

Inflammatory bowel disease in Africa: what is the current state of knowledge?

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Inflammatory bowel disease (IBD) is increasingly recognized as a global disease in the twenty-first century; however, little is known about its epidemiology in Africa. We conducted a literature review in order to assess what is currently known on this subject, the results of which are reported here. Based on available observational studies, it appears that the incidence of IBD in Africa is rising, although comprehensive epidemiological data are lacking. This is likely due to multiple factors, including shifting trends in diet and exposure to environmental pathogens. Many challenges relating to IBD exist for healthcare systems in Africa, including the need for improved access to diagnostic facilities such as endoscopy and histopathology, and the potential economic burden of treatment. Intestinal TB also represents a significant confounding factor in the diagnosis of IBD in Africa.

Keywords: inflammatory bowel disease, inflammatory bowel diseases, ulcerative colitis, Crohn's, epidemiology

Introduction

The inflammatory bowel diseases (IBDs) ulcerative colitis (UC) and Crohn's disease are chronic inflammatory conditions of the intestine, the exact causes of which are unknown. Current thinking is that they are likely to be the result of dysregulation of the intestinal immune response to components of the gut microbiota in genetically susceptible individuals.^{1,2} This could be thought of as a loss of oral tolerance, which is the lack of an immune response to soluble antigens in the intestinal luminal stream. Although long thought of as diseases of the West, these diseases have emerged over the past decade as a global public health challenge.^{3–6} This is particularly striking in Asia, where the prevalence of UC in parts of eastern Asia has been shown to be as high as 57.3/100 000.³ An increasing number of case reports and series from Africa suggest that the incidence on this continent is also rising. However, there are few data pertaining to the prevalence of IBD outside of North African countries and South Africa.^{7–9}

Methods

We searched MEDLINE via PubMed from initiation up to and including 8 September 2019 for all studies relating to UC, Crohn's

disease or IBD in Africa. The combination of terms and keywords used for this search was 'inflammatory bowel disease OR ulcerative colitis OR Crohn's disease AND Africa'. The search identified 395 articles, and two additional studies were identified from citations. The initial stage of the review consisted of screening abstracts and titles of search results, following which 150 articles reporting on aspects of epidemiology, pathophysiology, diagnostic techniques or treatment were identified for full-text review.

Early reports

In 1946, Kibaya¹⁰ described the first likely case of Crohn's disease in Africa in a 36-year-old Rwandan herdsman presenting with chronic intestinal obstruction with symptoms of constipation, vomiting after eating and anorexia. He was found to have an ileocaecal mass, which was resected, and histopathology showed that the caecal wall was ulcerated and the submucosa was congested. However, there was no evidence of TB, syphilis or amoebiasis and the appearance 'resemble[d] those seen in Crohn's ileitis'.

Following this, Billingham and Welchman¹¹ reported four cases of UC in Kampala, Uganda in 1966, with the diagnosis based on typical sigmoidoscopic or radiographic appearances,

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failure to identify any infective cause and response to corticosteroids. There were further case reports in the 1960s and 1970s, largely from South Africa, but there were also reports of UC from Nigeria, Tanzania, Kenya, Senegal and Zimbabwe.¹²⁻¹⁷ Despite this, Walker reported in 1979 that the disease was extremely rare among the rural South African black population, although the prevalence of UC in the white population of South Africa was similar to that of Western countries. He postulated that changes in environmental factors such as diet, smoking, atmospheric pollution and 'stresses linked with urbanization and rise in class' were likely to account for this.¹⁸

For many years the majority of publications on IBD came from South Africa. Some comparison of incidence in different ethnic groups was attempted, although it should be borne in mind that there was a wide disparity in access to healthcare between black and white South Africans. A report published in 1980 from Baragwanath Hospital, Johannesburg suggested that although UC remained rare in black populations, the incidence (or at least diagnostic frequency) appeared to be increasing.¹⁹ This was based on the observation that only 18 cases were reported in sub-Saharan Africa up to 1975, but over a period of 4 years following this, 13 cases had been reported at this single centre. Epidemiological studies of IBD patients diagnosed in Cape Town between 1975 and 1980 reported that UC was a more common diagnosis than Crohn's, with 220 new cases of UC compared with 117 cases of Crohn's. A total of 3% of the UC patients were black, compared with only 1% of the Crohn's patients.^{20,21} From 1980 to 1984, the incidence of UC in the black population in Cape Town was calculated to be 0.3/100 000 per year, compared with 2.6/100 000 per year in the white population.²² Interestingly, a separate study of UC in the Indian population of Durban, South Africa, between 1983 and 1987 reported an incidence of 2.7/100 000 per year,²³ comparable to that of the white population of Cape Town around that time. A case series of the first 46 black South African patients to be treated for UC at Baragwanath Hospital reported that 34 of these patients were women (female:male ratio 28:1), 94% were from urban areas and the patients generally had higher levels of education (67% having attended high school as opposed to only 27% of the general Sowetan black population at this time) and were from 'higher occupational categories' (23% being from professional occupations compared with only 6% of the general Sowetan black population).²⁴

Temporal trends

The relative frequency of UC diagnosis when compared with Crohn's in Johannesburg was borne out by reports from Cairo, where data from a cohort of IBD patients diagnosed between 1995 and 2009 reported that the ratio of UC to Crohn's was 6:1.⁷ It was also noted that the frequency of diagnoses of both Crohn's and UC increased markedly over the latter 5 y of the study, with 88 cases being diagnosed over this time period as compared with only 70 cases in the 10 y period leading up to this.⁷ The male:female ratio in this study was 1:1.15, whereas Crohn's seemed to occur predominantly in males, with the ratio being 2.6:1.

This trend mirrors that originally noted in industrialized countries, where UC was initially more common but has

now been overtaken by Crohn's.⁵ For example, the reported prevalence of Crohn's in North America reached 319/100 000 in Nova Scotia, Canada, as opposed to the highest prevalence for UC which was 286/100 000 in Olmsted County, MN, USA.³ It seems that this is already the case in areas of North Africa, with the prevalence of UC in Constantine, Algeria reported to be lower than that of Crohn's (the highest estimate being 19/100 000 vs only 11/100 000 for UC).⁸ Similarly in Tunisia, where IBD incidence appears to be increasing, Crohn's seems to be diagnosed with more frequency than UC, representing 55.5% of the 202 diagnoses of IBD that were made between 1991 and 2005. This represented a change from the first part of the study period (1991-1993), where UC was diagnosed more frequently before being overtaken by Crohn's for the remainder of the study period.²⁵

IBD in Africa in the twenty-first century

Larger epidemiological studies relating to IBD in Africa are lacking. In a recent systematic review of population-based studies of IBD, only one study from the continent met the requirements for inclusion, and this was from Algeria, where 299 cases of IBD (180 Crohn's, 100 UC and 19 unclassified) were registered at the University Hospital in Constantine between January 2003 and December 2007, giving an average annual incidence of 5.87/100 000 for Crohn's and 3.29/100 000 for UC. In addition, this study reported that the incidence of UC had risen during the 5 y period of the study from 2.76/100 000 in 2003 to 5.12/100 000 in 2007.⁸

In sub-Saharan Africa, the majority of data relating to IBD incidence come from South Africa, where patient cohorts are primarily white, Asian or of mixed-race descent. For example, a retrospective analysis of a cohort of IBD patients seen at the Groote Schuur Hospital in Cape Town between 2002 and 2009 identified 1388 IBD patients who had attended the clinic, with only 5% of these being black. These patients were predominantly female (63%) and the majority had Crohn's (53%).²⁶ A later study from Cape Town investigating the relationship between race and Crohn's phenotype in patients seen at the Groote Schuur Hospital between September 2011 and January 2013 included 194 patients, only 7 (4%) of whom were black, with the majority (78%) being 'Cape Coloured' (a term applied to people of mixed genetic origin including Europe, Africa and the Indian Ocean littoral) and 18% being white.²⁷ There was no significant difference in disease behaviour between the white and Cape Coloured patients at initial diagnosis; however, over the course of follow-up (median disease duration 16 y), significantly more Cape Coloured patients developed complicated disease as defined by stricturing, penetrating or perianal disease or disease requiring surgical intervention (60% vs 9%). Although black patients were excluded from statistical analysis due to their relatively small numbers, all of these patients either had complicated disease at the time of diagnosis or developed complicated disease during follow-up. Interestingly, a positive family history of IBD in a first-degree relative was much more common among white patients (14%) as compared with only 6% of the Cape Coloured patients. None of the black patients had a first-degree relative with IBD. Although these numbers are small, this might suggest that genetic predisposition in IBD may vary with ethnicity.

Table 1. Case numbers reported from sub-Saharan African countries excluding South Africa (a full list of references included in the table is available in [Appendix 1](#))

Country	Total cases reported, n	Crohn's, n	UC, n	Indeterminate, n	Reference
Burkina Faso	4	2	2		Bougouma et al. 2002
Cameroon	1	1	0		Alegbeleye 2019
Côte d'Ivoire	3	1	2		Casanelli et al. 2004, Okon et al. 2012
Ethiopia	13	8	5		Kefenie et al. 1987, Mengesha et al. 1997, Mengesha and Tsega 1989
Ghana	45	4	24	17	Archampong and Nkrumah 2013
Kenya	18	2	16		Awori et al. 1972, Ogutu et al. 1998, Steury and Templeton 1980
Nigeria	26	8	18		Adi and Lloyd 2010, Akere et al. 2016, Alatise et al. 2012, Alese and Irabor 2008, Khwaja et al. 1982, Naish et al. 1970, Senbanjo et al. 2012, Ukwanya et al. 2011
Rwanda	3	1	2		Clerinx et al. 1995, Kibaya 1946
Senegal	12	3	9		Carayon et al. 1968, Derrien et al. 1970, Dia et al. 2014, Diop et al. 2014, Peghini et al. 1988, Peghini et al. 1990
Tanzania	4	0	4		Jones et al. 1977, Spencer and Nhonoli 1972
Togo	1	0	1		Agoda-Koussema et al. 2012
Uganda	4	0	4		Billinghurst and Welchman 1966
Zimbabwe	10	0	10		Jena 1980, Muguti 1989, Sealey and Gelfand 1968, Stein and Levy 1982

Outside of South Africa and North African countries, data remain scarce at the beginning of the twenty-first century. [Table 1](#) summarizes all cases reported in sub-Saharan countries (excluding South Africa) to date based on our literature search. Two recent case series from Nigeria suggest that diagnosis of UC occurs late after onset of symptoms, indicating that underdiagnosis may be leading to a false perception of the scarcity of the disease.^{28,29} A prospective study of patients attending a clinic in southwest Nigeria for colonoscopy, where the most common indication was haematochezia, showed that UC was in fact a relatively common finding, present in 1.3% of participants.³⁰

In sub-Saharan Africa excluding South Africa, Ghana has reported the largest number of IBD cases. A retrospective cohort study from Accra describing patterns of IBD diagnoses between 1997 and 2011 found that the number of diagnoses rose from 17 patients over the initial 7-y period of the study from 1997 to 2004 to 28 patients in the latter 7 y of the study period, representing a 65% increase in the number of diagnoses.⁹ The majority of these patients were male, with a male:female ratio of 2.83 between 2004 and 2011. The patients in Accra largely presented late (between 1 and 5 y after symptom onset) and with severe endoscopic colitis, and the authors observed that many had tolerated their symptoms or sought relief from traditional medicine, such as herbal remedies, prior to consultation. Interestingly, however, the majority responded to medical treatment with corticosteroids or sulfasalazine, and there were no recorded incidences of surgery being required for treatment-refractory colitis.

A similar phenomenon of late and severe presentation but rapid response to treatment was observed in a retrospective study of patients presenting to the National Centre for Gastrointestinal and Liver disease conducted in Khartoum, Sudan between 1990 and 2001. This study identified 85 patients who had been diagnosed with IBD during this time period (73 with UC and 12 with Crohn's);³¹ 55% of these patients had severe symptoms at the time of presentation (passing more than five stools per day), but 82% improved with medical therapy (corticosteroids and 5-aminosalicylic acid) and only 4 of the UC patients had been referred for surgery. Again, the majority of these patients (67%) belonged to a high or middle socio-economic class and, similar to the cohort in Accra, the majority were male (male:female ratio 1.6:1).

Genetic studies

A genome-wide association study of 2345 African American IBD patients in the USA identified that the strongest associations for UC were located within the *HLA-DRB1* gene, which is well established as a risk locus in other populations.³² This study also identified African-specific risk loci for UC (SNPs in *ZNF649* and *LSAMP*); however, it did not identify any associations of genome-wide significance for Crohn's.³³

There are increasing numbers of case-control studies investigating potential genetic risk loci in African IBD patients. *NOD2* (previously known as *CARD15*) was the first susceptibility gene for Crohn's to be identified,³⁴ and it remains the strongest

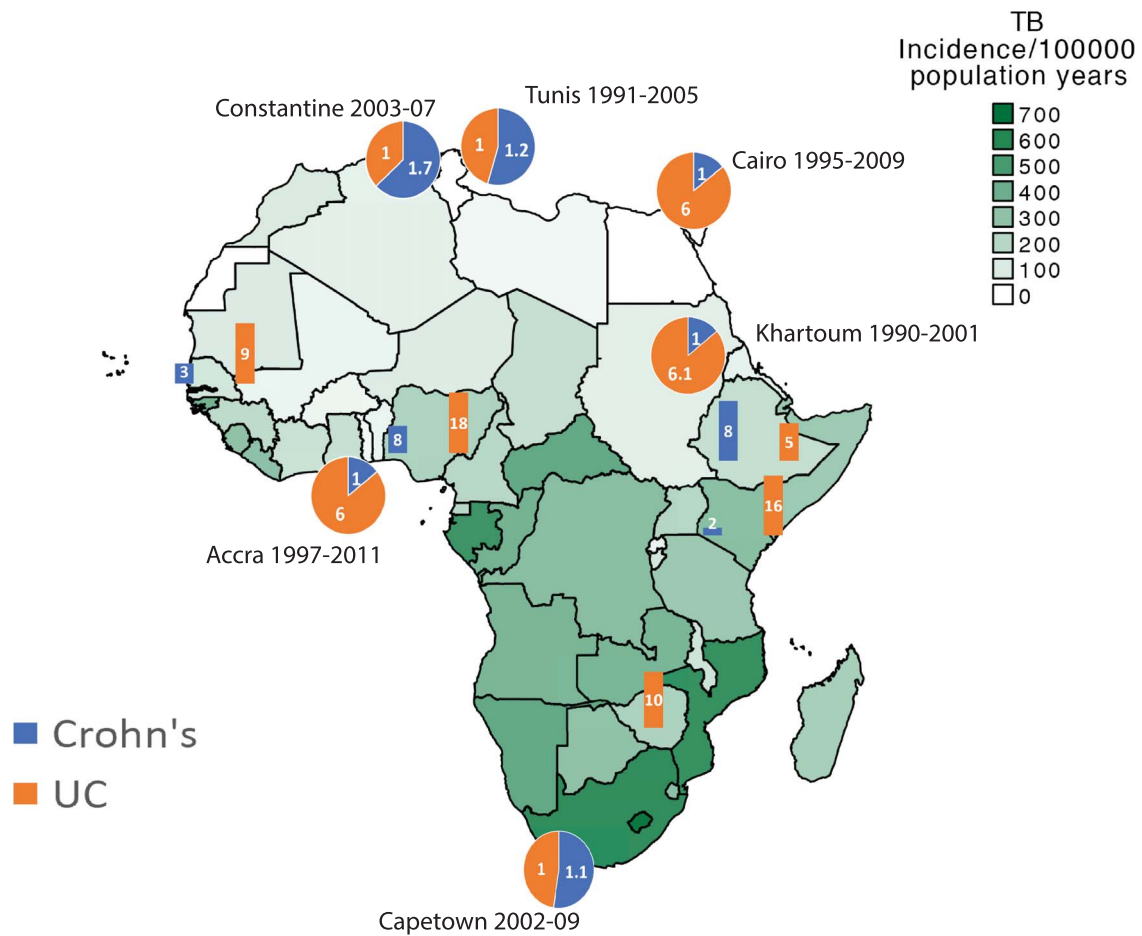


Figure 1. Map of TB incidence per 100 000 population. Pie charts represent areas with reported Crohn's:UC ratio. Where ratios are not known, bar charts show numbers of cases reported (from countries where ≥ 10 cases are reported).

Table 2. Known areas of IBD incidence

Area	Race	Incidence/100 000 population	
		Crohn's	UC
Constantine, Algeria, 2003–2007		5.87	3.29
Durban, South Africa, 1983–1987			2.7
Cape Town, South Africa, 1980–1984	Black	0.3	0.6
	White	2.6	5.0
	Cape Coloured	1.8	1.9

known association for this disease. A Tunisian case-control study investigating the significance of variants of this gene in Crohn's showed that the variants previously shown to be associated with Crohn's in other populations were not as frequent in the Tunisian patients, and in fact there was no significant difference in their frequency between cases and controls.³⁵ Similarly, in a cohort of IBD patients in Morocco, which has a significantly heterogeneous population in terms of ethnic diversity, it was reported that there was no significant difference in the frequency of the

three common Crohn's-associated variants in *NOD2* between patients and controls (although analysis was not stratified by ethnic group).³⁶ The same was true for variants of *IL23R* and *ATG16L1* (other established risk loci of Crohn's) in another case-control study from the same group.³⁷ In South Africa, where variants of *NOD2* were investigated in a cohort of 'South African coloured' IBD patients, again no statistically significant differences between cases and population-matched controls were identified.³⁸ In a case-control study in Algeria, the observed

frequency of *NOD2* mutant alleles was similar to that reported in European populations and a higher proportion of Crohn's patients were carriers of at least one mutant allele in any variant (18.6% Crohn's patients vs 10.2% controls); however, this association did not reach statistical significance. The authors postulated that this may be due to the lack of exposure to environmental factors that are fundamental to the pathophysiology of the disease.³⁹

The reported non-association of *NOD2* variations and the paucity of other apparent risk loci for Crohn's in these populations may be a result of the small numbers involved in these studies. However, given the lack of associations of genome-wide significance found in a cohort of 1646 African American Crohn's patients,³³ it may also imply a genetic characteristic specific to populations in this region; perhaps that there is greater genetic heterogeneity underlying Crohn's than in previously studied populations or that genetic susceptibility confers a lesser degree of risk.

Environmental factors/exposome

Diet and the microbiome

One early theory relating to the increase in incidence of IBD in line with the demographic transition relates to the change in diet from a traditional rural diet that included a high intake of fibre and complex carbohydrate to one characterized by a high intake of fat and a high proportion of energy from animal protein; the so-called nutrition transition.^{40,41} It is postulated that 'super-efficient' carbohydrate absorption may lead to a reduced concentration of the short-chain fatty acids (SCFAs) acetate, propionate and butyrate generated in the colon. These changes in diet, particularly a reduction in fibre and complex carbohydrate intake, may result in an increased risk for gastrointestinal diseases more common in industrialized societies, including adenomas and colorectal cancers, diverticular disease and UC.^{42,43}

Non-digestible carbohydrates (dietary fibre) cannot be absorbed in the small intestine and reach the colon where they are fermented by the resident microbiota, generating SCFAs. SCFAs trigger signalling cascades by inhibition of histone deacetylases and activation of G-protein-coupled receptors (GPCRs) in intestinal epithelial cells and immune cells. The importance of this SCFA-GPCR pathway in IBD has been demonstrated in animal models; for example, *Gpcr43* knockout mice have been shown to develop more severe inflammation and higher levels of tumour necrosis factor (TNF)- α and interleukin-17 than wild-type mice in dextran sulphate sodium (DSS)-induced colitis. Furthermore, although the severity of DSS-induced colitis is inversely proportional to the amount of fibre that had been fed to the mice, this is not the case in *Gpr43* knockout mice, suggesting that the demonstrated effect of dietary fibre content as a protective factor in colitis is mediated through this SCFA-GPCR pathway.⁴⁴ A study from North India showed that there were reduced concentrations of the SCFAs butyrate and acetate in faecal samples from patients with UC, resulting from depleted levels of butyrate-producing bacteria.⁴⁵

Hygiene hypothesis

It has been proposed that living in an urban area is itself a risk factor for IBD, with a recent prospective population-based

study in Asia reporting that higher population density was associated with increased risk of both UC and Crohn's, and that the increased incidence of IBD in China is positively associated with gross domestic product.⁴⁶ This may be explained by the hygiene hypothesis: improved sanitation in wealthy urban areas means that people are not exposed to enteric pathogens in childhood that they would have otherwise encountered if living in a less sanitized, poorer rural environment and this increases the risk of inappropriate response of the mucosal immune system when presented with these pathogens in later life. A recent case-control study conducted in patients with Crohn's in South Africa showed that having piped tap water or bottled water as the primary source of drinking water between the ages of 0 and 10 y was associated with the development of Crohn's.⁴⁷ A meta-analysis of studies conducted in Europe, North America and Asia has shown an inverse association between access to bathrooms or hot water and UC, although no association was found with Crohn's. Interestingly, this association was only evident in non-white populations.⁴⁸

Another case-control study conducted in South Africa that lends credence to this hypothesis found that 61.6% of IBD patients reported childhood helminth exposure compared with 91.3% of non-IBD controls ($p < 0.001$), suggesting that childhood helminth exposure may be a protective factor for IBD.⁴⁹ Helminthic infection is known to be associated with chronic immune downregulation through its effect on regulatory T-cell activity and this has been shown to have significant implications for the natural history and treatment of certain infections, for example hepatitis C virus in the context of schistosomiasis, as well as for the efficacy of childhood vaccines.⁵⁰⁻⁵² It is possible, however, that this immune dysregulation may also confer a protective effect from autoimmune disorders such as IBD and this hypothesis has led to the exploration of therapeutic applications of helminth infections in IBD.⁵³

Helicobacter pylori

An Egyptian cohort study of 30 patients newly diagnosed with UC at Tanta University Hospital, Tanta, Egypt proposes that there may be an association between *Helicobacter pylori* and UC, with 40% of these patients testing positive for *H. pylori* by Giemsa staining of colonoscopic biopsies and 56.6% testing positive by immunohistochemistry, which was significantly more than in the control group, where only 13.3% were positive by Giemsa and 10% by immunohistochemistry. Furthermore, it was noted that four of the control cases who tested positive for *H. pylori* also had histopathological features of UC despite not having colitis that was evident at endoscopy. Given that the prevalence of *H. pylori* in the general Egyptian population has been reported to be as high as 88%, as the authors point out, the prevalence in the control group is unlikely to be reflective of prevalence in general, making the significance of these findings unclear.⁵⁴

IBD vs TB

No review of IBD in Africa would be complete without also discussing TB. The challenge of differentiating between the diagnosis of Crohn's and intestinal TB (ITB) is becoming increasingly relevant in areas of the world where the incidence of IBD

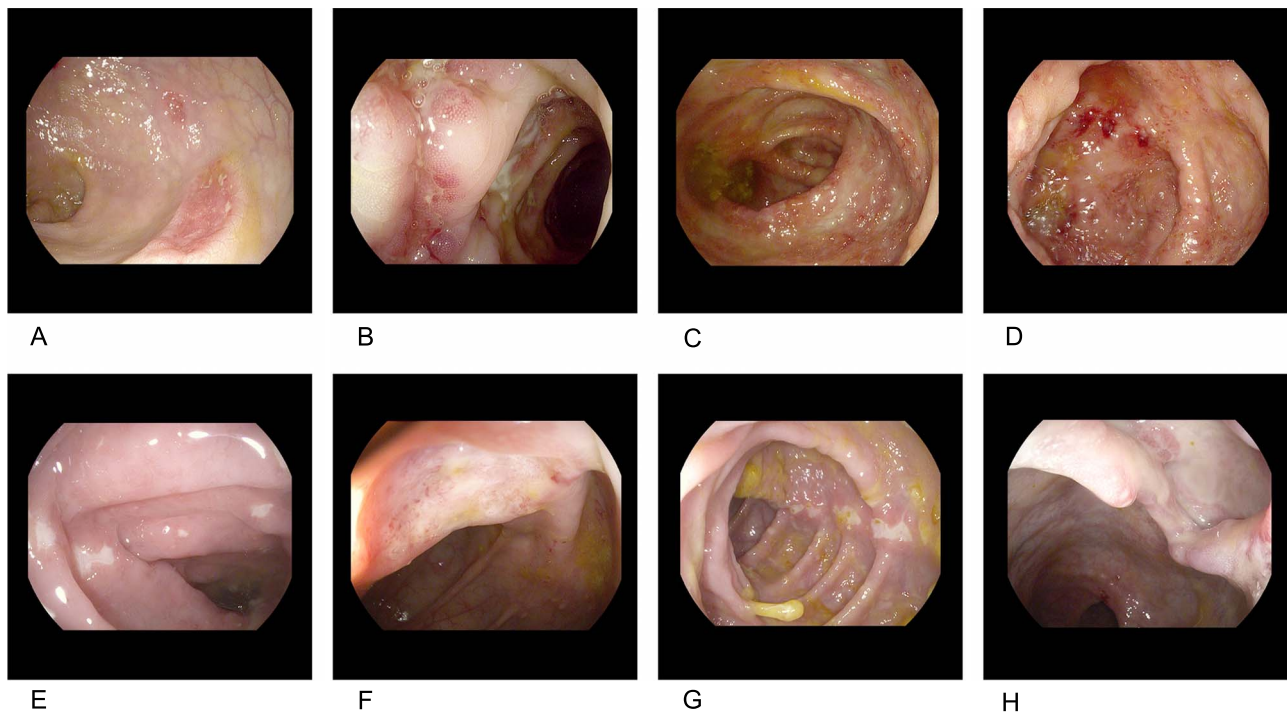


Figure 2. Endoscopic images (A–D) show appearances of intestinal tuberculosis, images (E–H) show colonic Crohn's. Areas of atypical ulceration (see A) are suspicious for TB; however, this can also closely mimic Crohn's (see the discrete and linear ulceration in E and G). Patency of the ileocaecal valve (see D) is said to be typical of intestinal TB. All pleomorphic ulcers must be biopsied and histological analysis must include TB culture or polymerase chain reaction.

is increasing in parallel with urbanization, as both are chronic granulomatous conditions with a predilection for the ileocaecal valve. This was recognized in South Africa by Segal,⁵⁵ who described the clinicopathological similarities between ITB and Crohn's in an urban black population in 1984. In the retrospective study of IBD patients in Khartoum described above,³¹ 42% of the patients who were eventually diagnosed with Crohn's had initially been diagnosed with and treated for ITB. We will not discuss in detail the endoscopic, histological and radiological techniques used for differentiation between the two conditions, as these have been summarized in a recent review.⁵⁶ Staining intestinal biopsies remains an important part of investigation, especially where granulomata are present. Although the sensitivity of Ziehl-Neelsen staining for diagnosis of ITB is low (2.7–37.5%),⁵⁶ it may reveal the presence of fungal organisms, as may periodic acid-Schiff staining, which in colonic biopsies can also be used to detect *Entamoeba histolytica*. These differentials are critical when approaching granulomatous intestinal diseases in tropical settings. Since formalin-fixed biopsies cannot be used for culture, it is vital that additional biopsies are collected for TB culture at index endoscopy.

As well as the diagnostic difficulties outlined above, TB also represents a challenge in terms of treatment of IBD, as immunosuppressive treatments used in IBD pose a risk of reactivation of latent TB; experience using these therapies is largely in the context of populations where TB prevalence is low. At present there is a TB epidemic, with TB being one of the top 10 causes of death worldwide and, at 567/100 000, South Africa has the

second highest TB incidence in the world.⁵⁷ Deetlefs et al.²⁶ conducted a retrospective analysis of a cohort of IBD patients seen in the gastroenterology clinic at Groote Schuur Hospital in Cape Town from 2002 to 2009 and found that of 1388 patients who had attended the clinic, 72 (11.7%) had been diagnosed with TB either before or after being diagnosed with IBD. A total of 30 of these patients had developed TB after IBD diagnosis and 7 of these had been exposed to immunosuppressive treatment for IBD (either azathioprine or the anti-TNF agent infliximab) within the 6 months prior to their TB diagnosis.

ITB is still likely to be more common than Crohn's in Africa, although comprehensive epidemiological data are lacking. The similar presenting symptoms of these two diseases, combined with a lack of awareness in both clinicians and patients, as well as limited access to diagnostic resources make this a genuine diagnostic challenge. An incorrect diagnosis may have disastrous consequences, as immunosuppressive agents can potentially be fatal if the correct diagnosis is ITB. In practice, where there is diagnostic doubt, a trial of anti-TB treatment prior to making a diagnosis of Crohn's may still be necessary.

Conclusions and future areas for research

Available evidence suggests that the incidence of IBD in Africa is increasing and, if this follows the same epidemiological trends as in the West and Asia, this is likely to represent a significant public health challenge in the near future. Larger epidemiological studies and establishment of local and regional registries are

needed, and all of this will require greatly increased access to endoscopy and histology services. The most pressing research need is to establish data on prevalence, but improved services are also needed to aid with diagnostic challenges such as differentiation of IBD from ITB, as discussed above, and to assess response to treatment. This epidemiological transition may offer further insights into environmental risk factors that play a role in the pathophysiology of IBD.

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Appendix 1

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