SYSTEMATIC REVIEWS AND META-ANALYSES

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Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review



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BACKGROUND & AIMS:	The incidence of inflammatory bowel diseases (IBD) is increasing in Latin America. We per- formed a systematic review to identify clinical and epidemiologic features of IBD in Latin America (including Mexico, Central America, and South America) and the Caribbean.
METHODS:	We searched MEDLINE, EMBASE, and SciELO databases for clinical or epidemiologic studies of Crohn's disease (CD) or ulcerative colitis (UC) from Latin American and Caribbean countries and territories that reported incidence, prevalence, ratio of UC:CD, IBD phenotype, and treat- ment, through September 12, 2018. Data were extracted from 61 articles for analysis.
RESULTS:	The incidence and prevalence of IBD have been steadily increasing in Latin America and the Caribbean. The incidence of CD in Brazil increased from 0.08 per 100,000 person-years in 1988 to 0.68 per 100,000 person-years in 1991–1995 to 5.5 per 100,000 person-years in 2015. The highest reported prevalence of IBD was in Argentina, in 2007, at 15 and 82 per 100,000 person-years for CD and UC, respectively. The ratio of UC:CD exceeded 1 in all regions throughout Latin America and the Caribbean with the exception of Brazil. Treatment with tumor necrosis factor antagonists increased steadily for patients with CD (43.4% of all patients in Brazil were treated in 2014) but less so for patients with UC (4.5% of all patients were treated in 2014). Surgery for IBD decreased with time. In Chile, surgeries were performed on 57.0% of patients with CD and 18.0% of patients with UC during the period of 1990–2002; these values decreased to 38.0% and 5.0%, respectively, during the period of 2012–2015. In Peru, 6.9% of patients with UC received colectomies in the period of 2001–2003 and 6.2% in 2004–2014.
CONCLUSIONS:	In a systematic review, we found the incidence of IBD to be increasing throughout Latin America and the Caribbean. Population-based epidemiology studies are needed to evaluate the increase in IBD in these regions, which differ from other global regions in climate, culture, de- mographics, diet, healthcare delivery and infrastructure, and socioeconomic status.

Keywords: Anti-TNF; Ethnicity; Race; Risk Factor; Incidence; Prevalence; Inflammatory Bowel Disease.

Abbreviations used in this paper: CD, Crohn's disease; IBD, inflammatory bowel diseases; TNF, tumor necrosis factor; UC, ulcerative colitis.

I n the 21st century, the incidence of Crohn's disease (CD) and ulcerative colitis (UC) stabilized in the Western world.^{1,2} The prevalence of the inflammatory bowel diseases (IBD) exceeded 0.3% of the population in North America, Europe, and Oceania.² In contrast, the prevalence of IBD in Asia, Africa, and South America was a fraction of the Western world. However, as newly industrialized countries experienced Westernization, a wave of steadily rising incidence has followed.^{2–5}

Population-based studies in Latin America and the Caribbean, regions including countries and territories in North America (ie, Mexico), Central America, and South America, have demonstrated rising incidence of IBD.^{6–11} However, data from the Southwest Hemisphere have been scarcer and less well-organized because of less developed healthcare infrastructure available to capture clinical outcomes in registries and administrative healthcare databases.^{2,6}

We conducted a systematic literature review of all CD and UC studies in Latin America and the Caribbean that reported phenotypic characteristics, hospitalization, surgery, drug penetration, incidence, or prevalence of IBD patients of any age or sex.

Methods

Literature Search

Cohort and cross-sectional studies from all Latin American and Caribbean countries and territories that reported incidence, prevalence, hospitalization, surgery, medication, or phenotypic characteristics of IBD patients were identified by searching MEDLINE and EMBASE to September 12, 2018. SciELO, an Open Access database focused predominantly on research in Latin America,¹² was also searched to uncover articles that were not indexed in MEDLINE or EMBASE. Studies were limited to regional or national samples as well as population-based studies in the following regions: Latin America, Central America, the Caribbean, and South America. Appendix 1 provides a list of countries and territories that were searched in each database. The systematic review was performed in accordance with the quality of reporting guidelines according to MOOSE¹³ and PRISMA.¹⁴ The search was not limited by language. The search was performed by an author with postgraduate training in systematic review (F.E.U.).

Study Selection

Search results were reviewed by 2 independent reviewers (P.G.K., F.E.U.), first as abstracts and then as fulltexts. Abstracts were excluded if they did not report on IBD populations in Latin America or the Caribbean. Review articles were set aside for hand searching of their reference lists for any studies not found in the database search. Additional articles were found from expert

What You Need to Know

Background

We performed a systematic review to identify clinical and epidemiologic features of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, in Latin America (including Mexico, Central America, and South America) and the Caribbean.

Findings

The incidence and prevalence of IBD are increasing throughout Latin America and the Caribbean. Population-based epidemiology studies are needed to evaluate the increase in IBD in these regions, which differ from other global regions in climate, culture, demographics, diet, healthcare delivery and infrastructure, and socioeconomic status.

Implications for patient care

Physicians in Latin America and the Caribbean should be aware that more patients will be presenting with IBD.

knowledge of the IBD literature in Latin America. Articles in Portuguese or Spanish were reviewed and translated by P.G.K. Disagreements were resolved through discussion with a third reviewer (G.G.K.). Abstracts were accepted if no follow-up, full-text study had yet been published.

Data Extraction

Data were extracted independently by P.G.K. and F.E.U. Data extracted included first author, country or territory (including states within Brazil), local region, study period, age groups, incidence, prevalence, hospitalization (crude values), in addition to numbers and percentages of patients, medications prescribed, proportion of surgical treatment in the cohorts, and phenotypic characteristics (ie, Montreal classification). When multiple studies used the same data source, we extracted relevant data from the most recent study population. Disagreements were resolved through discussion with a third reviewer (G.G.K.). If necessary, authors were contacted to provide details of the data presented in their studies. Quality of the studies was assessed independently by using a modified version of the Cochrane Collaboration-endorsed Newcastle-Ottawa Quality Assessment Scale.¹⁵

Data Summarization

Tables and figures were created to describe different aspects of IBD populations in Latin America and the Caribbean in our review as follows: incidence per 100,000 person-years, prevalence per 100,000 persons, ratio of patients diagnosed with UC versus CD at time of study entry, proportion of age at study entry point, proportion of the patients' disease location and behavior at study entry, proportion of prescribed IBD medications (ie, steroids, mesalamine, immunomodulators, anti-tumor necrosis factor (TNF) agents), and proportion of the IBD population with an intestinal resection.

The UC:CD ratio represents the average of UC (combined with unclassified inflammatory bowel disease if reported separately) to CD ratios, per country or per Brazilian state, limited to one ratio per study (the longest period of data per study). The UC:CD ratio was illustrated as 6 map classes using Jenks Natural Breaks.¹⁶ The 6 selected classes were 0.48–0.68, 0.68–1.20, 1.20–1.94, 1.94–3.38, 3.38–4.87, and 4.87–5.84 (a value greater than 1 denotes an area where UC is more common than CD). The static maps were created by using QGIS 2.18 (Open Source Geospatial Foundation, Chicago, IL).

An interactive Web-linked map was created to provide a narrative description of the key clinical and epidemiologic findings for each region. The interactive map (https://wpsites.ucalgary.ca/gilkaplan/ibd-in-latinamerica-and-the-caribbean/) was created with ArcGIS Pro 2.3.0 and ArcGIS Online (Environmental Systems Research Institute, Redlands, CA).

Results

Studies Selected

We identified 1434 articles that fulfilled our selection criteria: 255 from MEDLINE, 722 from EMBASE, and 457

from SciELO. Eighty-three articles were selected for fulltext review from MEDLINE and EMBASE, and 43 articles were selected from SciELO. After full-text review, 41 articles were selected from MEDLINE and EMBASE, 25 articles were selected from SciELO, and 4 articles were discovered outside of the database searches. In total, 61 articles were used for data extraction (Appendix 2). An article matrix (Appendix 3) denotes the IBD information provided in each study in the systematic review, with some studies providing information on more than 1 health measure: incidence (9), prevalence (8), UC:CD ratio (35), phenotype (46), medication (27), hospitalization (8), and surgery (38). Appendix 4 reports the quality assessment of the studies, Appendix 5 lists the MOOSE¹³ checklist, and Appendix 6 lists the PRISMA¹⁴ checklist.

Incidence

The incidence of both CD and UC steadily increased during the last decades (Figure 1, Table 1). For example, the incidence of IBD in Brazil was reported as 0.08 per 100,000 person-years in 1988,¹⁷ yet the incidence of CD rose sharply from 0.68 in 1991–1995¹¹ to 3.50 in 2001–2005,¹¹ reaching a peak incidence of CD of 5.48 in 2015,¹⁸ whereas from 1991–1995 to 2001–2005 UC incidence rose from 3.86¹¹ to 5.3,¹⁹ with a peak of 8.00 in 2015.¹⁸ In Puerto Rico, incidence for CD and UC more than doubled from 1996 to 2000 (3.07 to 7.74).²⁰ Argentina, Uruguay, Guadeloupe and Martinique, and Panama all reported incidence values between 0.39 and 4.39.^{7,21,22}



Figure 1. Incidence. CD, Crohn's disease; UC, ulcerative colitis.

Table 1. Incidence per 100,000 Person-Years

First author and publication year	Country	Study period	IBD incidence	CD incidence	UC incidence
de la Cal 1999 ²¹	Argentina	1987–1993			2.17
Edwards 2008 ⁸	Barbados	1980–1984	1.58	0.28	1.30
Edwards 2008 ⁸	Barbados	1985–1989	2.56	0.64	1.92
Edwards 2008 ⁸	Barbados	1990–1994	3.60	1.30	2.30
Edwards 2008 ⁸	Barbados	1995–1999	3.05	0.71	2.34
Edwards 2008 ⁸	Barbados	2000-2004	2.19	0.61	1.58
Victoria 2009 ¹¹	Brazil	1986–1990	0.98	0.24	0.74
Parente 2015 ¹⁷	Brazil	1988	0.08	0.08	0.00
Victoria 2009 ¹¹	Brazil	1991–1995	4.54	0.68	3.86
Parente 2015 ¹⁷	Brazil	1998	0.34	0.20	0.14
Victoria 2009 ¹¹	Brazil	1996–2000	8.24	1.48	6.76
Victoria 2009 ¹¹	Brazil	2001-2005	7.98	3.50	4.48
Parente 2015 ¹⁷	Brazil	2008	1.39	0.54	0.85
Parente 2015 ¹⁷	Brazil	2012	1.26	0.61	0.65
Gasparini 2018 ¹⁸	Brazil	2012	13.57	6.83	6.73
Gasparini 2018 ¹⁸	Brazil	2013	13.55	6.62	6.92
Lima-Martins 2018 ¹⁹	Brazil	2014	7.7	2.4	5.3
Gasparini 2018 ¹⁸	Brazil	2014	12.65	5.66	6.99
Gasparini 2018 ¹⁸	Brazil	2015	13.49	5.48	8.00
Edouard 2005 ⁷	Guadeloupe and Martinique	1997–1999	4.39	1.95	2.44
de la Cal 1999 ²¹	Panama	1987–1993			1.20
Appleyard 2004 ²⁰	Puerto Rico	1996	3.07	0.49	2.57
Appleyard 2004 ²⁰	Puerto Rico	1997	4.1	1.2	2.8
Appleyard 2004 ²⁰	Puerto Rico	1998	5.0	0.9	4.0
Appleyard 2004 ²⁰	Puerto Rico	1999	4.7	1.2	3.4
Appleyard 2004 ²⁰	Puerto Rico	2000	7.74	1.96	5.78
Buenavida 2011 ²²	Uruguay	2007–2008	2.63	0.39	2.25

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Prevalence

Prevalence of IBD steadily rose in Latin America and the Caribbean (Figure 2, Table 2). For example, the prevalence of CD in Brazil rose from 0.24 per 100,000 persons $(1986-1990)^{11}$ to 24.1 (2014),¹⁹ whereas the prevalence of UC rose from 0.99¹¹ to 14.1¹⁹ in the same period (Table 2). Prevalence of IBD was also high in Argentina (97.2),²³ Barbados (61),⁸ Colombia (57.62 in 2012²⁵), and Puerto Rico (38.22 in 2005).²⁶

Ulcerative Colitis:Crohn's Disease Ratio

The ratio of UC to CD patients at study entry was greater than 1 in all regions with the exception of 3 Brazilian states (Figure 3). Within Brazil, which had an overall country UC:CD ratio of 1.081 and a range of 0.481–1.936, the Brazilian states of Alagoas, Rio de Janeiro, and Mato Grosso do Sul had UC:CD ratios of 0.481, 0.679, and 0.596, respectively. France's regions, Guadeloupe and Martinique, had a UC:CD ratio of 1.200. UC was more common than CD in Argentina (4.308), Cuba (4.867), Chile (2.914), Colombia (5.837), Mexico (4.798), Peru (3.375), Uruguay (4.160), and Venezuela (4.668) (Figure 3). The UC:CD ratios of the remaining countries were 2.429, 2.574, and 2.572 for Trinidad and Tobago, Barbados, and the U.S. territory Puerto Rico, respectively.

Phenotypes (Montreal Classification)

Phenotypic characteristics of CD and UC varied across Latin America and the Caribbean (Appendix 7). The most common phenotypic characteristics for CD were age of diagnosis between 17 and 40 years (Montreal classification A2), ileocolonic disease extent (L3), and inflammatory disease behavior (B1). Perianal CD varied from 12% in a Brazilian study²⁷ up to 53% in a study from Peru.²⁸ Disease extent of UC varied; distal proctitis (Montreal classification E1) spanned from 0% in a Brazilian study²⁹ to 55.35% in a study from Puerto Rico,³⁰ left-sided colitis (Montreal classification E2) varied from 11.1%³¹ to 62.9%³² in different studies from Peru, and extensive colitis (Montreal classification E3) was 12% in a Brazilian study³³ and up to 77% in Argentina³⁴ (Appendix 7).

Medications

The mesalamine compounds were commonly used for CD, varying from 21.2% in Brazil³⁵ to 100% in Cuba.³⁶ High percentages of mesalamine use were noted in UC patients, from $56.36\%^{19}$ to 100%.³⁷ Use of mesalamine for CD patients in Brazil had fallen from 81.6% in 1970–1998³⁸ to 31.46% in 2013–2014,¹⁹ whereas use for UC patients fell from 93.2% in 1980–1999¹⁰ to 56.36% in 2013–2014¹⁹ (Appendix 8). Steroids were still widely used in the region, with percentages varying in CD and UC



Figure 2. Prevalence. CD, Crohn's disease; UC, ulcerative colitis.

from $13.3\%^{39}$ to $87.5\%^{40}$ Immunomodulator use for CD patients in Brazil rose from 8.3% in $1970-1998^{38}$ to 71.7% in 2013-2014,¹⁹ whereas use for UC patients rose from 5.4% in $1980-1999^{10}$ to 19.4% in $2013-2014^{19}$ (Appendix 8).

Since approval of anti-TNF use in 2000, the proportion of patients with CD prescribed infliximab or adalimumab has risen steadily (Figure 4*A*, Appendix 8). For example, in Brazil, 29.6% of CD patients received anti-TNF from 2005 to 2012,⁴¹ rising to 43.4% in 2013–2014¹⁹ (Figure 4*A*, Appendix 8). In contrast, the proportion of UC patients prescribed anti-TNF after 2006 remained consistently low. For example, only 4.5% of UC patients were prescribed anti-TNF in Brazil in 2013–2014¹⁹ and 7% and 1.4% in Uruguay in 2016–2017⁴² (Figure 4*B*, Appendix 8).

Hospitalization and Surgery

Hospitalizations were highest in Colombia⁴⁰ (CD, 75.0%; UC, 42.9%) and Peru⁴³ (CD, 75.0%; UC, 51.8%) and lowest in Brazil, where CD hospitalization had fallen from 83.3% in 1980–1999¹⁰ to 29.2% in 2006,⁴⁴ and UC hospitalization had fallen from 63.0% in 1980–1999¹⁰ to 43.8% in 2011–2012⁴⁵ (Appendix 9).

Surgery for CD and UC steadily declined over time in several regions of Latin America: in Brazil from $1980-1999^{10}$ (CD, 57.8%; UC, 21.9%) to $2016-2017^{46}$ (CD, 31.7%; UC, 5.8%) and in Peru from 70.5% (CD) in $1990-2010^{28}$ to 50.0% (CD) in $2004-2014^{43}$ (Figure 4, Appendix 10). In contrast, the proportion of colectomy for UC remained stable in many regions: in Peru from 6.9% in $2001-2003^{32}$ to 6.2% in $2004-2014^{43}$ and in

First author and publication year	Country	Study period	IBD prevalence	CD prevalence	UC prevalence
Sobrero 2009 ²³	Argentina	2007	97.2	15.0	82.2
Edwards 2008 ⁸	Barbados	2004	61.0	16.7	44.3
Victoria 2009 ¹¹	Brazil	1988	1.23	0.24	0.99
Victoria 2009 ¹¹	Brazil	1993	5.67	0.90	4.77
Victoria 2009 ¹¹	Brazil	1998	13.52	2.32	11.2
Victoria 2009 ¹¹	Brazil	2003	20.46	5.65	14.81
Parente 2015 ¹⁷	Brazil	2012	12.8		
Lima-Martins 2018 ¹⁹	Brazil	2014	38.2	24.1	14.1
Yepes-Barreto 2010 ²⁴	Colombia	2006	29	7	22
Juliao 2018 ²⁵	Colombia	2012	57.62	5.85	51.77
Vendrell 2013 ²⁶	Puerto Rico	2002	33.23	11.43	21.72
Vendrell 2013 ²⁶	Puerto Rico	2003	32.42	11.96	20.46
Vendrell 2013 ²⁶	Puerto Rico	2004	37.26	12.93	24.33
Vendrell 2013 ²⁶	Puerto Rico	2005	38.22	14.9	23.32

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.



Figure 3. UC:CD ratio. CD, Crohn's disease; UC, ulcerative colitis.

Uruguay from 1951–2003⁴⁷ (UC, 8.3%) to 1985–2015⁴² (UC, 10.5%) (Figure 4, Appendix 10).

Discussion

Our systematic review identified significant gaps in high quality population-based studies of IBD in Latin America and the Caribbean. Nonetheless, the available data indicate notable heterogeneity between the countries that may be driven by factors such as historical colonization, culture, socioeconomic status, genetic background, lifestyle, and diet. Future studies should focus on developing large population-based registries that describe the epidemiology, natural history, and outcomes of IBD.

Despite important variation in the incidence of both UC and CD in Latin America and the Caribbean, our review suggests that incidence has steadily increased during the past decades. In a descriptive review of the incidence and prevalence of IBD in Latin America, Farrukh and Mayberry⁹ speculated that epidemiologic patterns have mirrored the evolution of IBD in Spain during the 20th century. Historically, UC was diagnosed more commonly than CD in the Western world. During the 20th century, numerous studies confirmed a transition in the UC:CD ratio such that CD approximated the diagnosis of UC and in many Western countries became more common. Similar to the Western world, regions within Latin America that are associated with higher economic development, industrialization, and Westernization of environmental exposures (eg, diet) reported higher proportions of CD. Improved healthcare access and delivery may also influence the diagnosis of CD.

After decades of rising incidence, the prevalence of IBD has been expanding. Consequently, the prevalence of IBD in Latin America is equivalent to many countries in Asia and is approximating countries in Southern and Eastern Europe. As more individuals live with IBD, caring for these patients will exact a tremendous stress on the healthcare systems within Latin America and the Caribbean. Expansion of national registries of IBD is necessary for surveillance of the burden of IBD across these countries.

Important variation in the prescription of medications was observed throughout the continent. The use of corticosteroids was high for both diseases. Moreover, the use of mesalamine compounds for CD is common, probably because of difficult access to biologics in some areas. The proportion of patients treated with anti-TNF therapy was also variable between the countries. Some studies demonstrated approximately 40% of biologic penetration for CD in more developed areas. Case series from other countries did not have such a high penetration, possibly because of difficulties in patient care, access to these agents, and the lack of specific local IBD study groups or associations that could increase the level of patient care.

With the rising prevalence of IBD, countries in Latin America and the Caribbean can expect higher rates of hospitalization and surgeries and, in turn, greater utilization of expensive biologics to treat flares and prevent complications of IBD. Our review demonstrated an increase in the use of anti-TNF therapy in the management of CD, mostly after the approval of infliximab around the year 2000. In juxtaposition, surgery for CD decreased in the same period. Increased use of anti-TNF therapy for



Figure 4. Proportion of patients with Crohn's disease (A) and ulcerative prescribed colitis (B) anti-TNF therapy and undergoing intestinal an resection. CD. Crohn's disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

CD was likely related to greater disease awareness, better diagnostic techniques, and management strategies. In contrast, surgery rates for UC in the 21st century were relatively stable throughout Latin America. Similarly, the use of anti-TNF therapy for UC did not increase significantly in Latin American and Caribbean countries after 2006 when the ACT randomized controlled studies demonstrated the efficacy of infliximab in UC.⁴⁸ These findings may be explained by difficulties in accessing anti-TNF therapies for UC, mostly on the basis of limited reimbursement from both public and private payors in many countries. As access to biologics expands and increased awareness of therapeutic strategies for managing IBD (eg, less reliance on mesalamine for treatment of CD) rises, we can anticipate that rates of hospitalization and surgery will continue to fluctuate in this region of the globe.

The major strength of our review was the inclusion of a local database (SciELO) in addition to MEDLINE and EMBASE. By including articles written in local languages, more data could be captured, and we believe this could be used as an example in methodology for future reviews in different parts of the world. This systematic review has some limitations that may influence the

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interpretation of our results. The information collected varied between studies, and data were based predominantly on cross-sectional studies. Most of the data were derived from tertiary centers from larger cities. Variables such as frequency of medication use, hospitalization, and surgery are described in crude values, with no defined follow-up. As the healthcare infrastructure in Latin American and Caribbean regions advances to include greater use of electronic administrative databases, a more complete picture of the health services and outcomes of IBD will become available. Furthermore, temporal trend analyses on incidence and prevalence of IBD were derived from a few population-based studies with sufficient longitudinal data, and thus extrapolation of the rising incidence and prevalence of IBD throughout Latin America and the Caribbean is an assumption that needs to be confirmed in future population-based studies.

Finally, the quality assessment demonstrated that the majority of included studies were of low quality. For example, only 16 of the 61 studies were populationbased. Outcomes such as medication usage and surgery need to be interpreted cautiously and in the context of the limitation of including lower quality studies. Moreover, the paucity of high quality studies highlights an important gap in the literature and serves as a clarion call to invest in the infrastructure, resources, and personnel necessary to conduct non-biased observational research in Latin America and the Caribbean.

In summary, this systematic review on the clinical and epidemiologic characteristics of IBD in Latin America and the Caribbean demonstrated that the incidence and prevalence of IBD may be increasing and that the UC:CD ratios are evolving throughout the continent. The phenotypes of IBD observed varied slightly between the countries but are consistent to what is seen in other parts of the world. The increase in the use of anti-TNF agents for CD may be correlated to a decrease in surgery; the same pattern was not observed in UC. This comprehensive systematic review outlines the important burden of IBD in Latin America and the Caribbean and emphasizes the need for better registries and populationbased studies in this region of the world.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.06.030.

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Conflicts of interest

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