ and
47 comparison of enteral with parenteral nutrition showed no difference in efficacy¹⁷⁶ implying
48 no efficacy for enteral nutrition either. Whether enteral nutrition is effective as primary
49 therapy in isolated colonic Crohn's disease is controversial. Relatively few studies provide
50 separate data on patients with isolated colonic Crohn's disease (Table 10). Five of the six
51 studies are in children. Two studies^{178,179} report poorer results in children with isolated
52 colonic disease compared with those with small intestinal involvement. Numbers are small
53 though (19 cases of isolated colonic disease across the two trials) and the other studies
54 (including 72 cases of isolated colonic disease across four trials) found no significant
55 difference in remission rates for those with isolated colonic disease compared with other
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3 sites. Further trials of exclusive enteral nutrition are needed in patients with isolated colonic
4 disease.
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6 7 **Surgery**

8 *Faecal diversion*

9 Colonic Crohn's disease commonly responds to "bowel rest" induced by a defunctioning
10 ileostomy whereas ulcerative colitis does not.^{11, 12} Instillation of unfiltered ileostomy
11 contents into the defunctioned colon induced relapse whereas instillation of content that
12 had passed through a 0.22micron pore diameter filter did not, implying a role for bacteria in
13 pathogenesis.¹⁸³ Defunctioning ileostomy has become less commonly performed for the
14 treatment of uncomplicated colonic Crohn's disease since it was shown that at least 50%
15 relapsed after continuity was restored.¹⁸⁴
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18 *Resection*

19 The cumulative risk of surgery for isolated colonic Crohn's disease is reported as 22-33% by
20 10 years after diagnosis compared with around 75-90% for ileal disease.^{17,67} Partial
21 resection, either right hemicolectomy for proximal disease or a segmental resection for
22 more distal disease has been shown to be successful therapy for colonic Crohn's disease^{185,}
23 ¹⁸⁶ as is colectomy with ileo-rectal anastomosis for more extensive disease if the rectum is
24 uninvolved^{187,188}. Approximately 75% of patients with ileo-rectal anastomosis will still have a
25 functioning anastomosis after 10 years and about two thirds of those treated by segmental
26 resection will not have required a further resection.¹⁸⁸ Recurrence rates are similar after
27 either procedure.¹⁸⁹ This contrasts with left-sided ulcerative colitis, where the tempting
28 option of left hemicolectomy with right-sided colo-anal anastomosis consistently fails,
29 usually with rapid recurrence of colitis in the retained colon.¹⁹⁰ It should be noted though
30 that segmental resection for colon cancer complicating colonic Crohn's disease has been
31 associated with high (39%) risk for metachronous colon cancer¹⁹¹ suggesting that
32 panproctocolectomy might be a safer option for such patients.
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37 *Ileo-anal pouch reconstruction*

38 Crohn's disease has generally been considered a contra-indication for restorative ileo-anal
39 pouch surgery and even in selected patients pouch failure of 57% has been reported from
40 the UK.¹⁹² Others have suggested that it may be successful in very carefully selected
41 patients. Thus, a series of 3,707 patients with ileal-pouch anal anastomosis from the
42 Cleveland Clinic included 150 with Crohn's disease, of whom 32 had a pre-operative
43 diagnosis, the remainder diagnosed by post-operative histopathology or on follow-up.
44 Amongst 59 patients with Crohn's disease reaching 10 year follow-up, pouch survival was
45 80%.¹⁹³ Forty nine of 132 patients (37%) needing pouch excision had a histological diagnosis
46 of Crohn's disease. Considering that a pre-operative diagnosis of Crohn's disease was only
47 present in less than 1% of patients receiving pouch-anal anastomosis these data do not
48 make a strong case for this procedure in patients with a definite diagnosis of colonic Crohn's
49 disease.
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55 **CONCLUSION**

56 Current data suggest that the genetics, microbiota, serology and smoking association of
57 isolated colonic Crohn's disease lie between those of ileo/ileocolonic Crohn's disease and
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3 ulcerative colitis and make a strong case for this phenotype being considered separately
4 (Table 11). Genetic data in particular show good separation from ileal/ileocolonic Crohn's
5 disease and the low rate of progression from isolated colonic to ileo-colonic disease help to
6 justify this distinction. There is a disappointing paucity of good quality therapeutic data but
7 the lack of response to mesalazine, whose target cell is the surface epithelium, suggests a
8 different pathophysiology to ulcerative colitis and there are important differences from
9 ulcerative colitis in surgical outcomes, including a good response to segmental resection in
10 selected cases and a generally poor response to pouch reconstruction. Taken together this
11 implies a compelling need for isolated colonic Crohn's disease to be identified separately
12 from ileal/ileocolonic disease and from ulcerative colitis. This is particularly important when
13 future therapeutic trials are designed and when cohort studies are reported.
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15

16
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19

20
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22 pharmaceuticals, Shire and received educational grant from MSD, Abbvie, Actavis and is an
23 advisory board member for Abbvie, Dr Falk pharmaceuticals, Janssen and Vifor
24 pharmaceuticals. JMR is or has been a member of advisory boards for Atlantic,
25 Pharmacosmos, Procter and Gamble, Vifor and Falk, has received speaking honoraria from
26 Abbott, Falk, Ferring, Glaxo Smith Kline, Merck, Procter and Gamble, Schering Plough, Shire,
27 and Wyeth, and with the University of Liverpool and Provox UK, holds a patent for use of a
28 soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent pending
29 for its use in antibiotic-associated diarrhoea.
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32 Provenance and peer review: Commissioned; externally peer reviewed.
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36 **LEGENDS TO FIGURES:**

37 1. Comparison between Crohn's disease genetic risk score and ulcerative colitis genetic
38 risk score for different locations of Crohn's disease, ulcerative colitis and IBD unclassified
39 (from Cleynen et al,¹⁷ with permission. This shows that isolated colonic Crohn's lies
40 approximately equidistant genetically between ileal Crohn's disease and ulcerative
41 colitis.
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43
44 2A. Isolated colonic Crohn's as percentage of all Crohn's disease by year in studies
45 reporting sequential data from the same centres or geographical areas.

46 2B. Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all
47 studies.
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53 Supplementary Files

- 54 1. PRISMA flow diagram.
- 55 2. PRISMA checklist.
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REFERENCES

1. Bargen JA, Weber HM. Regional migratory chronic ulcerative colitis. *Surg Gynecol Obstet* 1930;1:964-72.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathologic and clinical entity. *J Amer Med Assoc* 1932;99:1323-9.
3. Moschcowitz E, Wilensky AO. Non-specific granulomata of the intestine. *Am J Med Sci* 1923;166:48-66.
4. Colp R. A case of nonspecific granuloma of the terminal ileum and caecum. *Surg Clin N America* 1934;14:443-9.
5. Crohn BB, Rosenak BD. A combined form of ileitis and colitis. *J Amer Med Assoc* 1936;106:1-7.
6. Neuman HW, Bargen JA, Judd ES. A clinical study of two hundred and one cases of regional (segmental) colitis. *Surg Gynecol Obstet* 1954;99:563-71.
7. Wells C. Ulcerative colitis and Crohn's disease. *Ann Roy Coll Surg Engl* 1952;11:105-20.
8. Goldgraber MB, Kirsner JB, Palmer WL. The histopathology of chronic ulcerative colitis and its pathogenic implications. *Gastroenterology* 1960;38:596-604.
9. 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.
10. Cornes JS, Stecher M. Primary Crohn's disease of the colon and rectum. *Gut* 1961;2:189-201.
11. Truelove SC, Ellis H, Webster CD. The place of a double-barrelled ileostomy in ulcerative colitis and Crohn's disease of the colon: a preliminary report. *Brit Med J* 1965;1:150-3.
12. 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.
13. 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;13:611-4.
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.
15. Price AB. Overlap in the spectrum on non-specific inflammatory bowel disease – "colitis indeterminate". *J Clin Pathol* 1978;31:567-77.
16. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus and implications. *Gut* 2006;55:749-53.
17. 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.
18. Hadfield G. The primary histological lesion of regional ileitis. *Lancet* 1939;2:773-5.
19. Warren BF. Classic pathology of ulcerative and Crohn's colitis. *J Clin Gastroenterol* 2004;38:S33-5.
20. Morson BC. Crohn's disease. *Proc Roy Soc Med* 1968;61:79-81.
21. 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.
22. Bull DM. Crohn's disease of the colon. *Gastroenterology* 1979;76:607-21.
23. 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.
24. 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.
25. 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.
 26. 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 (S3):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 patten over the course of he disease. *Gut* 2001;49:777-82.
 31. Chow DKL, Leong RWL, 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, Prosberg 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;52:552-57.
 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;27:211-9.
 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 JH1, Phillips SF, Melton LJ 3rd, *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 WG1, Brown JS, Parks TG. Crohn's disease in Northern Ireland--a retrospective study of 440 cases. *Ulster Med J* 1990;59:30-5.
 42. Ekbohm 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

- 1
2
3 update for 1991-1995. *Eur J Gastroenterol Hepatol* 2000;12:907-11.
- 4 44. Jayanthi V, Probert CS, Pinder D, *et al.* Epidemiology of Crohn's disease in Indian
5 migrants and the indigenous population in Leicestershire. *Q J Med* 1992;82:125-38.
- 6 45. Cottone M, Brignola C, Rosselli M, *et al.* Relationship between site of disease and familial
7 occurrence in Crohn's disease. *Dig Dis Sci* 1997;42:129-32.
- 8 46. Jacobsen BA, Fallingborg J, Rasmussen HH, *et al.* Increase in incidence and prevalence of
9 inflammatory bowel disease in northern Denmark: a population-based study, 1978-
10 2002. *Eur J Gastroenterol Hepatol* 2006;18:601-6.
- 11 47. Wright JP, Froggatt J, O'Keefe EA, *et al.* The epidemiology of inflammatory bowel disease
12 in Cape Town 1980-1984. *S Afr Med J* 1986;70:10-5.
- 13 48. Manninen P, Karvonen AL, Huhtala H, *et al.* The epidemiology of inflammatory bowel
14 diseases in Finland. *Scand J Gastroenterol* 2010;45:1063-7.
- 15 49. Economou M, Filis G, Tsianou Z, *et al.* Crohn's disease incidence evolution in North-
16 western Greece is not associated with alteration of NOD2/CARD15 variants. *World J*
17 *Gastroenterol* 2007;13:5116-20
- 18 50. Rhodes JM, Cockel R, Allan RN, *et al.* Colonic Crohn's disease and the contraceptive pill.
19 *British Medical Journal* 1984;288: 595-596.
- 20 51. Gower-Rousseau C, Salomez JL, Dupas JL, *et al.* Incidence of inflammatory bowel disease
21 in northern France (1988-1990). *Gut* 1994;35:1433-8.
- 22 52. Auvin S, Molinié F, Gower-Rousseau C, *et al.* Incidence, clinical presentation and location
23 at diagnosis of pediatric inflammatory bowel disease: a prospective population-based
24 study in northern France (1988-1999). *J Pediatr Gastroenterol Nutr* 2005;41:49-55.
- 25 53. Spanish Epidemiological and Economic Study Group on Crohn's disease. Epidemiological
26 and clinical features of Spanish patients with Crohn's disease. *Eur J Gastroenterol*
27 *Hepatol* 1999;11:1121-7.
- 28 54. Jess T, Riis L, Vind I, *et al.* Changes in clinical characteristics, course, and prognosis of
29 inflammatory bowel disease during the last 5 decades: a population-based study from
30 Copenhagen, Denmark. *Inflamm Bowel Dis* 2007;13:481-9.
- 31 55. Chow DK, Leong RW, Lai LH, *et al.* Changes in Crohn's disease phenotype over time in
32 the Chinese population: validation of the Montreal classification system. *Inflamm Bowel*
33 *Dis* 2008;14:536-41.
- 34 56. Romberg-Camps MJL, Dagnelle PC, Kester ADM, *et al.* Influence of phenotype at
35 diagnosis and of other potential prognostic factors on the course of inflammatory bowel
36 disease. *Am J Gastroenterol* 2009;104:371-83.
- 37 57. Björnsson S, Tryggvason FP, Jónasson JG, *et al.* Incidence of inflammatory bowel disease
38 in Iceland 1995 - 2009. A nationwide population-based study. *Scand J Gastroenterol*
39 2015;50:1368-75.
- 40 58. Tozun N, Atug O, Imeryuz N, *et al.* Members of the Turkish IBD Study Group. Clinical
41 characteristics of inflammatory bowel disease in Turkey: a multicenter epidemiologic
42 survey. *J Clin Gastroenterol* 2009;43:51-7.
- 43 59. Lakatos L, Kiss LS, David G, *et al.* Incidence, disease phenotype at diagnosis, and early
44 disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. *Inflamm*
45 *Bowel Dis* 2011;17:2558-65.
- 46 60. Nguyen GC, Torres EA, Regueiro M, *et al.* Inflammatory bowel disease characteristics
47 among African Americans, Hispanics, and non-Hispanic Whites: characterization of a
48 large North American cohort. *Am J Gastroenterol* 2006;101:1012-23.
- 49
50
51
52
53
54
55
56
57
58
59
60

- 1
- 2
- 3 61. Ott C, Obermeier F, Thieler S, *et al.* The incidence of inflammatory bowel disease in a
- 4 rural region of Southern Germany: a prospective population-based study. *Eur J*
- 5 *Gastroenterol Hepatol* 2008;20:917-23.
- 6
- 7 62. Siddique I, Alazmi W, Al-Ali J, *et al.* Clinical epidemiology of Crohn's disease in Arabs
- 8 based on the Montreal Classification. *Inflamm Bowel Dis* 2012;18:1689-97.
- 9
- 10 63. Chen H, Lee A, Bowcock A, *et al.* Influence of Crohn's disease risk alleles and smoking on
- 11 disease location. *Dis Colon Rectum* 2011;54:1020-5.
- 12
- 13 64. Lucendo AJ, Hervías D, Roncero Ó, *et al.* Epidemiology and temporal trends (2000-2012)
- 14 of inflammatory bowel disease in adult patients in a central region of Spain. *Eur J*
- 15 *Gastroenterol Hepatol* 2014;26:1399-407.
- 16
- 17 65. Henckaerts L, Pierik M, Joossens M, *et al.* Mutations in pattern recognition receptor
- 18 genes modulate seroreactivity to microbial antigens in patients with inflammatory
- 19 bowel disease. *Gut* 2007;56:1536-42.
- 20
- 21 66. Herrinton LJ, Liu L, Lewis JD, *et al.* Incidence and prevalence of inflammatory bowel
- 22 disease in a Northern California managed care organization, 1996-2002. *Am J*
- 23 *Gastroenterol* 2008;103:1998-2006.
- 24
- 25 67. Hancock L, Beckly J, Geremia A, *et al.* Clinical and molecular characteristics of isolated
- 26 colonic Crohn's disease. *Inflamm Bowel Dis* 2008;14:1667-77.
- 27
- 28 68. Aloï M, Lionetti P, Barabino A, *et al.* SIGENP IBD Group. Phenotype and disease course of
- 29 early-onset pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2014;20:597-605.
- 30
- 31 69. Aljebreen AM, Alharbi OR, Azzam NA, *et al.* Clinical epidemiology and phenotypic
- 32 characteristics of Crohn's disease in the central region of Saudi Arabia. *Saudi J*
- 33 *Gastroenterol* 2014;20:162-9.
- 34
- 35 70. Burisch J, Pedersen N, Cukovic-Cavka S, *et al.* Environmental factors in a population-
- 36 based inception cohort of inflammatory bowel disease patients in Europe--an ECCO-
- 37 EpiCom study. *J Crohns Colitis* 2014;8:607-16.
- 38
- 39 71. Eglinton TW, Roberts R, Pearson J, *et al.* Clinical and genetic risk factors for perianal
- 40 Crohn's disease in a population-based cohort. *Am J Gastroenterol* 2012;107:589-96.
- 41
- 42 72. Ng SC, Tang W, Ching JY, *et al.* Incidence and phenotype of inflammatory bowel disease
- 43 based on results from the Asia-pacific Crohn's and colitis epidemiology study.
- 44 *Gastroenterology* 2013;145(1):158-165.
- 45
- 46 73. Somerville KW, Logan RFA, Edmond M, *et al.* Smoking and Crohn's disease. *Brit Med J*
- 47 1984;289:954-6.
- 48
- 49 74. Holdstock G, Savage D, Harman M, *et al.* Should patients with inflammatory bowel
- 50 disease smoke? *Brit Med J* 1984;288:362.
- 51
- 52 75. Tobin MV, Logan RFA, Langman MJS, *et al.* Cigarette smoking and inflammatory bowel
- 53 disease. *Gastroenterology* 1987;93:316-21.
- 54
- 55 76. Lindberg E, Järnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and
- 56 clinical course. *Gut* 1992;33:779-82.
- 57
- 58 77. Breuer-Katschinski B, Hollander N, Goebell H. Effect of cigarette smoking on the course
- 59 of Crohn's disease. *Europ J Gastroenterol Hepatol* 1996;8:225-8.
- 60
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. 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.
 83. 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.
 84. Chivese 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.
 85. Cleynen I, Gonzalez JR, Figueroa *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
 86. World Health Organisation. WHO Report on the global tobacco epidemic 2008: The MPOWER package. www.who.int/tobacco/mpower/2008/en/
 87. 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.
 88. 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.
 89. 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.
 90. 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.
 91. 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.
 92. Sandler RS, Wurzelmann JI, Lyles CM. Oral contraceptive use and the risk of inflammatory bowel disease. *Epidemiology* 1992;3:374-8
 93. Persson PG, Leijonmarck CE, Bernell O, *et al.* Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;22:268-72.
 94. 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.
 95. Khalili H, Higuchi LM, Ananthakrishnan AN, *et al.* Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut* 2013;62:1153-9.
 96. Khalili H, Chan AT. Author response: oral contraceptives and Crohn's disease. *Gut* 2015;64:854.
 97. 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.
 98. 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.
 99. Deana DG1, Dean PJ. Reversible ischemic colitis in young women. Association with oral

- 1
2
3 contraceptive use. *Am J Surg Pathol* 1995;19:454-62.
- 4 100. Tedesco FJ, Volpicelli NA, Moore FS. Estrogen- and progesterone-associated colitis: a
5 disorder with clinical and endoscopic features mimicking Crohn's colitis. *Gastrointest*
6 *Endosc* 1982;28:247-9.
- 7 101. Tsai HH, Howden CW, Thomson TJ. Probable Crohn's colitis mimicking ischaemic
8 colitis in a young adult. *Scott Med J* 1989;34:406-7
- 9 102. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease.
10 *Gut* 2000;46:140
- 11 103. Economou M1, Trikalinos TA, Loizou KT, *et al.* Differential effects of NOD2 variants
12 on Crohn's disease risk and phenotype in diverse populations: a metaanalysis. *Am J*
13 *Gastroenterol* 2004;99:2393-404.
- 14 104. Ahmad T, Marshall SE, Jewell D. Genetics of inflammatory bowel disease: The role of
15 the HLA complex. *World J Gastroenterol* 2006;12:3628-35.
- 16 105. Paul T, Birnbaum A, Pal DK, *et al.* Distinct phenotype of early childhood
17 inflammatory bowel disease. *J Clin Gastroenterol* 2006;40:583-6.
- 18 106. Maisawa S, Sasaki M, Ida S, *et al.* Characteristics of inflammatory bowel disease with
19 an onset before eight years of age: a multicenter epidemiological survey in Japan. *J*
20 *Gastroenterol Hepatol* 2013;28:499-504.
- 21 107. Marks DJ, Miyagi K, Rahman FZ, *et al.* Inflammatory bowel disease in CGD
22 reproduces the clinicopathological features of Crohn's disease. *Am J Gastroenterol*
23 2009;104:117-24.
- 24 108. Uhlig HH, Schwerd T, Koletzko S, *et al.* The diagnostic approach to monogenic very
25 early onset inflammatory bowel disease. *Gastroenterology* 2014;147:990-1007.
- 26 109. Moran CJ1, Klein C, Muise AM, *et al.* Very early-onset inflammatory bowel disease:
27 gaining insight through focused discovery. *Inflamm Bowel Dis* 2015;21:1166-75.
- 28 110. Zeissig Y, Petersen BS, Milutinovic S, *et al.* XIAP variants in male Crohn's disease. *Gut*
29 2015;64:66-76.
- 30 111. Elkadri AA, Stempak JM, Walters TD, *et al.* Serum antibodies associated with
31 complex inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1499-505.
- 32 112. Zhang Z, Li C, Zhao X, Lv C, *et al.* Anti-Saccharomyces cerevisiae antibodies associate
33 with phenotypes and higher risk for surgery in Crohn's disease: a meta-analysis. *Dig Dis*
34 *Sci* 2012;57:2944-54.
- 35 113. Kaul A, Hutfless S, Liu L, *et al.* Serum anti-glycan antibody biomarkers for
36 inflammatory bowel disease diagnosis and progression: a systematic review and meta-
37 analysis. *Inflamm Bowel Dis* 2012;18:1872-84.
- 38 114. Reese GE, Constantinides VA, Simillis C, *et al.* Diagnostic precision of anti-
39 Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic
40 antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006;101:2410-22.
- 41 115. Duerr RH, Targan SR, Landers CJ, *et al.* Anti-neutrophil cytoplasmic antibodies in
42 ulcerative colitis. Comparison with other colitides/diarrheal illnesses. *Gastroenterology*
43 1991;100:1590-6.
- 44 116. Cambridge G, Rampton DS, Stevens TR, *et al.* Anti-neutrophil antibodies in
45 inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1992;33:668-74.
- 46 117. Joossens S, Reinisch W, Vermeire S, *et al.* The value of serologic markers in
47 indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002;122:1242-
48 7.
- 49
50
51
52
53
54
55
56
57
58
59
60

118. 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.
119. Annese 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.
120. 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.
121. Vind I, Riis L, Jespersgaard C, Jess T, *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.
122. 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.
123. 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.
124. 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.
125. Prideaux L, De Cruz P, Ng SC, *et al.* Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2012;18:1340-55.
126. 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;20:1192-1210.
127. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014;146:1489-99.
128. Gevers D, Kugathasan S, Denson LA, *et al.* The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014;15:382-92.
129. 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.
130. Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, Järnerot G, Tysk C, Jansson JK, *et al.* A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. *Gastroenterology* 2010;139:1844-1854.
131. Willing B, 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.
132. 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.
133. 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.

134. Haberman Y, Tickle TL, Dexheimer PJ, *et al.* Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 2014;124:3617-33. Erratum in: *J Clin Invest* 2015;125:1363.
135. 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.
136. Lim WC, Hanauer S. Aminosaliclates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010;(12):CD008870.
137. 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.
138. 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.
139. 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.
140. 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.
141. 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.
142. 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.
143. 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.
144. 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.
145. 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.
146. 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.
147. Summers RW, Switz DM, Sessions JT Jr, *et al.* National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847-69.
148. Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;86:249-66.
149. Khan, K.J., 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.
150. Nitzan, O., Elias M, Peretz A *et al.*, Role of antibiotics for treatment of inflammatory bowel disease. *World J Gastroenterol* 2016;22:1078-87.
151. 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.
152. Prantera C, Lochs H, Grimaldi M *et al.* Rifaximin-extended intestinal release induces

- 1
2
3 remission in patients with moderately active Crohn's disease. *Gastroenterology* 2012;
4 142:473-481.
- 5 153. Blichfeldt, P, Blomhoff JP, Myhre E, *et al.* Metronidazole in Crohn's disease. A double
6 blind cross-over clinical trial. *Scand J Gastroenterol* 1978;13:123-7.
- 7 154. Sutherland L, Singleton J, Sessions J *et al.*, Double blind, placebo controlled trial of
8 metronidazole in Crohn's disease. *Gut* 1991;32:1071-5.
- 9 155. Steinhart AH, Feagan BG, Wong CJ *et al.* Combined budesonide and antibiotic
10 therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology*
11 2002;123:33-40.
- 12 156. Selby W, Pavli P, Crotty B *et al.* Two-year combination antibiotic therapy with
13 clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology*
14 2007;132:2313-9.
- 15 157. Tromm A, Bunganic I, Tomsova E, *et al.* Budesonide 9 mg is at least as effective as
16 mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease.
17 *Gastroenterology* 2011;140:425-434.
- 18 158. Bar-Meir S, Chowers Y, Lavy A, *et al.*, Budesonide versus prednisone in the treatment
19 of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology*
20 1998;115:835-40.
- 21 159. Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short-term study of chimeric
22 monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's
23 Disease cA2 Study Group. *N Engl J Med* 1997; 337: 1029–35.
- 24 160. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's
25 disease: the ACCENT I randomised trial. *Lancet* 2002; 359: 1541–9.
- 26 161. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor
27 monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.
28 *Gastroenterology* 2006; 130: 323–33.
- 29 162. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance
30 treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; 56: 1232–9.
- 31 163. Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn's
32 disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;
33 146: 829–38.
- 34 164. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of
35 clinical response and remission in patients with Crohn's disease: the CHARM trial.
36 *Gastroenterology* 2007; 132: 52–65.
- 37 165. Sandborn WJ, Melmed GU, MCGovern DP *et al.* Certolizumab pegol for active Crohn's
38 disease: a placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol* 2011; 9:670-
39 678.
- 40 166. Arnott, I.D., McNeill G, Satsangi J. An analysis of factors influencing short-term and
41 sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther*
42 2003;17:1451-7.
- 43 167. Laharie D, Salzmann M, Boubekour H *et al.* Predictors of response to infliximab in
44 luminal Crohn's disease. *Gastroenterol Clin Biol* 2005;29:145-9.
- 45 168. Vermeire S, Louis E, Carbonez A *et al.* Demographic and clinical parameters
46 influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment
47 in Crohn's disease. *Am J Gastroenterol* 2002;97:2357-63.
- 48
49
50
51
52
53
54
55
56
57
58
59
60

169. 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.
170. 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;18:10-6.
171. 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.
172. Kansal S, Wagner J, Kirkwood CD, *et al.* Enteral nutrition in Crohn's disease: an underused therapy. *Gastroenterol Res Pract* 2013;2013:482108.
173. Lee D, Albenberg L, Compher C, *et al.* Diet in the pathogenesis and treatment of inflammatory bowel diseases. *Gastroenterology* 2015;148:1087-106.
174. 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
175. 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.
176. 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.
177. 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.
178. Wilschanski M, Sherman P, Pencharz P, *et al.* Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996;38:543-8.
179. 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.
180. 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.
181. 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.
182. 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.
183. 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.
184. 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.
185. 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;13:611-4.
186. Andersson P, Olaison G, Hallböök O, *et al.* Segmental resection or subtotal colectomy in Crohn's colitis? *Dis Colon Rectum* 2002;45:47-53.
187. Bernell O, Lapidus A, Hellers G. Recurrence after colectomy in Crohn's colitis. *Dis*

- 1
2
3 *Colon Rectum* 2001;44:647-54.
- 4 188. Martin ST, Vogel JD. Restorative procedures in colonic crohn disease. *Clin Colon*
5 *Rectal Surg* 2013;26:100-5.
- 6 189. Kiran RP, Nisar PJ, Church JM, *et al.* The role of primary surgical procedure in
7 maintaining intestinal continuity for patients with Crohn's colitis. *Ann Surg*
8 2011;253:1130-5.
- 9 190. Schwarz RJ, Pezim ME. Failure of right-sided coloanal anastomosis for treatment of
10 left-sided ulcerative colitis. Report of a case. *Dis Colon Rectum* 1991;34:618-21.
- 11 191. Maser EA, Sachar DB, Kruse D, *et al.* High rates of metachronous colon cancer or
12 dysplasia after segmental resection or subtotal colectomy in Crohn's colitis. *Inflamm*
13 *Bowel Dis* 2013;19:1827-32.
- 14 192. Tekkis PP, Heriot AG, Smith O, *et al.* Long-term outcomes of restorative
15 proctocolectomy for Crohn's disease and indeterminate colitis. *Colorectal Dis*
16 2005;7:218-23.
- 17 193. Fazio VW, Kiran RP, Remzi FH, *et al.* Ileal pouch anal anastomosis: analysis of
18 outcome and quality of life in 3707 patients. *Ann Surg* 2013;257:679-85.
- 19
20
21
22
23
24
25
26
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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
Comes ¹⁰	UK	1961	131	46	34	60	38	41-50	-
Gollop ³⁹	USA	1943-82	103	64	36	68	62	25-34	-
Loftus ⁴⁰	USA	1940-93	225	54	32	-	-	-	-
Humphreys ⁴¹	UK	1966-81	440	58	40	-	-	-	-
Ekbom ⁴²	Sweden	1965-83	1469	53	25	-	-	33 (mean)	-
Kyle ³⁵	UK	1955-88	856	63	41	63	63	40-49	-
" "	" "	1964-69	122	-	30	-	-	-	-
" "	" "	1970-75	167	-	40	-	-	-	-
" "	" "	1976-81	204	-	46	-	-	-	-
" "	" "	1982-87	263	-	54	-	-	-	-
Lapidus ³⁷	Sweden	1955-59	83	61	14	-	-	-	-
		1960-64	145	48	15	-	-	-	-
		1965-69	270	51	21	-	-	-	-
		1970-74	364	53	26	-	-	-	-
		1975-79	331	54	26	-	-	-	-
		1980-84	348	58	32	-	-	-	-
		1985-89	395	49	32	-	-	-	-
Gunesh ³⁶	UK (Cardiff)	1950-60	40	-	13	-	-	-	-
" "	" "	1960-70	89	-	17	-	-	-	-
" "	" "	1970-80	148	-	34	-	-	-	-
" "	" "	1980-90	217	-	38	-	-	-	-
Yapp ⁴³	UK (Cardiff)	1991-95	84	68	43	-	-	-	-
Gunesh ³⁶	" "	1996-2005	212	61	43	68	55	-	-
Jayanthi ⁴⁴	UK	1972-89	235	50	25 (incr from 1972 to 89)	-	-	-	-
Cottone ⁴⁵	Italy	1975-95	882	-	18	-	-	-	-
Jacobsen ⁴⁶	Denmark	1978-87	196	67 (1978-87)	32	-	-	-	-
" "	" "	1988-97	354	" "	42	-	-	-	-
" "	" "	1998-2002	230	" "	51	-	-	-	-
Wright ⁴⁷	S.Africa	1980-84	134	69	27	-	-	-	0.44
Manninen ⁴⁸	Finland	1986-99	470	50	40% 1986 31% 1999	-	-	-	0.56

Economou ⁴⁹	Greece	1983-2005	105	37	40	-	-	-	0.40
Rhodes ⁵⁰	UK	1984	395	55	22	72	50	28 (subset)	-
Gower-Rousseau ⁵¹	France	1994	674	57	19	-	-	28	1.15
Auvin ⁵²	France	1988-99	367 (< 17y)	47	10	-	-	-	0.54
Spanish ⁵³	Spain	1997	635	52	17	-	-	-	-
Jess ⁵⁴	Denmark	1962-87	374	58	30	-	-	-	-
" "	" "	1991-93	58	66	43	-	-	-	-
" "	" "	2003-04	209	54	37	-	-	-	-
Chow ⁵⁵	China	1987-2005	109	29	35	-	-	-	-
Chouraki ³⁸	France	1988-2007	7409	56	11	-	-	-	0.90
" "	" "	1988-90	544	-	23	-	-	-	-
" "	" "	1997-99	1044	-	13	-	-	-	-
" "	" "	2006-07	533	-	5	-	-	-	-
Romberg-Camps ⁵⁶	Netherlands	1991-2003	476	61	27	66	59	34 (mean)	0.63
Bjornsson ⁵⁷	Iceland	1995-2009	279	54	55	-	-	-	0.08
Tozun ⁵⁸	Turkey	2001-03	216	44	26	-	-	-	-
Lakatos ⁵⁹	Hungary	2002-06	163	48	36	-	-	-	-
Nguyen ⁶⁰	USA/Canada	2003-05	579	-	19	-	-	-	0.30
Ott ⁶¹	Germany	2004-06	168	55	18	-	-	-	0.43
Siddique ⁶²	Kuwait	2005-6	206	52	14	-	-	-	-
Chen ⁶³	USA	2005-10	628	55	21	50	56	-	-
Lucendo ⁶⁴	Spain	2000-12	599	49	24	-	-	-	0.10
Henckaerts ⁶⁵	Belg	2007	874	-	17	-	-	-	0.03
Herrinton ⁶⁶	USA	2008	948	55	40	-	-	-	0.10
Hancock ⁶⁷	UK	2008	675	62	20	74	59	31 (mean)	-
Aloj ⁶⁸	Italy	2009-13	10 (<5y)	-	50	-	-	-	-
" "	" "	" "	215 (6-18y)	-	15	-	-	-	1.00
Aljebreen ⁶⁹	Saudi	2009-13	497	41	8	-	-	-	-
Burisch ⁷⁰	Western europe	2010	345	48	26	-	-	-	1.19
" "	Eastern europe	2010	99	41	20	-	-	-	0.30
Eglinton ⁷¹	NZ	2011	507	63	42	-	-	-	-
Ng ⁷²	Asia-pacific	2011-12	166	Asia 39% Austr 52%	24	-	-	-	0.53
Cleynen ¹⁷	16 countries	2015	16,902	56	24	-	-	-	0.06

Table 1. Studies of Crohn's disease age and sex distribution and proportion of total, where isolated colonic Crohn's disease separately identified (in approximate median date order).

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 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 ⁷⁴	1984	UK	150	Consecutive outpatients	-	25 (smokers with isolated colon CD had more relapses P=0.028)	35	52	-	8
Tobin ⁷⁵	1987	UK	137	Case control	RR for smoking at onset and CD: Small bowel only 1.4 (0.5-4.0) Ileum and asc 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 ⁷⁶	1992	Sweden	231	Postal questionnaire (95% response)	-	42	51	53	-	-
Breuer-Katschinski ⁷⁷	1995	Germany	346	Postal questionnaire (82% response)	-	49	50	49	-	-
Ruszel ⁷⁸	1998	Europe (20 centres, 13 countries)	457	Prospective consecutive cases	-	35	47	59	-	16
Cosnes ⁷⁹	1999	France	622	Consecutive outpatients	-	54	49	49	-	-
Cosnes ⁸⁰	2004	France	688 all colonic	Consecutive outpatients	-	61	-	-	-	42
Aldhous ⁸¹	2007	UK (Scotland)	408	Retrospective outpatients	-	33	43	50	-	-
Hancock ⁶⁷	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 ⁸²	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 ⁸³	2013	Spain	3224	National registry	-	26	34	35	-	-
Chivese ⁸⁴	2015	S. Africa	194	Prospective consecutive cases	RR 3.63 (1.32-9.98) for ileo-colonic 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"

Table 2. Studies of smoking in Crohn's disease where isolated colonic disease 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 ⁵⁰	Case control matched for age and year of onset	37	9/12 75%	11/25 44%	-	NS increased P=0.09
Vessey ⁹⁰	Cohort study in patients attending family planning clinics	18	4/7 57%	4/11 36%	-	NS increased 0.63
Lashner ⁹¹	Case control	51 (incl 8 isolated colonic)	-	-	Isolated colonic OR0.50(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 Crohns)
Sandler ⁹²	Case control Age matched and excluding onset before menarche	184 (incl 26 isolated colonic)	-	-	Isolated colonic OR2.63 (1.00-7.11) Small bowel only 1.33 (0.70-2.53) Ileocolonic 1.52 (0.82-2.83)	NS increased
Persson ⁹³	Case control age 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 ⁹⁴	Case control pre-menopausal	90 (incl 30 isolated colonic)	-	-	Isolated colonic RR3.2 (1.1-15.3) Small bowel only RR4.7 (1.6-17.8) Ileocolonic RR 3.8 (1.3 -17.0)	NS reduced
Khalili ^{95,96}	Cohort – Nurses Health	315 (incl 141 isolated colonic)	-	-	Isolated colonic HR4.13 (1.77-9.68) Ileal only HR2.99 (1.06-8.49)	NS increased

Table 3 – Studies of oral contraceptive usage in Crohn's disease where isolated colonic disease separately identified.

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 ¹¹⁵	1991	Prospective	18	-	-	-	5/18 (28%)	-	-	pANCA 34/40 (85%)	pANCA+ in isolated colonic CD not signif commoner than diarrhea-predom IBS (4/27 15%)
Cambridge ¹¹⁶	1992	Stored sera IBD and healthy controls	18	-	-	-	1/18 (6%)	-	-	pANCA 27/50 (54%)	pANCA+ in 4/32 CD with small bowel involt
Joossens ¹¹⁷	2002	Prospective follow-up of 97 patients with initial diag 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 ¹¹⁸	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 ¹¹⁹	2004	Prospective	61	NA	NA	25/61 (41%)	-	-	-	ASCA 32/197 (16%)	ASCA in CD overall 51%
Ferrante ¹²⁰	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 ¹²¹	2008	Prospective cohort	60	NA	NA	5/60 (8%)	15/60 (25%)	-	-	ASCA 14% pANCA 55%	ASCA CD overall 22%
Lakatos ¹²²	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 ¹²³	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 (nonL2) CD ASCA 55/137 (40.1%) other (nonL2) CD
Bertin ¹²⁴	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 ¹¹¹	2013	Prospective cohort adults and children	55	NA	NA	NA but OR 0.25 (0.12-0.51; P=0.0002) for assocn with isolated colonic disease vs other sites	NA but OR 2.27 (1.50 – 4.92; P<0.03 for assocn 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

Table 4. Serological test results in isolated colonic Crohn's disease and ulcerative colitis.

Author/ref	Year	Specimen type	Number of cases CD	Ileal CD	Ileocolonic CD	Isolated colonic CD	Ulcerative colitis	Healthy controls	Conclusions
Naftali ¹³³	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 ¹³⁴	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 ¹³²	2014	Ileum and colon	45	19 Reduction in <i>F. prausnitzii</i> , <i>E. 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 ^{#130,131}	2009, 2010	Ileum and colon	14	6 Increased Enterobacteriaceae and Ruminococcus gnavus; decreased Faecalibacteria and Roseburia and compared to healthy controls. Increased <i>E. coli</i> .	8 No reduction in Faecalibacterium or Roseburia. Some increase in <i>E. coli</i> but less marked than ileo-colonic.	6 Colonic CD microbiome intermediate between ileal CD and healthy controls.			
Baumgart ¹²⁹	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>Faecalibacteria</i> and <i>Subdoligranula</i>)	8 Results not presented separately	8 Enterobacteriaceae not increased and Faecalibacteria not reduced.	NA	7	Ileal CD and colonic CD microbiome were distinct. Colonic CD more closely resembled healthy controls

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

#Willing 2010, similar patient cohort to Willing (2009) but sequencing methodology compared to terminal-restriction fragment length polymorphism in Willing (2009).

†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.

Table 5: Studies of mucosal microbiota in Crohn's disease where isolated colonic disease separately identified

Author/Ref	N (isolated colonic CD)	5ASA	Placebo	P value	Conclusions
Singleton ¹⁴⁰	64	CDAI mean change: -77 (+/-27) at 2g/day -81 (+/-31) at 4g/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-aminosalicylic acid in isolated colonic Crohn's disease
(i) induction

Author/Ref	N (isolated colonic CD)	5ASA relapse rate 12months	Placebo relapse rate 12 months	P value	Conclusions
International ¹⁴¹	56	32.1% (9/28)	38.9% (11/28)	0.49	5ASA only showed benefit in ileal disease
Prantera ¹⁴²	18	40% (2/5)	55% (6/?11) extrapolated from table	NS	5ASA only showed benefit in ileal disease
Gendre ¹⁴³	48	-	-	-	5ASA better (P<0.003) than placebo in all CD patients in remission <3m at onset, no sig difference according to disease location
De Franchis ¹⁴⁴	36	45% (8/17)(extrapolated from figure)	45% (9/19)	1.0	5ASA ineffective in ileal, colonic, or ileocolonic

(a) Placebo-controlled trials of oral 5-aminosalicylic acid in isolated colonic Crohn's disease
(ii) maintenance

Author/Ref	N (isolated colonic CD)	Sulphasalazine remission	Placebo remission	P value	Conclusions
Singleton ¹⁴⁶	20	-	-	NS	Both groups also received tapering prednisolone. Placebo better than sulphasalazine in patients with ileal disease.
Summers ¹⁴⁷	17	-	-	0.006 (comparison of outcome ranks)	Sulphasalazine better than placebo in colonic CD (also effective in ileocolonic but not ileal only)
Malchow ¹⁴⁸	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 sulphasalazine in isolated colonic Crohn's disease (i) induction

Author/Ref	N (isolated colonic CD)	Sulphasalazine relapse rate 12months	Placebo relapse rate 12 months	P value	Conclusions
Singleton ¹⁴⁶	20	-	-	NS	Sulphasalazine not significantly different from placebo in CD overall and no relation to disease location
Summers ¹⁴⁷	19	-	-	NS	No significant effect (judged by outcome rank based on CDAI)

(b) Placebo-controlled trials of oral sulphasalazine in isolated colonic Crohn's disease (ii) maintenance

Author/Ref	N (isolated colonic CD)	Olsalazine relapse /failure rate 12 months	Placebo relapse /failure rate 12 months	P value	Comments
Mahmud ¹⁴⁵	145	65.4%	53.6%	0.035 (Olsalazine worse)	Olsalazine induces diarrhea, no evidence of efficacy

(c) Placebo-controlled trial of olsalazine in isolated colonic Crohn's maintenance

Table 6. Trials of 5ASA preparations where data presented separately for isolated colonic Crohn's disease.

Author/Ref	N (isolated colonic CD)	Comparator	Primary end point	Rifaximin remission rate	Placebo remission rate	P value	Conclusions
Prantera ¹⁵²	190 active; 76 placebo (from supplement table 2)	Placebo	Week 12 remission (CDAI <150)	3 doses: 400mg bd; 800 mg bd; 1200 mg bd; 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 ¹⁵³	6	Placebo (crossover)	Week 8 response	100%	?	NS overall	Metronidazole 1g daily improved symptoms and lab values in all six with colonic disease
Sutherland ¹⁵⁴	12 (4 received 10 mg/kg; 4 received 20mg/kg; placebo)	Placebo	Week 16 response	Mean CDAI drop 145, 95% CI 26-265, 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

Table 7. Trials of antibiotics where data provided separately for patients with isolated colonic Crohn's disease.

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 ¹⁵⁷	50 (distal colon excluding rectum) of 307 in trial	Budesonide 9mg od vs 3mg tds vs Mesalamine 1.5g tds	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 signif better than mesalamine
Bar-Meir ¹⁵⁸	27 of 201 in trial	Budesonide 9mg od vs Prednisone 40mg od 2wks 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 ¹⁴⁶	34 of 295 in trial (Pt1)	Prednisone up to 60mg /day (n=8) vs Azathioprine 2.5 mg/kg (n=9) vs Sulfasalazine 1g/15kg (n=8) vs Placebo (n=9)	Week 17 remission	Data presented as rank outcome	Data presented as rank outcome	0.465	Prednisone not effective in colon only disease (but only n=8 treated)
Malchow ¹⁴⁷	49 of 215 in trial (induction data from table 11)	Sulfasalazine or combination of sulfasalazine and 6-methyl Prednisolone	Remission by week 18	6/8 (75%)	Placebo 2/14 (14%) Sulphasalazine 4/13 (31%) Combination 13/14 (93%)	<0.01 for Sulfasalazine and 6-methylprednisolone and <0.001 for combination	All active treatments better than placebo but combination superior to either agent alone

(b) Controlled trials of oral Prednis(ol)one

Table 8. Trials of oral corticosteroids where data provided separately for isolated colonic Crohn's disease.

Author	Year	Type of study	Study agent	Total number of patients	Number with colonic CD	Endpoint	Main findings	P value (for colonic vs other sites unless stated)	Conclusion
Sandborn ¹⁶⁵	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
Arnott ¹⁶⁶	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 ¹⁶⁷	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 ¹⁶⁸	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 – 3.597	0.046	Better efficacy in colonic than combined ileal/ileocolonic. Remission also more likely in isolated colonic (P=0.019)
Dupont-Lucas ¹⁶⁹	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%). iHR 2.72 (95% CI 1.30-5.71) for loss of response in isolated colonic CD vs other sites	0.008	Isolated colonic disease more likely to lose response
Cohen ¹⁷⁰	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 ¹⁷¹	2013	RCT	Vedolizumab	1115	316 (273 active, 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 ¹⁷¹	2013	RCT	Vedolizumab	461	117	Remission at week 52 over placebo	Remission 8wkly vedo: 18.9% difference from placebo for colonic vs 11.8% for ileal	0.11 0.19	No difference between isolated colonic and other Crohn's for

							vs 19.9% for ileocolonic Remission 4wkly vedo: 12.7% for colonic vs 25.4% for ileal vs 12% for ileocolonic		maintenance with vedolizumab
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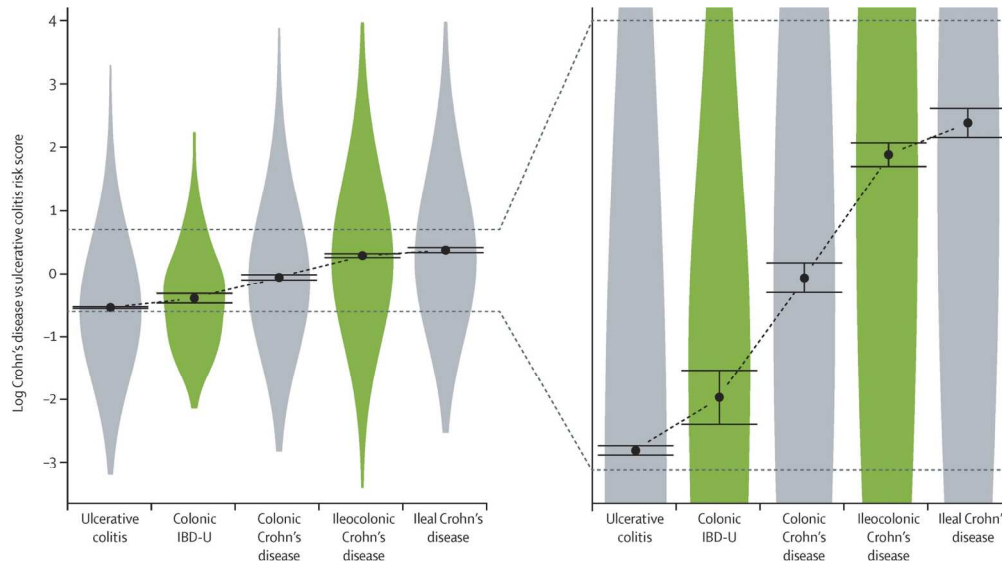
Table 9: Randomized controlled trials (RCTs) and cohort studies of biological therapy in Crohn's disease where data were provided separately for patients with isolated colonic disease.

Author/ref	Year	Nature of study	Adults/ children	n=	Intervention	Duration	Primary endpoint	Results in patients with ileal involvement	Results in isolated colonic CD	P*
Lochs ¹⁷⁷	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 till remission 26 days	Mean time till remission 31 days	NS
Wilschanski ¹⁷⁸	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
Afzal ¹⁷⁹	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 ¹⁸⁰	2009	Prospective cohort	Children Median age 12	110 (19 colon only)	Exclusive polymeric (Modulen) in 105, elemental in 5	8 weeks	Remission (improvt in all domains of global assesst)	Remission 73/91 (80.2%)	Remission 15/19 (78.9%)	NS
Rubio ¹⁸¹	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		NS
De Bie ¹⁸²	2013	Retrospective cohort	Children Median age 14	76 (18 colon only)	Exclusive polymeric or semi-polymeric	6 weeks	Remission defined as no diarrhea, pain or wt loss	Remission 32/51 (63%)	Remission 8/15 (53%)	NS

Table 10. Results of exclusive enteral nutrition as primary therapy in Crohn's disease where data provided separately for isolated colonic Crohn's disease.

	Ileal/Ileocolonic Crohn's disease	Isolated colonic Crohn's disease	Ulcerative colitis
Sex	Slightly commoner in females (c55%)	Commoner in females (c65%)	Equal or slight male predominance
Genetics	Crohn's-associated genotype including NOD2/CARD15	Genotype midway between Crohn's 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>E. 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

Table 11. A summary of the distinguishing features of the three inflammatory bowel diseases: ileal/ileocolonic Crohn's disease, isolated colonic Crohn's disease, ulcerative colitis.

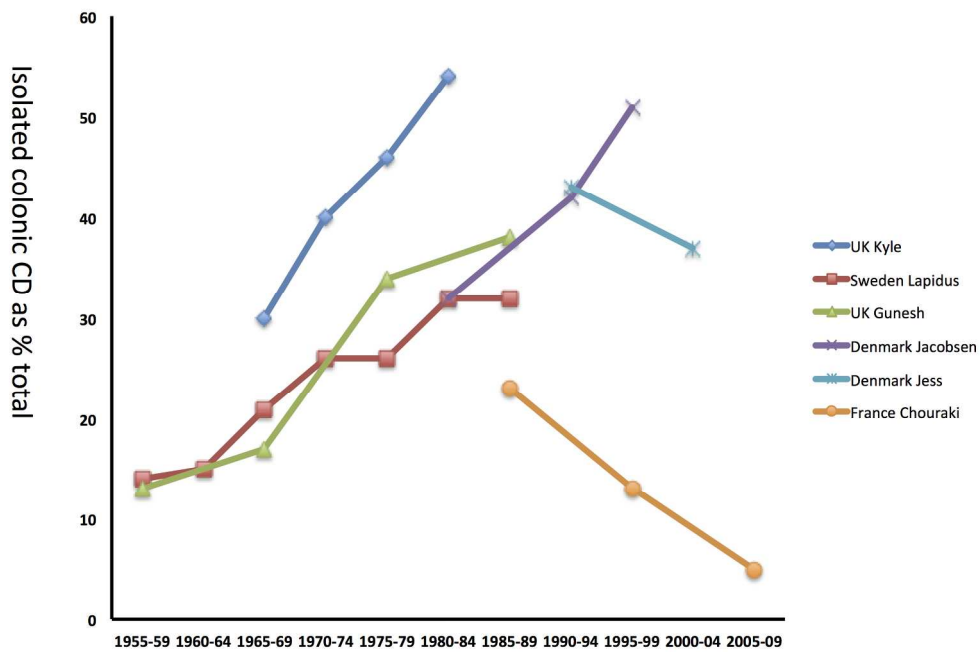


Comparison between Crohn's disease genetic risk score and ulcerative colitis genetic risk score for different locations of Crohn's disease, ulcerative colitis and IBD unclassified (from Cleyney et al,17 with permission.

This shows that isolated colonic Crohn's lies approximately equidistant genetically between ileal Crohn's disease and ulcerative colitis.

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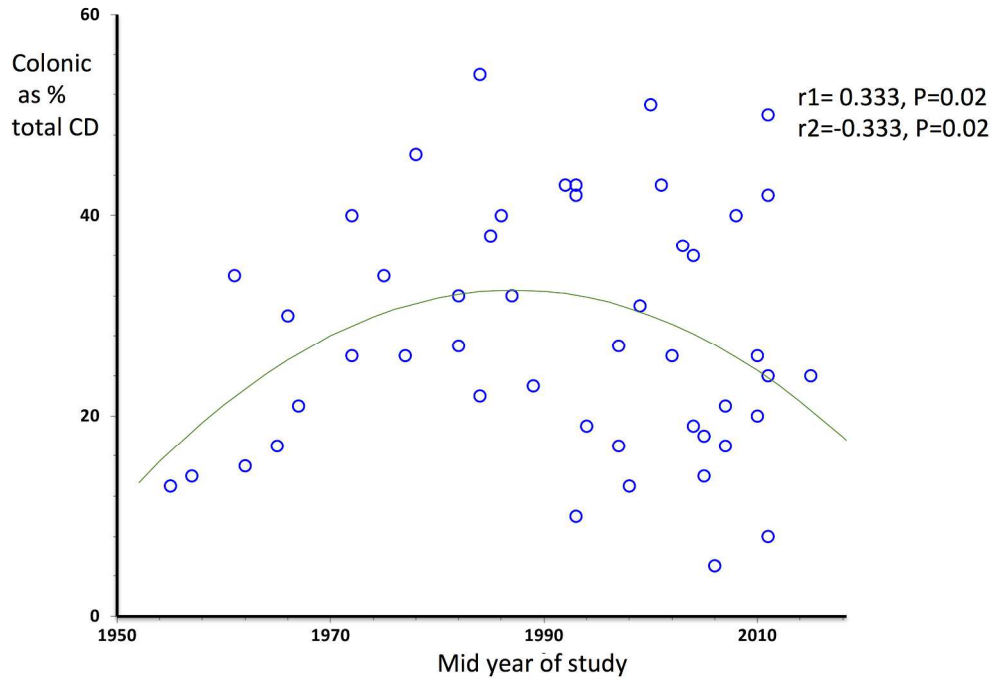
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Isolated colonic Crohn's as percentage of all Crohn's disease by year in studies reporting sequential data from the same centres or geographical areas.
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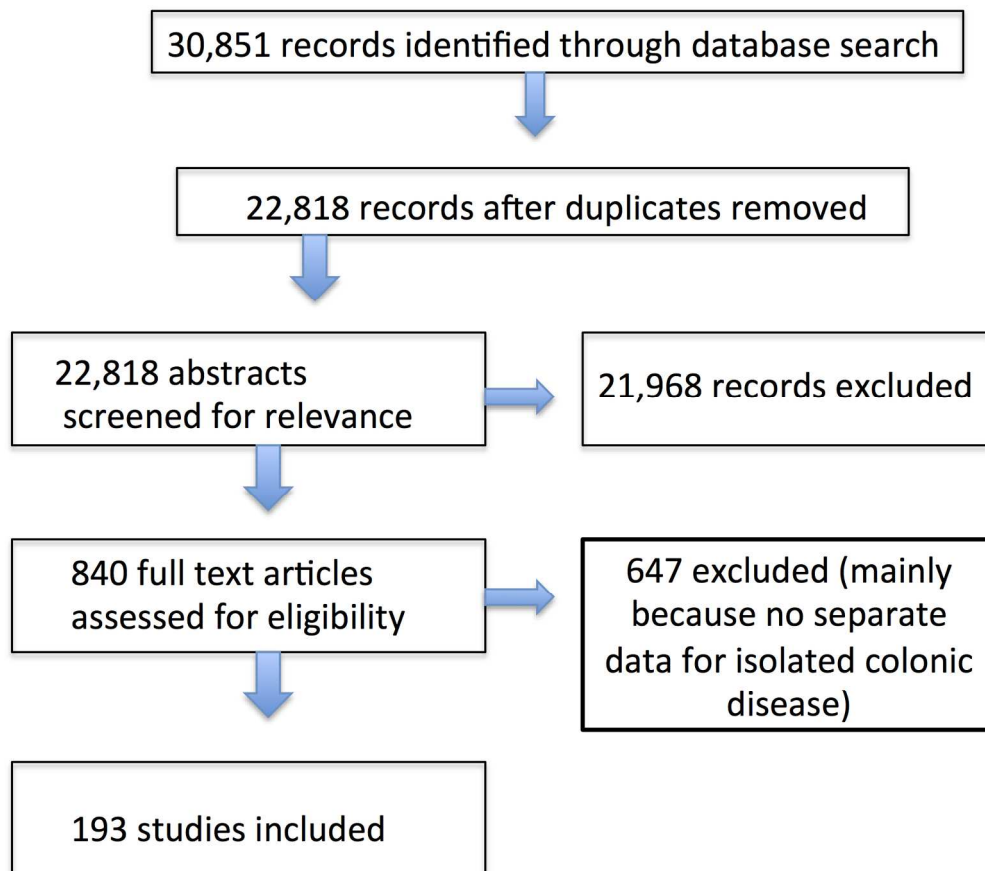
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Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all studies.
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ABSTRACT

The genetics of isolated colonic Crohn's disease place it approximately midway between Crohn's disease with small intestinal involvement and ulcerative colitis, 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 ulcerative colitis, no response to mesalazine, but possibly better response to anti-TNF than Crohn's disease at other sites. Diagnostic distinction from ulcerative colitis 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 involvement² although non-tuberculous granulomatous involvement of ileum and colon had been reported in 1923³ and later by others.^{4,5} From the 1930's to the 1950's, 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 ulcerative colitis.⁸ Identification of Crohn's disease of the colon separately from ulcerative colitis was strongly reinforced by Lockhart-Mummery and Morson, (1960) who described 25 cases with features including non-bloody diarrhoea, anal fistulae, rectal sparing, skip lesions and strictures.⁹ 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 Stecher reported 45 patients with isolated colonic Crohn's disease, with fistulation in nearly two thirds, and skip lesions in 20%.¹⁰

Later evidence that colonic Crohn's disease, unlike ulcerative colitis, 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 ulcerative colitis.

Distinction of colonic Crohn's disease from ulcerative colitis 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 "inflammatory bowel disease unclassified" (IBD-U) was recommended for such cases.¹⁶

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3 The scene is now changing again – extensive data show that isolated colonic Crohn’s disease
4 is genetically separable from Crohn’s disease involving the small intestine.¹⁷ When the ratio
5 of Crohn’s-associated genes to ulcerative colitis-associated is compared with disease
6 phenotype isolated colonic Crohn’s disease lies approximately midway between ileal
7 Crohn’s and ulcerative colitis. IBD-U, although statistically separable from ulcerative colitis
8 overlaps it considerably and ileo-colonic Crohn’s disease similarly overlaps ileal Crohn’s
9 disease (Figure 1). This finding led to recommendation that Crohn’s disease with ileal
10 involvement (ileal and ileocolonic), isolated colonic Crohn’s disease and ulcerative colitis
11 should be considered as three separate conditions.
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15 It is therefore timely to review the epidemiology, genetics, serology, microbiology, and
16 response to treatment of isolated colonic Crohn’s disease and to reconsider whether this
17 “evidence” favours isolated colonic Crohn’s disease as a variant of Crohn’s disease, as a
18 variant of ulcerative colitis, or as a separate condition.
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20 21 **METHODS**

22 The medical literature was searched using National Library of Medicine/Pubmed to 1st
23 December 2015 using the terms “colonic and Crohn’s” “Crohn’s and colitis” “epidemiology
24 and Crohn’s”. We conducted additional searches for “smoking and Crohn’s disease” and
25 “oral contraception and Crohn’s”. Later (to 1st June 2016) additional searches for “Crohn’s”
26 and each of the therapies covered were performed. After removal of duplicates and
27 screening of abstracts for relevance, 840 were selected for further review (Supplementary
28 Figures 1 & 2). Whilst the literature search was fully systematic, the subject of this review is
29 necessarily much broader than that of a conventional systematic review. We have only
30 included full publications in English language and have not attempted to judge quality of the
31 data. For epidemiological studies we included all reports that (a) contained data on at least
32 100 patients with Crohn’s disease and (b) included separate data for isolated colonic
33 Crohn’s disease (Montreal classification L2). Where published studies had overlapping
34 patient base and time period we used only the more completely described data set to avoid
35 duplication. For other aspects of the review (genetics, serological testing, response to
36 therapies and association with environmental factors) we included all studies that identified
37 isolated colonic Crohn’s disease separately. For therapeutic studies we have separately
38 identified data that have been obtained from randomized clinical trials and those that have
39 been obtained from cohort studies. It should be noted that, whereas pure ileal Crohn’s and
40 pure colonic Crohn’s should be readily distinguished by a comprehensive diagnostic
41 assessment including ileal intubation, incomplete assessment could mislabel ileocolonic as
42 colonic. This should be taken into account particularly in respect of older studies but we
43 have taken care to ensure that all data included here regarding isolated colonic disease
44 relate to patients thought at the time of publication not to have ileal disease. Statistical
45 analysis was performed using StatsDirect3 v 3.0.171 StatsDirect Ltd, UK.
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51 **PATHOLOGY, DIFFERENTIAL DIAGNOSIS, AND DISEASE COURSE – DEFINING THE** 52 **CONDITION**

53 The histological features of isolated colonic Crohn’s disease were first defined by Lockhart-
54 Mummery and Morson.⁹ They labeled patients with this diagnosis because “they had the
55 same characteristic pathology in the large intestinal lesions as that described by Hadfield¹⁸
56 for the disease as it affects the small intestine”. Gross appearances of the colon following
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3 colectomy include less sharp demarcation of ulceration than typically seen in ulcerative
4 colitis and with areas of intact intervening mucosa. In some cases, very marked fibrous
5 thickening with associated stricturing was present. Fibrosis and oedema sometimes
6 extended into the pericolic fat and enlargement of regional lymph nodes was marked.
7 Warren later split the macroscopic features into three patterns: isolated rectal disease;
8 stricturing colonic disease; diffuse colitis – usually with rectal sparing, and noted that
9 approximately 75% develop perianal pathology during their disease course.¹⁹
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12 Microscopic features described by Morson included discontinuous inflammation and
13 ulceration which could extend into the submucosa or deeper into the wall as the basis of
14 fistula formation, plus focal crypt irregularity. Non-caseating epithelioid granulomas were
15 present in the majority, distributed through all layers of the bowel wall as well as regional
16 lymph nodes. Other features included submucosal lymphangiectasia and neuromatous
17 hyperplasia.²⁰ It has subsequently been noted that the earliest lesions – aphthous ulcers –
18 which usually overlie lymphoid follicles, are preceded by a “red ring” sign on colonoscopy,
19 biopsy of which reveals a lymphoid follicle surrounded by reactive hypervascularisation.²¹
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23 Histopathology alone is diagnostic only in the minority – in a series of 103 cases of Crohn’s
24 colitis, diagnosis was determined by microscopy alone in 28%, by distribution (rectal sparing
25 and/or discontinuity) alone in 22% and by combination of the two in 50%.²² Particularly
26 discriminatory features suggesting Crohn’s colitis rather than ulcerative colitis include
27 granulomata, submucosal inflammation, and relative preservation of goblet cells.^{23,24} At an
28 international workshop expert pathologists “correctly” identified only 64% of cases with
29 Crohn’s colitis and 74% with ulcerative colitis²⁵ leading the European consensus on
30 histopathology of inflammatory bowel disease (2013) to note that “accurate discrimination
31 between the two diseases (Crohn’s colitis and ulcerative colitis) is not yet optimal amongst
32 expert gastrointestinal pathologists”. Given that inflammatory disease pathogenesis is
33 multifactorial an alternative interpretation would be that there is a continuous phenotypic
34 spectrum that runs through from “typical” ulcerative colitis, through IBD-unclassified to
35 “typical” Crohn’s colitis.
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39 Early studies reported an additional incidence peak of Crohn’s disease in the elderly
40 resulting from cases particularly affecting the sigmoid colon.²⁶ Following the later
41 clarification of segmental colitis associated with diverticular disease (SCAD) this seems
42 probably attributable to SCAD. SCAD can be indistinguishable histologically from
43 inflammatory bowel disease and includes a “Crohn’s-like” variant with granulomata.²⁷ This
44 reflects emphasis often placed on the diagnostic specificity of the granuloma. However,
45 granulomas are only found in colonoscopic biopsies at diagnosis in about 66% of adults with
46 colonic Crohn’s disease, falling to 18% at follow-up.²⁸ Moreover granulomas, particularly in
47 association with crypts, can be found in ulcerative colitis.²⁹ Other forms of colitis that may
48 need to be considered in the differential include ischemic colitis (see earlier) and infections
49 including amoebiasis and tuberculosis but it is beyond the scope of this review to consider
50 these further.
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55 Localisation of disease to the colon remains fairly constant over time. The largest published
56 data set by far is the 16,902 Crohn’s disease cohort, including 2,933 with isolated colonic
57 disease, in the recent genotype/phenotype association study.¹⁷ This confirmed previous
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reports of low rates of progression to ileo-colonic 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, eg 0/45 cases in a Belgian series³³ whereas penetrating disease (B3) as defined by the Vienna classification (ie including perianal fistulae) occurred in 23% in the same series, less frequently than in patients with ileal disease (46%; $P=0.0003$) or ileocolonic (28.6%; NS). The much larger genotype/phenotype association study confirmed that cumulative probability of progression to B2 and B3 combined over ten 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 ten years (22%) than for ileo-colonic (42%) or ileal disease (62%). A recent meta-analysis showed that colon cancer risk in isolated colonic Crohn's disease is similar to ulcerative colitis of equivalent extent with a pooled standardized incidence ratio (SIR) of 1.7; 0.9-2.6 95%CI (population based data) compared with SIR 1.8; 1.2-2.4 for ulcerative colitis but rising to SIR 18.2; 7.8-35.8 for extensive colonic Crohn's disease in a referral centre population compared with SIR 21.6; 15.0-31.0 for extensive ulcerative colitis.³⁴

EPIDEMIOLOGY

Changes over time

Studies reporting sequential data from a single centre or region show interesting time trends. Studies from 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 which 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 – eg median 25 years in the 16,902 patients studied by Cleynen et al¹⁷. Older age of isolated colonic versus other sites of Crohn's disease was also confirmed by the IBDchip European Project.⁸⁵ The preponderance of isolated colonic disease amongst children with very early onset Crohn's disease is discussed later.

Smoking

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3 Cigarette smoking is associated with increased risk for development and progression of
4 Crohn's disease but reduced risk for ulcerative colitis. Smoking is more strongly associated
5 with risk for ileal and ileo-colonic Crohn's disease than for isolated colonic disease (Table 2).
6 Only one study (of nine)⁷⁹ reported a higher rate of smoking amongst patients with isolated
7 colonic Crohn's disease. If the South African data⁸⁴ which reported exceptionally high rates
8 (73%) across all groups are excluded, the other studies report rates for smoking amongst
9 patients with isolated colonic disease that averaged 37.8% compared with 49.8% (P=0.008
10 by paired t test) for other Crohn's disease sites. This smoking rate is probably slightly higher
11 than for the general population – approximately 30% European adults were smokers in 2008
12 (WHO).⁸⁶
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16 Smoking worsens prognosis of Crohn's disease overall and cessation of smoking improves
17 it.^{87,88} This has been studied less in isolated colonic disease but the conclusion is similar. The
18 largest study⁸⁰ included 688 patients with Crohn's colitis, 978 with ulcerative colitis and 118
19 with "indeterminate" colitis. Sixty-one per cent of patients with ulcerative colitis or
20 indeterminate colitis had stopped smoking before disease onset compared with only 12% in
21 isolated colonic Crohn's disease. In women but not men with isolated colonic disease the
22 risk of needing immunosuppression was increased amongst smokers (10-yr cumulative risk
23 48% in non-smokers vs 58% in smokers, P<0.01). An earlier study⁷⁴ showed that smokers
24 with Crohn's colitis relapsed approximately 50% more often (P=0.028) and with more pain
25 (P<0.007) than non-smokers.
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29 Thus smoking at best has a neutral effect on isolated colonic Crohn's disease but more likely
30 is harmful.
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33 Oral contraception

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35 Meta-analysis of 14 studies, with adjustment for smoking, showed a relative risk of 1.51
36 (95%CI 1.17-1.96, P=0.002) for Crohn's disease amongst women currently taking oral
37 contraception⁸⁹. The relative risk for ulcerative colitis was also increased at 1.53 (1.21-1.94,
38 P=0.001). Six of the seven studies that reported risk associated with oral contraception
39 separately for isolated colonic disease found a significant association (Table 3) with
40 relatively high odds ratio (2.63), risk ratios (3.6 and 3.23) or hazard ratio (4.13). The sole
41 exception⁹¹ only included 8 cases with isolated colonic Crohn's disease and showed no
42 overall association between oral contraception and risk for Crohn's disease. Excluding the
43 latter study⁹¹, five of the other six show higher risks amongst oral contraceptive users for
44 isolated colonic Crohn's than for other sites.
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47 *Oestrogen-associated ischaemic colitis as a confounder*

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50 An early study from Birmingham⁵⁰ reported patients with apparent oral contraceptive-
51 associated colonic Crohn's disease who had non-granulomatous colitis with rectal sparing.
52 Ischaemic colitis is a rare but recognized complication of oral contraception that might
53 cause diagnostic confusion.^{97,98,99} Most cases have a short duration with typical features of
54 ischaemic colitis including abdominal pain, and rectal bleeding. Colonoscopy shows mucosal
55 friability but no linear ulceration and the proximal colon and rectum are typically normal.
56 Such cases should be readily distinguishable from colonic Crohn's disease but Tedesco¹⁰⁰
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3 reported five cases of oral contraceptive-associated colitis with features that overlapped
4 more with colonic Crohn's disease than ischaemic colitis. Moreover, colonic
5 "thumbprinting", a characteristic feature of ischaemic colitis, has been reported in Crohn's
6 disease.¹⁰¹ It is unclear whether diagnostic overlap with milder cases of oral contraceptive-
7 associated ischaemic colitis contributes to the female preponderance of isolated colonic
8 Crohn's disease. If it does then the change to lower oestrogen dosing in later versions of the
9 contraceptive pill might be a plausible explanation for the apparent fall off in cases in recent
10 decades.¹⁰² Clinicians should be aware of the possible associations between oral
11 contraception and inflammatory bowel disease or ischaemic colitis and advise patients
12 accordingly – such advice should usually include at least a temporary cessation of oral
13 contraception to assess impact on the colitis.
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16 17 **GENETICS**

18 The strongest genetic association with IBD is the link between NOD2/CARD15 and Crohn's
19 disease. Meta-analysis of 42 studies showed that this association was stronger for Crohn's
20 disease with small bowel involvement than for those without (OR 2.53; 95%CI 2.01-3.16).¹⁰³
21 Subsequent study of 1528 patients with Crohn's disease from 8 centres (in 7 European
22 countries) (IBDchip) confirmed the association of NOD2/CARD15 with ileal involvement and
23 also showed that Interleukin23 receptor polymorphisms were more strongly associated with
24 isolated colonic Crohn's (OR 2.20; 95%CI 1.17-4.57).⁸⁵
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28 The most consistent genetic link with ulcerative colitis is with the rare Major
29 histocompatibility Complex (MHC) / Human Leucocyte Antigen (HLA) Class II allele HLA-
30 DRB*0103. This occurs in less than 2% in European and white North American populations
31 and is absent in the Japanese. It is strongly associated with colonic Crohn's disease where it
32 is present at up to 32% frequency with Odds Ratios for isolated colonic disease of 5.1-18.5
33 compared with Crohn's disease at other sites.¹⁰⁴
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36 The largest study to compare genetic associations with Crohn's disease phenotype included
37 19713 patients from 49 centres across 16 countries in Europe, North American and
38 Australasia.¹⁷ This confirmed that the strongest association with isolated colonic Crohn's
39 disease was HLA-DRB1*01:03 ($p=1.47 \times 10^{-23}$, ileal vs colonic OR 0.32, 95%CI 0.29-0.41;
40 ileocolonic vs colonic OR 0.47, 95%CI 0.39-0.57). The only other loci that were significant
41 across all analyses in this study were NOD2 (16q12), again associated with increased risk for
42 ileal involvement (OR ileocolonic vs colonic 1.61, 1.59, and 1.89 for the three NOD2
43 polymorphisms tested) and also MST1 (macrophage stimulating -1 that encodes a protein
44 which induces macrophage phagocytosis) polymorphisms which were more weakly
45 associated with ileal involvement (OR 1.07 -1.10 according to polymorphism and whether
46 comparing ileal or ileocolonic with colonic disease). When overall genetic risk scores for
47 Crohn's disease and ulcerative colitis were computed as a ratio and compared with
48 phenotype, isolated colonic Crohn's disease was found to be approximately "balanced" in
49 respect of Crohn's disease versus ulcerative colitis genetic risk factors (Figure 1). It was
50 found though that even the combination of smoking status with the strongest genetic
51 predictors could only explain 6.8% of the variance for disease location.
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56 **ISOLATED COLONIC CROHN'S DISEASE IN CHILDHOOD AND SINGLE GENE DISORDERS**

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3 Amongst children with very early onset Crohn's disease there is a marked preponderance of
4 cases with isolated colonic disease eg 76.5% before age 5¹⁰⁵ and 42% before age 8.¹⁰⁶
5 Amongst younger cases there is a strong male preponderance – eg 1.6:1 across all Crohn's
6 disease presenting <5¹⁰⁵ and some of this is accounted for by X-linked single gene disorders.
7 The first such condition to be identified was X-linked Chronic Granulomatous Disease.
8 Chronic Granulomatous Disease is associated with defects in neutrophil function leading to
9 skin lesions and in around 40% with a form of inflammatory bowel disease that is
10 indistinguishable from Crohn's disease, typically with predominant colorectal and perianal
11 involvement.¹⁰⁷ It is due to mutations in one of four NADPH oxidase complex component
12 genes of which the commonest (CYBB) located on the X chromosome accounts for about
13 65% cases.
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17 Rapid developments in DNA sequencing have allowed identification of over 50 further single
18 gene disorders that present as inflammatory bowel disease, typically as colonic disease and
19 with presentation before age 6, defined as Very Early Onset IBD or VEO-IBD.¹⁰⁸ VEO-IBD
20 cases account for 4-10% of paediatric inflammatory bowel disease.¹⁰⁹ One of the commoner
21 single gene variants is in the coding region of X-linked inhibitor of apoptosis protein (XIAP)
22 that accounts for about 4% of male patients with paediatric onset Crohn's disease.¹¹⁰
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27 **SEROLOGY INCLUDING ANTI-MICROBIAL AND ANTI-NEUTROPHIL ANTIBODIES**

28 Anti-microbial antibodies such as Anti-Saccharomyces cerevesiae (ASCA) and antibodies to
29 outer membrane protein (ompC) are found less often and/or at lower titre in isolated
30 colonic Crohn's than in other Crohn's phenotypes.¹¹¹ Meta-analyses confirm this particularly
31 for ASCA.¹¹²⁻¹¹⁴ Average sensitivity of ASCA for isolated colonic Crohn's disease diagnosis is
32 31% but with a wide range (8-59%) and an average 14% positivity rate in ulcerative colitis
33 (Table 4). The clinical utility of ompC antibodies has been less studied but reported
34 positivity/sensitivity in isolated colonic Crohn's disease is substantially lower than that for
35 ASCA.
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38 Anti-neutrophil antibodies, particularly an atypical peri-nuclear antibody (pANCA), are
39 present in around 55% of patients with ulcerative colitis¹¹⁴ and 23% of patients with isolated
40 colonic Crohn's disease (Table 4). This compares with pANCA positivity of around 11% in
41 Crohn's disease overall and 3% in non-IBD controls.¹¹⁴
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44 A combination of positive ASCA and negative pANCA is more discriminatory eg positivity
45 rate in isolated colonic Crohn's disease of 52% compared with 9% in ulcerative colitis¹²² but
46 is still insufficiently predictive for routine clinical use.¹²⁵
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49 Thus the frequency in isolated colonic Crohn's disease of both ASCA and pANCA antibodies
50 lies somewhere in between that found in Crohn's disease with ileal involvement (more likely
51 ASCA+, and pANCA-) and that found in ulcerative colitis (more likely ASCA- and pANCA+).
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55 **MICROBIOTA**

56 The faecal microbiota in active inflammatory bowel disease is commonly dysbiotic with
57 reduced bacterial diversity.^{126,127} This could be secondary to inflammation yet still significant
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3 in maintaining chronicity. The large study of pre-treatment Crohn's disease by Gevers
4 showed only a mild dysbiosis in the faecal microbiota and much greater separation of
5 Crohn's disease from healthy controls when the mucosa-associated microbiota was
6 studied.¹²⁸ Ileal and rectal mucosal samples typically showed a reduction in *Firmicutes* such
7 as *Faecalibacterium prausnitzii* and an increase in *Proteobacteria* such as *Escherichia coli* as
8 well as in *Veillonella*, *Haemophilus* and *Fusibacteria*. This confirmed many previous studies
9 showing an increase in mucosa-associated *E. coli* in Crohn's disease as well as several
10 showing a reduction in *F. prausnitzii*¹²⁹⁻¹³².

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13 The faecal and mucosa-associated microbiota in isolated colonic Crohn's disease are
14 generally closer to that of healthy controls than is found in patients with ileal or ileocolonic
15 Crohn's disease (Table 5). Thus Baumgart *et al*¹²⁹ found that an increase in ileal mucosa-
16 associated *E. coli* and reduction in ileal *F. prausnitzii* was only present in patients with
17 Crohn's disease who had ileal involvement and not in those with isolated colonic disease.
18 Similarly, a study of twins with/without Crohn's disease showed that faecal microbial
19 diversity was only reduced and *Proteobacteria* increased in patients with ileal involvement
20 and not in patients with isolated colonic disease.¹³⁰ A previous report by the same group
21 also showed a reduction in *F. prausnitzii* in Crohn's patients with ileal involvement but not in
22 isolated colonic disease.¹³¹ Both the twin study by Willing¹³¹ and the large study in
23 children¹²⁸ and adolescents¹³⁴ did however show differences between the mucosa-
24 associated microbiota in isolated colonic Crohn's disease and ulcerative colitis. 16sRNA
25 pyrosequencing of mucosal samples¹³³ confirms the increase in *E. coli* and reduced *F.*
26 *prausnitzii* in Crohn's disease with ileal involvement with milder changes in isolated colonic
27 disease, although the latter did show some reduction in *F. prausnitzii* compared with
28 healthy controls. This study also confirmed that the mucosa-associated microbiota are
29 consistent at different sites from ileum to rectum in the same individual.
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35 In conclusion, mucosa-associated microbiota changes in Crohn's disease are more marked
36 than faecal changes. The microbiota in isolated colonic Crohn's disease, show changes that
37 tend to be less marked and less consistent than those found in Crohn's disease with ileal
38 involvement.
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43 **RESPONSE TO TREATMENT**

44 **Mesalazine**

45 Systematic reviews show no convincing benefit of oral mesalazine (5-aminosalicylic acid)
46 over placebo either in induction of remission or in maintenance of medically induced
47 remission in Crohn's disease as a whole^{134,138} although they may have a modest benefit in
48 maintaining surgically-induced remission.¹³⁹ Sulphasalazine (sulphapyridine linked via azo
49 bond to 5-aminosalicylate) has possible modest efficacy in induction of remission.^{134, 136}
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55 Amongst trials that have reported data separately for isolated colonic Crohn's disease, only
56 one trial studied the effect of oral mesalazine in remission induction¹⁴⁰ and four studied its
57 effect in maintenance of medically-induced remission¹⁴¹⁻¹⁴⁴ (Table 6). In none of these was
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mesalazine significantly more effective than placebo but in two studies^{141,142} 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 diarrhea.¹⁴⁵ Sulphasalazine was no better than placebo in two trials of maintenance^{146,147} but there was a weak signal of efficacy in remission induction in two trials^{147,148} but 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. Sulphasalazine 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 though these have included diverse antibiotics and small trials.¹⁴⁹⁻¹⁵¹ The largest study to date is for rifaximin.¹⁵² Three doses were tested: 400, 800, 1200mg or placebo twice daily for 12 weeks with good efficacy overall but no dose response. Amongst 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 (Blichfeldt¹⁵³: n=6 crossover; Sutherland¹⁵⁴: 8 active and 4 placebo). In a study of 134 patients randomly assigned to ciprofloxacin and metronidazole, both 500mg twice daily, or placebo in combination with budesonide 9mg daily¹⁵⁵ 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 randomized 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).¹⁵⁶ No differential response was seen according to disease location but data were not presented separately for patients with isolated colonic disease.

Rifaximin and metronidazole thus show some evidence of efficacy in patient 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.^{147,148} Each of these included only 8 steroid-treated patients with isolated colonic disease (Table 8) with one trial¹⁴⁷ showing no benefit and the other¹⁴⁸ showing efficacy. There has never been a trial to assess dose-responsiveness to

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3 conventional corticosteroids in Crohn's disease so optimal dosage is unknown. More data
4 are available for budesonide but trials have focused predominantly on patients with ileal or
5 ileo-colonic disease so data in isolated colonic disease are again very sparse. The data from
6 one comparison with mesalazine¹⁵⁷, support efficacy in isolated colonic Crohn's disease,
7 possibly with a weaker effect than conventional corticosteroids¹⁵⁸, but reduced
8 corticosteroid side-effects.
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10 11 12 13 **Anti-TNF**

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17 None of the randomised trials of infliximab^{159,160} or adalimumab¹⁶¹⁻¹⁶⁴ reported subgroup
18 analyses of outcomes based on disease location. In a randomised, placebo controlled trial of
19 certolizumab pegol, patients with colonic (OR 2.39, 95% CI 0.99-5.75, P=0.052) and
20 ileocolonic disease (OR 2.07, 95% CI 1.01-4.28, P=0.048) were more likely to achieve
21 remission at week 6 compared to ileal disease (OR 0.42, 95% CI=0.18-0.99, P=0.048)¹⁶⁵ (Table
22 9)
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25 Several cohort studies have assessed colonic disease location as a predictor of response to
26 anti-TNF agents, four with infliximab and one with adalimumab. Three cohort studies
27 assessing induction therapy with infliximab¹⁶⁶⁻¹⁶⁸ all showed better response rates in
28 isolated colonic disease than for disease at other sites. Paradoxically, cohort studies of
29 infliximab maintenance in children¹⁶⁹ and of adalimumab maintenance in adults¹⁷⁰ both
30 showed higher risk of lost response or dose escalation in isolated colonic disease. Overall,
31 the evidence supports good efficacy for anti-TNF therapy in induction of remission in
32 isolated colonic Crohn's disease but possibly with a higher subsequent rate of loss of
33 response.
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36 37 **Vedolizumab**

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39 In the combined induction and maintenance study of vedolizumab there was no significant
40 difference in efficacy in isolated colonic disease compared with other locations.¹⁷¹ (Table 9)
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42 43 **Enteral nutrition**

44 Exclusive enteral nutrition is effective as primary therapy in patients with active Crohn's
45 disease^{172,173} and partial enteral nutrition has shown efficacy in maintenance of remission.¹⁷⁴
46 In ulcerative colitis total parenteral nutrition and bowel rest are ineffective¹⁷⁵ and
47 comparison of enteral with parenteral nutrition showed no difference in efficacy¹⁷⁶ implying
48 no efficacy for enteral nutrition either. Whether enteral nutrition is effective as primary
49 therapy in isolated colonic Crohn's disease is controversial. Relatively few studies provide
50 separate data on patients with isolated colonic Crohn's disease (Table 10). Five of the six
51 studies are in children. Two studies^{178,179} report poorer results in children with isolated
52 colonic disease compared with those with small intestinal involvement. Numbers are small
53 though (19 cases of isolated colonic disease across the two trials) and the other studies
54 (including 72 cases of isolated colonic disease across four trials) found no significant
55 difference in remission rates for those with isolated colonic disease compared with other
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3 sites. Further trials of exclusive enteral nutrition are needed in patients with isolated colonic
4 disease.
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6 7 **Surgery**

8 *Faecal diversion*

9 Colonic Crohn's disease commonly responds to "bowel rest" induced by a defunctioning
10 ileostomy whereas ulcerative colitis does not.^{11, 12} Instillation of unfiltered ileostomy
11 contents into the defunctioned colon induced relapse whereas instillation of content that
12 had passed through a 0.22micron pore diameter filter did not, implying a role for bacteria in
13 pathogenesis.¹⁸³ Defunctioning ileostomy has become less commonly performed for the
14 treatment of uncomplicated colonic Crohn's disease since it was shown that at least 50%
15 relapsed after continuity was restored.¹⁸⁴
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18 *Resection*

19 The cumulative risk of surgery for isolated colonic Crohn's disease is reported as 22-33% by
20 10 years after diagnosis compared with around 75-90% for ileal disease.^{17,67} Partial
21 resection, either right hemicolectomy for proximal disease or a segmental resection for
22 more distal disease has been shown to be successful therapy for colonic Crohn's disease^{185,}
23 ¹⁸⁶ as is colectomy with ileo-rectal anastomosis for more extensive disease if the rectum is
24 uninvolved^{187,188}. Approximately 75% of patients with ileo-rectal anastomosis will still have a
25 functioning anastomosis after 10 years and about two thirds of those treated by segmental
26 resection will not have required a further resection.¹⁸⁸ Recurrence rates are similar after
27 either procedure.¹⁸⁹ This contrasts with left-sided ulcerative colitis, where the tempting
28 option of left hemicolectomy with right-sided colo-anal anastomosis consistently fails,
29 usually with rapid recurrence of colitis in the retained colon.¹⁹⁰ It should be noted though
30 that segmental resection for colon cancer complicating colonic Crohn's disease has been
31 associated with high (39%) risk for metachronous colon cancer¹⁹¹ suggesting that
32 panproctocolectomy might be a safer option for such patients.
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37 *Ileo-anal pouch reconstruction*

38 Crohn's disease has generally been considered a contra-indication for restorative ileo-anal
39 pouch surgery and even in selected patients pouch failure of 57% has been reported from
40 the UK.¹⁹² Others have suggested that it may be successful in very carefully selected
41 patients. Thus, a series of 3,707 patients with ileal-pouch anal anastomosis from the
42 Cleveland Clinic included 150 with Crohn's disease, of whom 32 had a pre-operative
43 diagnosis, the remainder diagnosed by post-operative histopathology or on follow-up.
44 Amongst 59 patients with Crohn's disease reaching 10 year follow-up, pouch survival was
45 80%.¹⁹³ Forty nine of 132 patients (37%) needing pouch excision had a histological diagnosis
46 of Crohn's disease. Considering that a pre-operative diagnosis of Crohn's disease was only
47 present in less than 1% of patients receiving pouch-anal anastomosis these data do not
48 make a strong case for this procedure in patients with a definite diagnosis of colonic Crohn's
49 disease.
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55 **CONCLUSION**

56 Current data suggest that the genetics, microbiota, serology and smoking association of
57 isolated colonic Crohn's disease lie between those of ileo/ileocolonic Crohn's disease and
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3 ulcerative colitis and make a strong case for this phenotype being considered separately
4 (Table 11). Genetic data in particular show good separation from ileal/ileocolonic Crohn's
5 disease and the low rate of progression from isolated colonic to ileo-colonic disease help to
6 justify this distinction. There is a disappointing paucity of good quality therapeutic data but
7 the lack of response to mesalazine, whose target cell is the surface epithelium, suggests a
8 different pathophysiology to ulcerative colitis and there are important differences from
9 ulcerative colitis in surgical outcomes, including a good response to segmental resection in
10 selected cases and a generally poor response to pouch reconstruction. Taken together this
11 implies a compelling need for isolated colonic Crohn's disease to be identified separately
12 from ileal/ileocolonic disease and from ulcerative colitis. This is particularly important when
13 future therapeutic trials are designed and when cohort studies are reported.
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19

20
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22 pharmaceuticals, Shire and received educational grant from MSD, Abbvie, Actavis and is an
23 advisory board member for Abbvie, Dr Falk pharmaceuticals, Janssen and Vifor
24 pharmaceuticals. JMR is or has been a member of advisory boards for Atlantic,
25 Pharmacosmos, Procter and Gamble, Vifor and Falk, has received speaking honoraria from
26 Abbott, Falk, Ferring, Glaxo Smith Kline, Merck, Procter and Gamble, Schering Plough, Shire,
27 and Wyeth, and with the University of Liverpool and Provox UK, holds a patent for use of a
28 soluble fibre preparation as maintenance therapy for Crohn's disease plus a patent pending
29 for its use in antibiotic-associated diarrhoea.
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32 Provenance and peer review: Commissioned; externally peer reviewed.
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36 LEGENDS TO FIGURES:

37 1. Comparison between Crohn's disease genetic risk score and ulcerative colitis genetic
38 risk score for different locations of Crohn's disease, ulcerative colitis and IBD unclassified
39 (from Cleynen et al,¹⁷ with permission. This shows that isolated colonic Crohn's lies
40 approximately equidistant genetically between ileal Crohn's disease and ulcerative
41 colitis.
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44 2A. Isolated colonic Crohn's as percentage of all Crohn's disease by year in studies
45 reporting sequential data from the same centres or geographical areas.

46 2B. Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all
47 studies.
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52 Supplementary Files

- 53 1. PRISMA flow diagram.
- 54 2. PRISMA checklist.
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REFERENCES

1. Barga JA, Weber HM. Regional migratory chronic ulcerative colitis. *Surg Gynecol Obstet* 1930;1:964-72.
2. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathologic and clinical entity. *J Amer Med Assoc* 1932;99:1323-9.
3. Moschowitz E, Wilensky AO. Non-specific granulomata of the intestine. *Am J Med Sci* 1923;166:48-66.
4. Colp R. A case of nonspecific granuloma of the terminal ileum and caecum. *Surg Clin N America* 1934;14:443-9.
5. Crohn BB, Rosenak BD. A combined form of ileitis and colitis. *J Amer Med Assoc* 1936;106:1-7.
6. Neuman HW, Barga JA, Judd ES. A clinical study of two hundred and one cases of regional (segmental) colitis. *Surg Gynecol Obstet* 1954;99:563-71.
7. Wells C. Ulcerative colitis and Crohn's disease. *Ann Roy Coll Surg Engl* 1952;11:105-20.
8. Goldgraber MB, Kirsner JB, Palmer WL. The histopathology of chronic ulcerative colitis and its pathogenic implications. *Gastroenterology* 1960;38:596-604.
9. 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.
10. Cornes JS, Stecher M. Primary Crohn's disease of the colon and rectum. *Gut* 1961;2:189-201.
11. Truelove SC, Ellis H, Webster CD. The place of a double-barrelled ileostomy in ulcerative colitis and Crohn's disease of the colon: a preliminary report. *Brit Med J* 1965;1:150-3.
12. 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.
13. 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;13:611-4.
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.
15. Price AB. Overlap in the spectrum on non-specific inflammatory bowel disease – "colitis indeterminate". *J Clin Pathol* 1978;31:567-77.
16. Satsangi J, Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus and implications. *Gut* 2006;55:749-53.
17. 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.
18. Hadfield G. The primary histological lesion of regional ileitis. *Lancet* 1939;2:773-5.
19. Warren BF. Classic pathology of ulcerative and Crohn's colitis. *J Clin Gastroenterol* 2004;38:S33-5.
20. Morson BC. Crohn's disease. *Proc Roy Soc Med* 1968;61:79-81.
21. 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.
22. Bull DM. Crohn's disease of the colon. *Gastroenterology* 1979;76:607-21.
23. 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.
24. 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.
25. 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.
 26. 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 (S3):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 DKL, Leong RWL, 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, Prosberg 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;52:552-57.
 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;27:211-9.
 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 JH1, Phillips SF, Melton LJ 3rd, *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 WG1, Brown JS, Parks TG. Crohn's disease in Northern Ireland--a retrospective study of 440 cases. *Ulster Med J* 1990;59:30-5.
 42. Ekbohm 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;70:10-5.
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, Cockel R, Allan RN, *et al.* Colonic Crohn's disease and the contraceptive pill. *British Medical Journal* 1984;288: 595-596.
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. 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.
56. 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.
57. Björnsson S, Tryggvason FP, 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.
58. Tozun N, Atug O, Imeryuz 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.
59. 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.
60. 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.

- 1
- 2
- 3 61. Ott C, Obermeier F, Thielier S, *et al.* The incidence of inflammatory bowel disease in a
- 4 rural region of Southern Germany: a prospective population-based study. *Eur J*
- 5 *Gastroenterol Hepatol* 2008;20:917-23.
- 6
- 7 62. Siddique I, Alazmi W, Al-Ali J, *et al.* Clinical epidemiology of Crohn's disease in Arabs
- 8 based on the Montreal Classification. *Inflamm Bowel Dis* 2012;18:1689-97.
- 9
- 10 63. Chen H, Lee A, Bowcock A, *et al.* Influence of Crohn's disease risk alleles and smoking on
- 11 disease location. *Dis Colon Rectum* 2011;54:1020-5.
- 12
- 13 64. Lucendo AJ, Hervías D, Roncero Ó, *et al.* Epidemiology and temporal trends (2000-2012)
- 14 of inflammatory bowel disease in adult patients in a central region of Spain. *Eur J*
- 15 *Gastroenterol Hepatol* 2014;26:1399-407.
- 16
- 17 65. Henckaerts L, Pierik M, Joossens M, *et al.* Mutations in pattern recognition receptor
- 18 genes modulate seroreactivity to microbial antigens in patients with inflammatory
- 19 bowel disease. *Gut* 2007;56:1536-42.
- 20
- 21 66. Herrinton LJ, Liu L, Lewis JD, *et al.* Incidence and prevalence of inflammatory bowel
- 22 disease in a Northern California managed care organization, 1996-2002. *Am J*
- 23 *Gastroenterol* 2008;103:1998-2006.
- 24
- 25 67. Hancock L, Beckly J, Geremia A, *et al.* Clinical and molecular characteristics of isolated
- 26 colonic Crohn's disease. *Inflamm Bowel Dis* 2008;14:1667-77.
- 27
- 28 68. Aloï M, Lionetti P, Barabino A, *et al.* SIGENP IBD Group. Phenotype and disease course of
- 29 early-onset pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2014;20:597-605.
- 30
- 31 69. Aljebreen AM, Alharbi OR, Azzam NA, *et al.* Clinical epidemiology and phenotypic
- 32 characteristics of Crohn's disease in the central region of Saudi Arabia. *Saudi J*
- 33 *Gastroenterol* 2014;20:162-9.
- 34
- 35 70. Burisch J, Pedersen N, Cukovic-Cavka S, *et al.* Environmental factors in a population-
- 36 based inception cohort of inflammatory bowel disease patients in Europe--an ECCO-
- 37 EpiCom study. *J Crohns Colitis* 2014;8:607-16.
- 38
- 39 71. Eglinton TW, Roberts R, Pearson J, *et al.* Clinical and genetic risk factors for perianal
- 40 Crohn's disease in a population-based cohort. *Am J Gastroenterol* 2012;107:589-96.
- 41
- 42 72. Ng SC, Tang W, Ching JY, *et al.* Incidence and phenotype of inflammatory bowel disease
- 43 based on results from the Asia-pacific Crohn's and colitis epidemiology study.
- 44 *Gastroenterology* 2013;145(1):158-165.
- 45
- 46 73. Somerville KW, Logan RFA, Edmond M, *et al.* Smoking and Crohn's disease. *Brit Med J*
- 47 1984;289:954-6.
- 48
- 49 74. Holdstock G, Savage D, Harman M, *et al.* Should patients with inflammatory bowel
- 50 disease smoke? *Brit Med J* 1984;288:362.
- 51
- 52 75. Tobin MV, Logan RFA, Langman MJS, *et al.* Cigarette smoking and inflammatory bowel
- 53 disease. *Gastroenterology* 1987;93:316-21.
- 54
- 55 76. Lindberg E, Järnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and
- 56 clinical course. *Gut* 1992;33:779-82.
- 57
- 58 77. Breuer-Katschinski B, Hollander N, Goebell H. Effect of cigarette smoking on the course
- 59 of Crohn's disease. *Europ J Gastroenterol Hepatol* 1996;8:225-8.
- 60
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. 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.
 83. 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.
 84. Chivese 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.
 85. Cleyne I, Gonzalez JR, Figueroa *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
 86. World Health Organisation. WHO Report on the global tobacco epidemic 2008: The MPOWER package. www.who.int/tobacco/mpower/2008/en/
 87. 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.
 88. 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.
 89. 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.
 90. 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.
 91. 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.
 92. Sandler RS, Wurzelmann JI, Lyles CM. Oral contraceptive use and the risk of inflammatory bowel disease. *Epidemiology* 1992;3:374-8
 93. Persson PG, Leijonmarck CE, Bernell O, *et al.* Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;22:268-72.
 94. 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.
 95. Khalili H, Higuchi LM, Ananthakrishnan AN, *et al.* Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut* 2013;62:1153-9.
 96. Khalili H, Chan AT. Author response: oral contraceptives and Crohn's disease. *Gut* 2015;64:854.
 97. 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.
 98. 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.
 99. Deana DG1, Dean PJ. Reversible ischemic colitis in young women. Association with oral

- 1
2
3 contraceptive use. *Am J Surg Pathol* 1995;19:454-62.
- 4 100. Tedesco FJ, Volpicelli NA, Moore FS. Estrogen- and progesterone-associated colitis: a
5 disorder with clinical and endoscopic features mimicking Crohn's colitis. *Gastrointest*
6 *Endosc* 1982;28:247-9.
- 7 101. Tsai HH, Howden CW, Thomson TJ. Probable Crohn's colitis mimicking ischaemic
8 colitis in a young adult. *Scott Med J* 1989;34:406-7
- 9 102. Alic M. Epidemiology supports oral contraceptives as a risk factor in Crohn's disease.
10 *Gut* 2000;46:140
- 11 103. Economou M1, Trikalinos TA, Loizou KT, *et al.* Differential effects of NOD2 variants
12 on Crohn's disease risk and phenotype in diverse populations: a metaanalysis. *Am J*
13 *Gastroenterol* 2004;99:2393-404.
- 14 104. Ahmad T, Marshall SE, Jewell D. Genetics of inflammatory bowel disease: The role of
15 the HLA complex. *World J Gastroenterol* 2006;12:3628-35.
- 16 105. Paul T, Birnbaum A, Pal DK, *et al.* Distinct phenotype of early childhood
17 inflammatory bowel disease. *J Clin Gastroenterol* 2006;40:583-6.
- 18 106. Maisawa S, Sasaki M, Ida S, *et al.* Characteristics of inflammatory bowel disease with
19 an onset before eight years of age: a multicenter epidemiological survey in Japan. *J*
20 *Gastroenterol Hepatol* 2013;28:499-504.
- 21 107. Marks DJ, Miyagi K, Rahman FZ, *et al.* Inflammatory bowel disease in CGD
22 reproduces the clinicopathological features of Crohn's disease. *Am J Gastroenterol*
23 2009;104:117-24.
- 24 108. Uhlig HH, Schwerd T, Koletzko S, *et al.* The diagnostic approach to monogenic very
25 early onset inflammatory bowel disease. *Gastroenterology* 2014;147:990-1007.
- 26 109. Moran CJ1, Klein C, Muise AM, *et al.* Very early-onset inflammatory bowel disease:
27 gaining insight through focused discovery. *Inflamm Bowel Dis* 2015;21:1166-75.
- 28 110. Zeissig Y, Petersen BS, Milutinovic S, *et al.* XIAP variants in male Crohn's disease. *Gut*
29 2015;64:66-76.
- 30 111. Elkadri AA, Stempak JM, Walters TD, *et al.* Serum antibodies associated with
31 complex inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1499-505.
- 32 112. Zhang Z, Li C, Zhao X, Lv C, *et al.* Anti-Saccharomyces cerevisiae antibodies associate
33 with phenotypes and higher risk for surgery in Crohn's disease: a meta-analysis. *Dig Dis*
34 *Sci* 2012;57:2944-54.
- 35 113. Kaul A, Hutfless S, Liu L, *et al.* Serum anti-glycan antibody biomarkers for
36 inflammatory bowel disease diagnosis and progression: a systematic review and meta-
37 analysis. *Inflamm Bowel Dis* 2012;18:1872-84.
- 38 114. Reese GE, Constantinides VA, Simillis C, *et al.* Diagnostic precision of anti-
39 Saccharomyces cerevisiae antibodies and perinuclear antineutrophil cytoplasmic
40 antibodies in inflammatory bowel disease. *Am J Gastroenterol* 2006;101:2410-22.
- 41 115. Duerr RH, Targan SR, Landers CJ, *et al.* Anti-neutrophil cytoplasmic antibodies in
42 ulcerative colitis. Comparison with other colitides/diarrheal illnesses. *Gastroenterology*
43 1991;100:1590-6.
- 44 116. Cambridge G, Rampton DS, Stevens TR, *et al.* Anti-neutrophil antibodies in
45 inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1992;33:668-74.
- 46 117. Joossens S, Reinisch W, Vermeire S, *et al.* The value of serologic markers in
47 indeterminate colitis: a prospective follow-up study. *Gastroenterology* 2002;122:1242-
48 7.
- 49
50
51
52
53
54
55
56
57
58
59
60

- 1
- 2
- 3 118. Lawrance IC, Murray K, Hall A, *et al.* A prospective comparative study of ASCA and
- 4 pANCA in Chinese and Caucasian IBD patients. *Am J Gastroenterol* 2004;99:2186-94.
- 5 119. Annese V, Piepoli A, Perri F, *et al.* Anti-Saccharomyces cerevisiae mannan antibodies
- 6 in inflammatory bowel disease: comparison of different assays and correlation with
- 7 clinical features. *Aliment Pharmacol Ther* 2004;20:1143-52.
- 8 120. Ferrante M, Henckaerts L, Joossens M, *et al.* New serological markers in
- 9 inflammatory bowel disease are associated with complicated disease behaviour. *Gut*
- 10 2007;56:1394-403.
- 11 121. Vind I, Riis L, Jespersgaard C, Jess T, *et al.* Genetic and environmental factors as
- 12 predictors of disease severity and extent at time of diagnosis in an inception cohort of
- 13 inflammatory bowel disease, Copenhagen County and City 2003-2005. *J Crohns Colitis*
- 14 2008;2:162-9.
- 15 122. Lakatos PL, Altorjay I, Szamosi T, *et al.* Pancreatic autoantibodies are associated with
- 16 reactivity to microbial antibodies, penetrating disease behavior, perianal disease, and
- 17 extraintestinal manifestations, but not with NOD2/CARD15 or TLR4 genotype in a
- 18 Hungarian IBD cohort. *Inflamm Bowel Dis* 2009;15:365-74.
- 19 123. Bogdanos DP, Roggenbuck D, Reinhold D, *et al.* Pancreatic-specific autoantibodies to
- 20 glycoprotein 2 mirror disease location and behaviour in younger patients with Crohn's
- 21 disease. *BMC Gastroenterol* 2012;12:102.
- 22 124. Bertin D, Grimaud JC, Lesavre N, *et al.* Targeting tissular immune response improves
- 23 diagnostic performance of anti-Saccharomyces cerevisiae antibodies (ASCA) in Crohn's
- 24 disease. *PLoS One* 2013;8:e80433.
- 25 125. Prideaux L, De Cruz P, Ng SC, *et al.* Serological antibodies in inflammatory bowel
- 26 disease: a systematic review. *Inflamm Bowel Dis* 2012;18:1340-55.
- 27 126. Hold G, Smith M, Grange C, *et al.* Role of the gut microbiota in inflammatory bowel
- 28 disease pathogenesis: What have we learnt in the past 10 years? *World J Gastro*
- 29 2014;20:1192-1210.
- 30 127. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease:
- 31 current status and the future ahead. *Gastroenterology* 2014;146:1489-99.
- 32 128. Gevers D, Kugathasan S, Denson LA, *et al.* The treatment-naive microbiome in new-
- 33 onset Crohn's disease. *Cell Host Microbe* 2014;15:382-92.
- 34 129. Baumgart M, Dogan B, Rishniw M, *et al.* Culture independent analysis of ileal mucosa
- 35 reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to
- 36 depletion of Clostridiales in Crohn's disease involving the ileum. *ISME J* 2007;1:403-18.
- 37 130. Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, Zheng Z, Järnerot G, Tysk
- 38 C, Jansson JK, *et al.* A pyrosequencing study in twins shows that gastrointestinal
- 39 microbial profiles vary with inflammatory bowel disease phenotypes. *Gastroenterology*
- 40 2010;139:1844-1854.
- 41 131. Willing B, Halfvarson J, Dicksved J, *et al.* Twin studies reveal specific imbalances in
- 42 the mucosa-associated microbiota of patients with ileal Crohn's disease. *Inflamm Bowel*
- 43 *Dis* 2009;15:653-60.
- 44 132. Lopez-Siles M, Martinez-Medina M, Busquets D, *et al.* Mucosa-associated
- 45 *Faecalibacterium prausnitzii* and *Escherichia coli* co-abundance can distinguish Irritable
- 46 Bowel Syndrome and Inflammatory Bowel Disease phenotypes. *Int J Med Microbiol*
- 47 2014;304:464-75.
- 48 133. Naftali T, Reshef L, Kovacs A, *et al.* Distinct Microbiotas are Associated with Ileum-
- 49 Restricted and Colon-Involving Crohn's Disease. *Inflamm Bowel Dis* 2016;22:293-302.
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

134. Haberman Y, Tickle TL, Dexheimer PJ, *et al.* Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 2014;124:3617-33. Erratum in: *J Clin Invest* 2015;125:1363.
135. 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.
136. Lim WC, Hanauer S. Aminosaliclates for induction of remission or response in Crohn's disease. *Cochrane Database Syst Rev* 2010;(12):CD008870.
137. 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.
138. 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.
139. 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.
140. 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.
141. 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.
142. 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.
143. 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.
144. 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.
145. 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.
146. 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.
147. Summers RW, Switz DM, Sessions JT Jr, *et al.* National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847-69.
148. Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;86:249-66.
149. Khan, K.J., 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.
150. Nitzan, O., Elias M, Peretz A *et al.*, Role of antibiotics for treatment of inflammatory bowel disease. *World J Gastroenterol* 2016;22:1078-87.
151. 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.
152. Prantera C, Lochs H, Grimaldi M *et al.* Rifaximin-extended intestinal release induces

- 1
2
3 remission in patients with moderately active Crohn's disease. *Gastroenterology* 2012;
4 142:473-481.
- 5 153. Blichfeldt, P, Blomhoff JP, Myhre E, *et al.* Metronidazole in Crohn's disease. A double
6 blind cross-over clinical trial. *Scand J Gastroenterol* 1978;13:123-7.
- 7 154. Sutherland L, Singleton J, Sessions J *et al.*, Double blind, placebo controlled trial of
8 metronidazole in Crohn's disease. *Gut* 1991;32:1071-5.
- 9 155. Steinhart AH, Feagan BG, Wong CJ *et al.* Combined budesonide and antibiotic
10 therapy for active Crohn's disease: a randomized controlled trial. *Gastroenterology*
11 2002;123:33-40.
- 12 156. Selby W, Pavli P, Crotty B *et al.* Two-year combination antibiotic therapy with
13 clarithromycin, rifabutin, and clofazimine for Crohn's disease. *Gastroenterology*
14 2007;132:2313-9.
- 15 157. Tromm A, Bunganic I, Tomsova E, *et al.* Budesonide 9 mg is at least as effective as
16 mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease.
17 *Gastroenterology* 2011;140:425-434.
- 18 158. Bar-Meir S, Chowers Y, Lavy A, *et al.*, Budesonide versus prednisone in the treatment
19 of active Crohn's disease. The Israeli Budesonide Study Group. *Gastroenterology*
20 1998;115:835-40.
- 21 159. Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short-term study of chimeric
22 monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's
23 Disease cA2 Study Group. *N Engl J Med* 1997; 337: 1029–35.
- 24 160. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's
25 disease: the ACCENT I randomised trial. *Lancet* 2002; 359: 1541–9.
- 26 161. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor
27 monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.
28 *Gastroenterology* 2006; 130: 323–33.
- 29 162. Sandborn WJ, Hanauer SB, Rutgeerts P, *et al.* Adalimumab for maintenance
30 treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; 56: 1232–9.
- 31 163. Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn's
32 disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;
33 146: 829–38.
- 34 164. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of
35 clinical response and remission in patients with Crohn's disease: the CHARM trial.
36 *Gastroenterology* 2007; 132: 52–65.
- 37 165. Sandborn WJ, Melmed GU, MCGovern DP *et al.* Certolizumab pegol for active Crohn's
38 disease: a placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol* 2011; 9:670-
39 678.
- 40 166. Arnott, I.D., McNeill G, Satsangi J. An analysis of factors influencing short-term and
41 sustained response to infliximab treatment for Crohn's disease. *Aliment Pharmacol Ther*
42 2003;17:1451-7.
- 43 167. Laharie D, Salzmann M, Boubekour H *et al.* Predictors of response to infliximab in
44 luminal Crohn's disease. *Gastroenterol Clin Biol* 2005;29:145-9.
- 45 168. Vermeire S, Louis E, Carbonez A *et al.* Demographic and clinical parameters
46 influencing the short-term outcome of anti-tumor necrosis factor (infliximab) treatment
47 in Crohn's disease. *Am J Gastroenterol* 2002;97:2357-63.
- 48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 169. Dupont-Lucas C, Sternszus R, Ezri J *et al.* Identifying patients at high risk of loss of
4 response to infliximab maintenance therapy in paediatric Crohn's disease. *J Crohns*
5 *Colitis* 2016;10:795-804.
6
7 170. Cohen RD, Lewis JR, Turner H *et al.* Predictors of adalimumab dose escalation in
8 patients with Crohn's disease at a tertiary referral center. *Inflamm Bowel Dis*
9 2012;18:10-6.
10 171. Sandborn,WJ, Feagan BG, Rutgeerts P *et al.* Vedolizumab as induction and
11 maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711-21.
12 172. Kansal S, Wagner J, Kirkwood CD, *et al.* Enteral nutrition in Crohn's disease: an
13 underused therapy. *Gastroenterol Res Pract* 2013;2013:482108.
14 173. Lee D, Albenberg L, Compher C, *et al.* Diet in the pathogenesis and treatment of
15 inflammatory bowel diseases. *Gastroenterology* 2015;148:1087-106.
16 174. El-Matary W, Otley A, Critch J, *et al.* Enteral Feeding Therapy for Maintaining
17 Remission in Crohn's Disease: A Systematic Review. *J Parenter Enteral Nutr* 2015; Dec 8.
18 pii: 0148607115621051
19 175. Dickinson RJ, Ashton MG, Axon AT, *et al.* Controlled trial of intravenous
20 hyperalimentation and total bowel rest as an adjunct to the routine therapy of acute
21 colitis. *Gastroenterology* 1980;79:1199-204.
22 176. González-Huix F, Fernández-Bañares F, Esteve-Comas M, *et al.* Enteral versus
23 parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol*
24 1993;88:227-32.
25 177. Lochs H, Steinhardt HJ, Klaus-Wentz B, *et al.* Comparison of enteral nutrition and
26 drug treatment in active Crohn's disease. Results of the European Cooperative Crohn's
27 Disease Study. IV. *Gastroenterology* 1991;101:881-8.
28 178. Wilschanski M, Sherman P, Pencharz P, *et al.* Supplementary enteral nutrition
29 maintains remission in paediatric Crohn's disease. *Gut* 1996;38:543-8.
30 179. Afzal NA, Davies S, Paintin M, *et al.* Colonic Crohn's disease in children does not
31 respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci*
32 2005;50:1471-5.
33 180. Buchanan E, Gaunt WW, Cardigan T, *et al.* The use of exclusive enteral nutrition for
34 induction of remission in children with Crohn's disease demonstrates that disease
35 phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009;30:501-7.
36 181. Rubio A, Pigneur B, Garnier-Lengliné H, *et al.* The efficacy of exclusive nutritional
37 therapy in paediatric Crohn's disease, comparing fractionated oral vs. continuous enteral
38 feeding. *Aliment Pharmacol Ther* 2011;33:1332-9.
39 182. de Bie C, Kindermann A, Escher J. Use of exclusive enteral nutrition in paediatric
40 Crohn's disease in the Netherlands. *J Crohn's Colitis* 2013;7:263-70.
41 183. Harper PH, Lee EC, Kettlewell MG, *et al.* Role of the faecal stream in the
42 maintenance of Crohn's colitis. *Gut* 1985;26:279-84.
43 184. Harper PH, Truelove SC, Lee EC *et al.* Split ileostomy and ileocolostomy for Crohn's
44 disease of the colon and ulcerative colitis: a 20 year survey. *Gut* 1983;24:106-13.
45 185. Allan A, Andrews H, Hilton CJ, *et al.* Segmental colonic resection is an appropriate
46 operation for short skip lesions due to Crohn's disease in the colon. *World J Surg*
47 1989;13:611-4.
48 186. Andersson P, Olaison G, Hallböök O, *et al.* Segmental resection or subtotal colectomy
49 in Crohn's colitis? *Dis Colon Rectum* 2002;45:47-53.
50 187. Bernell O, Lapidus A, Hellers G. Recurrence after colectomy in Crohn's colitis. *Dis*
51
52
53
54
55
56
57
58
59
60

- 1
2
3 *Colon Rectum* 2001;44:647-54.
- 4 188. Martin ST, Vogel JD. Restorative procedures in colonic crohn disease. *Clin Colon*
5 *Rectal Surg* 2013;26:100-5.
- 6 189. Kiran RP, Nisar PJ, Church JM, *et al.* The role of primary surgical procedure in
7 maintaining intestinal continuity for patients with Crohn's colitis. *Ann Surg*
8 2011;253:1130-5.
- 9 190. Schwarz RJ, Pezim ME. Failure of right-sided coloanal anastomosis for treatment of
10 left-sided ulcerative colitis. Report of a case. *Dis Colon Rectum* 1991;34:618-21.
- 11 191. Maser EA, Sachar DB, Kruse D, *et al.* High rates of metachronous colon cancer or
12 dysplasia after segmental resection or subtotal colectomy in Crohn's colitis. *Inflamm*
13 *Bowel Dis* 2013;19:1827-32.
- 14 192. Tekkis PP, Heriot AG, Smith O, *et al.* Long-term outcomes of restorative
15 proctocolectomy for Crohn's disease and indeterminate colitis. *Colorectal Dis*
16 2005;7:218-23.
- 17 193. Fazio VW, Kiran RP, Remzi FH, *et al.* Ileal pouch anal anastomosis: analysis of
18 outcome and quality of life in 3707 patients. *Ann Surg* 2013;257:679-85.
- 19
20
21
22
23
24
25
26
27
28
29
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31
32
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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
Comes ¹⁰	UK	1961	131	46	34	60	38	41-50	-
Gollop ³⁹	USA	1943-82	103	64	36	68	62	25-34	-
Loftus ⁴⁰	USA	1940-93	225	54	32	-	-	-	-
Humphreys ⁴¹	UK	1966-81	440	58	40	-	-	-	-
Ekbom ⁴²	Sweden	1965-83	1469	53	25	-	-	33 (mean)	-
Kyle ³⁵	UK	1955-88	856	63	41	63	63	40-49	-
" "	" "	1964-69	122	-	30	-	-	-	-
" "	" "	1970-75	167	-	40	-	-	-	-
" "	" "	1976-81	204	-	46	-	-	-	-
" "	" "	1982-87	263	-	54	-	-	-	-
Lapidus ³⁷	Sweden	1955-59	83	61	14	-	-	-	-
		1960-64	145	48	15	-	-	-	-
		1965-69	270	51	21	-	-	-	-
		1970-74	364	53	26	-	-	-	-
		1975-79	331	54	26	-	-	-	-
		1980-84	348	58	32	-	-	-	-
		1985-89	395	49	32	-	-	-	-
Gunesh ³⁶	UK (Cardiff)	1950-60	40	-	13	-	-	-	-
" "	" "	1960-70	89	-	17	-	-	-	-
" "	" "	1970-80	148	-	34	-	-	-	-
" "	" "	1980-90	217	-	38	-	-	-	-
Yapp ⁴³	UK (Cardiff)	1991-95	84	68	43	-	-	-	-
Gunesh ³⁶	" "	1996-2005	212	61	43	68	55	-	-
Jayanthi ⁴⁴	UK	1972-89	235	50	25 (incr from 1972 to 89)	-	-	-	-
Cottone ⁴⁵	Italy	1975-95	882	-	18	-	-	-	-
Jacobsen ⁴⁶	Denmark	1978-87	196	67 (1978-87)	32	-	-	-	-
" "	" "	1988-97	354	" "	42	-	-	-	-
" "	" "	1998-2002	230	" "	51	-	-	-	-
Wright ⁴⁷	S.Africa	1980-84	134	69	27	-	-	-	0.44
Manninen ⁴⁸	Finland	1986-99	470	50	40% 1986 31% 1999	-	-	-	0.56

Economou ⁴⁹	Greece	1983-2005	105	37	40	-	-	-	0.40
Rhodes ⁵⁰	UK	1984	395	55	22	72	50	28 (subset)	-
Gower-Rousseau ⁵¹	France	1994	674	57	19	-	-	28	1.15
Auvin ⁵²	France	1988-99	367 (< 17y)	47	10	-	-	-	0.54
Spanish ⁵³	Spain	1997	635	52	17	-	-	-	-
Jess ⁵⁴	Denmark	1962-87	374	58	30	-	-	-	-
" "	" "	1991-93	58	66	43	-	-	-	-
" "	" "	2003-04	209	54	37	-	-	-	-
Chow ⁵⁵	China	1987-2005	109	29	35	-	-	-	-
Chouraki ³⁸	France	1988-2007	7409	56	11	-	-	-	0.90
" "	" "	1988-90	544	-	23	-	-	-	-
" "	" "	1997-99	1044	-	13	-	-	-	-
" "	" "	2006-07	533	-	5	-	-	-	-
Romberg-Camps ⁵⁶	Netherlands	1991-2003	476	61	27	66	59	34 (mean)	0.63
Bjornsson ⁵⁷	Iceland	1995-2009	279	54	55	-	-	-	0.08
Tozun ⁵⁸	Turkey	2001-03	216	44	26	-	-	-	-
Lakatos ⁵⁹	Hungary	2002-06	163	48	36	-	-	-	-
Nguyen ⁶⁰	USA/Canada	2003-05	579	-	19	-	-	-	0.30
Ott ⁶¹	Germany	2004-06	168	55	18	-	-	-	0.43
Siddique ⁶²	Kuwait	2005-6	206	52	14	-	-	-	-
Chen ⁶³	USA	2005-10	628	55	21	50	56	-	-
Lucendo ⁶⁴	Spain	2000-12	599	49	24	-	-	-	0.10
Henckaerts ⁶⁵	Belg	2007	874	-	17	-	-	-	0.03
Herrinton ⁶⁶	USA	2008	948	55	40	-	-	-	0.10
Hancock ⁶⁷	UK	2008	675	62	20	74	59	31 (mean)	-
Aloi ⁶⁸	Italy	2009-13	10 (<5y)	-	50	-	-	-	-
" "	" "	" "	215 (6-18y)	-	15	-	-	-	1.00
Aljebreen ⁶⁹	Saudi	2009-13	497	41	8	-	-	-	-
Burisch ⁷⁰	Western europe	2010	345	48	26	-	-	-	1.19
" "	Eastern europe	2010	99	41	20	-	-	-	0.30
Eglinton ⁷¹	NZ	2011	507	63	42	-	-	-	-
Ng ⁷²	Asia-pacific	2011-12	166	Asia 39% Austr 52%	24	-	-	-	0.53
Cleynen ¹⁷	16 countries	2015	16,902	56	24	-	-	-	0.06

Table 1. Studies of Crohn's disease age and sex distribution and proportion of total, where isolated colonic Crohn's disease separately identified (in approximate median date order).

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 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 ⁷⁴	1984	UK	150	Consecutive outpatients	-	25 (smokers with isolated colon CD had more relapses P=0.028)	35	52	-	8
Tobin ⁷⁵	1987	UK	137	Case control	RR for smoking at onset and CD: Small bowel only 1.4 (0.5-4.0) Ileum and asc 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 ⁷⁶	1992	Sweden	231	Postal questionnaire (95% response)	-	42	51	53	-	-
Breuer-Katschinski ⁷⁷	1995	Germany	346	Postal questionnaire (82% response)	-	49	50	49	-	-
Ruszel ⁷⁸	1998	Europe (20 centres, 13 countries)	457	Prospective consecutive cases	-	35	47	59	-	16
Cosnes ⁷⁹	1999	France	622	Consecutive outpatients	-	54	49	49	-	-
Cosnes ⁸⁰	2004	France	688 all colonic	Consecutive outpatients	-	61	-	-	-	42
Aldhous ⁸¹	2007	UK (Scotland)	408	Retrospective outpatients	-	33	43	50	-	-
Hancock ⁶⁷	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 ⁸²	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 ⁸³	2013	Spain	3224	National registry	-	26	34	35	-	-
Chivese ⁸⁴	2015	S. Africa	194	Prospective consecutive cases	RR 3.63 (1.32-9.98) for ileo-colonic 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"

Table 2. Studies of smoking in Crohn's disease where isolated colonic disease 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 ⁵⁰	Case control matched for age and year of onset	37	9/12 75%	11/25 44%	-	NS increased P=0.09
Vessey ⁹⁰	Cohort study in patients attending family planning clinics	18	4/7 57%	4/11 36%	-	NS increased 0.63
Lashner ⁹¹	Case control	51 (incl 8 isolated colonic)	-	-	Isolated colonic OR0.50(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 Crohns)
Sandler ⁹²	Case control Age matched and excluding onset before menarche	184 (incl 26 isolated colonic)	-	-	Isolated colonic OR2.63 (1.00-7.11) Small bowel only 1.33 (0.70-2.53) Ileocolonic 1.52 (0.82-2.83)	NS increased
Persson ⁹³	Case control age 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 ⁹⁴	Case control pre-menopausal	90 (incl 30 isolated colonic)	-	-	Isolated colonic RR3.2 (1.1-15.3) Small bowel only RR4.7 (1.6-17.8) Ileocolonic RR 3.8 (1.3 -17.0)	NS reduced
Khalili ^{95,96}	Cohort – Nurses Health	315 (incl 141 isolated colonic)	-	-	Isolated colonic HR4.13 (1.77-9.68) Ileal only HR2.99 (1.06-8.49)	NS increased

Table 3 – Studies of oral contraceptive usage in Crohn's disease where isolated colonic disease separately identified.

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 ¹¹⁵	1991	Prospective	18	-	-	-	5/18 (28%)	-	-	pANCA 34/40 (85%)	pANCA+ in isolated colonic CD not signif commoner than diarrhea-predom IBS (4/27 15%)
Cambridge ¹¹⁶	1992	Stored sera IBD and healthy controls	18	-	-	-	1/18 (6%)	-	-	pANCA 27/50 (54%)	pANCA+ in 4/32 CD with small bowel involt
Joossens ¹¹⁷	2002	Prospective follow-up of 97 patients with initial diag 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 ¹¹⁸	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 ¹¹⁹	2004	Prospective	61	NA	NA	25/61 (41%)	-	-	-	ASCA 32/197 (16%)	ASCA in CD overall 51%
Ferrante ¹²⁰	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 ¹²¹	2008	Prospective cohort	60	NA	NA	5/60 (8%)	15/60 (25%)	-	-	ASCA 14% pANCA 55%	ASCA CD overall 22%
Lakatos ¹²²	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 ¹²³	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 (nonL2) CD ASCA 55/137 (40.1%) other (nonL2) CD
Bertin ¹²⁴	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 ¹¹¹	2013	Prospective cohort adults and children	55	NA	NA	NA but OR 0.25 (0.12-0.51; P=0.0002) for assocn with isolated colonic disease vs other sites	NA but OR 2.27 (1.50 – 4.92; P<0.03 for assocn 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

Table 4. Serological test results in isolated colonic Crohn's disease and ulcerative colitis.

Author/ref	Year	Specimen type	Number of cases CD	Ileal CD	Ileocolonic CD	Isolated colonic CD	Ulcerative colitis	Healthy controls	Conclusions
Naftali ¹³³	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 ¹³⁴	2015	Ileal biopsy	243 (Paediatric)	180 <u>Persistent reduction in Lachnospiraceae, Bifidobacteriaceae, Clostridiales, and Erysipelotrichaceae in all forms of CD, with expansion of Veillonellaceae, Pasteurellaceae, Neisseriaceae, Gemellaceae, Fusobacteriaceae, and Enterobacteriaceae</u>	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 ¹³²	2014	Ileum and colon	45	19 Reduction in <i>F. prausnitzii</i> , <i>E. 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 ^{#130,131}	2009, 2010	Ileum and colon	14	6 Increased Enterobacteriaceae and Ruminococcus gnavus; decreased Faecalibacteria and Roseburia and compared to healthy controls. Increased <i>E. coli</i> .	8 No reduction in Faecalibacterium or Roseburia. Some increase in <i>E. coli</i> but less marked than ileo-colonic.	6 Colonic CD microbiome intermediate between ileal CD and healthy controls.			
Baumgart ¹²⁹	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>Faecalibacteria</i> and <i>Subdoligranula</i>)	8 Results not presented separately	8 Enterobacteriaceae not increased and Faecalibacteria not reduced.	NA	7 Ileal CD and colonic CD microbiome were distinct. Colonic CD more closely resembled healthy controls	

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

#Willing 2010, similar patient cohort to Willing (2009) but sequencing methodology compared to terminal-restriction fragment length polymorphism in Willing (2009).

†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.

Table 5: Studies of mucosal microbiota in Crohn's disease where isolated colonic disease separately identified

Author/Ref	N (isolated colonic CD)	5ASA	Placebo	P value	Conclusions
Singleton ¹⁴⁰	64	CDAI mean change: -77 (+/-27) at 2g/day -81 (+/-31) at 4g/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-aminosalicylic acid in isolated colonic Crohn's disease
(i) induction

Author/Ref	N (isolated colonic CD)	5ASA relapse rate 12months	Placebo relapse rate 12 months	P value	Conclusions
International ¹⁴¹	56	32.1% (9/28)	38.9% (11/28)	0.49	5ASA only showed benefit in ileal disease
Prantera ¹⁴²	18	40% (2/5)	55% (6/?11) extrapolated from table	NS	5ASA only showed benefit in ileal disease
Gendre ¹⁴³	48	-	-	-	5ASA better (P<0.003) than placebo in all CD patients in remission <3m at onset, no sig difference according to disease location
De Franchis ¹⁴⁴	36	45% (8/17)(extrapolated from figure)	45% (9/19)	1.0	5ASA ineffective in ileal, colonic, or ileocolonic

(a) Placebo-controlled trials of oral 5-aminosalicylic acid in isolated colonic Crohn's disease
(ii) maintenance

Author/Ref	N (isolated colonic CD)	Sulphasalazine remission	Placebo remission	P value	Conclusions
Singleton ¹⁴⁶	20	-	-	NS	Both groups also received tapering prednisolone. Placebo better than sulphasalazine in patients with ileal disease.
Summers ¹⁴⁷	17	-	-	0.006 (comparison of outcome ranks)	Sulphasalazine better than placebo in colonic CD (also effective in ileocolonic but not ileal only)
Malchow ¹⁴⁸	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 sulphasalazine in isolated colonic Crohn's disease (i) induction

Author/Ref	N (isolated colonic CD)	Sulphasalazine relapse rate 12months	Placebo relapse rate 12 months	P value	Conclusions
Singleton ¹⁴⁶	20	-	-	NS	Sulphasalazine not significantly different from placebo in CD overall and no relation to disease location
Summers ¹⁴⁷	19	-	-	NS	No significant effect (judged by outcome rank based on CDAI)

(b) Placebo-controlled trials of oral sulphasalazine in isolated colonic Crohn's disease (ii) maintenance

Author/Ref	N (isolated colonic CD)	Olsalazine relapse /failure rate 12 months	Placebo relapse /failure rate 12 months	P value	Comments
Mahmud ¹⁴⁵	145	65.4%	53.6%	0.035 (Olsalazine worse)	Olsalazine induces diarrhea, no evidence of efficacy

(c) Placebo-controlled trial of olsalazine in isolated colonic Crohn's maintenance

Table 6. Trials of 5ASA preparations where data presented separately for isolated colonic Crohn's disease.

Author/Ref	N (isolated colonic CD)	Comparator	Primary end point	Rifaximin remission rate	Placebo remission rate	P value	Conclusions
Prantera ¹⁵²	190 active; 76 placebo (from supplement table 2)	Placebo	Week 12 remission (CDAI <150)	3 doses: 400mg bd; 800 mg bd; 1200 mg bd; 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 ¹⁵³	6	Placebo (crossover)	Week 8 response	100%	?	NS overall	Metronidazole 1g daily improved symptoms and lab values in all six with colonic disease
Sutherland ¹⁵⁴	12 (4 received 10 mg/kg; 4 received 20mg/kg; placebo)	Placebo	Week 16 response	Mean CDAI drop 145, 95% CI 26-265, 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

Table 7. Trials of antibiotics where data provided separately for patients with isolated colonic Crohn's disease.

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 ¹⁵⁷	50 (distal colon excluding rectum) of 307 in trial	Budesonide 9mg od vs 3mg tds vs Mesalamine 1.5g tds	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 signif better than mesalamine
Bar-Meir ¹⁵⁸	27 of 201 in trial	Budesonide 9mg od vs Prednisone 40mg od 2wks 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 ¹⁴⁶	34 of 295 in trial (Pt1)	Prednisone up to 60mg /day (n=8) vs Azathioprine 2.5 mg/kg (n=9) vs Sulfasalazine 1g/15kg (n=8) vs Placebo (n=9)	Week 17 remission	Data presented as rank outcome	Data presented as rank outcome	0.465	Prednisone not effective in colon only disease (but only n=8 treated)
Malchow ¹⁴⁷	49 of 215 in trial (induction data from table 11)	Sulfasalazine or combination of sulfasalazine and 6-methyl Prednisolone	Remission by week 18	6/8 (75%)	Placebo 2/14 (14%) Sulphasalazine 4/13 (31%) Combination 13/14 (93%)	<0.01 for Sulfasalazine and 6-methylprednisolone and <0.001 for combination	All active treatments better than placebo but combination superior to either agent alone

(b) Controlled trials of oral Prednis(ol)one

Table 8. Trials of oral corticosteroids where data provided separately for isolated colonic Crohn's disease.

Author	Year	Type of study	Study agent	Total number of patients	Number with colonic CD	Endpoint	Main findings	P value (for colonic vs other sites unless stated)	Conclusion
Sandborn ¹⁶⁵	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
Arnott ¹⁶⁶	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 ¹⁶⁷	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 ¹⁶⁸	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 – 3.597	0.046	Better efficacy in colonic than combined ileal/ileocolonic. Remission also more likely in isolated colonic (P=0.019)
Dupont-Lucas ¹⁶⁹	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%). iHR 2.72 (95% CI 1.30-5.71) for loss of response in isolated colonic CD vs other sites	0.008	Isolated colonic disease more likely to lose response
Cohen ¹⁷⁰	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 ¹⁷¹	2013	RCT	Vedolizumab	1115	316 (273 active, 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 ¹⁷¹	2013	RCT	Vedolizumab	461	117	Remission at week 52 over placebo	Remission 8wkly vedo: 18.9% difference from placebo for colonic vs 11.8% for ileal	0.11 0.19	No difference between isolated colonic and other Crohn's for

							vs 19.9% for ileocolonic Remission 4wkly vedo: 12.7% for colonic vs 25.4% for ileal vs 12% for ileocolonic		maintenance with vedolizumab
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Table 9: Randomized 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/ref	Year	Nature of study	Adults/ children	n=	Intervention	Duration	Primary endpoint	Results in patients with ileal involvement	Results in isolated colonic CD	P*
Lochs ¹⁷⁷	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 till remission 26 days	Mean time till remission 31 days	NS
Wilschanski ¹⁷⁸	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
Afzal ¹⁷⁹	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 ¹⁸⁰	2009	Prospective cohort	Children Median age 12	110 (19 colon only)	Exclusive polymeric (Modulen) in 105, elemental in 5	8 weeks	Remission (improvt in all domains of global assesst)	Remission 73/91 (80.2%)	Remission 15/19 (78.9%)	NS
Rubio ¹⁸¹	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		NS
De Bie ¹⁸²	2013	Retrospective cohort	Children Median age 14	76 (18 colon only)	Exclusive polymeric or semi-polymeric	6 weeks	Remission defined as no diarrhea, pain or wt loss	Remission 32/51 (63%)	Remission 8/15 (53%)	NS

Table 10. Results of exclusive enteral nutrition as primary therapy in Crohn's disease where data provided separately for isolated colonic Crohn's disease.

	Ileal/Ileocolonic Crohn's disease	Isolated colonic Crohn's disease	Ulcerative colitis
Sex	Slightly commoner in females (c55%)	Commoner in females (c65%)	Equal or slight male predominance
Genetics	Crohn's-associated genotype including NOD2/CARD15	Genotype midway between Crohn's 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>E. 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

Table 11. A summary of the distinguishing features of the three inflammatory bowel diseases: ileal/ileocolonic Crohn's disease, isolated colonic Crohn's disease, ulcerative colitis.