Inflammatory Bowel Disease in Latin America: a systematic review

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Key words: Inflammatory bowel disease, ulcerative colitis, crohn's disease, epidemiology, burden of disease, Latin America & Caribbean

Abstract

Background: Inflammatory Bowel Disease(IBD) is the name given to two inflammatory entities of the colon and/or small intestine: Crohn's disease(CD) and Ulcerative Colitis(UC). There is no information summarizing the complete body of evidence about IBD in developing regions, including Latin-American.

Objective: To estimate the burden of IBD in Latin-America.

Methods: We conducted a systematic review searching published and unpublished studies on the main international and regional databases from January 2000 to September 2015. Outcomes considered were incidence, prevalence, mortality, hospitalization attributable, treatment patterns, comparative effectiveness, patients reported outcomes and adherence to treatment. Pairs of reviewers independently selected, extracted and assessed the risk of bias of the studies. Discrepancies were solved by consensus.

Results: We retrieved 3445 references finally including 25 studies. Only 19% of observational studies had low risk of bias for participant selection and 60% were based on registries. The incidence ranged in 0.74 to 6.76/100,000 person-year for UC and 0.24 to 3.5/100,000 person-year for CD. The prevalence ranges in 0.99 to 44.3/100,000 inhabitants for UC and 0.24 to 16.7/100,000 for CD. Mortality rates were from 0.60 to 1.02 for UC and from 0.23 to 0.40 for CD. Patient reported outcomes showed a decrease in quality of life associated with depression and anxiety and correlated with the time of diagnosis. The treatment most used in the studies was mesalazine.

Conclusion: The burden of IBD in Latin-America seems to be important but there is a considerable gap of high quality evidence in the region.

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Key words: inflammatory bowel disease, ulcerative colitis, crohn’s disease, epidemiology, burden of disease, Latin-America & Caribbean

Background

Inflammatory Bowel Disease (IBD) is the name given to two inflammatory diseases of the colon and/ or small intestine: Crohn's disease (CD) and Ulcerative Colitis (UC).[1] Diagnosis is based on clinical presentation, endoscopic findings and other imaging and histopathologic findings. Both diseases are chronic and intermittent with remissions and relapses, possibly because of an interaction between genetic and environmental factors. Differentiation between UC and CD is not always clear as the extra-intestinal clinical heterogeneity can be similar in both diseases resulting in cases that remain with a non-specific diagnosis.[2] Treatment of inflammatory bowel disease includes lifestyle alterations (e.g., smoking cessation for patients with CD), medical management, and surgical interventions. A seminal advance was the introduction of the treatment with anti–TNFα monoclonal antibodies, which are particularly effective in CD.[1]

IBDs have a major impact on life expectancy, quality of life and medical costs. According to a meta-analysis, patients with Crohn's disease have a risk of dying over 50% higher than someone in the general population of the same age. Moreover, CD diagnosed before the age of 20 reduces life expectancy 7 to 13 years. Although the risk of death by UC is low, it increases the risk of colorectal cancer with an incidence rate of 1.58 per 1000 patient-years [CI 95% 1.39–1.76].[3] IBD burden derives in an important increase of the direct medical costs. A Canadian study shows that an IBD case doubles the cost of controls. Additionally, CD was on average 20% costlier than UC.[4]

IBD is well characterized in developed countries. In United States of America, incidence rates range from 2.2 to 19.2 cases per 100,000 person-years for UC and 3.1 to 20.2 cases per 100,000 person-years for CD.[5, 6] Recently, efforts have been made to describe IBD in some developing regions such as Latin-America showing differences in the burden of the disease among countries.[7] Environmental factors such as socio-economic status, exposure to infections, use of antibiotics and issues of hygiene, might help explain the epidemiological differences between populations.[6]

Information about IBD in the region could assist Latin-American decision makers to design proper health policies to better address IBD related problems and finally todeliver high-quality patient-

centered care for this disease. Therefore, it is imperative to summarize all the complete body of evidence of IBD in Latin-America. Our objective was to estimate the epidemiology and burden of inflammatory bowel disease in Latin-America through a systematic review of literature.

Methods

We followed the Meta-Analysis of Observational Studies in Epidemiology guidelines[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA statement)[9, 10] for reporting systematic reviews and meta-analyses.

Search strategy and selection criteria

We searched published and unpublished studies on the main international and regional databases: MEDLINE, EMBASE, LILACS, and CENTRAL. We included randomized controlled trials, cohort studies, case-control studies, cross sectional studies, case series and economic evaluations that only include Latin-American participants. Outcomes considered were incidence, prevalence, mortality, hospitalization attributable, treatment patterns, comparative effectiveness, patients reported outcomes and adherence to treatment. Studies were included only if they reported at least 50 cases. No language restriction was performed. Only studies published or reported since 2000 were included. We searched unpublished studies in the reference list of included studies and looking for the full-text of the abstract of medical congresses obtained from the search strategy.

If we found data or data subsets reported in more than one publication or overlapping from the same period of time, we selected the one with the largest sample size and most representative of the country's population. Search strategy is detailed in Appendix 1.

Screening and data extraction

Pairs of independent reviewers screened titles and abstracts of all identified references. They categorized the articles into one of the following categories: excluded, related reference, related

review (references were searched), low/moderate probability of inclusion, high probability of inclusion. We obtained the full-text versions of all articles not excluded. Except those categorized as excluded, the rest of the articles were retrieved in full text for further analysis. As a second screening process, two reviewers independently extracted and assessed the risk of bias of each full text article. All phases of the study selection were completed using EROS® (Early Review Organizing Software, IECS, Buenos Aires), a web-based platform designed to facilitate the independent selection and quality assessment of studies for systematic reviews. [11]

Authors of articles were contacted when necessary to obtain missing or supplementary information.

Assessment of risk of bias

The risk of bias of observational studies were assessed using a checklist of essential items based in STROBE[12] (Strengthening the Reporting of Observational studies in Epidemiology), and complemented with several methodological articles: Sanderson et al.[13] and Fowkeset al.[14], QATSO[15], Berra[16]. Risk of bias was assessed using a checklist of essential items: selection of participants, control of confounders, measurement of exposure and outcome and conflict of interest.

Randomized controlled trials, quasi-randomized controlled trials, cohort studies, case-control studies, were assessed considering non-comparative data (i.e. control arms of intervention studies or the whole population if the expositions represented the expositions of IBD patients).

Randomized controlled trials for comparative data were assessed with the Cochrane tool.[17]

Pairs of independent reviewers assessed the risk of bias through EROS®. Discrepancies were solved by consensus of the whole team.

The protocol was registered in PROSPERO, an international prospective register of systematic review protocols (Registration Number CRD42016035479).

Results

The search retrieved 3445 references after removing duplicates, and 3048 references were excluded by title and abstract. Out of 397 full texts studies retrieved for detailed evaluation, 25 met the inclusion criteria. The flow diagram of the systematic review is shown in **Figure 1.**

Most studies were conducted in South America (68%), particularly in Brazil (48%). The years of publication of included studies ranged from 2002 to 2015, with a mode in 2011. Moreover, the majority of the included studies reported only UC and CD jointly (56%). Out of the 25 included studies, 1 was case series (4%), 15 registries / surveillance studies (60%), 7 cross-sectional (28%) and two control arms of randomized controlled trials (8%). The main characteristics of included studies are shown in **Table 1.**

The risk of bias was reported separately by type of study and by risk of bias domain (**Table 2**). Most observational studies had moderate risk of bias for participant selection and one of the two randomized controlled trials had high risk of bias in most of the risk of bias domains.

Incidence

Six studies described incidence of IBD in Latin-America. Three were Brazilian studies and reported data from hospital records in different study periods: 1988 - 2012, 1986 - 2005 and 1980 - 1999 [18, 19]˙[20]. The remaining three studies were from Uruguay[21], Puerto Rico[22] and Barbados[23] and used data from their national registries. For UC,, incidences ranged from 0.74 to 6.76 per 100000 inhabitants, for CD; from 0.24 to 3.50, and for non-specified IBD 0,42 to 2,46 per 100000 inhabitants. Only one studied reported outcomes without specifying the IBD type.

All the information from the studies and study period are detailed by type of IBD in **Table 3.**

Prevalence

Five studies described prevalence of IBD. Four of them were previously characterized on Table 3 [18, 19, 22, 23] . The fifth study[24] was based on information from a major health insurance company in Puerto Rico which offered commercial health insurance and a government-sponsored managed care plan for the low-income medically indigent population that previously received services directly from the Puerto Rico Department of Health. All the studies and their results are shown in **Table 4.** The prevalence for UC ranged from 0.99 to 44.3 per 100000 inhabitants; 0,24 to 14,90 per 100000 inhabitants for CD and; 0.42 to 38.22 for non-specified IBD.

Mortality rate

Only one study[25] reported mortality rate in Latin-America. This study compared the geographic distribution of mortality of peptic ulcer compared with IBD. Mortality rates data from 27 countries were analyzed including three in Latin-American. Causes of death were recorded according to the 9th and 10th revisions of the International Classification of Diseases (ICD). The annual mortality rate is shown in Table 5.

Case Fatality rate

The main results of the included studies for case fatality rate are described in **Table 6.** We found four studies that described this outcome in the IBD population from Latin-America[20, 26-28].

A Brazilian study[20] showed case fatality rate of IBD (UC and rectocolitis) in a university hospital. Another study carried out in Brazil[26] retrieved information on the incidence of intestinal and extra intestinal neoplasia among patients with IBD attending a tertiary health care hospital.

A descriptive observational study from Colombia[27] included all patients with IBD that attended the emergency unit or ambulatory care services or were hospitalized. The last study from Cuba[28] described the frequency and socio-epidemiological characteristics of all the patients under 19 years with verified diagnosis of IBD based on a surveillance in pediatric centers.

Hospitalization rate and length of stay

Hospitalization rate and length of stay are shown in the **Appendix 2 Table 1 and Table 2** respectively. Four out of five included studies were from Brazil[20, 29-31]; the remaining one was from Colombia[27]. One of the Brazilian studies evaluated the classification and severity (hospitalization in the last year) of CD in different racial groups and found a greater frequency of hospitalization in the last year in non-white patients compared to white patients (14.3 vs 36.4 p=0.07).[29] The Colombian study[27] found an association between hospitalization rate and the use of steroids for UC ($p < 0.001$) and CD ($p = 0.039$) and between hospitalization rate and the use of biological therapy in UC (91.7%; $p < 0.001$) and CD (93.3%; $p = 0.041$).

One of the studies that described length of stay was a descriptive epidemiological study[30]. The other one was a controlled randomized clinical trials[31] that evaluated the effect of azathioprine (AZA) compared with mesalazine on incidence of re-hospitalizations due to all causes and to CD-related surgeries.

Patient Reported Outcomes

Three Brazilian studies[32-34] evaluated quality of life (QoL) in adults with IBD. The population, QoL tools used and main results are described in **Appendix 2 Table 3**

Treatment Pattern

The main results of studies reporting treatment patterns are shown in **Appendix 2 Table 4.** Only one of the included studies was from Brazil[33], two were from Chile[35, 36], two from Mexico [37-39] and one from Puerto Rico[40]. One of the Chilean studies was descriptive and retrospective[35] and characterized the clinical features of IBD comparing the experience of patients from two medical centers. From the three Mexican studies, one was a large cohort from a referral hospital in Mexico City[37], and the remaining two were descriptive retrospective studies[38, 39]. The study from Puerto Rico [40] retrieved data from the Registry of IBD, a database of demographic and medical information obtained by interviews and medical record reviews of patients with IBD and collected nationwide.

Adherence to treatment

The only study[41] that evaluated the prevalence of non-adherence to therapy in patients with CD and determined possible associated risk factors was from Brazil. This cross sectional study included 100 patients between 18 and 65 years old that attended the Center for Inflammatory Bowel Diseases. Before their doctor's appointment, patients were asked to respond to the modified Morisky & Green Test to assess their adherence to therapy. This questionnaire showed a prevalence of non-adherence of 64%. When analyzing possible risk factors, the study demonstrated an increase of non-adherence between younger (P = 0,07) and non-white patients (P = 0,06). No correlation was observed with psychological or drug therapy variables.

Comparative Effectiveness

We found one study conducted in Brazil[42] that determined the effectiveness of AZA for the prevention of recurrent bowel obstruction. Data was drawn from a 3-year multicenter randomized, investigator -blind, controlled trial that compared AZA with mesalazine in 72 CD's patients. According to this study, the cumulative rate was significantly lower in patients with recurrent sub-occlusion in the AZA group (56%) compared with the mesalazine group (79%; OR 3.34, 95% CI 1.67–8.6; *P*=0.003). The number needed to treat in order to prevent one sub-occlusion episode was of 3.7 favoring AZA. The occlusion-free time interval was longer in the AZA group compared with the mesalazine group (28.8 *vs.* 18.3 months; *P*=0.000). The occlusion-free survival at 12, 24, and 36 months was significantly higher in the AZA group (91%, 81%, and 72%, respectively) than in the mesalazine group (64.7%, 35.3%, and 23.5%, respectively; *P*<0.05 for all comparisons).

Economic evaluations

We only found two economic evaluations in Latin America but there were not included because were abstracts presented in medical congresses.

Discussion

In this report, we have presented a comprehensive review following a rigorous systematic methodology about IBD data in Latin-America. We identified 25 studies addressing the incidence, prevalence, mortality, patient reported outcomes, treatment patterns, adherence to treatment, and comparative effectiveness in Latin-American population.

Three studies from Brazil reported IBD incidence based on non-nationwide registries since 1986 to 2012. They reported data from the state of Piuai (described as region with poor living condition)[18] and Sao Paulo (industrialized region)[19, 20]. The incidence was lower in the study from Piuau in comparison with the results from Sao Paulo, however it showed an increase from 1998 to 2007 (0.08 to 1.53 per 100,000 person-years). Despite the data periods, the other two Brazilian studies from Sao Paulo were different compared with each other. This difference can be partially explained by hospital's databases differences: higher incidences were reported in the study in which the database was from a referral medical center of the 30 municipal districts[19] than in the study using data from a medical school university.[20] Moreover, the second study measured ulcerative rectocolitis instead of ulcerative colitis. A nationwide study from Puerto Rico showed an increase in the incidence of UC, CD and non-specified IBD from 1996 to 2000.[22] Another study from Barbados presented results by periods showing an increase of the incidence from 1980 to 1994 followed by a decrease until 2004.[23] A multicenter study from Uruguay reported a punctual incidence from 2007 to 2008 within the range of the other studies.[21] Incidences of UC were consistently higher than incidences of CD. Incidence in developed countries ranged from 2.2 to 19.2 cases per 100,000 person-years for UC and 3.1 to 20.2 cases per 100,000 person-years for CD.[5, 6]

One Brazilian study[18] reported an IBD prevalence of 12.8 per 100,000 inhabitants and another Brazilian study[19] presented data from periods until 2005 reaching 14.81 for UC, 5.65 for CD and 2.14 for non-specified IBD per 100,000 inhabitants. One study from Puerto Rico presenting data from a major health insurance showed higher prevalences in 2005 of 23.32 for UC, 14.90 for CD per 100,000 inhabitants..[24] Another study from Puerto Rico (nationwide) showed a remarkable lower prevalence per 100,000 inhabitants from 1996 to 2000 with 12.53 for UC, 5.89 for CD and 6.39 for non-specific IBD.[22]. In contrast, a high prevalence was reported in the study from

Barbados:44,3 per 100,000 persons for UC.[23] The highest reported prevalence rates for IBD are from Europe (UC, 505 per 100,000 persons; CD, 322 per 100,000 persons) and North America (UC, 249 per 100,000 persons; CD, 319 per 100,000 persons) while Latin-America has reported considerably lower prevalence rates than other regions.[5]

The only study describing mortality rates[25] showed data from Argentina, Chile and Mexico with rates lower than 1.5 per 100,000 inhabitants. These rates are remarkably lower compared to other countries such as United Kingdom in which the mortality rate for IBD was 17.1 per 1000 person-years overall and a high hazard ratio for UC was among the 40-59-year age group (1.79 IC95% 1.42-2.27) and for CD among 20-39 year-olds (3.82 IC95% 2.17-6.75).[43] The great variability of Latin-American rates and the differences with other regions could be probably explained by deficiencies of the registries including lack of standard protocols.

Case fatality rates of IBD were up to 12% in the selected studies. Hospitalization rate information was heterogeneous among studies with a range of 43 to 63% in UC, 29 to 83% in CD and 28% in non-specified IBD.

We also found that the time elapsed since diagnosis was associated to more anxiety and depression and that IBD was highly correlated with worse quality of life. These results were consistent with other studies that evaluated quality of life reporting its decrease in people with IBD. One study from United States of America showed that the main aspect that determined the loss of quality of life was stage of disease activity and severity.[44]

Surgery was more used in CD than UC, less than 50% of the UC patients reported in these studies were treated with surgery. Less than 13% of patients used anti-TNF in UC and the most frequently used medication was mesalazine. The only study reporting adherence to treatment[41] showed a result of 64% (64/100) related to young age and non-white race, without a clear association with physiological or therapeutic aspects. There is only one identified randomized controlled trial that studied comparative effectiveness in Latin-American population and showed that AZA was better than mesalazine at the prevention of sub-occlusions in CD patient.

Despite the rigorous methodology followed, our study has limitations. The most important one is the heterogeneity that precludes to perform-meta-analysis, and the scarcity of high quality epidemiologic studies about IBD in Latin-America. Moreover, the majority of the studies were based on registries and not on population-based data which would have been more representative of the country. Despite these difficulties, our study provides an exhaustive picture of the available evidence in the region and has highlighted important evidence gasps.

Conclusion

The burden of inflammatory bowel disease in Latin-America seems to be important but there is a considerable gap of evidence in the region. More studies of adequate methodological quality from representative samples and the use of standardized definitions and outcomes are required. This information could assist Latin-American decision makers to design strategies to deliver high-quality, patient-centered care for the population of patients with IBD.

Conflict of Interest: The authors declare no conflicts of interest

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References

1. Abraham C, Cho JH. Inflammatory bowel disease. The New England journal of medicine. 2009; 361: 2066-78.
2. Hendrickson BA, Gokhale R, Cho JH. Clinical aspects and pathophysiology of inflammatory bowel disease. Clinical microbiology reviews. 2002; 15: 79-94.
3. Castano-Milla C, Chaparro M, Gisbert JP. Systematic review with meta-analysis: the declining risk of colorectal cancer in ulcerative colitis. Alimentary pharmacology & therapeutics. 2014; 39: 645-59.
4. Bernstein CN, Longobardi T, Finlayson G, et al. Direct medical cost of managing IBD patients: a Canadian population-based study. Inflammatory bowel diseases. 2012; 18: 1498-508.
5. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012; 142: 46-54 e42; quiz e30.
6. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004; 126: 1504-17.
7. KOTZE PG. RESEARCH IN INFLAMMATORY BOWEL DISEASES IN LATIN AMERICA: a challenge ahead. Arquivos de Gastroenterologia. 2014; 51: 269-70.
8. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA : the journal of the American Medical Association. 2000; 283: 2008-12.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009; 6: e1000100.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6: e1000097.
11. Bardach A, Ciapponi A, Garcia-Marti S, et al. Epidemiology of acute otitis media in children of Latin America and the Caribbean: A systematic review and meta-analysis. Int J Pediatr Otorhinolaryngol. 2011; 75: 1062-70.
12. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007; 370: 1453-7.

13. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 2007; 36: 666-76.
14. Fowkes F, Fulton P. Critical appraisal of published research: introductory guidelines. BMJ 1991 302: 1136-40.
15. Wong WC, Cheung CS, Hart GJ. Development of a quality assessment tool for systematic reviews of observational studies (QATSO) of HIV prevalence in men having sex with men and associated risk behaviours. Emerg Themes Epidemiol. 2008; 5: 23.
16. Berra S, Elorza-Ricart JM, Estrada M-D, et al. Instrumento para la lectura crítica y la evaluación de estudios epidemiológicos transversales. Gaceta Sanitaria. 2008; 22: 492-7.
17. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011; 343: d4002.
18. Parente JML, Coy CSR, Campelo V, et al. Inflammatory bowel disease in an underdeveloped region of Northeastern Brazil. World Journal of Gastroenterology. 2015: 1197-206.
19. Victoria CR, Sassak LY, Nunes HR. Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of Sao Paulo State, Brazil. Arq Gastroenterol. 2009: 20-5.
20. Souza MH, Troncon LE, Rodrigues CM, et al. [Trends in the occurrence (1980-1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in southeastern Brazil]. Arq Gastroenterol. 2002; 39: 98-105.
21. Buenavida G, Casanias A, Vasquez C, et al. Incidence of inflammatory bowel disease in five geographical areas of Uruguay in the biennial 2007-2008. Acta gastroenterologica Latinoamericana. 2011; 41: 281-7.
22. Appleyard CB, Hernandez G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. Inflammatory bowel diseases. 2004: 106-11.
23. Edwards CN, Griffith SG, Hennis AJ, et al. Inflammatory bowel disease: Incidence, prevalence, and disease characteristics in Barbados, West Indies. Inflammatory bowel diseases. 2008: 1419-24.
24. Vendrell R, Venegas HL, Perez CM, et al. Differences in prevalence of inflammatory bowel disease in Puerto Rico between commercial and government-sponsored managed health care insured individuals. Boletin de la Asociacion Medica de Puerto Rico. 2013; 105: 15-9.
25. Sonnenberg A. Similar geographic variations in mortality from peptic ulcer and inflammatory bowel disease. Inflammatory bowel diseases. 2007: 763-8.
26. Campos FG, Teixeira MG, Scanavini A, et al. Intestinal and extraintestinal neoplasia in patients with inflammatory bowel disease in a tertiary care hospital. Arq Gastroenterol. 2013: 123-9.
27. Juliao Baños F, Ruiz Vélez MH, Flórez Arango JF, et al. Fenotipo e historia natural de la enfermedad inflamatoria intestinal en un centro de referencia en Medellín-Colombia. Revista Colombiana de Gastroenterologia. 2010; 25: 240-51.

28. Fragoso Arbelo T, García Bacallao E, García Pérez W, et al. Estudio epidemiológico de la enfermedad inflamatoria intestinal en niños y adolescentes cubanos (estudio multicéntrico). Revista Cubana de Pediatría. 2002; 74: 195-202.
29. Santana GO, Lyra LG, Santana TC, et al. Crohn's disease in one mixed-race population in Brazil. World J Gastroenterol. 2007: 4489-92.
30. Oliveira FM, Emerick APdC, Soares EG. Aspectos epidemiológicos das doenças intestinais inflamatórias na macrorregião de saúde leste do Estado de Minas Gerais. Ciência & Saúde Coletiva. 2010; 15: 1031-7.
31. de Souza GS, Vidigal FM, Chebli LA, et al. Effect of azathioprine or mesalazine therapy on incidence of re-hospitalization in sub-occlusive ileocecal Crohn's disease patients. Medical science monitor : international medical journal of experimental and clinical research. 2013; 19: 716-22.
32. Cohen D, Bin CM, Fayh AP. Assessment of quality of life of patients with inflammatory bowel disease residing in Southern Brazil. Arq Gastroenterol. 2010: 285-9.
33. Souza MMd, Barbosa DA, Espinosa MM, et al. Qualidade de vida de pacientes portadores de doença inflamatória intestinal. Acta Paulista de Enfermagem. 2011; 24: 479-84.
34. Freitas TH, Andreoulakis E, Alves GS, et al. Associations of sense of coherence with psychological distress and quality of life in inflammatory bowel disease. World J Gastroenterol. 2015: 6713-27.
35. Figueroa C C, Quera P R, Valenzuela E J, et al. Enfermedades inflamatorias intestinales: Experiencia de dos centros chilenos. Revista médica de Chile. 2005; 133: 1295-304.
36. Meyer L, Simian D, Lubascher J, et al. Eventos adversos en la terapia farmacológica de la enfermedad inflamatoria intestinal. Revista médica de Chile. 2015; 143: 7-13.
37. Yamamoto-Furusho JK. Clinical epidemiology of ulcerative colitis in Mexico: A single hospital-based study in a 20-year period (1987-2006). Journal of Clinical Gastroenterology. 2009: 221-4.
38. Bosques-Padilla FJ, Sandoval G, Atilde, et al. Epidemiología y características clínicas de la colitis ulcerosa crónica idiopática en el noreste de México Revista de Gastroenterologia de Mexico. 2011: 34-8.
39. De la Cruz-Guillén AA, Cortés-Espinosa T, Sánchez-Chávez X, et al. Comportamiento clínico de la colitis ulcerosa crónica inespecífica en pacientes del CMN 20 de Noviembre, ISSSTE , y comparación con la bibliografía americana. Medicina Interna de Mexico. 2011: 224-30.
40. Melendez JD, Larregui Y, Vazquez JM, et al. Medication profiles of patients in the University of Puerto Rico inflammatory bowel disease registry. Puerto Rico health sciences journal. 2011; 30: 3-8.
41. Cornelio Rde C, Pinto AL, Pace FH, et al. [Non-adherence to the therapy in Crohn's disease patients: prevalence and risk factors]. Arq Gastroenterol. 2009; 46: 183-9.
42. Vidigal FM, de Souza GS, Chebli LA, et al. Azathioprine is more effective than mesalazine at preventing recurrent bowel obstruction in patients with ileocecal Crohn's disease. Medical

science monitor : international medical journal of experimental and clinical research. 2014; 20: 2165-70.

43. Card T, Hubbard R, Logan RF. Mortality in inflammatory bowel disease: a population-based cohort study. Gastroenterology. 2003; 125: 1583-90.

44. Bernklev T, Jahnsen J, Aadland E, et al. Health-related quality of life in patients with inflammatory bowel disease five years after the initial diagnosis. Scandinavian journal of gastroenterology. 2004; 39: 365-73.