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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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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 1930[1] as "regional migratory ulcerative colitis". Crohn's classic 1932 paper did not include cases with colonic involvement[2] although non-tuberculous granulomatous involvement of ileum and colon had been reported in 1923[3] 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 resection[13], 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]

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

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

METHODS

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

PATHOLOGY, DIFFERENTIAL DIAGNOSIS, AND DISEASE COURSE – DEFINING THE CONDITION

The histological features of isolated colonic Crohn's disease were first defined by Lockhart-Mummery and Morson.[9] They labeled patients with this diagnosis because "they had the same characteristic pathology in the large intestinal lesions as that described by Hadfield[18] for the disease as it affects the small intestine". Gross appearances of the colon following

colectomy include less sharp demarcation of ulceration than typically seen in ulcerative colitis and with areas of intact intervening mucosa. In some cases, very marked fibrous thickening with associated stricturing was present. Fibrosis and oedema sometimes extended into the pericolic fat and enlargement of regional lymph nodes was marked. Warren later split the macroscopic features into three patterns: isolated rectal disease; stricturing colonic disease; diffuse colitis – usually with rectal sparing, and noted that approximately 75% develop perianal pathology during their disease course.[19]

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

Histopathology alone is diagnostic only in the minority – in a series of 103 cases of Crohn's colitis, diagnosis was determined by microscopy alone in 28%, by distribution (rectal sparing and/or discontinuity) alone in 22% and by combination of the two in 50%.[22] Particularly discriminatory features suggesting Crohn's colitis rather than ulcerative colitis include granulomata, submucosal inflammation, and relative preservation of goblet cells.[23,24] At an international workshop expert pathologists "correctly" identified only 64% of cases with Crohn's colitis and 74% with ulcerative colitis[25] leading the European consensus on histopathology of inflammatory bowel disease (2013) to note that "accurate discrimination between the two diseases (Crohn's colitis and ulcerative colitis) is not yet optimal amongst expert gastrointestinal pathologists". Given that inflammatory disease pathogenesis is multifactorial an alternative interpretation would be that there is a continuous phenotypic spectrum that runs through from "typical" ulcerative colitis, through IBD-unclassified to "typical" Crohn's colitis.

Early studies reported an additional incidence peak of Crohn's disease in the elderly resulting from cases particularly affecting the sigmoid colon.[26] Following the later clarification of segmental colitis associated with diverticular disease (SCAD) this seems probably attributable to SCAD. SCAD can be indistinguishable histologically from inflammatory bowel disease and includes a "Crohn's-like" variant with granulomata.[27] This reflects emphasis often placed on the diagnostic specificity of the granuloma. However, granulomas are only found in colonoscopic biopsies at diagnosis in about 66% of adults with colonic Crohn's disease, falling to 18% at follow-up.[28] Moreover granulomas, particularly in association with crypts, can be found in ulcerative colitis.[29] Other forms of colitis that may need to be considered in the differential include ischemic colitis (see earlier) and infections including amoebiasis and tuberculosis but it is beyond the scope of this review to consider these further.

Localisation of disease to the colon remains fairly constant over time. The largest published data set by far is the 16,902 Crohn's disease cohort, including 2,933 with isolated colonic disease, in the recent genotype/phenotype association study.[17] This confirmed previous

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 series [33] whereas penetrating disease (B3) as defined by the Vienna classification (ie including peri-anal fistulae) occurred in 23% in the same series, less frequently than in patients with ileal disease (46%; P=0.0003) or ileocolonic (28.6%; 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 Sweden[37] 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 France[38] 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 al[17]. 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

Cigarette smoking is associated with increased risk for development and progression of Crohn's disease but reduced risk for ulcerative colitis. Smoking is more strongly associated with risk for ileal and ileo-colonic Crohn's disease than for isolated colonic disease (Table 2). Only one study (of nine)[79] reported a higher rate of smoking amongst patients with isolated colonic Crohn's disease. If the South African data[84] which reported exceptionally high rates (73%) across all groups are excluded, the other studies report rates for smoking amongst patients with isolated colonic disease that averaged 37.8% compared with 49.8% (P=0.008 by paired t test) for other Crohn's disease sites. This smoking rate is probably slightly higher than for the general population – approximately 30% European adults were smokers in 2008 (WHO).[86]

Smoking worsens prognosis of Crohn's disease overall and cessation of smoking improves it.[87,88] This has been studied less in isolated colonic disease but the conclusion is similar. The largest study[80] included 688 patients with Crohn's colitis, 978 with ulcerative colitis and 118 with "indeterminate" colitis. Sixty-one per cent of patients with ulcerative colitis or indeterminate colitis had stopped smoking before disease onset compared with only 12% in isolated colonic Crohn's disease. In women but not men with isolated colonic disease the risk of needing immunosuppression was increased amongst smokers (10-yr cumulative risk 48% in non-smokers vs 58% in smokers, P<0.01). An earlier study[74] showed that smokers with Crohn's colitis relapsed approximately 50% more often (P=0.028) and with more pain (P<0.007) than non-smokers.

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

Oral contraception

Meta-analysis of 14 studies, with adjustment for smoking, showed a relative risk of 1.51 (95%CI 1.17-1.96, P=0.002) for Crohn's disease amongst women currently taking oral contraception[89]. The relative risk for ulcerative colitis was also increased at 1.53 (1.21-1.94, P=0.001). Six of the seven studies that reported risk associated with oral contraception separately for isolated colonic disease found a significant association (Table 3) with relatively high odds ratio (2.63), risk ratios (3.6 and 3.23) or hazard ratio (4.13). The sole exception[91] only included 8 cases with isolated colonic Crohn's disease and showed no overall association between oral contraception and risk for Crohn's disease. Excluding the latter study[91], five of the other six show higher risks amongst oral contraceptive users for isolated colonic Crohn's than for other sites.

Oestrogen-associated ischaemic colitis as a confounder

An early study from Birmingham[50] reported patients with apparent oral contraceptive-associated colonic Crohn's disease who had non-granulomatous colitis with rectal sparing. Ischaemic colitis is a rare but recognized complication of oral contraception that might cause diagnostic confusion. [97,98,99] Most cases have a short duration with typical features of ischaemic colitis including abdominal pain, and rectal bleeding. Colonoscopy shows mucosal friability but no linear ulceration and the proximal colon and rectum are typically normal. Such cases should be readily distinguishable from colonic Crohn's disease but Tedesco[100]

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

GENETICS

The strongest genetic association with IBD is the link between NOD2/CARD15 and Crohn's disease. Meta-analysis of 42 studies showed that this association was stronger for Crohn's disease with small bowel involvement than for those without (OR 2.53; 95%CI 2.01-3.16).[103] Subsequent study of 1528 patients with Crohn's disease from 8 centres (in 7 European countries) (IBDchip) confirmed the association of NOD2/CARD15 with ileal involvement and also showed that Interleukin23 receptor polymorphisms were more strongly associated with isolated colonic Crohn's (OR 2.20; 95%CI 1.17-4.57).[85]

The most consistent genetic link with ulcerative colitis is with the rare Major histocompatibility Complex (MHC) / Human Leucocyte Antigen (HLA) Class II allele HLA-DRB*0103. This occurs in less than 2% in European and white North American populations and is absent in the Japanese. It is strongly associated with colonic Crohn's disease where it is present at up to 32% frequency with Odds Ratios for isolated colonic disease of 5.1-18.5 compared with Crohn's disease at other sites.[104]

The largest study to compare genetic associations with Crohn's disease phenotype included 19713 patients from 49 centres across 16 countries in Europe, North American and Australasia.[17] This confirmed that the strongest association with isolated colonic Crohn's disease was HLA-DRB1*01:03 ($p=1.47 \times 10^{-23}$, ileal vs colonic OR 0.32, 95%CI 0.29-0.41; ileocolonic vs colonic OR 0.47, 95%CI 0.39-0.57). The only other loci that were significant across all analyses in this study were NOD2 (16q12), again associated with increased risk for ileal involvement (OR ileocolonic vs colonic 1.61,1.59, and 1.89 for the three NOD2 polymorphisms tested) and also MST1 (macrophage stimulating -1 that encodes a protein which induces macrophage phagocytosis) polymorphisms which were more weakly associated with ileal involvement (OR 1.07 -1.10 according to polymorphism and whether comparing ileal or ileocolonic with colonic disease). When overall genetic risk scores for Crohn's disease and ulcerative colitis were computed as a ratio and compared with phenotype, isolated colonic Crohn's disease was found to be approximately "balanced" in respect of Crohn's disease versus ulcerative colitis genetic risk factors (Figure 1). It was found though that even the combination of smoking status with the strongest genetic predictors could only explain 6.8% of the variance for disease location.

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

Amongst children with very early onset Crohn's disease there is a marked preponderance of cases with isolated colonic disease eg 76.5% before age 5[105] and 42% before age 8.[106] Amongst younger cases there is a strong male preponderance – eg 1.6:1 across all Crohn's disease presenting <5[105] and some of this is accounted for by X-linked single gene disorders. The first such condition to be identified was X-linked Chronic Granulomatous Disease. Chronic Granulomatous Disease is associated with defects in neutrophil function leading to skin lesions and in around 40% with a form of inflammatory bowel disease that is indistinguishable from Crohn's disease, typically with predominant colorectal and perianal involvement .[107] It is due to mutations in one of four NADPH oxidase complex component genes of which the commonest (CYBB) located on the X chromosome accounts for about 65% cases.

Rapid developments in DNA sequencing have allowed identification of over 50 further single gene disorders that present as inflammatory bowel disease, typically as colonic disease and with presentation before age 6, defined as Very Early Onset IBD or VEO-IBD.[108] VEO-IBD cases account for 4-10% of paediatric inflammatory bowel disease.[109] One of the commoner single gene variants is in the coding region of X-linked inhibitor of apoptosis protein (XIAP) that accounts for about 4% of male patients with paediatric onset Crohn's disease.[110]

SEROLOGY INCLUDING ANTI-MICROBIAL AND ANTI-NEUTROPHIL ANTIBODIES

Anti-microbial antibodies such as Anti-Saccharomyces cerevesiae (ASCA) and antibodies to outer membrane protein (ompC) are found less often and/or at lower titre in isolated colonic Crohn's than in other Crohn's phenotypes.[111] Meta-analyses confirm this particularly for ASCA.[112-114] Average sensitivity of ASCA for isolated colonic Crohn's disease diagnosis is 31% but with a wide range (8-59%) and an average 14% positivity rate in ulcerative colitis (Table 4). The clinical utility of ompC antibodies has been less studied but reported positivity/sensitivity in isolated colonic Crohn's disease is substantially lower than that for ASCA.

Anti-neutrophil antibodies, particularly an atypical peri-nuclear antibody (pANCA), are present in around 55% of patients with ulcerative colitis[114] and 23% of patients with isolated colonic Crohn's disease (Table 4). This compares with pANCA positivity of around 11% in Crohn's disease overall and 3% in non-IBD controls.[114]

A combination of positive ASCA and negative pANCA is more discriminatory eg positivity rate in isolated colonic Crohn's disease of 52% compared with 9% in ulcerative colitis[122] but is still insufficiently predictive for routine clinical use.[125]

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

MICROBIOTA

The faecal microbiota in active inflammatory bowel disease is commonly dysbiotic with reduced bacterial diversity.[126,127] This could be secondary to inflammation yet still significant

in maintaining chronicity. The large study of pre-treatment Crohn's disease by Gevers showed only a mild dysbiosis in the faecal microbiota and much greater separation of Crohn's disease from healthy controls when the mucosa-associated microbiota was studied.[128] Ileal and rectal mucosal samples typically showed a reduction in *Firmicutes* such as *Faecalibacterium prausnitzii* and an increase in *Proteobacteria* such as *Escherichia coli* as well as in *Veillonella*, *Haemophilus* and *Fusibacteria*. This confirmed many previous studies showing an increase in mucosa-associated *E. coli* in Crohn's disease as well as several showing a reduction in *F. prausnitzii*[129-132].

The faecal and mucosa-associated microbiota in isolated colonic Crohn's disease are generally closer to that of healthy controls than is found in patients with ileal or ileocolonic Crohn's disease (Table 5). Thus Baumgart *et al*[129] found that an increase in ileal mucosa-associated *E. coli* and reduction in ileal *F. prausnitzii* was only present in patients with Crohn's disease who had ileal involvement and not in those with isolated colonic disease. Similarly, a study of twins with/without Crohn's disease showed that faecal microbial diversity was only reduced and *Proteobacteria* increased in patients with ileal involvement and not in patients with isolated colonic disease.[130] A previous report by the same group also showed a reduction in *F. prausnitzii* in Crohn's patients with ileal involvement but not in isolated colonic disease.[131] Both the twin study by Willing[131] and the large study in children[128] and adolescents[134] did however show differences between the mucosa-associated microbiota in isolated colonic Crohn's disease and ulcerative colitis. 16sRNA pyrosequencing of mucosal samples[133] confirms the increase in *E. coli* and reduced *F. prausnitzii* in Crohn's disease with ileal involvement with milder changes in isolated colonic disease, although the latter did show some reduction in *F. prausnitzii* compared with healthy controls. This study also confirmed that the mucosa-associated microbiota are consistent at different sites from ileum to rectum in the same individual.

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

RESPONSE TO TREATMENT

Mesalazine

Systematic reviews show no convincing benefit of oral mesalazine (5-aminosalicyclic acid) over placebo either in induction of remission or in maintenance of medically induced remission in Crohn's disease as a whole[1345138] although they may have a modest benefit in maintaining surgically-induced remission.[139] Sulphasalazine (sulphapyridine linked via azo bond to 5-aminosalicylate) has possible modest efficacy in induction of remission.[134, 136]

Amongst trials that have reported data separately for isolated colonic Crohn's disease, only one trial studied the effect of oral mesalazine in remission induction[140] and four studied its effect in maintenance of medically-induced remission[141-144] (Table 6). In none of these was

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 (Blichfeldt[153]: n=6 crossover; Sutherland[154]: 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 daily[155] 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 trial[147]showing no benefit and the other[148]showing efficacy. There has never been a trial to assess dose-responsiveness to

conventional corticosteroids in Crohn's disease so optimal dosage is unknown. More data are available for budesonide but trials have focused predominantly on patients with ileal or ileo-colonic disease so data in isolated colonic disease are again very sparse. The data from one comparison with mesalazine[157], support efficacy in isolated colonic Crohn's disease, possibly with a weaker effect than conventional corticosteroids[158], but reduced corticosteroid side-effects.

Anti-TNF

None of the randomised trials of infliximab[159,160] or adalimumab[161-164] reported subgroup analyses of outcomes based on disease location. In a randomised, placebo controlled trial of certolizumab pegol, patients with colonic (OR 2.39, 95% CI 0.99-5.75, P=0.052) and ileocolonic disease (OR 2.07, 95% CI 1.01-4.28, P=0.048) were more likely to achieve remission at week 6 compared to ileal disease (OR 0.42, 95% CI=0.18-0.99, P=0.048)[165](Table 9)

Several cohort studies have assessed colonic disease location as a predictor of response to anti-TNF agents, four with infliximab and one with adalimumab. Three cohort studies assessing induction therapy with infliximab[166-168] all showed better response rates in isolated colonic disease than for disease at other sites. Paradoxically, cohort studies of infliximab maintenance in children[169] and of adalimumab maintenance in adults[170] both showed higher risk of lost response or dose escalation in isolated colonic disease. Overall, the evidence supports good efficacy for anti-TNF therapy in induction of remission in isolated colonic Crohn's disease but possibly with a higher subsequent rate of loss of response.

Vedolizumab

In the combined induction and maintenance study of vedolizumab there was no significant difference in efficacy in isolated colonic disease compared with other locations.[171] (Table 9)

Enteral nutrition

Exclusive enteral nutrition is effective as primary therapy in patients with active Crohn's disease[172,173] and partial enteral nutrition has shown efficacy in maintenance of remission.[174] In ulcerative colitis total parenteral nutrition and bowel rest are ineffective[175] and comparison of enteral with parenteral nutrition showed no difference in efficacy[176] implying no efficacy for enteral nutrition either. Whether enteral nutrition is effective as primary therapy in isolated colonic Crohn's disease is controversial. Relatively few studies provide separate data on patients with isolated colonic Crohn's disease (Table 10). Five of the six studies are in children. Two studies[178,179] report poorer results in children with isolated colonic disease compared with those with small intestinal involvement. Numbers are small though (19 cases of isolated colonic disease across the two trials) and the other studies (including 72 cases of isolated colonic disease across four trials) found no significant difference in remission rates for those with isolated colonic disease compared with other

sites. Further trials of exclusive enteral nutrition are needed in patients with isolated colonic disease.

Surgery

Faecal diversion

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

Resection

The cumulative risk of surgery for isolated colonic Crohn's disease is reported as 22-33% by 10 years after diagnosis compared with around 75-90% for ileal disease.[17,67] Partial resection, either right hemicolectomy for proximal disease or a segmental resection for more distal disease has been shown to be successful therapy for colonic Crohn's disease[185, 186] as is colectomy with ileo-rectal anastomosis for more extensive disease if the rectum is uninvolved[187,188]. Approximately 75% of patients with ileo-rectal anastomosis will still have a functioning anastomosis after 10 years and about two thirds of those treated by segmental resection will not have required a further resection.[188] Recurrence rates are similar after either procedure.[189] This contrasts with left-sided ulcerative colitis, where the tempting option of left hemicolectomy with right-sided colo-anal anastomosis consistently fails, usually with rapid recurrence of colitis in the retained colon.[190] It should be noted though that segmental resection for colon cancer complicating colonic Crohn's disease has been associated with high (39%) risk for metachronous colon cancer[191] suggesting that panproctocolectomy might be a safer option for such patients.

Ileo-anal pouch reconstruction

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

CONCLUSION

Current data suggest that the genetics, microbiota, serology and smoking association of isolated colonic Crohn's disease lie between those of ileo/ileocolonic Crohn's disease and

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

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LEGENDS TO FIGURES:

1. 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 Cleynen et al,[17] with permission. This shows that isolated colonic Crohn's lies approximately equidistant genetically between ileal Crohn's disease and ulcerative colitis.

2A. 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.
2B. Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all studies.

Supplementary Files

1. PRISMA flow diagram.
2. PRISMA checklist.

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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
Cornes[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 ("enriched")	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	-	-
Russel[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 involvt
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 *Escherichia* and reduced *Faecalibacterium;* disease activity correlated with abundance of *Fusobacterium*	8* Similar to colonic CD apart from *Faecalibacterium* abundance 2.7-fold lower than in isolated colonic CD (not significant)	8* Higher levels of *Faecalibacterium* and 2 unidentified genera of the Clostridiales and Ruminococceaea; 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 *F. prausnitzii*, *E. coli* moderately increased.	13 Reduction in *F. prausnitzii*	13 *F. prausnitzii* comparable to UC; *E. coli* commoner than UC particularly in ulcerated zones	28 *F. prausnitzii* abundance intermediate between CD and HC.	28	***F. prausnitzii/ E. coli* (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 *E. coli*.		8 No reduction in Faecalibacterium or Roseburia. Some increase in *E. coli* 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, (*E. coli, Shigella*) reduction in Lachnospiraceae, (*Ruminococci*, *Roseburia* and *Coprococci*) and Clostridiales (*Faecalibacteria* and *Subdoligranula)*	8 Results not presented separately	8 Enterobacteraciae 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 </=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 >/= 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 >/=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) Subgroup analysis based on 62 active and 43 placebo.	Remission (CDAI </=150) at week 6 over placebo, Response (CDAI fall >/=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

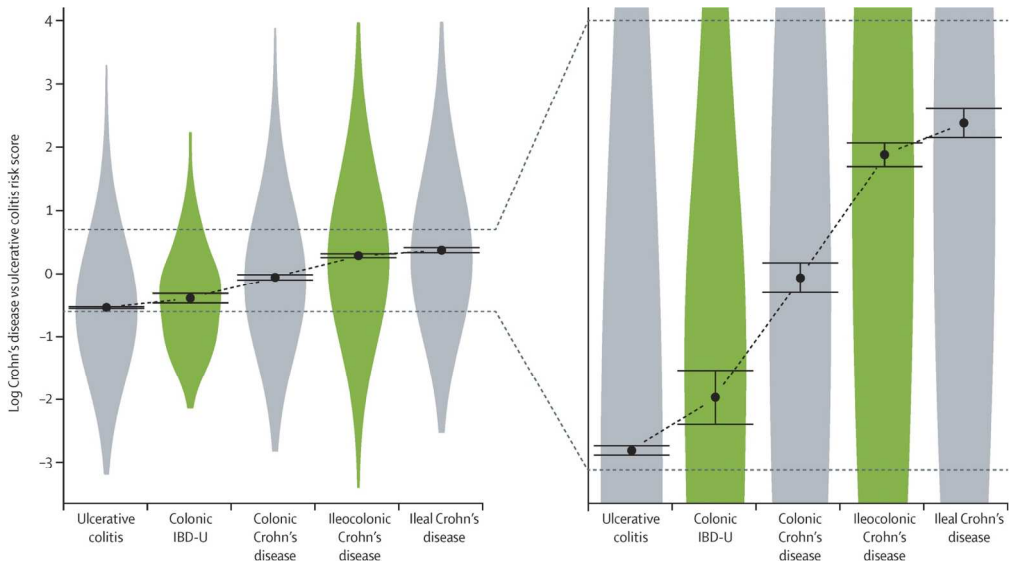
Table 9: Randomized controlled trials (RCTs) and cohort studies of biological therapy in Crohn's disease where data were provided separately for patients with isolated colonic disease.

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	4weeks 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	8weeks	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/ileolonic CD pANCA positive in minority	ASCA usually negative pANCA commonly positive
Mucosa-associated Microbiota	Marked changes commonly including increased Proteobacteria (eg *E. coli*) and Fusobacteria, reduced Firmicutes (eg *F. prausnitzii*	Intermediate changes similar to ileal/ileo-colonic CD but less consistent	Modest changes, including slight increase in *E. coli* but no reduction in *F. prausnitzii*
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 excusive 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 Cleynen et al,17 with permission. This shows that isolated colonic Crohn's lies approximately equidistant genetically between ileal Crohn's disease and ulcerative colitis.
Crohn's disease similarly ov
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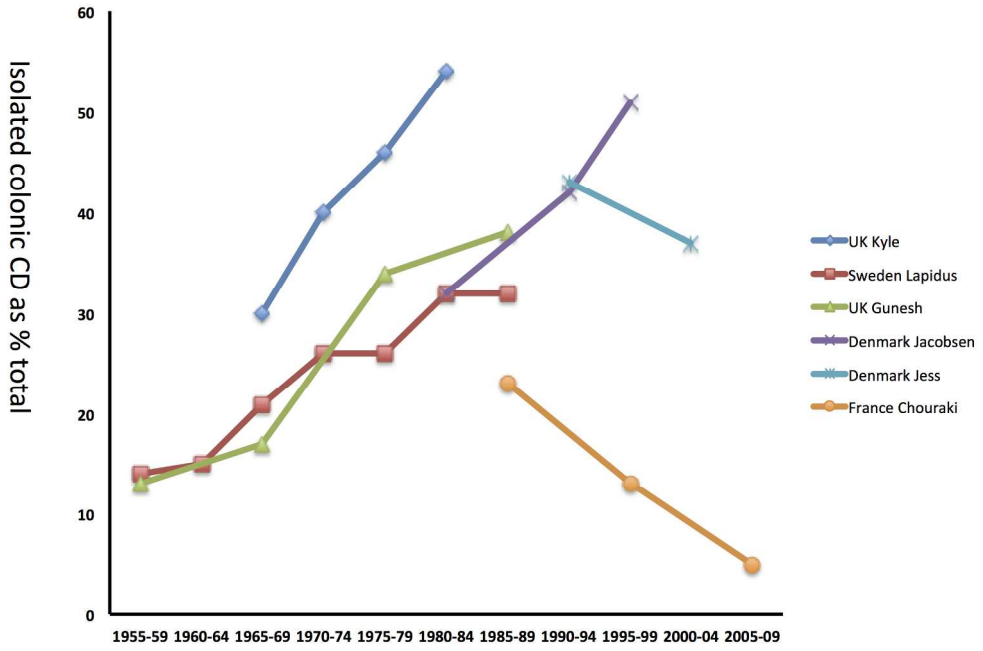

Isolated colonic Crohn's as percentage of all Crohn's disease by year in studies reporting sequential data from the same centres or geographical areas.
total Crohn's from 1970 to 1
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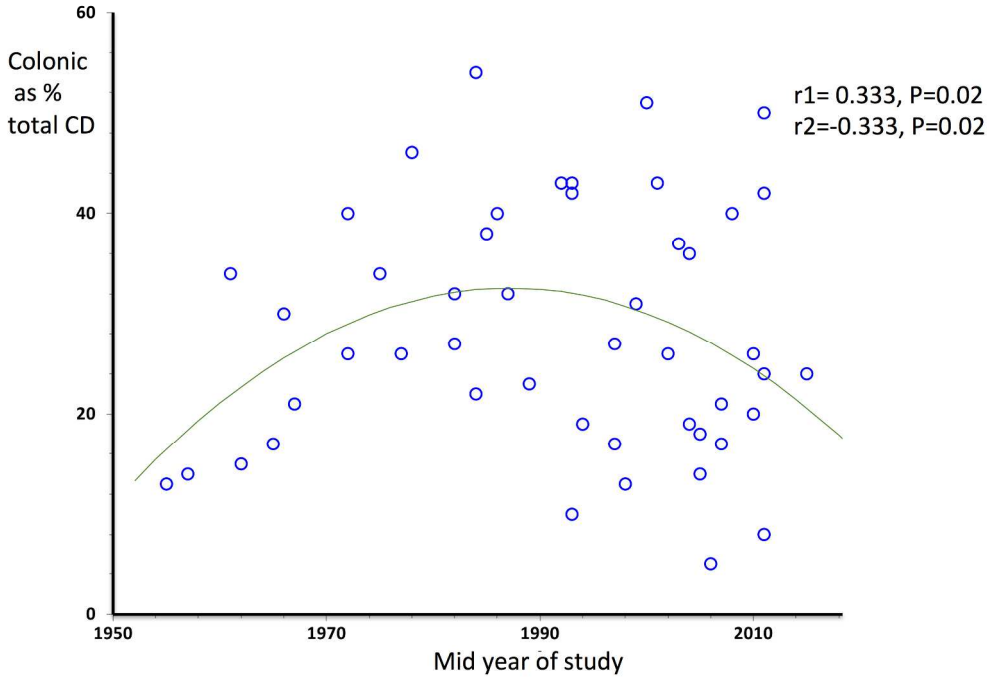

Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all studies.
(p=0.02 by polynomial regressi
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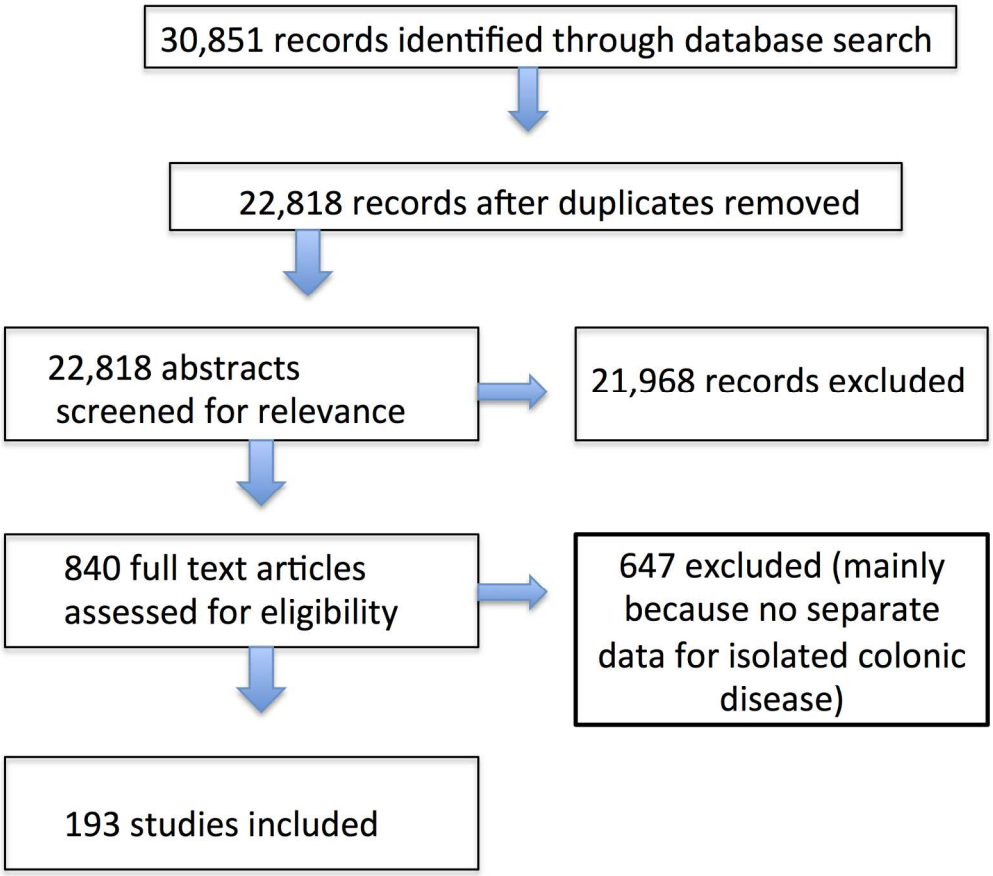

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Recent advances in clinical practice: a systematic review of isolated colonic Crohn's disease – the third inflammatory bowel disease?

5355 words

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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 1930[1] as "regional migratory ulcerative colitis". Crohn's classic 1932 paper did not include cases with colonic involvement[2] although non-tuberculous granulomatous involvement of ileum and colon had been reported in 1923[3] 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 resection[13], 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]

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

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

METHODS

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

PATHOLOGY, DIFFERENTIAL DIAGNOSIS, AND DISEASE COURSE – DEFINING THE CONDITION

The histological features of isolated colonic Crohn's disease were first defined by Lockhart-Mummery and Morson.[9] They labeled patients with this diagnosis because "they had the same characteristic pathology in the large intestinal lesions as that described by Hadfield[18] for the disease as it affects the small intestine". Gross appearances of the colon following

colectomy include less sharp demarcation of ulceration than typically seen in ulcerative colitis and with areas of intact intervening mucosa. In some cases, very marked fibrous thickening with associated stricturing was present. Fibrosis and oedema sometimes extended into the pericolic fat and enlargement of regional lymph nodes was marked. Warren later split the macroscopic features into three patterns: isolated rectal disease; stricturing colonic disease; diffuse colitis – usually with rectal sparing, and noted that approximately 75% develop perianal pathology during their disease course.[19]

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

Histopathology alone is diagnostic only in the minority – in a series of 103 cases of Crohn's colitis, diagnosis was determined by microscopy alone in 28%, by distribution (rectal sparing and/or discontinuity) alone in 22% and by combination of the two in 50%.[22] Particularly discriminatory features suggesting Crohn's colitis rather than ulcerative colitis include granulomata, submucosal inflammation, and relative preservation of goblet cells.[23,24] At an international workshop expert pathologists "correctly" identified only 64% of cases with Crohn's colitis and 74% with ulcerative colitis[25] leading the European consensus on histopathology of inflammatory bowel disease (2013) to note that "accurate discrimination between the two diseases (Crohn's colitis and ulcerative colitis) is not yet optimal amongst expert gastrointestinal pathologists". Given that inflammatory disease pathogenesis is multifactorial an alternative interpretation would be that there is a continuous phenotypic spectrum that runs through from "typical" ulcerative colitis, through IBD-unclassified to "typical" Crohn's colitis.

Early studies reported an additional incidence peak of Crohn's disease in the elderly resulting from cases particularly affecting the sigmoid colon.[26] Following the later clarification of segmental colitis associated with diverticular disease (SCAD) this seems probably attributable to SCAD. SCAD can be indistinguishable histologically from inflammatory bowel disease and includes a "Crohn's-like" variant with granulomata.[27] This reflects emphasis often placed on the diagnostic specificity of the granuloma. However, granulomas are only found in colonoscopic biopsies at diagnosis in about 66% of adults with colonic Crohn's disease, falling to 18% at follow-up.[28] Moreover granulomas, particularly in association with crypts, can be found in ulcerative colitis.[29] Other forms of colitis that may need to be considered in the differential include ischemic colitis (see earlier) and infections including amoebiasis and tuberculosis but it is beyond the scope of this review to consider these further.

Localisation of disease to the colon remains fairly constant over time. The largest published data set by far is the 16,902 Crohn's disease cohort, including 2,933 with isolated colonic disease, in the recent genotype/phenotype association study.[17] This confirmed previous

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 series [33] whereas penetrating disease (B3) as defined by the Vienna classification (ie including peri-anal fistulae) occurred in 23% in the same series, less frequently than in patients with ileal disease (46%; P=0.0003) or ileocolonic (28.6%; 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 Sweden[37] 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 France[38] 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 al[17]. 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

Cigarette smoking is associated with increased risk for development and progression of Crohn's disease but reduced risk for ulcerative colitis. Smoking is more strongly associated with risk for ileal and ileo-colonic Crohn's disease than for isolated colonic disease (Table 2). Only one study (of nine)[79] reported a higher rate of smoking amongst patients with isolated colonic Crohn's disease. If the South African data[84] which reported exceptionally high rates (73%) across all groups are excluded, the other studies report rates for smoking amongst patients with isolated colonic disease that averaged 37.8% compared with 49.8% (P=0.008 by paired t test) for other Crohn's disease sites. This smoking rate is probably slightly higher than for the general population – approximately 30% European adults were smokers in 2008 (WHO).[86]

Smoking worsens prognosis of Crohn's disease overall and cessation of smoking improves it.[87,88] This has been studied less in isolated colonic disease but the conclusion is similar. The largest study[80] included 688 patients with Crohn's colitis, 978 with ulcerative colitis and 118 with "indeterminate" colitis. Sixty-one per cent of patients with ulcerative colitis or indeterminate colitis had stopped smoking before disease onset compared with only 12% in isolated colonic Crohn's disease. In women but not men with isolated colonic disease the risk of needing immunosuppression was increased amongst smokers (10-yr cumulative risk 48% in non-smokers vs 58% in smokers, P<0.01). An earlier study[74] showed that smokers with Crohn's colitis relapsed approximately 50% more often (P=0.028) and with more pain (P<0.007) than non-smokers.

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

Oral contraception

Meta-analysis of 14 studies, with adjustment for smoking, showed a relative risk of 1.51 (95%CI 1.17-1.96, P=0.002) for Crohn's disease amongst women currently taking oral contraception[89]. The relative risk for ulcerative colitis was also increased at 1.53 (1.21-1.94, P=0.001). Six of the seven studies that reported risk associated with oral contraception separately for isolated colonic disease found a significant association (Table 3) with relatively high odds ratio (2.63), risk ratios (3.6 and 3.23) or hazard ratio (4.13). The sole exception[91] only included 8 cases with isolated colonic Crohn's disease and showed no overall association between oral contraception and risk for Crohn's disease. Excluding the latter study[91], five of the other six show higher risks amongst oral contraceptive users for isolated colonic Crohn's than for other sites.

Oestrogen-associated ischaemic colitis as a confounder

An early study from Birmingham[50] reported patients with apparent oral contraceptive-associated colonic Crohn's disease who had non-granulomatous colitis with rectal sparing. Ischaemic colitis is a rare but recognized complication of oral contraception that might cause diagnostic confusion. [97,98,99] Most cases have a short duration with typical features of ischaemic colitis including abdominal pain, and rectal bleeding. Colonoscopy shows mucosal friability but no linear ulceration and the proximal colon and rectum are typically normal. Such cases should be readily distinguishable from colonic Crohn's disease but Tedesco[100]

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

GENETICS

The strongest genetic association with IBD is the link between NOD2/CARD15 and Crohn's disease. Meta-analysis of 42 studies showed that this association was stronger for Crohn's disease with small bowel involvement than for those without (OR 2.53; 95%CI 2.01-3.16).[103] Subsequent study of 1528 patients with Crohn's disease from 8 centres (in 7 European countries) (IBDchip) confirmed the association of NOD2/CARD15 with ileal involvement and also showed that Interleukin23 receptor polymorphisms were more strongly associated with isolated colonic Crohn's (OR 2.20; 95%CI 1.17-4.57).[85]

The most consistent genetic link with ulcerative colitis is with the rare Major histocompatibility Complex (MHC) / Human Leucocyte Antigen (HLA) Class II allele HLA-DRB*0103. This occurs in less than 2% in European and white North American populations and is absent in the Japanese. It is strongly associated with colonic Crohn's disease where it is present at up to 32% frequency with Odds Ratios for isolated colonic disease of 5.1-18.5 compared with Crohn's disease at other sites.[104]

The largest study to compare genetic associations with Crohn's disease phenotype included 19713 patients from 49 centres across 16 countries in Europe, North American and Australasia.[17] This confirmed that the strongest association with isolated colonic Crohn's disease was HLA-DRB1*01:03 ($p=1.47 \times 10^{-23}$, ileal vs colonic OR 0.32, 95%CI 0.29-0.41; ileocolonic vs colonic OR 0.47, 95%CI 0.39-0.57). The only other loci that were significant across all analyses in this study were NOD2 (16q12), again associated with increased risk for ileal involvement (OR ileocolonic vs colonic 1.61,1.59, and 1.89 for the three NOD2 polymorphisms tested) and also MST1 (macrophage stimulating -1 that encodes a protein which induces macrophage phagocytosis) polymorphisms which were more weakly associated with ileal involvement (OR 1.07 -1.10 according to polymorphism and whether comparing ileal or ileocolonic with colonic disease). When overall genetic risk scores for Crohn's disease and ulcerative colitis were computed as a ratio and compared with phenotype, isolated colonic Crohn's disease was found to be approximately "balanced" in respect of Crohn's disease versus ulcerative colitis genetic risk factors (Figure 1). It was found though that even the combination of smoking status with the strongest genetic predictors could only explain 6.8% of the variance for disease location.

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

Amongst children with very early onset Crohn's disease there is a marked preponderance of cases with isolated colonic disease eg 76.5% before age 5[105] and 42% before age 8.[106] Amongst younger cases there is a strong male preponderance – eg 1.6:1 across all Crohn's disease presenting <5[105] and some of this is accounted for by X-linked single gene disorders. The first such condition to be identified was X-linked Chronic Granulomatous Disease. Chronic Granulomatous Disease is associated with defects in neutrophil function leading to skin lesions and in around 40% with a form of inflammatory bowel disease that is indistinguishable from Crohn's disease, typically with predominant colorectal and perianal involvement .[107] It is due to mutations in one of four NADPH oxidase complex component genes of which the commonest (CYBB) located on the X chromosome accounts for about 65% cases.

Rapid developments in DNA sequencing have allowed identification of over 50 further single gene disorders that present as inflammatory bowel disease, typically as colonic disease and with presentation before age 6, defined as Very Early Onset IBD or VEO-IBD.[108] VEO-IBD cases account for 4-10% of paediatric inflammatory bowel disease.[109] One of the commoner single gene variants is in the coding region of X-linked inhibitor of apoptosis protein (XIAP) that accounts for about 4% of male patients with paediatric onset Crohn's disease.[110]

SEROLOGY INCLUDING ANTI-MICROBIAL AND ANTI-NEUTROPHIL ANTIBODIES

Anti-microbial antibodies such as Anti-Saccharomyces cerevesiae (ASCA) and antibodies to outer membrane protein (ompC) are found less often and/or at lower titre in isolated colonic Crohn's than in other Crohn's phenotypes.[111] Meta-analyses confirm this particularly for ASCA.[112-114] Average sensitivity of ASCA for isolated colonic Crohn's disease diagnosis is 31% but with a wide range (8-59%) and an average 14% positivity rate in ulcerative colitis (Table 4). The clinical utility of ompC antibodies has been less studied but reported positivity/sensitivity in isolated colonic Crohn's disease is substantially lower than that for ASCA.

Anti-neutrophil antibodies, particularly an atypical peri-nuclear antibody (pANCA), are present in around 55% of patients with ulcerative colitis[114] and 23% of patients with isolated colonic Crohn's disease (Table 4). This compares with pANCA positivity of around 11% in Crohn's disease overall and 3% in non-IBD controls.[114]

A combination of positive ASCA and negative pANCA is more discriminatory eg positivity rate in isolated colonic Crohn's disease of 52% compared with 9% in ulcerative colitis[122] but is still insufficiently predictive for routine clinical use.[125]

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

MICROBIOTA

The faecal microbiota in active inflammatory bowel disease is commonly dysbiotic with reduced bacterial diversity.[126,127] This could be secondary to inflammation yet still significant

in maintaining chronicity. The large study of pre-treatment Crohn's disease by Gevers showed only a mild dysbiosis in the faecal microbiota and much greater separation of Crohn's disease from healthy controls when the mucosa-associated microbiota was studied.[128] Ileal and rectal mucosal samples typically showed a reduction in *Firmicutes* such as *Faecalibacterium prausnitzii* and an increase in *Proteobacteria* such as *Escherichia coli* as well as in *Veillonella*, *Haemophilus* and *Fusibacteria*. This confirmed many previous studies showing an increase in mucosa-associated *E. coli* in Crohn's disease as well as several showing a reduction in *F. prausnitzii*[129-132].

The faecal and mucosa-associated microbiota in isolated colonic Crohn's disease are generally closer to that of healthy controls than is found in patients with ileal or ileocolonic Crohn's disease (Table 5). Thus Baumgart *et al*[129] found that an increase in ileal mucosa-associated *E. coli* and reduction in ileal *F. prausnitzii* was only present in patients with Crohn's disease who had ileal involvement and not in those with isolated colonic disease. Similarly, a study of twins with/without Crohn's disease showed that faecal microbial diversity was only reduced and *Proteobacteria* increased in patients with ileal involvement and not in patients with isolated colonic disease.[130] A previous report by the same group also showed a reduction in *F. prausnitzii* in Crohn's patients with ileal involvement but not in isolated colonic disease.[131] Both the twin study by Willing[131] and the large study in children[128] and adolescents[134] did however show differences between the mucosa-associated microbiota in isolated colonic Crohn's disease and ulcerative colitis. 16sRNA pyrosequencing of mucosal samples[133] confirms the increase in *E. coli* and reduced *F. prausnitzii* in Crohn's disease with ileal involvement with milder changes in isolated colonic disease, although the latter did show some reduction in *F. prausnitzii* compared with healthy controls. This study also confirmed that the mucosa-associated microbiota are consistent at different sites from ileum to rectum in the same individual.

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

RESPONSE TO TREATMENT

Mesalazine

Systematic reviews show no convincing benefit of oral mesalazine (5-aminosalicyclic acid) over placebo either in induction of remission or in maintenance of medically induced remission in Crohn's disease as a whole[1345138] although they may have a modest benefit in maintaining surgically-induced remission.[139] Sulphasalazine (sulphapyridine linked via azo bond to 5-aminosalicylate) has possible modest efficacy in induction of remission.[134, 136]

Amongst trials that have reported data separately for isolated colonic Crohn's disease, only one trial studied the effect of oral mesalazine in remission induction[140] and four studied its effect in maintenance of medically-induced remission[141-144] (Table 6). In none of these was

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 (Blichfeldt[153]: n=6 crossover; Sutherland[154]: 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 daily[155] 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 trial[147]showing no benefit and the other[148]showing efficacy. There has never been a trial to assess dose-responsiveness to

conventional corticosteroids in Crohn's disease so optimal dosage is unknown. More data are available for budesonide but trials have focused predominantly on patients with ileal or ileo-colonic disease so data in isolated colonic disease are again very sparse. The data from one comparison with mesalazine[157], support efficacy in isolated colonic Crohn's disease, possibly with a weaker effect than conventional corticosteroids[158], but reduced corticosteroid side-effects.

Anti-TNF

None of the randomised trials of infliximab[159,160] or adalimumab[161-164] reported subgroup analyses of outcomes based on disease location. In a randomised, placebo controlled trial of certolizumab pegol, patients with colonic (OR 2.39, 95% CI 0.99-5.75, P=0.052) and ileocolonic disease (OR 2.07, 95% CI 1.01-4.28, P=0.048) were more likely to achieve remission at week 6 compared to ileal disease (OR 0.42, 95% CI=0.18-0.99, P=0.048)[165](Table 9)

Several cohort studies have assessed colonic disease location as a predictor of response to anti-TNF agents, four with infliximab and one with adalimumab. Three cohort studies assessing induction therapy with infliximab[166-168] all showed better response rates in isolated colonic disease than for disease at other sites. Paradoxically, cohort studies of infliximab maintenance in children[169] and of adalimumab maintenance in adults[170] both showed higher risk of lost response or dose escalation in isolated colonic disease. Overall, the evidence supports good efficacy for anti-TNF therapy in induction of remission in isolated colonic Crohn's disease but possibly with a higher subsequent rate of loss of response.

Vedolizumab

In the combined induction and maintenance study of vedolizumab there was no significant difference in efficacy in isolated colonic disease compared with other locations.[171] (Table 9)

Enteral nutrition

Exclusive enteral nutrition is effective as primary therapy in patients with active Crohn's disease[172,173] and partial enteral nutrition has shown efficacy in maintenance of remission.[174] In ulcerative colitis total parenteral nutrition and bowel rest are ineffective[175] and comparison of enteral with parenteral nutrition showed no difference in efficacy[176] implying no efficacy for enteral nutrition either. Whether enteral nutrition is effective as primary therapy in isolated colonic Crohn's disease is controversial. Relatively few studies provide separate data on patients with isolated colonic Crohn's disease (Table 10). Five of the six studies are in children. Two studies[178,179] report poorer results in children with isolated colonic disease compared with those with small intestinal involvement. Numbers are small though (19 cases of isolated colonic disease across the two trials) and the other studies (including 72 cases of isolated colonic disease across four trials) found no significant difference in remission rates for those with isolated colonic disease compared with other

sites. Further trials of exclusive enteral nutrition are needed in patients with isolated colonic disease.

Surgery

Faecal diversion

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

Resection

The cumulative risk of surgery for isolated colonic Crohn's disease is reported as 22-33% by 10 years after diagnosis compared with around 75-90% for ileal disease.[17,67] Partial resection, either right hemicolectomy for proximal disease or a segmental resection for more distal disease has been shown to be successful therapy for colonic Crohn's disease[185, 186] as is colectomy with ileo-rectal anastomosis for more extensive disease if the rectum is uninvolved[187,188]. Approximately 75% of patients with ileo-rectal anastomosis will still have a functioning anastomosis after 10 years and about two thirds of those treated by segmental resection will not have required a further resection.[188] Recurrence rates are similar after either procedure.[189] This contrasts with left-sided ulcerative colitis, where the tempting option of left hemicolectomy with right-sided colo-anal anastomosis consistently fails, usually with rapid recurrence of colitis in the retained colon.[190] It should be noted though that segmental resection for colon cancer complicating colonic Crohn's disease has been associated with high (39%) risk for metachronous colon cancer[191] suggesting that panproctocolectomy might be a safer option for such patients.

Ileo-anal pouch reconstruction

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

CONCLUSION

Current data suggest that the genetics, microbiota, serology and smoking association of isolated colonic Crohn's disease lie between those of ileo/ileocolonic Crohn's disease and

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

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LEGENDS TO FIGURES:

1. 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 Cleynen et al,[17] with permission. This shows that isolated colonic Crohn's lies approximately equidistant genetically between ileal Crohn's disease and ulcerative colitis.

2A. 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.
2B. Isolated colonic Crohn's disease as percentage of all Crohn's disease by year in all studies.

Supplementary Files

1. PRISMA flow diagram.
2. PRISMA checklist.

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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
Cornes[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 ("enriched")	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	-	-
Russel[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 involvt
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 *Escherichia* and reduced *Faecalibacterium;* disease activity correlated with abundance of *Fusobacterium*	8* Similar to colonic CD apart from *Faecalibacterium* abundance 2.7-fold lower than in isolated colonic CD (not significant)	8* Higher levels of *Faecalibacterium* and 2 unidentified genera of the Clostridiales and Ruminococceaea; 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 *F. prausnitzii*, *E. coli* moderately increased.	13 Reduction in *F. prausnitzii*	13 *F. prausnitzii* comparable to UC; *E. coli* commoner than UC particularly in ulcerated zones	28 *F. prausnitzii* abundance intermediate between CD and HC.	28	***F. prausnitzii/ E. coli* (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 *E. coli*.		8 No reduction in Faecalibacterium or Roseburia. Some increase in *E. coli* 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, (*E. coli, Shigella*) reduction in Lachnospiraceae, (*Ruminococci*, *Roseburia* and *Coprococci*) and Clostridiales (*Faecalibacteria* and *Subdoligranula)*	8 Results not presented separately	8 Enterobacteraciae 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 </=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 >/= 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 >/=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) Subgroup analysis based on 62 active and 43 placebo.	Remission (CDAI </=150) at week 6 over placebo, Response (CDAI fall >/=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

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	4weeks 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	8weeks	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/ileolonic CD pANCA positive in minority	ASCA usually negative pANCA commonly positive
Mucosa-associated Microbiota	Marked changes commonly including increased Proteobacteria (eg *E. coli*) and Fusobacteria, reduced Firmicutes (eg *F. prausnitzii*	Intermediate changes similar to ileal/ileo-colonic CD but less consistent	Modest changes, including slight increase in *E. coli* but no reduction in *F. prausnitzii*
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 excusive 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.