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Systematic review: the costs of ulcerative colitis in Western countries

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SUMMARY

Background
Early onset and complications such as hospitalization and surgery contribute to the economic burden of ulcerative colitis.

Aim
To review systematically the literature on costs of ulcerative colitis in Western countries.

Methods
Studies estimating costs of ulcerative colitis in Western countries were identified using Medline, EMBASE and ISI Web of Science and were rated based on relevance and reliability of estimates. All costs were adjusted to 2008 currency values. A parallel review focused on the impact of disease severity on costs, hospitalizations and surgeries.

Results
Estimated annual per-patient direct medical costs of ulcerative colitis ranged from $6217 to $11 477 in the United States and from €8949 to €10 395 in Europe. Hospitalizations accounted for 41–55% of direct medical costs. Indirect costs accounted for approximately one-third of total costs in the United States and 54–68% in Europe. Total economic burden of ulcerative colitis was estimated at $8.1–14.9 billion annually in the United States and at €12.5–29.1 billion in Europe; total direct costs were $3.4–8.6 billion in the United States and €5.4–12.6 billion in Europe. Direct costs, hospitalizations and surgeries increased with worsening disease severity.

Conclusions
Ulcerative colitis is a costly disease. Hospitalizations contribute significantly to direct medical costs, and indirect costs are considerable, having previously been substantially underestimated.

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INTRODUCTION

Ulcerative colitis (UC), one of the two major types of inflammatory bowel disease (IBD), is a chronic condition with onset typically between the ages of 15 and 35 years.[1] The annual incidence of UC was 8.8 per 100 000-person-years in the United States in 1990–2000.[2] The prevalence estimate was 214 per 100 000 persons for the entire population in 2001,[2] and 238 and 28 per 100 000 for the adult and paediatric populations respectively in 2004.[3] In Europe, Scandinavian countries have the greatest reported incidence (9.2–20.3 per 100 000)[4] and East European and Baltic countries have the lowest (0.5 and 5.9 per 100 000 respectively).[5] The prevalence rate in some European countries (e.g. United Kingdom, Italy and Hungary) is similar to that reported in the United States, ranging from 121 to 243 per 100 000 in the 1990s.[4, 5]

Approximately 50–80% of patients with UC experience a relapsing and remitting course of disease with varying disease severity.[6] Another 15–30% have a more active course of UC in which sustained remission is difficult to achieve.[6] In addition, more than 50% of patients with UC restricted to proctosigmoiditis progressed over their lifetimes, particularly during the first year.[7] Because of the chronic and recurrent nature of the disease, patients with UC often require either continuous or intermittent treatment throughout the course of their disease. Nearly 40% of patients eventually require surgical intervention.[8] Treatment of the disease is further complicated by extraintestinal manifestations, as well as an increased risk of colorectal cancer (CRC). From a recent meta-analysis it is observed that the incidence rate of CRC in patients with UC was 3 per 1000-person-years compared with 0.6 per 1000-person-years in the general population.[9]

Because of the early onset, the chronic relapsing and remitting course, the likelihood of hospitalization or surgery, and the association with extra-intestinal manifestations, the treatment of UC requires considerable health care resources. When combined with the indirect costs related to lost work productivity and daily activity impairment, the overall costs of UC pose a significant economic burden to society. A variety of studies have attempted to estimate the economic impact of UC, and the range of cost estimates varies widely owing to different populations, time periods, data sources and estimation methods. These variations limit the ability to assess the actual economic burden of UC and thus the potential value of effective treatments. Although systematic reviews have estimated the potential economic impact of Crohn's disease,[10, 11] a comprehensive and critical synthesis of both the direct and indirect costs of UC is yet to be well-researched. We have conducted an updated review of the economic burden of UC in North America and Europe. Our analysis includes costs in subgroups of patients with UC, such as those requiring hospitalization and surgery, and also assesses the impact of disease severity on the cost of treating UC.

METHODS

Literature search

The studies reviewed for this analysis were identified by a systematic and comprehensive computerized search of the literature published in English from January 1970 to October 2009 in Medline, EMBASE and the ISI Web of Science citation database. For costs of UC, search terms included combinations of the following: 'ulcerative colitis' or 'inflammatory bowel disease' and 'cost', 'economics', 'health utilization', 'inpatient', 'hospitalization', 'surgery', 'disease activity', or 'severity'. The search strategy and the specific algorithm were determined based on the characteristics of each database.

During the initial screening, articles were excluded if they were irrelevant to the cost of illness of UC based on the titles and abstracts. If relevance could not be determined adequately from the initial screen, full texts were obtained for further review. In addition, the reference list of each relevant article was reviewed to identify other potential studies. The following inclusion/exclusion criteria were applied to select the final list of articles:

(i) Original, English-language studies with a targeted population in North America or Europe were included;

(ii) Studies reporting only costs for the IBD population as a whole were excluded, except for studies reporting indirect costs because few studies reported UC-specific indirect costs;

(iii) Studies that examined costs associated with a specific treatment (e.g. drug or complementary alternative medicine) were excluded; and

(iv) Cost-effectiveness studies were generally excluded, except for those with comprehensive estimates of medical costs or hospitalization or surgery

rates, from which the results for the standard-of-care group were extracted.

The search identified 32 articles meeting all the inclusion/exclusion criteria, of which 26 focused on costs of UC, five focused on hospitalization/surgery by disease subgroups and one focused on both. Of the 27 cost studies, 18 estimated costs for the general UC population, five described costs by disease activity or disease subgroups only and four included both the costs incurred by patients with UC in general and costs by disease severity.

Summary of the literature

All cost studies estimated one or more of the following cost components: direct medical costs (e.g. in-patient, out-patient, physician consultations, pharmacy, diagnostics and emergency department), in-patient costs (including surgery costs) or indirect costs. Data sources, methods and geographic region varied considerably across studies (Table 1).

Table 1. Characteristics of cost studies included in the review (n = 27)

Characteristics	Number of articles
Costs included	
Total costs (Direct + Indirect)	4
Direct costs*	16
In-patient costs	18
Surgery costs	6
Indirect costs	8
Methods†	
Medical algorithm	3
Claims database	10
Medical records	8
Physician or patient's survey	9
Region	
United States	17
Canada	3
United Kingdom	1
Germany	2
Italy	1
Spain	1
Sweden	1
Europe and Israel	1

* n = 12 excludes the studies focusing on hospitalization costs only and includes one study focusing on out-patient costs.
† Sum does not reflect the total number of studies because some studies used more than one method in their analysis.

The studies also varied by cost-reporting method (i.e. by patient vs. population), length of follow-up and year of cost accounting. To facilitate comparison across studies, we reported annualized costs per patient. We used annual direct costs attributable to UC (i.e. the costs associated with UC-related resource use or the incremental costs incurred by UC patients compared with their matched controls) to calculate the total direct cost incurred by UC patients. If annualized costs per patient were not provided in the original study, the values were derived as accurately as the available information would allow. In addition, if a study only reported charges, the charges were converted to cost via the cost-to-charge ratio.[12] For studies reporting only in-patient or surgery costs, we reported the average cost per admission/surgery. When total medical costs or total costs were included in the original study, in-patient costs or indirect costs were also reported as a percentage of direct medical costs or total costs (i.e. combination of direct medical costs, direct nonmedical costs, if available, and indirect costs).

As the studies spanned a wide time frame, all costs were converted to 2008 dollars or euros, unless otherwise specified. For US studies, costs were adjusted to 2008 dollars using the medical component of the consumer price index from the Bureau of Labor Statistics (or hospital or related services component for hospitalization costs).[13] Canadian cost data were adjusted for inflation using the Bank of Canada inflation calculator. European prices were adjusted using the inflation rate for the Unit Costs of Health and Social Care from the United Kingdom. For one study,[14] costs were converted from lire to euros using the currency conversion factor of 1936 lire per €1 (the conversion factor at the time Italy switched to euros).[15] Unless otherwise specified, all costs were reported as 2008 US dollars or 2008 euros in the results.

Studies on direct medical costs and in-patient costs were given a relevance–reliability (RR) rating based on overall study quality (primarily based on data sources, costs accounting methods, and comprehensiveness of the included cost components), the relevance of the study to the objective of this review and the reliability of the cost estimates. The assessment of RR also took into consideration year of publication, as UC treatment has evolved significantly since the introduction of biologics in the late 1990s. A low RR rating was assigned to studies with significant sampling bias (e.g. only 20 patients from one hospital), those with

substantial limitations in costing method (e.g. missing a major cost component) and those that were published before 1995. In contrast, studies that used objective cost-accounting methods and reliable data sources (e.g. claims data) included comprehensive cost components and were published after 2000 received a high RR rating. Medium RR–rated studies included those that were based on modelling or relied on survey data. If a study reported multiple cost categories, each category was rated independently. For example, a study reporting both direct and in-patient costs would receive a low RR rating for the direct medical costs estimate, if a major cost component was missing and a medium or high RR rating for in-patient costs if the methods and data were reliable. The large variation in the quality of the studies resulted in substantial variability in cost estimates; therefore, our evaluation focused on the estimates from studies with medium or high RR ratings when synthesizing costs across studies.

The RR rating system was not applied to indirect costs because neither the methods nor the cost components in these studies were comparable. For example, some studies used productivity loss from sick leave to estimate indirect costs, whereas others used labour force nonparticipation. Of note, estimates of indirect costs of IBD were also included in the evaluation of indirect costs because estimates of UC-specific indirect costs were scarce. No studies reported indirect costs per patient with UC in the United States; therefore, we derived these values using the cost per patient with IBD and the ratio of indirect costs of Crohn's disease and UC at the population level per the American Gastroenterological Association's (AGA) most recent analysis of disease burden for the year 1998.[16]

RESULTS

Direct medical costs

United States. In the United States, the estimated direct medical costs for UC (4 high RR studies, 2 low RR studies)[17–22] ranged from $3374 to $11 477 per patient per year (Table 2). All four studies that received high RR ratings used claims databases and were published in 2008.[17–20] The estimated annual direct medical costs

Table 2. Direct medical costs of ulcerative colitis

Study	Region	Data source	RR rating*	Original cost estimate in manuscript (per patient per year)		Estimate in 2008 currency
				Point estimate (year of currency)	CI/s.d. estimate	
Hillson *et al.*[17]	United States	Claims database	High	$8328 (2004)	NA	$9976
Gibson *et al.*[18]	United States	Claims database	High	$10 039 (2005)	NA	$11 477
Kappelman *et al.*[19]	United States	Claims database	High	$5066 (2003–2004)	$17 928 (s.d.)	$6217
Bickston *et al.*[20]	United States	Claims database	High	$10 019 (2005)	NA	$11 442
Hay and Hay[21]	United States	Claims database	Low	$4708 (1990)	$11 285 (s.d.)	$10 674
Hay and Hay[22]	United States	Modelling	Low	$1488 (1990)	NA	$3374
Pinchbeck *et al.*[23]†	Canada	Survey	Low	Can $3020 (1985)	NA	Can $4988
Bassi *et al.*[24]‡	United Kingdom	Medical records	High	£1286 (2000–2001) (6-months estimate)	£1018–1757 (CI)	€8949
Stark *et al.*[25]	Germany	Survey	Medium	€418 (2004) (4-weeks period)	€832–1258 (CI)	€10 395
Odes *et al.*[26]	8 European countries, Israel	Survey	Low	€1524 (2004)	€4101 (s.d.)	€2915
Martin *et al.*[13]§	Italy	Medical records	Low	820 000 lire (1981–1982)	NA	€2210

* RR ratings indicate the relevance and reliability of the studies.
† Direct medical costs included only physician costs and in-patient costs.
‡ Information on primary care costs were based on postal survey.
§ Based on a small sample size (N = 20).

(paid by the health plans) from these studies ranged from $6217 to $11 477 per patient per year.[17–20] Hillson *et al.*[17] used a large self-insured employer database to estimated the total medical costs of UC patient at $14 486 in 2004 US dollars, compared with $6158 for matched controls. Gibson *et al.*[18] used MarketScan database and estimated the total medical costs of UC at $15 020 in 2005 US dollars, compared with $4982 for the matched controls. The remaining two high-RR studies, Kappleman *et al.*[19] and Bickston *et al.*,[20] employed the PharMetrics database. While the study by Bickson *et al.* included patients of all ages and the data spanning from 2001 to 2005, the one by Kappleman *et al.* was restricted to patients younger than 65 years in 2003 and 2004. The former estimated the all-cause medical cost of UC at $13 233 per patient per year in 2005 US dollars, representing an incremental cost difference of $10 019 between participants with and without UC claims.[20] The latter estimated the incremental medical cost associated with UC at $5066 in 2003–2004 US dollars.[19]

Although the two studies published by Hay and Hay[21, 22] represent the seminal studies in the determination of the costs of inflammatory bowel diseases, they were given a low RR rating, primarily because the data are outdated. The first study by Hay and Hay[17] also used claims data from a large national insurer (Cigna Corporation) and estimated the total medical cost of UC to be $4708 in 1990 US dollars ($10 674 in 2008 US dollars). As determined by a medical algorithm, the other study by Hay and Hay[18] produced the lowest estimate of direct medical cost of UC ($3374). This medical algorithm was based on the disease course of a hypothetical patient cohort from the point of UC diagnosis through lifetime treatment, cure or remission. Such methods often underestimate the mean costs because they cannot account for patients with extremely high medical costs[21] and may not be consistent with the disease course in real life. The study also reported that the total annual medical costs for patients with UC in the United States were $0.8–1.2 billion, based on the prevalence of UC in 1990. This estimate was greater than the AGA's population-level estimate of $538 million (1998 US dollars) for the year 1998, which was calculated using secondary data from a series of national surveys.[16]

Europe. In Europe, estimates of annual direct medical costs of UC ranged from €2210 to €10 395 per patient (Table 2). Of the four qualifying studies, only the UK study by Bassi *et al.*[24] received a high RR rating. Using data from medical records, this study estimated total direct medical costs at €8949, and this estimate included costs of secondary care from a university hospital and, as a small fraction, primary care costs based on a postal survey. Despite the high RR rating, the study may be subject to sample bias because all patients were selected from a single hospital.

Cost estimates from the two studies that used survey data to estimate utilization (Stark *et al.*[25] and Odes *et al.*[26]) varied substantially. Of all European studies, the cost components in the study by Stark *et al.*[25] were the most complete; nevertheless, the study was given a medium RR rating because of the low participation rate (36.6%) and the sample bias toward non-hospitalized patients with UC. By estimating the costs of IBD and separate costs for Crohn's disease and UC in 8 European countries and Israel, the study by Odes *et al.*[26] represents the most comprehensive effort to estimate the economic burden of IBD in Europe. The study retrospectively collected utilization data for up to 10 years' follow-up via physician-reported survey forms compiled from medical records. When estimating costs, the study used the median price per resource in all nine countries as the unit cost instead of the price schedule in each individual country. This approach cannot reflect the actual costs of UC for each country; thus, a low rating was given to this study.

Direct medical costs by severity of UC

The typical clinical course of UC is characterized by phases of remission and active disease, and disease severity has a substantial impact on resource utilization and, thus, on direct medical costs. Although several UC disease activity indices have been developed to quantify better the disease severity,[27] the existing studies investigating direct medical costs of UC by disease severity were all based on qualitative measures (Table 3). The study by Hilson *et al.*[17] classified UC patients into mild, moderate and severe disease groups. Mild patients received only oral aminosalicylates or topical therapies; moderate patients received additional oral medications and/or biologics; and severe patients required hospitalizations for UC. They found that direct medical costs were more than tripled for severe UC patients compared with either mild and moderate patients ($24 817 vs. $7183 and $7874 respectively). Patients who required surgeries incurred even greater costs. Gibson *et al.* demonstrated that patients with

Table 3. Direct medical costs of ulcerative colitis by disease severity

Study	Region	RR rating*	Disease activity	Cost estimation: Point estimate (year of currency)	Cost estimation: 2008 costs per patient per year
Hillson *et al.*[17]	United States	High	Mild	$5996 (2004) (per year)	$7183
			Moderate	$6573 (2004) (per year)	$7874
			Severe	$20 717 (2004) (per year)	$24 817
Gibson *et al.*[18]	United States	High	Required surgery	$67 433 (2005) (per year)	$77 097
			No surgery	$7840 (2005) (per year)	$8964
Loftus EV *et al.*[28]	United States	High	Post-surgery	$90 455 (2007, 180 days, charge)	$78 140§
Mackowiak[29]	United States	Medium	After 5-ASA failure	$11 500 (2006) (first 6-months)	$25 251§
			After 5-ASA failure and require surgery	$54 404 (2006) (first 6-months)	$119 455
Bassi *et al.*[24]	United Kingdom	High	Quiescent†	£359 (2000–2001) (6-months estimate)	€2540
			Ambulatory with flares	£765 (2000–2001) (6-months estimate)	€5352
			Hospitalized	£8861 (2000–2001) (6-months estimate)	€61 667
Panes *et al.*[30]	Spain	Medium	Moderate to severe	€6740(2004) (12-months)	€12 893
Ebinger *et al.*[31]‡	Germany	Low	Remission	€161 (1997–2000) (per visit)	NA
			Active	€163 (1997–2000) (per visit)	NA
			Strongly active	€144 (1997–2000) (per visit)	NA

* RR ratings indicate the relevance and reliability of the studies.
† Defined as having no change in disease severity or treatment and no requirement for immunosuppressants or specialist consultations.
‡ Only out-patient costs were estimated.
§ May overestimate the total direct costs because the cost for the first 6 months after surgery or 5-ASA failure may be greater than the second half of the year.

surgeries during the year had an average of $77 079 in direct medical costs, which was $68 133 greater than for those without surgeries.[18] Loftus *et al.* estimated a similar direct medical cost for patients who underwent surgeries ($78 140).[28] In a model of treatment process and disease course in patients with UC who failed 5-aminosalcyclic acid (5-ASA) monotherapy, Mackowiak estimated that the per-patient direct medical costs for the first 6 months following 5-ASA failure were $25 251 for the overall sample and $119 455 for patients who required surgery.[29] These results suggest that the specific group of patients who are nonresponsive to traditional therapy and who require hospitalization and surgery are among the most costly UC cases.

European studies indicated similar patterns regarding disease severity and costs. Bassi *et al.*[24] evaluated the medical costs of disease flares in the United Kingdom and found that the direct costs incurred for out-patients with disease flares (€5352) more than doubled those of patients with quiescent disease (€2540) (Table 3). If the disease flare required hospitalization, direct medical costs increased by more than 20-fold (€61 667) compared with the quiescent cases. Another study by Panes *et al.*[30] used a Markov-based medical cost algorithm to estimate the annual direct medical costs for a patient with UC with a moderate to severe flare up in Spain. Their estimate of €12 893 was greater than the annual costs reported for the general UC population in Europe.[13, 24–26]

Bassi *et al.*[24] also evaluated the impact of UC severity using multiple-regression analysis and found that, on average, medical costs increased with worsening disease severity. Compared with patients in remission, medical costs were 1.8-times greater for patients with mild disease activity, 2.5-times greater for patients in a severe but drug-responsive state, 4.1-times greater for patients in a severe drug-dependent

or drug-refractory state and 8.3-times greater for patients in a surgical state. Overall, the top 10% most costly patients accounted for 62% of total direct UC medical costs.[24]

One German study by Ebinger *et al.*[31] (low RR rating) concluded that the costs per out-patient visit (including physician consultation, medical diagnostics, laboratory tests and radiology examinations) were not sensitive to the severity of UC (Table 3). However, the mean number of visits for each severity group was not presented and, thus, the study did not address the possibility that patients with greater disease activity may have had more visits, consequently reducing the average cost per visit compared with other severity groups.

In-patient costs

Annual cost per patient. Studies on in-patient costs were generally consistent in their finding that hospitalization is the single largest driver of direct medical costs in the treatment of UC. In the United States, seven studies[17–22, 32] reported that in-patient services accounted for 41–55% of the total direct medical costs of UC (Table 4). In the 4 studies with high RR ratings, the estimated in-patient costs ranged from $2523 to $6267 per patient per year, overall, for UC patients.[17–20] Sher *et al.*[32] estimated the costs of hospitalizations in 40 patients with severe UC ranged from $5447 to $6412 per patient per year. The study received a low RR rating because it had a very small sample size and the data, which were from 1991 to 1995, are outdated.[32] At the population level, AGA estimated that the total in-patient costs were $309.4 million (1998 US dollars) for the year 1998, accounting for 50% of direct medical costs.[16]

Similar results were found in the four European studies of in-patient costs, all of which received low RR ratings. In-patient costs for UC generally ranged from 32% to 56% of direct medical costs,[13, 26, 30] with the exception of a 9% estimate in one study by Stark *et al.*[25] However, this latter study, as noted by its authors, suffers from substantial selection bias in that

Table 4. In-patient costs of ulcerative colitis: annual costs per patient

Study	Region	RR rating*	Cost estimation		
			Point estimate† (year of currency)	2008 costs per UC patient per year	%‡
Hillson *et al.*[17]	United States	High	$3311 (2004)	$4264	43
Gibson *et al.*[18]	United States	High	$5145 (2005)	$6267	55
Kappelman *et al.*[19]	United States	High	$1906 (2003–2004)	$2523	41
Bickston *et al.*[20]	United States	High	$4805 (2005)	$5855	48
Hay and Hay[21]§	United States	Low	$3511 (1990)	$3330	31
Hay and Hay[22]	United States	Low	$702 (1990)	$1652	47
Sher *et al.*[32]¶	United States	Low	$28 477–38 041 (1996) during follow-up	$5447–$6412**	NA
Pinchbeck *et al.*[23]	Canada	Medium	Can $2070 (1985)	Can $3419	NA
Odes *et al.*[26]	8 European countries and Israel	Low	€689 (2004)	€1319	45
Stark *et al.*[25]	Germany	Low	€37 (2004) for a 4-week period	€920	9
Martin *et al.*[13]	Italy	Low	456 000 lire (1981–1982)	€1229	56
Panes *et al.*[30]††	Spain	Low	€2131 (2004)	€4077	32

* RR ratings indicate the relevance and reliability of the studies.
† Unless otherwise specified, cost is per patient per year.
‡ Percentage of direct medical costs. The percentages were calculated only when all three components (out-patient, in-patient and medications) were included in the study.
§ Costs reported are the amount charged in the claims instead of the amount paid.
¶ Estimated for patients with severe UC.
** Estimated by dividing the mean cost during the follow-up by the mean length of follow-up.
†† Estimated for patients with moderate to severe UC.

postal recruitment was used, which was likely to have missed patients who were hospitalized at the time of survey. The study by Odes *et al.*[26] reported the annual in-patient costs per patient with UC at €920 in 8 European countries and Israel, equivalent to 45% of the direct medical costs. Panes *et al.*[30] estimated the in-patient costs at €4077 per patient per year in Spain, which accounted for 32% of direct medical costs. The study received a low RR rating because it targeted UC patients with moderate and severe disease activity instead of the general UC population. Combining the estimates from other studies, the findings suggest that in-patient costs can increase substantially as disease severity worsens.

Per-admission costs. Estimates of cost per hospital admission were provided by several studies, of which only the studies by Nguyen *et al.*[33] and Bassi *et al.*[24] received high RR ratings. The three studies assessing in-patient costs in the United States used data from the National In-patient Sample (NIS). Nguyen *et al.*[33] examined the trend in UC-related hospitalizations, including hospitalizations with primary diagnoses of UC or UC-related complications, and found that mean hospital cost per admission increased from $10 860 in 1998 to $13 394 in 2004 (both in 2008 US dollars). They estimated that the total costs of hospitalizations attributable to UC and its complications amounted to $1.0 billion for the year 2004.[33] Similar to the studies by Nguyen *et al.*, Milenkovic *et al.*[34] estimated the mean cost per admission at $12 782 for regional enteritis and ulcerative colitis. Using 2003 NIS data, Ananthakrishnan *et al.*[35] reported that mean hospital cost per admission for UC with *Clostridium difficile* was $11 611. The study was given a low RR rating because charges for the general hospitalized patients with UC were not reported.

By reviewing the medical charts of all admissions related to UC (either UC or complications of UC), Bernstein *et al.*[36] estimated the per-admission cost in Canada to be Can $4394. The study further compared medical and surgical hospitalizations, finding that, on average, medical admissions were less costly than surgical admissions ($2926 per medical admission vs. $5269 per surgical admission). However, the authors noted that the study underestimated hospitalization costs because only direct patient care costs were included and nonpatient care costs (e.g. administrative overhead, facility maintenance) were excluded. In Europe, there was only one study from which the per-admission cost can be derived. From the study by Bassi *et al.*,[24] hospitalization cost per admission for UC was €19 449 in the United Kingdom.

Of all hospitalizations, surgeries were generally associated with greater costs than were medical hospitalizations. Three US studies estimated the costs of surgery specifically (Table 5).[37–39] Swenson *et al.*[38] first compared different types of ileal pouch anal anastomosis (IPAA), a surgery used primarily to treat severe ulcerative colitis. Using the hospital's cost-accounting database with specific cost-to-charge ratios, the authors estimated that total in-patient costs for all hospitalizations required for the planned surgery and related complications were $20 090 for 1-stage IPAA, $28 181 for 2-stage IPAA, $43 987 for 2-stage modified IPAA and $51 665 for 3-stage IPAA.[38] Using updated data, the authors subsequently compared the in-patient costs of 2-stage modified IPAA and 3-stage IPAA, finding results very similar to the first study.[37] An earlier study by Archer *et al.*[39] also estimated in-patient costs per surgery in patients with UC who underwent total colectomy and IPAA, estimating the total in-patient cost per surgery to be $16 442. However, this study received a low RR rating because of the small control group (n = 10) and outdated data (from 1997).

Hospitalizations and surgeries by severity. The hospitalization rate in the general UC population ranged from 5% for a 4-week period to 20% for 12 months.[13, 24, 25] The study with a high RR rating (Bassi *et al.*[24]) reported a 12.5% hospitalization rate for a 6-month period. In contrast, a US study reported a 28% hospitalization rate in patients with steroid-refractory UC during the first year after colectomy.[40] Drossman *et al.*[41] directly examined the relationship between symptom severity and hospitalization, finding that a 1-point increase in symptom severity score was associated with a 0.05 increase in the number of hospitalizations during the past 2 years and 0.07 increase in the number of lifetime surgeries. The results were not significant, however, possibly because other variables that were highly correlated with symptom severity (e.g. steroid dosage, the number of stools), were included in the model.[41] From these studies, it is evident that risk of UC-related hospitalization increases substantially as the disease becomes more severe.

Disease severity is associated not only with more hospitalizations but also with a longer length of stay

Table 5. In-patient costs of ulcerative colitis: costs per admission/surgery

Study	Region	RR rating*	Cost estimation	
			Point estimate (year of currency)	2008 cost value
All hospitalizations (per admission)				
Nguyen *et al.*[33]‡**	United States	High	$22 107–27 265 (2005, charge)	$10 860–$13 394
Milenkovic *et al.*[34]†**	United States	Low	$9200 (2004)	$12 782
Ananthakrishnan *et al.*[35]‡§**	United States	Low	$21 236 (2003, charge)	$11 661
Bernstein *et al.*[36]	Canada	Medium	Can $3726 (1995)	Can $4394
Bassi *et al.*[24]	United Kingdom	High	£5589 (2000–2001)††	€19 449
Surgical hospitalizations (per surgery)¶				
Swenson *et al.*[37]**	United States	Medium	$27 270–38 184 (2002)	$39 665–$55 541
Swenson *et al.*[38]**	United States	Medium	$12 738–32 758 (2001)	$20 090–$51 665
Archer *et al.*[39]‡**	United States	Low	$21 650 (1997, charge)	$16 442

* RR ratings indicate the relevance and reliability of the studies.
† Estimated for patients with UC and regional enteritis.
‡ Hospital charges were used.
§ Estimated for patients with UC with *Clostridium difficile*.
¶ Per-surgery costs were the sum of the costs for all planned surgical hospitalizations to complete the required surgery.
** Cost-to-charge ratios were used.
†† Based on the number of admissions per patient and percentage of total costs caused by hospitalizations reported in the article.

(LOS) for each admission. In the United States, the mean LOS for all hospitalized patients with UC was 6.1–7.2 days,[15, 33, 34] whereas, in severe UC, the LOS increased to an average of 20.5 days.[32] More directly, a study of 18 patients with moderate to severe UC in Italy reported that total hospitalization days decreased from 93 to 0 days when disease activity was reduced to remission or a mildly active state.[42]

Among all hospitalizations, the percentage of surgical hospitalizations varies substantially from country to country. Nguyen *et al.*[33] provided the rate of UC hospitalization and colectomy as 10.8 and 1.2 per 100 000 persons in the United States respectively, making 11.1% of UC hospitalizations attributable to colectomy. Bassi *et al.*[24] reported that 20% of hospitalizations involved surgery in the United Kingdom. In Canada, Bernstein *et al.*[36] reported that surgical hospitalizations accounted for 52% of the total hospitalizations for UC, a rate much greater than estimated for other countries. Regardless of the proportion, on average, surgeries consumed more resources than medical hospitalizations. Bernstein *et al.*[36] reported that the mean LOS for medical hospitalizations was 8.6 days, compared with 13.5 days for surgical hospitalizations. Similarly, Swenson *et al.*[37, 38] estimated that the average total LOS was 13.5 days for a 1-stage IPAA and 24–26 days for a 3-stage IPAA.

The percentage of patients with UC requiring surgery during their lifetime is strikingly high. One study in the United States estimated that the cumulative surgery rates (colectomy or ileostomy) in patients with UC were 24%, 34% and 44% respectively at 5, 10 and 20 years.[8] A Swedish study reported similar results, with the cumulative colectomy rates being 20%, 28% and 45% respectively at 5, 10 and 25 years.[43] Both studies included more than 1000 patients with UC, with an average follow-up period of 13 years.[8, 43] These two studies also found that surgery rate was associated with the extent of disease at diagnosis, and surgery rates were the greatest for patients initially diagnosed with pancolitis and the lowest in those with proctitis. The 10-year cumulative rates of surgery were 42–55% for patients with pancolitis and 12–21% for patients with proctitis.

Indirect costs

From a societal perspective, indirect costs consist of three major components: absence from paid work, including sick leave, early retirement and reduced employment (absenteeism); reduced productivity of

paid work (presenteeism); and reduced opportunities for unpaid activities (loss of leisure).[33] All of the studies presented here focused on costs associated with absenteeism; however, few estimated indirect costs result from early retirement and unemployment (two major and essential components in absenteeism). Presenteeism and loss of leisure are difficult to measure, and none of the identified studies included estimates for these components. In addition, only three of seven studies provided UC-specific indirect costs.

United States and Canada. Of the four studies reporting indirect costs in the United States,[15, 18, 21, 44] the study by Gibson *et al.*[18] and the AGA study[16] estimated UC-specific indirect costs (Table 6). Gibson *et al.*[18] estimated annual indirect costs of $8469 based on missing work days arising from absenteeism and short-term disability identified in employees' work records. The AGA estimated that indirect costs amounted to $50 million or 9% of the total costs of UC.[16] However, the study substantially underestimated the indirect costs because it only considered time spent in seeking health care (e.g. out-patient visits, emergency department visits and hospitalizations) and failed to include other major components (i.e. sick leave, early retirement, unemployment or disease-related underemployment).[16] Hay and Hay[21] provided a rough estimate of indirect costs of IBD, assuming 5–10% work disability in this patient group. The $0.8–1.6 billion in indirect costs, accounting for 15–44% of total costs of IBD, yielded an estimate of $1832–4580 per patient per year. Using regression analyses of national survey data in the United States, Longobardi *et al.*[44] estimated that a patient with IBD, on average, incurred $7970 annually in indirect costs resulting from labour force nonparticipation. The analysis is likely to have underestimated the indirect costs of UC because the study omitted productivity losses caused by sick leave, early retirement and unpaid employment.[44] The same authors also estimated indirect costs of IBD and similar bowel disorders at Can $1434 per patient per year in Canada.[45] In addition to the limitations mentioned for the US study, the Canadian study is also biased by the inclusion of chronic bowel disorders other than IBD in approximately half of the cases.[45]

Europe. In Europe, two studies estimated UC-specific indirect costs and one estimated the indirect costs of IBD as a whole. Stark *et al.*[25] measured productivity losses from short-term disability (sick leave and medical care) and long-term disability to estimate indirect costs of UC at €13 677 per patient per year. Bassi *et al.*[24] reported that 32% of employed patients with UC had loss of 'employment days' during a 6-month study, with the median annual indirect costs per patient amounting to €533. Blomqvist and Ekbom[46] evaluated productivity loss caused by sick leave, early retirement and death to estimate the indirect costs of IBD at $2248 per patient per year in Sweden. Excluding the study by Bassi *et al.*,[24] which considerably underestimated the actual indirect costs because labour force nonparticipation was omitted, indirect costs accounted for more than half of the total costs of UC or IBD in Europe (Table 6).[25, 46]

Total costs of UC

United States and Canada. In the United States, the annual total costs of UC per patient was $14 686 to $19 946, of which indirect costs accounted for approximately one-third of the total costs (Table 7). This estimate was derived from the direct medical costs and indirect costs reported by studies with high RR ratings.[18, 19] Furthermore, based on recently published prevalence rates of UC,[3, 4] the study estimated that 550 000–748 000 people are affected by UC in the United States. Therefore, the economic burden of UC was estimated to be $8.1–14.9 billion, of which $3.4–8.6 billion was direct medical costs.

Europe. Similar methods were applied to estimate the total costs of UC in the European Union (Table 8).[4, 24, 25, 48] Direct medical costs from the studies with medium-to-high RR ratings[24, 25] and indirect-to-direct medical costs ratios were derived from the studies by Stark *et al.*[25] The annual total costs per patient with UC ranged from €20 724 to €24 073, of which more than half was attributable to indirect costs. Based on the recently published prevalence rates,[4] the UC population in Europe was 603 000–1 210 000. Therefore, the economic burden in the European Union amounted to €12.5–29.1 billion, of which €5.4–12.6 billion was direct medical costs.

The United States and the European Union have very different policies regarding coverage for patients with disabilities, which may explain the difference in the percentages of indirect costs between these regions. Furthermore, the greater percentage of indirect costs in the European studies may reflect the inclusion of productivity losses caused by early retirement

Table 6. Indirect costs of ulcerative colitis

Study	Region	Relevance	Costs included	Cost estimation		
				One-year cost estimate (year of currency)	2008 cost per patient per year	%*
Gibson *et al.*[18]	United States	UC	Absenteeism and short-term disability	$7407 (2005)	$8469	33
Longobardi *et al.*[44]	United States	IBD	Labour-force nonparticipation	$5228 (1998) per patient	$7970	NA
AGA[15]	United States	UC	Loss of productivity resulting from medical care	$35.8 million (1998)	NA	9
Hay and Hay[21]	United States	IBD	Loss of productivity	$0.4–0.8 billion (1990)	$1832–$4580†	15–44‡
Longobardi *et al.*[45]	Canada	IBD and other similar bowel disorders	Labour-force nonparticipation	Can $868 (1998) per patient	Can$1434	NA
Bassi *et al.*[24]	United Kingdom	UC	Loss of productivity from work among employed patients	£239 median (2000), 6 months§	€533 (median)¶	5
Stark *et al.*[25]	Germany	UC	Loss of productivity resulting from sick leave, long-term disability, and medical care	€550 (2004) per patient, for a 4-week period	€13 677	54
Blomqvist & Ekbom[46]	Sweden	IBD	Loss of productivity caused by sick leave, early retirement, and death	$58.4 million (1994)	$2248†	68‡

* Percentage of total costs reported in study.
† Estimated using total costs and prevalence reported in the study.
‡ Percentage of total IBD costs.
§ Among employed patients who reported loss of employment days.
¶ Estimated using the reported median and percentage of patients with UC who had loss of employment days.

Table 7. Calculating total costs of UC in the United States (2008)

	Low estimate	High estimate	Source
(a) US population (in millions)	304	304	US Census[47]
(b) UC prevalence (per 100 000)	181	246	Kappelman *et al.*,[3*] Loftus[4]
(c) UC population (in 1000)	550	748	a × b
(d) Direct medical costs ($ per patient per year)	6217	11 477	Kappelman *et al.*[19], Gibson *et al.*[18]
(e) Indirect costs ($ per patient per year)	8469	8469	Gibson *et al.*[18]
(f) Total costs ($ per patient per year)	14 686	19 946	d + e
Total direct medical costs of UC (2008 $ billion)	3.4	8.6	c × d
Total costs of UC (2008 $ billion)	8.1	14.9	c × f

* Kappelman *et al.* reported the prevalence in paediatric and adult populations separately. The prevalence for the whole population was estimated using the 2008 population estimates in the respective age group.

Table 8. Calculating total costs of UC in the European Union (2008)

	Low estimate	High estimate	Source
(a) EU population (in millions)	498	498	Eurostat[48]
(b) UC prevalence (per 100 000)	121	243	Loftus[4]
(c) UC population (in 1000)	603	1210	a × b
(d) Direct medical costs (€ per patient per year)	8949	10 395	Bassi *et al.*[24], Stark *et al.*[25]
(e) Indirect costs to direct medical costs ratio	1.3	1.3	Stark *et al*[25]
(f) Indirect costs (€ per patient per year)	11 775	13 677	d × e
(j) Total costs (€ per patient per year)	20 724	24 072	d + e
Total direct medical costs of UC (2008 € billion)	5.4	12.6	c × d
Total costs of UC (2008 € billion)	12.5	29.1	c × f

and sick leave in addition to labour force nonparticipation.

DISCUSSION

Multiple studies have shown that UC is a costly disease. The medical costs and resources associated with UC are 3–4 times greater than the population average.[18–20] Yet, without a comprehensive and systematic review, the actual economic burden associated with the disease remained unclear. On the basis of the most reliable studies available, we critically evaluated the existing literature on the costs of UC in North America and Europe to provide a current and comprehensive analysis of the economic burden of the disease. Cost of illness literature based on claims analysis showed that, at the patient level, the total direct medical cost incurred by UC patients was comparable to that incurred by patients with rheumatoid arthritis (RA) ($9754 to $17 353 per patient per year for UC vs. $12 520 to $15 529 per patient per year for RA,[49] all in 2008 US dollars). Of the common gastrointestinal (GI) diseases, inflammatory bowel disease (UC and CD) incurred the greatest direct medical costs per patient compared with other types of GI diseases – 65% greater than for patients with irritable bowel syndrome and 41% greater than for patients with gastro-oesophageal reflux disease.[50]

As expected, costs of UC vary considerably between countries. This result most likely reflects differences in health care financing and delivery systems, as well as the methodologies used in the studies that estimated these costs. Despite the variations in the estimates, some findings were quite consistent across studies. Hospitalizations were the primary cost driver of direct medical costs, accounting for 41–60% of the total direct costs.[17–22] Medication costs, on the other hand, accounted for no more than a quarter of total direct medical costs.[20, 21, 24] Another common finding is that the cost distribution was highly skewed, with the few most costly patients with UC consuming the bulk of medical care resources.[21, 24] For example, the top 2%

patients in the Hay and Hay[21] study accounted for approximately 30% of UC-related costs and the top 10% of the patients with UC in the Bassi *et al.*[24] study incurred 62% of the total costs.

With respect to the impact of disease severity, our review found that, on average, patients with UC with moderate to severe disease activity or patients who were nonresponsive to traditional therapy incurred consistently greater direct medical costs[29, 30] compared with the general UC population. In the study that provided direct evidence of an association between medical costs and disease severity, patients with severe disease incurred 2.5–to 4.1-times greater direct medical costs than those in remission; if surgery was needed, the medical costs were 8.3-times greater.[24] Likewise, the rates of hospitalization and surgery, as well as the length of hospital stay, are much greater in patients with UC with severe or more extensive disease and, thus, are significant drivers of direct medical costs.[8, 15, 33, 34, 40, 43] In the United States, the rate of hospitalization has been increasing at 3% annually from 1998 to 2004.[33] In the absence of novel treatments for UC, direct medical costs of UC are likely to continue to increase.

Compared with direct costs, it is more challenging to synthesize data regarding indirect costs of UC and there are fewer studies addressing this issue. In this review, the estimate of indirect costs related to UC, including absenteeism and short-term disability, in the United States was $8469.[18] In Europe, the estimate was based on the indirect-to-direct costs ratio reported by the most accurate studies available.[25] From these studies, indirect costs account for approximately one-third of the total costs of UC in the United States and more than half in Europe. In some cases, indirect costs constitute a greater portion of the economic burden of UC than do direct costs. Moreover, the studies on indirect costs have substantially underestimated the true cost burden because none of the studies captured all relevant components of indirect costs, particularly the costs associated with presenteeism and loss of leisure time. Other studies have investigated the negative impact of UC or IBD on education and employment without giving cost estimates.[51, 52] For an accurate estimation of indirect costs, the effects of UC on individuals' career prospects and long-term earning potentials also need to be considered.

Overall, results of our systematic review suggest that the treatments most likely to reduce economic burden of UC are those that can reduce disease severity and decrease the rates of UC-related hospitalization and surgery. Nonetheless, it will be difficult to evaluate accurately the economic benefit of such treatments without new studies that provide precise, robust, and reliable cost estimates across a range of quantifiable disease severity measures (i.e. using the indices used in clinical trials). As indirect costs are a major component of the economic burden of UC, specific surveys should be conducted to assess comprehensively the indirect costs associated with UC.

We used the best evidence available in the existing literature to quantify the economic impact of UC in North America and Europe; however, estimates of costs of UC are only as good as the studies from which they were derived. Limitations such as substantial variation in data sources, patient samples, cost components assessed and accounting methods should be considered in interpreting our findings. Even studies with high RR ratings were subject to flaws that may have biased their estimates. For example, the use of claims-based databases omits the out-of-pocket costs borne by the majority of patients with UC. This limitation is illustrated in the study by Hay and Hay,[21] in which they found the ratio of Crohn's disease to UC was 5:1 in the claims database in contrast to a 1:1 ratio in the population-based epidemiological studies. In addition, by excluding languages other than English, this review is less comprehensive for the European countries than for North America. Lastly, this review could not compare each cost component across countries (e.g. out-patient costs, emergency visits etc.) because the studies varied with respect to the cost components assessed and research methodology. Moreover, the current literature only estimated the cost of UC at a certain time. The economic burden can also be assessed using the incidence approach to estimate lifetime cost associated with UC. Such an approach is especially important given the early onset of UC. Future studies could improve our understanding of the economic burden of the disease by including lifetime cost.

In summary, this systematic review of the costs of UC in the United States and other Western countries suggests that UC is a costly disease. Overall, health care systems bear $3.4–$8.6 billion in direct medical costs for UC in the United States and €5.4–12.6 billion in the European Union. Annual per-patient direct medical costs were the greatest in Germany

(€10 395)[25] followed by the United Kingdom (€8949)[24] and the United States ($6217–$11 477).[17–20] Hospitalization costs represent the primary driver of direct medical costs. The annual indirect costs per patient were estimated at $8469 in the United States and €11 775–€13 677 in Europe. Indirect costs from loss of productivity are a major component of total costs of UC and may exceed the direct medical costs in some countries. Based on the recently published prevalence rates of UC, the total economic burden of the disease is estimated at $8.1–14.9 billion in the United States and €12.5–29.1 billion in Europe (in 2008 values).

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