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Top-100 highest-cited original articles in inflammatory bowel disease

A bibliometric analysis

Xinrong Chen, MD[a,*], Kun Yang, PhD[b], Yujie Xu, MD[a], Ka Li, MD[c,*]

Abstract

Objectives: The use of citation analysis to identify the first 100 papers in inflammatory bowel disease (IBD) provides unique insights into advances in disease understanding and subsequent follow-up treatment innovations over time.

Methods: The Thomson Reuters Web of Science database with the search terms "inflammatory bowel disease" or "Crohn disease" or "ulcerative colitis" or "colitis" was used to identify all English language full manuscripts for the study. Title, first and senior authors, institution and department of first author, journal, country of origin, year, and topic of each manuscript were analyzed.

Results: The top 100 manuscripts were published between 1955 and 2013. 224,809 eligible papers were returned and the median (range) citation number was 1028.5 (719–3957). The country and year with the greatest number of publications were the USA (n = 47), and 2007 (n = 11). Gastroenterology published the highest number of papers (n = 18, 21,083 citations) and *The New England Journal of Medicine* had the most citations (n = 13, 25,035 citations).

Conclusions: This highly cited list of papers identifies the subjects and authors who have had the greatest impact on IBD research in the last decades, which serves as a reference for researchers and clinicians "highly citable" manuscripts.

Abbreviations: IBD = inflammatory bowel disease, CD = Crohn disease, UC = ulcerative colitis, ISI = Institute for Scientific Information.

Keywords: bibliometric analysis, Crohn disease, inflammatory bowel disease, ulcerative colitis

Key issues

- Over 242,272 manuscripts on IBD have been published to date.
- These manuscripts have shaped the current understanding of the aetiology of IBD, which is an interplay between host and environmental factors in a genetically predisposed host.
- Bibliometric citation analysis studies the clinical and scientific significance of manuscripts by analyzing the number of times a work has been cited in subsequent manuscripts. This type of analysis has never before been performed for inflammatory bowel disease.
- The journals publishing the top 100 cited IBD manuscripts are basic science, clinical, epidemiological, surgical, and genetic in nature.
- Rutgeerts P from the Katholieke Univ Leuven Hosp, Louvain, Belgium had the highest amount of authorships (3 first and 3 senior) and citations (n = 6714) followed by Colombel JF of the CHU Lille, Hop Claude Huriez, Dept Hepatogastroenterol, Rue Michel Polonovski, F-59037 Lille, France (Two first and 3 senior authorships, 6212 citations).
- The year that yielded the highest number of papers was 2007 (n = 11 manuscripts and 16,343 citations) followed by 2000, 2006, and 2008, each with 6 publications (Fig. 1) and 5928, 6750, and 6914 citations (Fig. 2), respectively.
- The institutions with the highest number of publications in the top 100 were NIAID Mucosal Immun Sect and Yale University USA, each with 5 papers generating 5694 and 8216 citations, respectively.

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All data generated or analyzed during this study are included in this published article.

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- The majority of top 100 manuscripts were written by first authors from the subspecialty of Gastroenterology (n = 27) followed by internal medicine (n = 22).
- Forty-seven percent of the manuscripts originated from the United States (Fig. 3). The Germany and England produced 13% and 10%, respectively.
- The majority of these works were published in high-impact journals reflecting the importance of the study of IBD in both scientific and clinical communities.
- This citation analysis provides a reference of what could be considered the most influential papers in IBD and may serve as a reference for clinicians and researchers as to what makes an influential paper in the study of disease pathology.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated inflammatory condition primarily involving the gastrointestinal tract. It includes Crohn disease (CD), ulcerative colitis (UC), and a less common phenotype-IBD unclassified. It is thought to result from a complex interplay of environmental, microbial, and host factors including genetic factors, although the exact mechanism is not known.[1] CD is a chronic bowel disease characterized by a relapsing inflammatory process. It can affect any part of the gastrointestinal tract and is associated with discontinuous, transmural lesions of the gut wall. UC is a typically relapsing, remitting inflammatory disease of the colon and rectum. The mucosal inflammation is continuous and most commonly progresses proximally from the rectum.[2]Although IBD is mostly seen in Western world, recent data suggests that the incidence and prevalence are increasing worldwide.[3] It can affect people of all ages, including children and geriatric populations, and can affect all aspects of life. The most accepted hypothesis of IBD pathogenesis is that complex interactions between genetics, environmental factors, and the host immune system lead to aberrant immune responses and chronic intestinal inflammation.[4] Currently, the treatment of IBD mainly includes drugs, surgery, and nutritional support. Among them, the commonly used therapeutic drugs, such as aminosalicylic acid, hormones, immunosuppressive agents, etc., have more limited therapeutic effects and more side effects .[5] With a lot of in-depth research, more treatments have been proposed. Such as biosimilar medicines, probiotics, faecal transplantation, diet therapy, and so on.[6–9]

Bibliometric citation analysis studies the clinical and scientific significance of manuscripts by analyzing the number of citations in subsequent manuscripts. A higher number of citations can represent the contribution of the manuscript to the current subject knowledge system. Bibliometric citations analysis has been utilized to report the top 100 cited papers in medicine and surgery including the subspecialties of orthopedic surgery, ophthalmology, gastric cancer, osteosarcoma, and pituitary adenoma .[10–14] To date, no study has been undertaken to determine the most influential papers in the field of inflammatory bowel disease. We aim to analyze the most cited papers in IBD to provide insights into how the understanding of disease pathophysiology and treatment over the past 100 years has evolved and to highlight the key work of clinicians and scientists.

2. Materials and methods

To identify the 100 most-cited articles in inflammatory bowel disease, we used Institute for Scientific Information (ISI) Web of Knowledge Journal Citation Reports Science Edition 2015 (Thomson Reuters, New York, NY). Since there was no use of human subjects, our study was exempt from the institutional review board approval. Two authors (XC and YX) extracted the data using a predetermined form. After extraction, data were compared by XC, with disagreements being solved by consensus. We contacted the authors of the original articles when we needed to clarify the study data. Any disagreements that arose were mutually resolved. The overall search was conducted in September 2018.

We selected the highest cited original articles and referred these as "citation classics." We included articles pertaining to inflammatory bowel disease limited to chronic relapsing inflammatory disorders Crohn disease and ulcerative colitis. The keywords used for the search were "inflammatory bowel disease" or "Crohn disease" or "ulcerative colitis" or "colitis" as the "topic" (title, abstract, author's keywords, and KeyWords Plus). The returned dataset was filtered to include only English language and full manuscripts and sorted by number of citations;

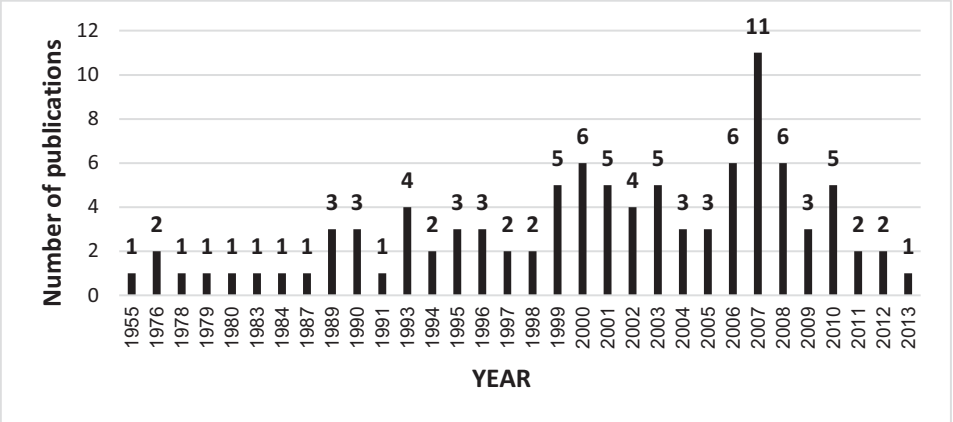

Figure 1. Number of top 100 of publications per year.

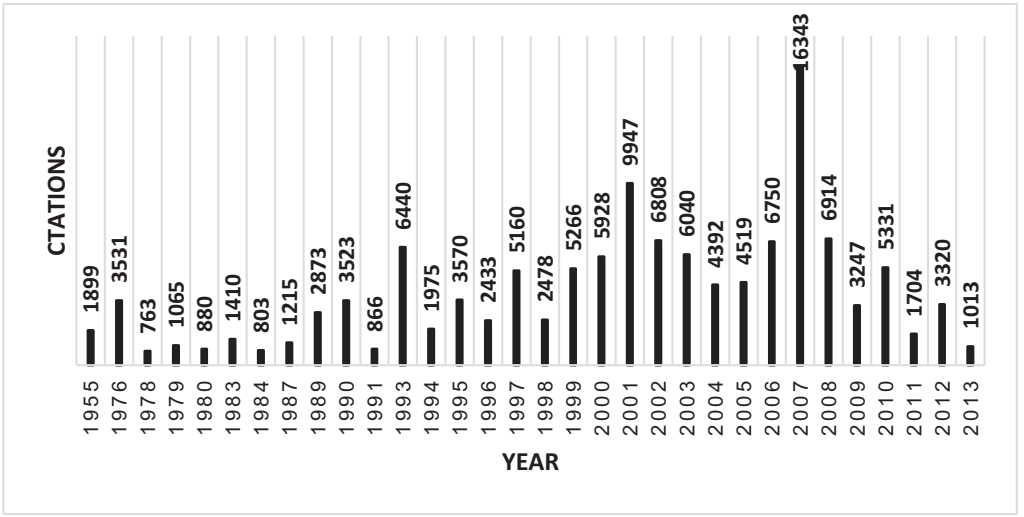

Figure 2. Number of top 100 citations per year.

a method initially developed by Paladugu et al.[15] Time limitations were not implemented in the investigation, and we did not impose any restrictions on the type of research, the availability of abstracts, and human and nonhuman research subjects. The results were organized from the most cited to the least cited publications. If we found identical numbers of total citations, the more recent articles were ranked higher. Data retrieved included journal name, publication date, first and senior authors, year of publication, country of origin, total number of citations for the article, overall citation rate (total citations/article age), current citation rate (measured as the number of citations in the year 2017), and research nature (basic science, clinical research or review).

3. Results

The Web of Knowledge search returned 242,272 works, of which 224,809 were in the English language. The top 100 cited manuscripts are listed in Table 1.[16–115] The citation count of articles ranged from 719 to 4957 (median number of citations, 1028.5). Citations Per Year The citations per year ranged from 18.29 to 400.33 (median, 70.49). The rank according to the average number of citations per year is shown in Table 1. The earliest and most cited manuscript was published in 1955 and focused on cortisone, the first treatment for UC.[27] The most recent was published in 2013 and focused on new insight into the mechanisms by which host–microbe interactions establish immunological homeostasis in the gut.[67]

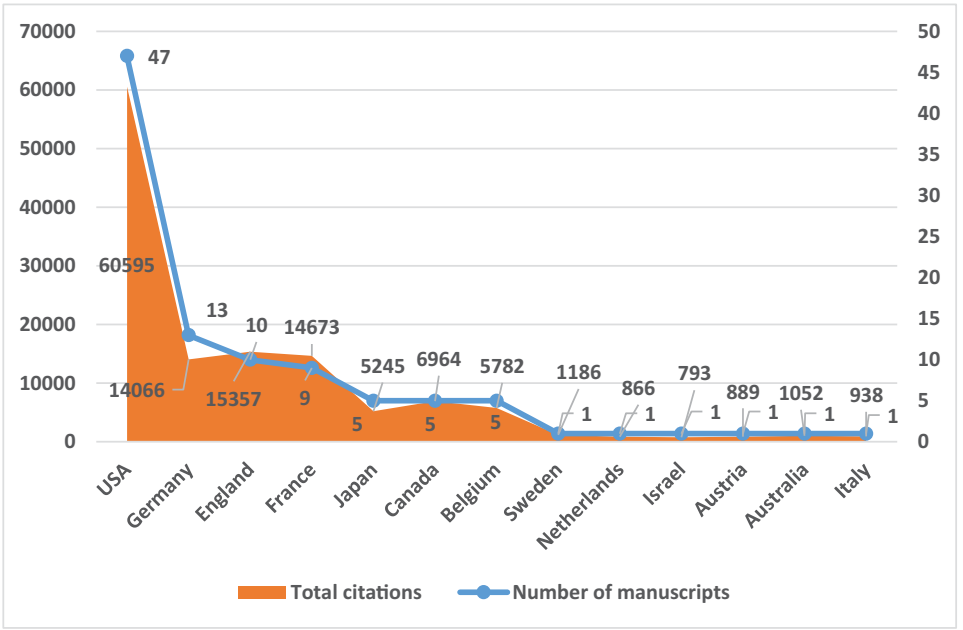

Figure 3. Countries of origin of top 100 papers.

Table 1

The 100 most-cited articles in inflammatory bowel disease.

Rank	Article	Citations	Citations/year since publication	Rank according to average citations per year	Citations in 2018	Year
1	Genome-wide association study of 14, 000 cases of seven common diseases and 3000 shared controls[16]	4957	413.08	1	176	2007
2	Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease[17]	3609	200.5	15	71	2001
3	A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease[18]	3329	184.94	21	66	2001
4	Interleukin-10-deficient mice develop chronic enterocolitis[19]	3017	116.04	2	54	1993
5	A CD4 (+) T-cell subset inhibits antigen-specific T-cell responses and prevents colitis[20]	2768	125.82	3	35	1997
6	Development of a Crohn-disease activity index - national cooperative Crohn's-disease study[21]	2579	59.98	10	57	1976
7	Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial[22]	2524	148.47	52	114	2002
8	Inflammatory bowel disease[23]	2453	144.29	29	46	2002
9	A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease[24]	2392	108.73	30	35	1997
10	Unravelling the pathogenesis of inflammatory bowel disease[25]	2106	175.5	17	107	2007
11	Infliximab for induction and maintenance therapy for ulcerative colitis[26]	1911	136.5	7	106	2005
12	Cortisone in ulcerative colitis - final report on a therapeutic trial[27]	1899	29.67	16	30	1955
13	A genome-wide association study identifies IL23R as an inflammatory bowel disease gene[28]	1892	145.54	13	50	2006
14	Infliximab for the treatment of fistulas in patients with Crohn's disease[29]	1757	87.85	8	30	1999
15	Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease[30]	1752	250.29	11	185	2012
16	Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases[31]	1752	146	23	136	2007
17	Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease[32]	1669	151.73	5	63	2008
18	Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences[33]	1619	107.93	41	70	2004
19	IKK beta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer[34]	1587	105.8	4	54	2004
20	Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of CD25 (+) CD4 (+) regulatory cells that control intestinal inflammation[35]	1570	82.63	73	19	2000
21	Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review[36]	1568	224	9	201	2012
22	Inflammatory bowel disease: etiology and pathogenesis[37]	1562	74.38	18	24	1998
23	Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients[38]	1462	132.91	19	128	2008
24	Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection[39]	1458	91.13	49	41	2003
25	Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology[40]	1443	103.07	85	98	2005
26	The risk of colorectal cancer in ulcerative colitis: a meta-analysis[41]	1436	79.78	50	63	2001
27	A novel method in the induction of reliable experimental acute and chronic ulcerative-colitis in mice[42]	1427	49.21	25	47	1990
28	Dysplasia in inflammatory bowel-disease - standardized classification with provisional clinical-applications[43]	1410	39.17	68	13	1983
29	Infliximab, azathioprine, or combination therapy for Crohn's disease[44]	1385	153.89	38	130	2010
30	Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci[45]	1378	153.11	70	85	2010
31	Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene[46]	1373	52.81	39	15	1993
32	Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease[47]	1326	82.88	43	44	2003
33	Hapten-induced model of chronic inflammation and ulceration in the rat colon[48]	1261	42.03	51	25	1989
34	Clinicopathological study of dextran sulfate sodium experimental murine colitis[49]	1257	48.35	54	57	1993
35	Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative-colitis - a randomized study[50]	1215	37.97	24	90	1987
36	Ulcerative-colitis and colorectal-cancer - a population-based study[51]	1187	40.93	88	24	1990
37	Infliximab maintenance therapy for fistulizing Crohn's disease[52]	1186	79.07	14	52	2004
38	Adalimumab for maintenance of clinical response and remission in patients with Crohn disease: The CHARM trial[53]	1181	98.42	59	86	2007
39	Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis[54]	1174	97.83	47	31	2007
40	Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract[55]	1165	83.21	40	29	2005
41	Mechanisms of disease inflammatory bowel disease[56]	1164	116.4	32	98	2009
42	Host recognition of bacterial muramyl dipeptide mediated through NOD2[57]	1157	72.31	20	25	2003

(*continued*)

Table 1

(continued).

Rank	Article	Citations	Citations/year since publication	Rank according to average citations per year	Citations in 2018	Year
43	A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1[58]	1153	96.08	26	39	2007
44	The immunological and genetic basis of inflammatory bowel disease[59]	1139	71.19	37	26	2003
45	Cyclosporine in severe ulcerative-colitis refractory to steroid-therapy[60]	1122	44.88	55	19	1994
46	An essential role for interleukin 10 in the function of regulatory T cells that inhibit intestinal inflammation[61]	1111	55.55	67	11	1999
47	The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications[62]	1104	84.92	22	80	2006
48	National Cooperative Crohn Disease Study - Results Of Drug-Treatment[63]	1065	26.63	57	4	1979
49	Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43[64]	1052	105.2	42	94	2009
50	IL-6 and Stat3 Are Required for Survival of Intestinal Epithelial Cells and Development of Colitis-Associated Cancer[65]	1031	103.1	89	75	2009
51	A microbial symbiosis factor prevents intestinal inflammatory disease[66]	1026	93.27	63	69	2008
52	Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells[67]	1013	168.83	44	192	2013
53	Antibodies to interleukin-12 abrogate established experimental colitis in mice[68]	1010	42.08	81	23	1995
54	Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1 beta production[69]	1008	91.64	77	80	2008
55	IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6[70]	998	76.77	93	34	2006
56	Experimental-models of inflammatory bowel-disease[71]	966	40.25	95	12	1995
57	Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach[72]	963	74.08	97	76	2006
58	Increased expression of interleukin 17 in inflammatory bowel disease[73]	960	60	58	42	2003
59	Microbial influences in inflammatory bowel diseases[74]	956	86.91	6	49	2008
60	Extra-intestinal complications of Crohn's-disease and ulcerative-colitis - study of 700 patients[75]	952	22.14	46	6	1976
61	The immunology of mucosal models of inflammation[76]	943	55.47	61	24	2002
62	Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: A double-blind, placebo-controlled trial[77]	938	49.37	31	14	2000
63	Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial[78]	932	71.69	69	55	2006
64	Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice[79]	916	43.62	62	28	1998
65	Predictability of the postoperative course of Crohn's-disease[80]	909	31.34	27	29	1990
66	Disparate CD4(+) lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease - Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5[81]	907	39.43	34	17	1996
67	Gastroenterology 2 - Inflammatory bowel disease: clinical aspects and established and evolving therapies[82]	898	74.83	80	58	2007
68	Inflammatory Bowel Disease[83]	889	98.78	75	51	2010
69	Mucosal flora in inflammatory bowel disease[84]	888	52.24	76	21	2002
70	The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management[85]	885	98.33	78	60	2010
71	Treatment of Crohn's-disease with 6-mercaptopurine - a long-term, randomized, double-blind-study[86]	880	22.56	45	11	1980
72	Treatment of Crohns-disease with antitumor necrosis factor chimeric monoclonal-antibody (CA2)[87]	875	36.46	82	10	1995
73	Genetics and pathogenesis of inflammatory bowel disease[88]	872	109	64	95	2011
74	Inflammatory bowel-disease .1[89]	866	30.93	53	16	1991
75	A simple classification of Crohn's disease: Report of the Working Party for the world congresses of gastroenterology[90]	863	45.42	33	13	2000
76	Treatment of murine colitis by Lactococcus lactis secreting interleukin-10[91]	862	45.37	83	17	2000
77	Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis[92]	861	66.23	84	58	2006
78	Differential alteration in intestinal epithelial cell expression of Toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease[93]	857	45.11	36	22	2000
79	Inhibition of TH1 responses prevents inflammatory bowel-disease in scid mice reconstituted with CD45RB(HI) CD4(+) T-CELLS[94]	853	34.12	56	19	1994
80	Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations[95]	852	47.33	99	10	2001
81	Gastroenterology 1 - Inflammatory bowel disease: cause and immunobiology[96]	845	70.42	66	46	2007

(*continued*)

Table 1

(continued).

Rank	Article	Citations	Citations/year since publication	Rank according to average citations per year	Citations in 2018	Year
82	Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: Evidence in Crohn disease and experimental colitis in vivo[97]	838	44.11	28	36	2000
83	Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils[98]	834	41.7	35	16	1999
84	Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease[99]	833	41.65	98	16	1999
85	NLRP6 Inflammasome Regulates Colonic Microbial Ecology and Risk for Colitis[100]	832	104	72	75	2011
86	Classification of inflammatory bowel-disease[101]	824	27.47	79	34	1989
87	European cooperative Crohn's-disease study (ECCDS) - results of drug-treatment[102]	803	22.94	92	6	1984
88	Inducible Foxp(3+) regulatory T-cell development by a commensal bacterium of the intestinal microbiota[103]	794	88.22	96	80	2010
89	A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells[104]	793	72.09	65	41	2008
90	Phenotypically distinct subsets of CD4(+) T-cells induce or protect from chronic intestinal inflammation in C - B-17 SCID mice[105]	793	30.5	74	17	1993
91	Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative-colitis - a randomized trial[106]	788	26.27	90	18	1989
92	Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4(+) TH1-like responses[107]	776	33.74	100	13	1996
93	Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility[108]	775	64.58	12	17	2007
94	Proctocolectomy without ileostomy for ulcerative-colitis[109]	763	18.61	86	22	1978
95	Chemically induced mouse models of intestinal inflammation[110]	756	63	48	52	2007
96	Mapping of a susceptibility locus for Crohn's disease on chromosome 16[111]	750	32.61	91	8	1996
97	The fundamental basis of inflammatory bowel disease[112]	746	62.17	87	26	2007
98	Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial[113]	731	36.55	71	9	1999
99	The natural history of corticosteroid therapy for inflammatory bowel disease: A population-based study[114]	721	40.06	60	18	2001
100	Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD)[115]	719	29.96	94	7	1995

Table 2

Journals publishing the top 100 cited IBD manuscripts.

Journal	Impact factor (IF)	IF without journal self-citations	5-y IF	Number of manuscripts in the top 100	Total citations	First issue
GASTROENTEROLOGY	20.773	20.006	19.131	18	21,083	1976
NATURE	41.577	41.015	44.958	13	25,035	1996
NEW ENGLAND JOURNAL OF MEDICINE	79.258	78.537	67.512	13	18,844	1980
LANCET	53.254	51.896	52.665	5	5850	1999
NATURE GENETICS	27.125	26.191	31.154	5	6149	2007
CELL	31.398	30.780	33.796	4	6809	1993
GUT	17.016	16.469	15.910	4	4463	2001
JOURNAL OF CLINICAL INVESTIGATION	13.251	13.093	14.434	3	2520	1996
JOURNAL OF EXPERIMENTAL MEDICINE	10.790	10.514	11.929	3	3691	1995
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	9.504	9.230	10.359	3	4008	2007
SCIENCE	41.058	40.616	40.627	3	3919	2000
ANNUAL REVIEW OF IMMUNOLOGY	22.714	22.551	35.512	2	1832	2002
BRITISH MEDICAL JOURNAL				2	2662	1976
IMMUNITY	19.734	19.100	23.618	2	1687	1996
INFECTION AND IMMUNITY	3.256	3.070	3.603	2	1773	1980
JOURNAL OF BIOLOGICAL CHEMISTRY	4.010	3.828	4.253	2	2615	1999
BMJ-BRITISH MEDICAL JOURNAL	23.259	21.852	20.375	1	788	2007

(*continued*)

Table 2

(continued).

Journal	Impact factor (IF)	IF without journal self-citations	5-y IF	Number of manuscripts in the top 100	Total citations	First issue
CANADIAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY	1.622	1.580	2.121	1	1443	1993
CANCER CELL	22.844	22.541	27.072	1	1031	2001
CLINICAL AND EXPERIMENTAL IMMUNOLOGY	3.542	3.446	3.234	1	719	1996
HUMAN PATHOLOGY	3.125	2.841	2.816	1	1410	1995
INFLAMMATORY BOWEL DISEASES	4.347	3.996	4.872	1	863	2007
INTERNATIONAL IMMUNOLOGY	5.189	5.147	3.837	1	793	2000
JOURNAL OF CROHNS & COLITIS	6.637	6.076	6.992	1	885	2010
JOURNAL OF IMMUNOLOGY	4.539	4.320	4.990	1	907	1976
LABORATORY INVESTIGATION	4.254	4.181	4.345	1	1257	1996
MEDICINE	2.028	1.891	2.193	1	952	1980
NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY				1	861	1999
NATURE MEDICINE	32.621	32.357	33.409	1	838	2007
NATURE PROTOCOLS	12.423	12.244	15.269	1	756	1993
NATURE REVIEWS IMMUNOLOGY	41.982	41.642	46.507	1	1139	2001
SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY	2.629	2.537	2.511	1	824	1989

The top 100 manuscripts were published in 32 journals (Table 2). These journals are basic science, clinical, epidemiological, surgical, and genetic in nature. Gastroenterology published the highest number of top 100 papers (n = 18 with 21,083 citations combined). This was followed by Nature with 13 manuscripts and 25,035 citations. Impact factors of the 32 journals ranged from 79.258 (*New England Journal Of Medicine*, 13 manuscripts and 18,844 citations) to 1.622 (*Canadian Journal of Gastroenterology and Hepatology*, 1 manuscript with 1443 citations).

The number of authors in each article ranged from 1 to 194 (median, 7). Eleven authors had more than 1 first authorship (Table 3). Seventeen had more than 5 senior authorship. Fifteen had at least 1 first and 1 or more senior authorships. Rutgeerts P from the Katholieke Univ Leuven Hosp, Louvain, Belgium had the highest amount of authorships (3 first and 3 senior) and citations (n = 6714) followed by Colombel JF of the CHU Lille, Hop Claude Huriez, Dept Hepatogastroenterol, Rue Michel Polonovski, F-59037 Lille, France (Two first and 3 senior authorships, 6212 citations).

The year which yielded the highest number of papers was 2007 (n = 11 manuscripts and 16,343 citations) followed by 2000, 2006, and 2008, each with 6 publications (Fig. 1) and 5928, 6750, and 6914 citations (Fig. 2), respectively. The articles were published between 1955 and 2013 and most were published in the 5-year periods 2005 to 2009 (n = 29) and 2000 to 2005 (n = 23). The most proliferative authors, as demonstrated by the first authorship of 3 or more of the manuscripts, hailed from 11 institutions. Ten of these institutions are located in the United States and 1 in Germany. The institutions with the highest number of publications in the top 100 were NIAID Mucosal Immun Sect and Yale University USA, each with 5 papers generating 5694 and 8216 citations, respectively (Table 4). Forty-seven percent of the manuscripts

Table 3

Authors with the highest number of manuscripts in the top 100.

Author's name	Number of first authorships	Number of citations from first authorships	Number of senior authorships	Number of citations from senior authorships
Hanauer SB	3	4363	2	3456
Rutgeerts P	3	3646	3	3068
Baumgart DC	2	1741	1	898
Colombel JF	2	2542	3	3670
Hampe J	2	2010	1	1153
Hugot JP	2	4365	1	750
Podolsky DK	2	3306	4	6282
Powrie F	2	1657	3	3216
Present DH	2	2620	1	1757
Sartor RB	2	1812	2	1817
Strober W	2	1763	3	2828
Akira S	0		3	2758
Cho JH	0		3	4808
Neurath MF	1	1026	3	2604
Loftus EV	1	1587	2	2340
Mazmanian SK	1	998	2	1820
Parkes M	1	775	2	2153
Parks AG	1	763	2	3342
Riddell RH	1	1443	2	2290
Sadlack B	1	1373	2	4390

Table 4

Academic departments represented in the top 100.

Institution	Country	Number of manuscripts	Number of citations
Yale Univ	USA	5	8216
NIAID, Mucosal Immun Sect	USA	5	5694
DNAX RES INST MOL & CELLULAR BIOL INC	USA	4	5609
Massachusetts Gen Hosp	USA	4	3959
Mayo Clin	USA	3	2866
Univ Calif San Diego	USA	3	3092
Univ Chicago	USA	3	2988
Univ N Carolina	USA	3	4653
CUNY, MT SINAI SCH MED	USA	3	2342
Humboldt Univ	Germany	3	3835
Harvard Univ	USA	3	2023

originated from the United States (Fig. 3). The Germany and England produced 13% and 10%, respectively.

Of the 100 articles, 51 were basic research, 31 were clinical research, and 18 were review papers (among the category "review papers" consensus papers were included). Considering the number of citations per type of article, a statistically significant difference was not found between the groups of basic research and clinical research (Mann–Whitney test $P = .699$; basic research: median = 1008 [range = 719–3609]; clinical research: median = 1122 [range = 721–2579] [Table 5]). We subdivided clinical research articles according to topics: diagnostic research (n = 6, 19.35%), epidemiology (n = 3, 9.68%), and medical and surgical treatment (n = 22, 70.97%). Eighteen articles were review articles (mean 1478 [range = 824–4957]; Table 5).

The topics covered in the top 100 are wide-ranging (Table 6). Molecules is the topic with the highest amount of publications (n = 27), followed by genetics (n = 26) and treatment (n = 16). Within the manuscripts that focused on molecules, factor-alpha is the topic of interest of the greatest number of manuscripts (n = 15), followed by interferon-gamma (n = 11), CD4+ T-cells (n = 10), and interleukin-10 (n = 9). Within the manuscripts that focused on treatment, 6-mercaptopurine, infliximab, and cyclosporin are the topic of interest of the greatest number of manuscripts (n = 4 each), followed by 5-aminosalicylic acid (n = 3). Eight manuscripts focus on the microbiome and 4 focus on epidemiology. Ulcerative Colitis (n = 45) and Crohn Disease (n = 43) are the main topics covered in top 100 manuscripts. Sixteen utilized animal models.

Table 6

Most referenced topics.

Topic	Number of manuscripts
Inflammatory bowel disease	47
Ulcerative colitis	45
Crohn disease	43
Treatment	16
NF-KAPPA-B	15
Factor-alpha	15
Interferon-gamma	11
Genome-wide association	10
CD4+ T-CELLS	10
Cytokine	10
Interleukin-10	9
Intestinal epithelial-cells	9
Microbiota	8
Animal models	16
Regulatory T-cells	7
Toll-like receptor	6
6-Mercaptopurine	4
Infliximab	4
Cyclosporin	4
5-Aminosalicylic acid	3
Epidemiology	3
Crohn disease activity index	3
Probiotics	2

Due to overlap of topics, cell numbers do not add up to 100.

4. Discussion

Bibliometric studies allow the reader to gain an insight into the history and development of a particular specialty over time.[116] Similarly, the identification of citation classics can promote understanding of academic advances in specific areas and help identify emerging themes and future directions in specific disciplines. These most cited works reflect important themes of the scientific and clinical IBD community. Our analysis has identified the most influential articles on the results of inflammatory bowel disease research in the past few decades. This study highlights the contribution of significant advances in inflammatory bowel disease research and points to current trends in the field. Similar to various other analyses, our bibliometric also has a peak period from 2000 to 2009, with more than half of the most-cited articles being published during this 10-year period. Only 3 articles published since 2012 made it to the list, likely because several years are needed for an article to gain a sufficient number of citations.

The ranking of articles on the basis of citations was considerably different from the original ranking based on citation counts only. However, the article "Genome-wide association study of 14,000 cases of 7 common diseases and 3000 shared controls" by Burton et al, both with the highest average citations per year and total citations, which was originally ranked at number 1. It was published in 2007 and highlights the importance of genome-wide association (GWA) to the identification of genes involved in common human diseases.

The publication of these top 100 manuscripts has several high impacts, reflecting their quality and interest in the science and

Table 5

Citations per type of article.

	Citations per type of article				P^*		
	N	Range (min/max)	Mean (±SD)	Median (Q25/Q75)	Gr1 vs Gr2	Gr1 vs Gr3	Gr2 vs Gr3
Basic research (Gr1)	51	719/3609	1243 (±651)	1008 (852/1427)	0.699	0.245	0.419
Clinical research (Gr2)	31	721/2579	1238 (±526)	122 (866/1385)			
Review article (Gr3)	18	824/4957	1478 (±983)	1160.5 (881.75/1580.75)			
Total	100	719/4957	1284 (±687)	1028.5 (862.25/1441.25)	*Mann–Whitney test		

clinical community. The impact factor of a journal quantifies the average citation of manuscripts published in journals over a specified period of time. Therefore, journals with higher impact factors are considered to be of higher quality and are more likely to contain influential publications. Journals with very high impact factors (79.258–31.398); *The New England Journal of Medicine*, *Lancent*, *Nature Reviews Immunology*, *Nature*, *Nature Medicine*, *Cell and Science* represent 40% of all publications in the top 100. Furthermore, the median impact factor was 12.423 and 15% of publications were in journals with an impact factor of 4.539 or less. A possible explanation for this involves the novelty of the results. Novelty can be classified as related to general science or only to inflammatory bowel disease. The findings that have been established in other cancers can then be reconstructed in inflammatory bowel disease. These manuscripts are unlikely to be published in high-impact journals, but they are likely to be considered influential in the context of this study.

Gastroenterology contributes the most articles to our list (n = 18), followed by *Nature* and *New England Journal of Medicine* (both n = 13). All these are specific journals catering to a particular field, and according to the Bradford law, this observation is justified.[117] However, several high-impact articles have been published in general medical journals such as *The Lancet* and *Science*. Bradford's Law means that some core journals in a particular field extract most of the citations, which is largely confirmed in our research. Therefore, for researchers, editors, and readers, the publications of journals in specific areas related to IBD may be more influential than publications in general medical journals.

The top 3 most-cited authors in this study period (Podolsky DK, Rutgeerts P, and Burton PR) contributed 14 articles as first and/or senior author, accruing a total of 18,212 citations. Of these 14 articles, 8 were from American institutions and 3 from Belgium. This highlights how a relatively few authors can substantially contribute to the impact of a journal or a field of research.[118] Twenty-seven were found to have 5 or more publications in the top 100 list. Among them, the author with the most articles is Rutgeerts, P. His name appears in more than one-tenth of all the articles on our list. This is a huge contribution to IBD. Other frequent contributors to this field are Colombel, JF and Hanauer, SB, with 10 and 9 publications, respectively. It can be inferred from this finding that a few eminent dedicated researchers contribute to IBD on a scale not observed in other bibliometrics. These researchers are more likely to receive academic promotions as a result of their notable contributions in the literature.[117]

The geographic location of the authors reflects disease distribution. IBD is primarily a disease of Western societies. Forty-one percent of manuscripts were from Europe and 47% from the United States. Conversely, no manuscripts originating from Africa were found and only 5 manuscripts were from Asia (all from Japan). The 100 most-cited articles in inflammatory bowel disease research were published in 32 journals, and 68 of the articles were published in 5 American journals. The American journal "Gastroenterology," established in 1943, topped the list with 18 articles.

A peak in cytokine research is seen in the early 1990s, when interleukins were a focus of many studies. Another peak in the number of manuscripts focusing on medical treatment is seen in the early 2000s, at the time of infliximab discovery. The number of genetics focused manuscripts rises throughout the different time periods. Typically in bibliometric analyses, years in which peaks in number of manuscripts or citations correspond to key events or discoveries in the field. In our analysis, 2007 was the year with the highest amount of publications followed by 2006 and 2008. Topics were varied and there was no discernable pattern within these years perhaps reflecting the complex etiology of the disease. For example, 1994 featured papers on treatment, genetics, cytokine, animal models of inflammatory bowel disease. This reflects the multiple varied aspects of disease.

When looking specifically at the topics which received a high amount of coverage in the top 100, the treatment in IBD is reflected by 16% of the top 100 (including 3 of the top 10 papers) focusing on the subject. Baumgart's 1980 paper confirmed 6-mercaptopurine (6-MP) was an effective and useful agent in the management of Crohn disease of 83 CD patients. It was reported that 6-MP was more effective than placebo in closing fistulas and in permitting discontinuation or reduction of steroid dosage.[86] Later Present's and Ekbom's work both replicated infliximab was an efficacious treatment for fistulas in patients with Crohn disease in a randomized, multicenter, double-blind, placebo-controlled trial.[29] This manuscript was followed by Colombel's research-authenticated patients with moderate-to-severe Crohn disease who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free Clinical remission than those receiving azathioprine monotherapy.[44] In addition, notable top 100 notable inclusions include Burton's 2007 landmark paper on the use of GWA to the identification of genes involved in IBD,[16] which offered new avenues for exploring the pathophysiology of these important disorders.

The topics covered in the genetics manuscripts were varied and included papers on genome-wide association study, metagenomic approach, genetic murine models of colitis, and cytokine associated genes.[16,28,32,39,54,58,59,72,91] The 1996 Nature manuscript by Strober et al[111] was the first to search genome-wide of IBD on 2 consecutive and independent panels of families with multiple affected members, using a nonparametric 2-point sibling-pair linkage method, identified a putative CD-susceptibility locus on chromosome 16. This authenticated that inherited factors may contribute in part to variation in individual susceptibility to IBD and provided a basis for the pathogenic mechanism of IBD. Number 61 on the list, Furusawa's 2006 paper on the first use of a comprehensive metagenomic approach to investigate the full range of intestinal microbial diversity, allowed us to detect a reduced complexity of the bacterial phylum Firmicutes as a signature of the faecal microbiota in patients with CD.[72] In addition, bowel inflammation in the mutants which originates from uncontrolled immune responses was stimulated by enteric antigens and IL-10 was an essential immunoregulator in the intestinal tract.[19]

Other works of note include Rutgeerts' paper that summarized the results of the ACCENT I and II trials proving the efficacy of infliximab, an antitumor necrosis factor agent (which was at the time being used to treat Crohn) in UC, revolutionizing treatment.[26] Okayasu's 1990 paper on the use of dextran sulfate sodium containing drinking water to induce a UC-like colitis in mice, which is the most commonly utilized nongenetic animal model of colitis, is found at number 6 in the list.[42] Oral administration of a new probiotic preparation (VSL#3) is effective in preventing flare-ups of chronic pouchitis.[77]

The main limitation of this manuscript is that there may be several types of biases that may affect the outcome. Disproportionate references may be due to institutional bias, language bias,

self-citation, or powerful person bias. In addition, older journals may receive more citations. Although trying to control this by using the Citation Index, it may take several years for an influential manuscript to generate a citation due to the time it takes to cite the manuscript. Therefore, the recently published manuscripts have been sufficiently cited to be included in the top 100, which has increased the importance. Another limitation is the institution that includes only the first author and the senior author, as well as the first author. It is possible that several first authors will coauthor other papers in the top 100 and therefore are not represented in the current research report.

5. Conclusion

In conclusion, this is, to our knowledge, the first bibliometric study to identify the 100 most cited papers in inflammatory bowel disease research. The most cited citations emphasized by IBD in the current work can be considered classic works in the field of research, as they have a great influence on subsequent works, which can be proved by their citations. These manuscripts describe the epidemiological, genetic, immunologic, pharmacologic, and surgically relevant disease features. The majority of these works were published in high impact journals reflecting the importance of the study of IBD in both scientific and clinical communities. In addition to providing a reference that can be considered the most influential paper in inflammatory bowel disease, this work provides a reference for researchers and clinicians to become a citable paper in the field of inflammatory bowel disease research.

Author contributions

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References

[1] Macdonald TT. New cytokine targets in inflammatory bowel disease. Gastroenterol Hepatol 2011;7:474–6.
[2] Silva FA, Rodrigues BL, Ayrizono ML, et al. The immunological basis of inflammatory bowel disease. Gastroenterol Res Pract 2016;2016:2097274.
[3] Burisch J, Munkholm P. Inflammatory bowel disease epidemiology. Curr Opin Gastroenterol 2013;29:357–62.
[4] Bernstein CN, Eliakim A, Fedail S, et al. Review TeamWorld Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. J Clin Gastroenterol 2016;50:803–18.
[5] Lee D, Albenberg L, Compher C, et al. Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology 2015;148:1087–106.
[6] Strik AS, Gr VDB, Ponsioen C, et al. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:1128–34.
[7] Danese S, Gomollon F. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). J Crohns Colitis 2013;7:586–9.
[8] Kao D, Hotte N, Gillevet P, et al. Fecal microbiota transplantation inducing remission in Crohn's colitis and the associated changes in fecal microbial profile. J Clin Gastroenterol 2014;48:625–8.
[9] Lewis JD, Abreu MT. Diet as a trigger or therapy for inflammatory bowel diseases. Gastroenterology 2016;152:398.e6–414.e6.
[10] Held M, Engelmann E, Dunn R, et al. Gunshot induced injuries in orthopaedic trauma research. A bibliometric analysis of the most influential literature. Orthop Traumatol Surg Res 2017;103: 801–7.
[11] Schargus M, Kromer R, Druchkiv V, et al. The top 100 papers in dry eye—a bibliometric analysis. Ocul Surf 2017;16:180–90.
[12] Powell AG, Hughes DL, Wheat JR, et al. The 100 most influential manuscripts in gastric cancer: a bibliometric analysis. Int J Surg 2016;28:83–90.
[13] Guo X, Gao L, Wang Z, et al. Top 100 most-cited articles on pituitary adenoma: a bibliometric analysis. World Neurosurg 2018;116:e1153–67.
[14] Hafeez MS, Malik AT, Noordin S. The top 100 most-cited articles on osteosarcoma: a bibliometric analysis. Int J Surg Oncol 2018;3:e62.
[15] Paladugu R, Schein M, Gardezi S, et al. One hundred citation classics in general surgical journals. World J Surg 2002;26:1099–105.
[16] Burton PR, Clayton DG, Cardon LR, et al. Genome-wide association study of 14, 000 cases of seven common diseases and 3, 000 shared controls. Nature 2007;447:661–78.
[17] Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599–603.
[18] Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature 2001;411:603–6.
[19] Kühn R, Löhler J, Rennick D, et al. Interleukin-10-deficient mice develop chronic enterocolitis. Cell 1993;75:263–74.
[20] Groux H, O'Garra A, Bigler M, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature 1997;389:737–42.
[21] Best WR, Becktel JM, Singleton JW, et al. Development of a crohns disease activity index: National Cooperative Crohns Disease Study. Gastroenterology 1976;70:439–44.
[22] Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–9.
[23] Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002;347:417–29.
[24] Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–35.
[25] Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007;448:427–34.
[26] Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–76.
[27] Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–8.
[28] Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314:1461–3.
[29] Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–405.
[30] Jostins L, Ripke SW, Rinse K, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119–24.
[31] Frank DN, Amand ALS, Feldman RA, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A 2007;104:13780–5.
[32] Barrett JC, Hansoul S, Dan LN, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40:955–62.
[33] LE Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504–17.
[34] Greten FR, Eckmann L, Greten TF, et al. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004;118:285–96.
[35] Read S, Malmstrom V, Powrie F, et al. T lymphocyteassociated antigen 4 plays an essential role in the function of CD25 (+)CD4 (+) regulatory

cells that control intestinal inflammation. J Exp Med 2000;192:295–302.
[36] 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.e42–54.e42.
[37] Fiocchi C. Inflammatory bowel disease: etiology and pathogenesis. Gastroenterology 2000;111:182–205.
[38] Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 2008;105:16731–6.
[39] Girardin SE, Boneca IG, Viala J, et al. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem 2003;278:8869–72.
[40] Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory boweldisease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19 suppl A:5A–36A.
[41] Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–35.
[42] Okayasu I, Hatakeyama S, Yamada M, et al. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology 1990;98:694–702.
[43] Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol 1983;14:931–68.
[44] Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–95.
[45] Franke A, Mcgovern DPB, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet 2010;42:1118–25.
[46] Sadlack B, Merz H, Schorle H, et al. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. Cell 1993;75:253–61.
[47] Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601–8.
[48] Morris GP, Beck PL, Herridge MS, et al. Hapten-induced model of chronic inflammation and ulceration in the rat colon. Gastroenterology 1989;96:795–803.
[49] Cooper HS, Murthy SN, Shah RS, et al. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. Lab Invest 1993;69:238–49.
[50] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–9.
[51] Ekbom A, Helmick C, Zack M, et al. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990;323:1228–33.
[52] Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–85.
[53] Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.
[54] Rioux JD, Xavier RJ, Taylor KD, et al. Genome-wide association study identifies five novel susceptibility loci for Crohn's disease and implicates a role for autophagy in disease pathogenesis. Nat Genet 2007;39:596–604.
[55] Kobayashi KS, Chamaillard M, Ogura Y, et al. Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science 2005;307:731–4.
[56] Abraham C, Cho JH. Mechanisms of disease: inflammatory bowel disease. *N Engl J Med*. 2009;(21):2066–2078.
[57] Inohara N, Ogura Y, Fontalba A, et al. Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. J Biol Chem 2003;278:5509–12.
[58] Hampe J, Franke A, Rosenstiel P, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet 2007;39:207–11.
[59] Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 2003;3:521–33.
[60] Gelernt I, Bauer J, Galler G. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330:1841–5.
[61] Asseman C, Mauze S, Leach MW, et al. An essential role for interleukin 10 in the function of regulatory T cells that inhibit intestinal inflammation. Nat Rev Immunol 1999;190:995–1004.
[62] Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–53.
[63] Summers RW, Switz DM, Sessions JT Jr, et al National Cooperative Crohn's Disease Study: results of drug treatment *Gastroenterology* 1979;77:847–869
[64] Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature 2009;461:1282–2119.
[65] Grivennikov S, Karin E, Terzic J, et al. IL-6 and STAT3 are required for survival of intestinal epithelial cells and development of colitis associated cancer. Cancer Cell 2009;15:91–102.
[66] Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 2008;453:620–5.
[67] Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504:446.
[68] Neurath MF, Fuss I, Kelsall BL, et al. Antibodies to interleukin 12 abrogate established experimental colitis in mice. J Exp Med 1995;182:1281–90.
[69] Saitoh T, Fujita N, Jang MH, et al. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1|[bgr]| production. Nature 2008;456:264–8.
[70] Yen D, Cheung J, Scheerens H, et al. IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest 2006;116:1310–6.
[71] Elson CO, Sartor RB, Tennyson GS, et al. Experimental models of inflammatory bowel disease. Acta Gastroenterol Belg 1994;57:306.
[72] Manichanh C, Rigottier-Gois L, Bonnaud E, et al. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut 2006;55:205–11.
[73] Fujino S, Andoh A, Bamba S, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut 2003;52:65–70.
[74] Sartor RB. Microbial influences in inflammatory bowel diseases. Gastroenterology 2008;134:577–94.
[75] Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. Medicine (Baltimore) 1976;55:401–12.
[76] Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. Annu Rev Immunol 2002;20:495–549.
[77] Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:305–9.
[78] Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (Adalimumab) in Crohn's disease: the CLASSIC-I Trial. Gastroenterology 2006;130:323–33.
[79] Sellon RK, Tonkonogy S, Schultz M, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. Infect Immun 1998;66:5224–31.
[80] Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology 1990;99:956–63.
[81] Fuss IJ, Neurath M, Boirivant M, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol 1996;157:1261–70.
[82] Baumgart DC, Sandborn WJ. Gastroenterology 2 Infl ammatory bowel disease: clinical aspects and established and evolving therapies. Lancet 2007;369:1641–57.
[83] Kaser A, Zeissig S, Blumberg RS, et al. Inflammatory bowel disease. Annu Rev Immunol 2010;28:573–621.
[84] Swidsinski A, Ladhoff A, Pernthaler A, et al. Mucosal flora in inflammatory bowel disease. Gastroenterology 2002;122:44–54.
[85] Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis 2010;4:7–27.
[86] van Dullemen HM, van Deventer SJ, Hommes DW, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 1995;109:129–35.

[87] Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981–7.
[88] Khor B, Gardet A, Xavier RJ, et al. Genetics and pathogenesis of inflammatory bowel disease. Nature 2011;474:307–17.
[89] Podolsky DK. Inflammatory bowel disease. N Engl J Med 1991;325:928–37.
[90] Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 2010;6:8–15.
[91] Steidler L, Hans W, Schotte L, et al. Treatment of murine colitis by lactococcus lactis secreting interleukin-10. Science 2000;289:1352–5.
[92] Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol 2006;3:390–407.
[93] Cario E, Podolsky DK. Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease. Infect Immun 2000;68:7010–7.
[94] Powrie F, Leach MW, Mauze S, et al. Inhibition of Thl responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBCD4T cells. Immunity 1994;1:553–62.
[95] Hampe J, Cuthbert A, Croucher PJ, et al. Association between insertion mutation in NOD2 gene and Crohn's disease in German and British populations. Lancet 2001;357:1925–8.
[96] Baumgart DC, Carding SR. Gastroenterology 1 Infl ammatory bowel disease: cause and immunobiology. Lancet 2007;369:1627–40.
[97] Atreya R, Mudter J, Finotto S, et al. Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in crohn disease and experimental colitis in vivo. Nat Med 2000;6:583–8.
[98] Takeda K, Clausen BE, Kaisho T, et al. Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. Immunity 1999;10:39–49.
[99] Rutgeerts P, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. Gastroenterology 1999;117:761–9.
[100] Elinav E, Strowig T, Kau AL, et al. NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell 2011;145:745–57.
[101] Lennard-Jones JE. Classification of inflammatory bowel-disease. Scand J Gastroenterol 1989;170:2–6.
[102] Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. Gastroenterology 1984;86:249–66.
[103] Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci U S A 2010;107:12204–9.
[104] Cadwell K, Liu JY, Brown SL, et al. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature 2009;456:259–63.
[105] Powrie F, Leach MW, Mauze S, et al. Phenotypically distinct subsets of CD4+ T cells induce or protect from chronic intestinal inflammation in C. B-17 scid mice. Int Immunol 1993;5:1461–71.
[106] Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ 1989;298:82–6.
[107] Berg DJ, Davidson N, Kühn R, et al. Enterocolitis and colon cancer in interleukin-10-deficient mice are associated with aberrant cytokine production and CD4 (+) TH1-like responses. J Clin Invest 1996;98:1010–20.
[108] Parkes M, Barrett JC, Prescott NJ, et al. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. Nat Genet 2007;39:830–2.
[109] Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. BMJ 1978;2:85–8.
[110] Wirtz S, Neufert C, Weigmann B, et al. Chemically induced mouse models of intestinal inflammation. Nat Protoc 2007;2: 541–6.
[111] Hugot JP, Laurent-Puig P, Gower-Rousseau C, et al. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature 1996;379:821–3.
[112] Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Invest 2007;117:514–21.
[113] Rembacken BJ, Snelling AM, Hawkey PM, et al. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet 1999;354:635–9.
[114] Faubion WA, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255–260.
[115] Duchmann R, Kaiser I, Hermann E, et al. Tolerance exists towards resident intestinal flora but is broken in active inflammatory bowel disease (IBD). Clin Exp Immunol 2010;102:448–55.
[116] Alotaibi NM, Nassiri F, Badhiwala JH, et al. The most cited works in aneurysmal subarachnoid hemorrhage: a bibliometric analysis of the 100 most cited articles. World Neurosurg 2016;89:587-592587.e6-592.e6.
[117] Stossel TP. Volume: papers and academic promotion. Ann Intern Med 1987;106:146–9.
[118] Chou CY, Chew SS, Patel DV, et al. Publication and citation analysis of the Australian and New Zealand Journal of Ophthalmology and Clinical and Experimental Ophthalmology over a 10-year period: the evolution of an ophthalmology journal. Clin Exp Ophthalmol 2010;37:868–73.