Costs and Resource Utilization for Diagnosis and Treatment During the Initial Year in a European Inflammatory Bowel Disease Inception Cohort: An ECCO-EpiCom Study

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Background: No direct comparison of health care cost in patients with inflammatory bowel disease across the European continent exists. The aim of this study was to assess the costs of investigations and treatment for diagnostics and during the first year after diagnosis in Europe.

Methods: The EpiCom cohort is a prospective population-based inception cohort of unselected inflammatory bowel disease patients from 31 Western and Eastern European centers. Patients were followed every third month from diagnosis, and clinical data regarding treatment and investigations were collected. Costs were calculated in euros (€) using the Danish Health Costs Register.

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Results: One thousand three hundred sixty-seven patients were followed, 710 with ulcerative colitis, 509 with Crohn's disease, and 148 with inflammatory bowel disease unclassified. Total expenditure for the cohort was €5,408,174 (investigations: €2,042,990 [38%], surgery: €1,427,648 [26%], biologicals: €781,089 [14%], and standard treatment: €1,156,520 [22%]). Mean crude expenditure per patient in Western Europe (Eastern Europe) with Crohn's disease: investigations €1803 (€2160) ($P = 0.44$), surgery €11,489 (€13,973) ($P = 0.14$), standard treatment €1027 (€824) ($P = 0.51$), and biologicals €7376 (€8307) ($P = 0.31$). Mean crude expenditure per patient in Western Europe (Eastern Europe) with ulcerative colitis: investigations €1189 (€1518) ($P < 0.01$), surgery €18,414 (€12,395) ($P = 0.18$), standard treatment €896 (€798) ($P < 0.05$), and biologicals €5681 (€72) ($P = 0.51$).

Conclusions: In this population-based unselected cohort, costs during the first year of disease were mainly incurred by investigative procedures and surgeries. However, biologicals accounted for >15% of costs. Long-term follow-up of the cohort is needed to assess the cost-effectiveness of biological agents.

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Key Words: epidemiology, outcomes research, Crohn's disease, ulcerative colitis, economics of IBD therapies

Inflammatory bowel disease (IBD) is associated with a high economic burden[1–6] but estimates of resource utilization and charges are difficult to compare due to the large differences in the health care policies between countries and differences in methodology between studies.[7] Specific cost data for IBD care are available for several Western European countries, including the European Collaborative Study Group on Inflammatory Bowel Disease,[8] which collected data from the first European population-based inception cohort, but those available largely represented the era preceding the advent of widespread biological therapy.[5] Data are lacking for Eastern Europe. Before the introduction of biological therapy in IBD care, costs were mainly driven by surgery and hospitalizations,[3] but recent studies indicate that this cost profile has changed and health care costs are now mainly driven by use of biological agents.[9] Growing constraints on health care costs demand up-to-date and accurate information regarding the cost of IBD care for decision makers. Therefore, unselected population-based cohort studies are needed to describe the health care costs in the general IBD population within the biological era.

The EpiCom cohort is a prospective population-based inception cohort of unselected IBD patients diagnosed in 31 centers in Europe. The aim of the collaboration was to investigate the occurrence and disease course of IBD, including Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBDU), in Europe.[1] Recently, we have reported on the European 2-to-1 West-East gradient in the incidence of IBD[10] and the unchanged initial disease course compared with the prebiological era, despite an earlier and more frequent use of biological agents and immunomodulating therapy.[11] The aim of this study was to determine the cost structure for establishing the diagnosis and within the first year after diagnosis in the EpiCom cohort across Europe.

METHODS

Study Centers and Cohort

The present cohort was derived from 31 centers from 14 Western and 8 Eastern European countries, covering a total background population of approximately 10.1 million people (6.8 million from Western and 3.3 million from Eastern Europe) and included a total number of incident 1560 adult and pediatric-onset IBD patients.[10] Patients were diagnosed with CD, UC, or IBDU according to the Copenhagen Diagnostic Criteria.[1,12,13] Israel was grouped with the Western European countries for the purpose of this research. A well-defined primary catchment area with up-to-date population data including age and gender distribution was a prerequisite for participation. Similarly, participation required an established network of gastroenterologists, colorectal surgeons, and general practitioners within the uptake area, who were contacted twice during the inclusion period, and identification of possible IBD clinics outside the uptake area to ensure complete coverage and inclusion of all patients diagnosed in 2010 and living in the predefined uptake areas. Ten centers (32%) reported having organized population-based cohorts before. Patients in the EpiCom cohort were followed prospectively at least every third month from diagnosis and throughout a follow-up period of 12 months. Online entry of the patient details in the web-based EpiCom database[14] allowed for ongoing data cleansing and immediate feedback to the investigators, thus ensuring accurate recording of the epidemiological, clinical, and cost data. Audit visits and built-in data control in the database guaranteed project protocol adherence and extensive training of participating physicians and nurses in methodology before and during the study period at the biannual EpiCom cohort meetings.[1]

Twenty-eight of the original 31 centers participated in this study (Table 1). One center from Eastern Europe only included pediatric-onset IBD patients, whereas 2 centers from Western Europe chose not to participate in the follow-up of the cohort. Of the 19 Western European centers, 13 were located in the northern and 6 in the southern part of Western Europe. Regarding the 9 Eastern European centers, the numbers were 4 and 5, respectively. Cases from age 15 years and older (no upper limit) were included in this study.

Resources

Resource utilization was assessed using the Danish Health Costs Register (diagnosis-related group)[15] representing the mean costs for hospital and outpatient procedures in Denmark and as the prices for medicine in the capital region of Denmark.[16] Because prices for medication were only available for the year

TABLE 1. List of Participating Centers in the Cost and Resource Utilization Analysis of a European Inception Cohort

	No. Patients	Type of Center	Catchment Area	Country Population
Western European centers				
Cyprus, Nicosia	27	Non-University	240,190	1,117,000
Denmark, Aarhus	55	University	259,739	5,573,000
Denmark, Amager	23	Non-University	133,939	5,573,000
Denmark, Funen	123	University	400,575	5,573,000
Denmark, Herlev	48	University	214,431	5,573,000
Denmark, Herning	49	Non-University	231,060	5,573,000
Denmark, Viborg	37	Non-University	150,370	5,573,000
Faroe Islands, nationwide	31	Non-University	38,053	49,000
Finland, Pirkanmaa	107	University	408,235	5,385,000
Greece, Ioanninia	15	University	162,955	11,390,000
Greenland, nationwide	9	Non-University	37,466	57,728
Ireland, Adelaide, and Meath	36	University	272,892	4,526,000
Israel, Beer Sheva	51	University	385,222	7,562,000
Italy, Northern Italy[a]	182	University/Non-university	1,674,798	60,789,000
Portugal, Vale de Sousa	31	University	278,722	10,690,000
Spain, Vigo	102	University	498,880	46,455,000
Sweden, Linköping	55	University	143,473	9,441,000
Sweden, Örebro	39	University	147,395	9,441,000
UK, Hull and East Yorkshire	91	University	502,900	62,417,000
Eastern European centers				
Croatia, Zagreb	12	University	190,558	4,396,000
Czech Republic, Prague	22	University	180,858	10,534,000
Czech Republic, South Bohemia	42	Non-University	545,786	10,534,000
Estonia, Southern Estonia	30	University	291,091	1,341,000
Hungary, Veszprem province	58	University	252,461	9,966,000
Lithuania, Kaunas	32	University	374,595	3,307,000
Moldova, Chisinau	10	University	232,597	3,545,000
Romania, Timis	24	University	581,850	21,346,000
Russia, Moscow	26	University	510,083	142,836,000

[a]The Italian centre consisted of 5 regions: Padua, Florence, Cremona and Crema, Forlì, and Reggio Emilia.

2013 and because price differences compared with 2010 were deemed to have no significant effect on the overall comparison, the diagnosis-related group charges for 2013 were used. Prices were converted from Danish Krone to Euro.[17] Indirect costs of IBD patients (transport costs, loss of study or work time, etc.) were not recorded.

Resource utilization referred to hospital and ambulatory procedures and therapies directly related to IBD as reported[5] and were grouped into 4 categories: investigations, standard medical treatment (excluding biologicals), biological therapy, and surgery. Investigations included both procedures performed to establish the IBD diagnosis and procedures performed during follow-up and comprised the full range of upper gastrointestinal endoscopy, colonoscopy, sigmoidoscopy, enteroscopy, and capsule endoscopy, and multiple radiological examinations, including ultrasound, barium studies, computerized tomography, and magnetic resonance imaging (MRI and magnetic resonance elastography). The term "standard medication" included medical treatment as follows: 5-aminosalicylates (5-ASA, oral and topical), corticosteroids (systemic/oral, locally acting steroids, and budesonide), and immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate). There was a separate category for biological therapy (infliximab or adalimumab; other biologicals were not used); costs for in-hospital administration of infliximab were incorporated. Surgical treatment was defined as any surgery due to IBD at diagnosis or within the first year after diagnosis; costs for hospitalization and pathology were included. All medical and surgical treatment initiated at initial presentation and while establishing the diagnosis were

TABLE 2. Demographic Characteristics of Incident Patients with Inflammatory Bowel Disease (aged 15–89 years) Recruited in 2010

	Western European Centers			Eastern European Centers		
	CD	UC	IBDU	CD	UC	IBDU
No. patients	405 (37%)	562 (51%)	142 (13%)	104 (40%)	148 (57%)	6 (2%)
Male	209 (52%)	325 (58%)	70 (49%)	61 (59%)	84 (57%)	4 (67%)
Female	196 (48%)	237 (42%)	72 (51%)	43 (41%)	64 (43%)	2 (33%)
Age at diagnosis, yr	35 (16–89)	40 (15–89)	38 (16–84)	32 (15–78)	37 (15–81)	30 (20–34)
Median time to diagnosis, mo	4.6 (0–31 yr)	2.5 (0–21 yr)	2.3 (0–30 yr)	3.4 (0–10 yr)	2.3 (0–20 yr)	2.7 (0–3 yr)
Never smoker	165 (43%)	279 (56%)	65 (52%)	38 (37%)	79 (54%)	4 (67%)
Current smoker	137 (35%)	47 (9%)	19 (15%)	39 (38%)	16 (11%)	2 (33%)
Former smoker	85 (22%)	174 (35%)	41 (33%)	25 (25%)	52 (35%)	0 (0%)
Disease extent						
E1: Proctitis		118 (21%)			32 (22%)	
E2: Left-sided		225 (41%)			67 (45%)	
E3: Extensive colitis		210 (38%)			49 (33%)	
Disease location						
L1: Terminal ileum	118 (30%)			40 (39%)		
L2: Colon	112 (28%)			20 (20%)		
L3: Terminal ileum + colon	87 (22%)			25 (25%)		
L4: Upper GI	30 (8%)			2 (2%)		
L1 + L4	23 (6%)			5 (5%)		
L2 + L4	11 (3%)			3 (3%)		
L3 + L4	18 (5%)			7 (7%)		
Disease behavior						
B1: nonstricturing, nonpenetrating	259 (64%)			70 (67%)		
B2: stricturing	79 (20%)			20 (19%)		
B3: penetrating	29 (7%)			6 (6%)		
B1p: B1 + perianal	16 (4%)			1 (1%)		
B2p: B2 + perianal	3 (1%)			0 (0%)		
B3p: B3 + perianal	19 (5%)			7 (7%)		
Highest level of treatment during follow-up						
No treatment	17 (4%)[a]	40 (7%)[a]	8 (6%)	1 (1%)	2 (1%)	0 (0%)
5-ASA	55 (14%)[a]	251 (45%)[a]	70 (49%)	29 (28%)	92 (62%)	4 (67%)
GCS	78 (19%)[a]	141 (25%)[a]	36 (25%)	24 (23%)	34 (23%)	1 (17%)
Immunomodulators	119 (29%)[a]	87 (15%)[a]	12 (8%)	32 (31%)	17 (11%)	1 (17%)
Biological therapy	71 (18%)[a]	23 (4%)[a]	11 (8%)	6 (6%)	1 (1%)	0 (0%)
Surgery	65 (16%)[a]	20 (4%)[a]	5 (4%)	12 (12%)	2 (1%)	0 (0%)

[a]Differences between geographic regions $P < 0.05$.
GI, gastrointestinal.

included in the calculations costs during the initial year after diagnosis. Antibiotics, nutritional supplements and iron preparation and supplementary preparations were documented but excluded from the analysis. Similarly, various stool and blood tests were omitted from the calculations. Excluded items had little impact on the overall cost of treatment.

Statistical Methods

Statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC). The cost of each resource was computed for each patient by multiplying the price of that resource by the quantity of resource used during follow-up. Results are given rounded to the nearest whole euro. Prices for biologicals and surgical procedures converted to costs per day. Predictors of total costs and costs for the different categories of medical and surgical treatment were analyzed using a multilevel regression model. The independent variables were age at diagnosis as a continuous variable, gender, diagnostic delay, type of diagnosis, geographic region, disease classification (behavior and location for CD, disease extent for UC), whereas the

participating centers were included as random effect. A P value of <0.05 was considered statistically significant.

Ethical Considerations

The study was approved by the local ethics committees according to local regulations.

RESULTS

Cohort Characteristics

A total of 1367 patients with IBD from the 28 participating centers were incorporated in this cost study. Data from time of diagnosis and until 12 months of follow-up were included in this study. Of the 1367 patients, 1109 cases (81%) were from Western Europe and 258 (19%) from Eastern Europe (Table 2). UC was the most common (710 cases, 52%), followed by CD (509 cases, 37%), and IBDU (148 cases, 11%). IBDU was detected in only 6 patients (0.4% of the total) in Eastern Europe. The patients' demographic characteristics and disease classification (using the Montreal Classification) did not differ statistically between the Western and Eastern European centers. However, regional differences in the highest treatment choices during follow-up were observed, including higher rates of biological therapy in Western Europe (Table 2). A subset of 148 (11%) patients had no follow-up after diagnosis, 3 because of death and 15 because they moved away from the uptake area. The remaining 130 patients gave no consent and came from countries where follow-up in that case was not allowed.

Resource Consumption and Cost

Treatment choices regarding medical and surgical (resections and/or colectomy only) therapy for the EpiCom cohort are illustrated in Figure 1. Patients on combination therapy were categorized in the highest hierarchic treatment step of the used treatment according to the conventional "step-up" strategy. The majority of patients with UC were treated with 5-ASA, whereas most patients with CD received treatment with immunomodulators and/or biologicals at some point during the follow-up period. The total expenditure on the 1367 patients in the cohort was €5,408,174 in the first year after diagnosis with €2,042,990 (38%) spent on investigations, €1,156,520 (21%) on standard medication, €781,017 (15%) on biologicals, and €1,427,648 (26%) on surgery. Total costs for all patients with CD were €2,523,939 in Western Europe and €500,470 in Eastern Europe. For UC, these amounts were €1,590,162 and €364,680, respectively. The outlays for IBDU were €418,043 and €10,881, respectively. Total expenditures and proportion of these used on the various categories are shown in Table 3 and Figure 2. The distribution of cumulative expenses regarding treatment choices and investigations for CD and UC patients overall during the first year from diagnosis is shown in Figures 3 and 4.

The total per patient cost for the initial year after diagnosis was €5942 for CD, €2753 for UC, and €2898 for IBDU patients. The observed costs of resource utilizations per patient are shown in Table 4. Predictors of total expenses and for the different groups of costs after 1 year of follow-up are shown in Tables 5 and 6. Given the smaller number of cases in Eastern Europe, it is remarkable that those countries too had considerable outlays in investigating and treating their patients with IBD in the first year of disease. This was particularly notable for diagnostic procedures in UC (upper gastrointestinal endoscopy, colonoscopy, and bowel x-ray), and the difference between Eastern and Western Europe regarding diagnostics in UC was found to be statistically significant. Median number of days to first treatment was for 5-ASA 0 days (range, 0–365 d) in Western Europe and 0 days (range, 0–333 d) in Eastern Europe; for glucocorticosteroids, 1 day (range, 0–365 d) and 1 day (range, 0–329 d); for immunomodulators, 90

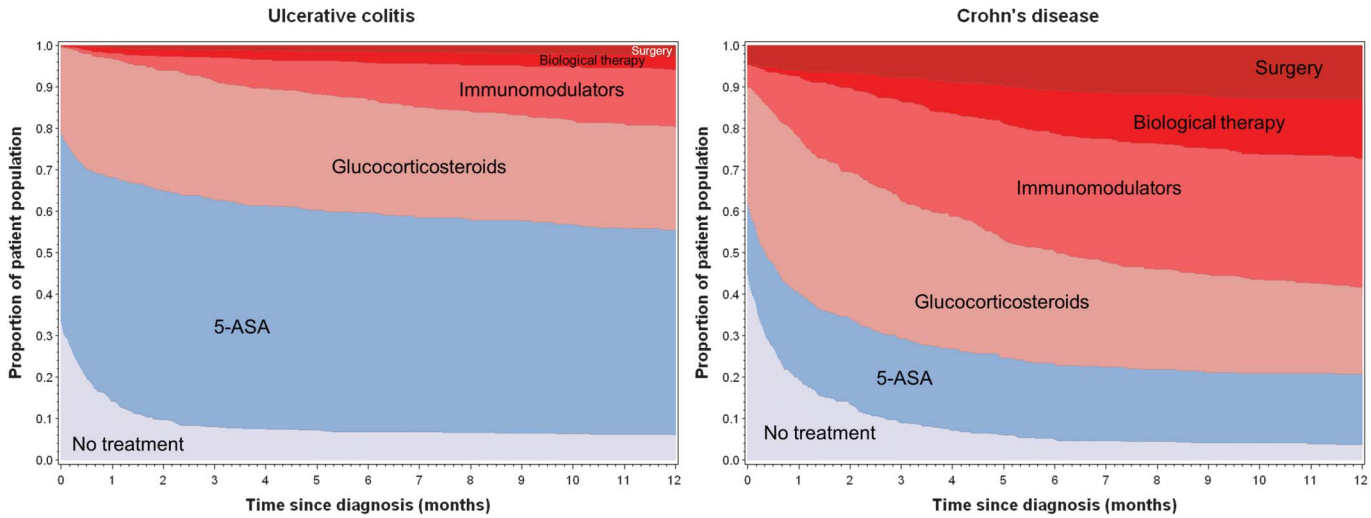

FIGURE 1. Distribution of UC and CD patients within the highest treatment steps during the first year of disease in Western and Eastern Europe combined.

TABLE 3. Total Cost (in euros) for Resources Used in the First Year of Follow-up of 1367 Patients with IBD

	CD			UC			IBDU		
	All	West	East	All	West	East	All	West	East
Investigations	945,264 (31%)	724,922 (29%)	220,342 (44%)	885,819 (45%)	661,163 (42%)	224,656 (62%)	211,907 (49%)	204,526 (49%)	7381 (68%)
5-ASA	166,873 (6%)	108,449 (4%)	58,424 (12%)	521,210 (27%)	417,574 (26%)	103,636 (28%)	86,381 (20%)	83,112 (20%)	3269 (30%)
Glucocorticosteroids	259,071 (9%)	236,400 (9%)	22,671 (5%)	20,334 (1%)	14,855 (1%)	5479 (2%)	16,581 (4%)	16,418 (4%)	163 (2%)
Immunomodulators	43,085 (1%)	39,285 (2%)	3801 (1%)	36,177 (2%)	30,131 (2%)	6045 (2%)	6807 (2%)	6740 (2%)	68 (1%)
Biologicals	594,731 (20%)	553,198 (22%)	41,533 (8%)	153,471 (8%)	153,399 (10%)	72 (0%)	32,815 (8%)	32,815 (8%)	0 (0%)
Surgery	1,015,384 (34%)	861,686 (34%)	153,699 (31%)	337,831 (17%)	313,040 (20%)	24,791 (7%)	74,432 (17%)	74,432 (18%)	0 (0%)
Total	3,024,409	2,523,939	500,470	1,954,842	1,590,162	364,680	428,924	418,043	10,881

days (range, 0–365 d) and 68 days (range, 0–365 d); and for biologicals 108 days (range, 0–362 d) and 165 days (range, 37–363 d), respectively.

Biological therapy accounted for 10% of UC, 22% of CD, and 8% of IBDU expenditure in Western Europe and 0% of UC, 8% of CD, and 0% of IBDU expenditure in Eastern Europe (Table 3). Overall, biological therapy was administered to 30 patients with UC (4.2% of UC cases), 82 with CD (15.1%), and 11 with IBDU (7.4%, all from Western Europe). Overall, 9.0% of patients received at least 1 series of biological therapy in the first 12 months of follow-up after diagnosis, patients with CD accounted for most of the expenses for biological therapy (Fig. 2). Most patients were started on infliximab (n = 102, 83%). Four patients changed from adalimumab to infliximab treatment, whereas 1 patient changed from infliximab to adalimumab during the observation time. In Western Europe, patients with CD received a median of 5 (range, 1–10) and patients with UC a median of 2 (range, 1–7) infliximab infusions, compared with 6 (range, 3–7) and 1 (range, 1) in Eastern Europe, respectively. Regarding adalimumab treatment, patients with CD in Western Europe received a median of 3 (range, 1–7) injections compared with 16 injections in the 1 Eastern European patient. The crude cost per patient receiving biologicals was €7184 for CD and €5290 for UC in Western Europe and €8307 and €72, in Eastern Europe, respectively.

Surgery was performed on 110 (8%) patients with IBD. In Western Europe, 74 (15%) patients with CD accounted for 51 intestinal resections, 8 hemicolectomies, 3 colectomies, and 30 anal surgeries (e.g., seton insertion, abscess incisions), 17 (3%) patients with UC for 17 colectomies and 1 intestinal resection, and 6 (4%) patients with IBDU for 1 hemicolectomy, 4 colectomies, and 2 anal surgeries. In Eastern Europe, 11 (11%) patients with CD accounted for 10 intestinal resections, 3 hemicolectomies, and 1 anal surgery, whereas UC patients had 2 colectomies (1%). CD carried the greatest proportion of costs for surgery (Fig. 2).

The frequency of diagnostic procedures is shown in Table 7. Eighteen (4%) CD and 37 (7%) UC patients in Western Europe compared with 3 (3%) CD and 20 (14%) UC patients in Eastern Europe had a sigmoidoscopy in addition to colonoscopy. In Western Europe, 40 (10%) CD and 12 (2%) UC patients had bowel barium x-ray in addition to a colonoscopy compared with 15 (14%) CD and 19 (13%) UC patients in Eastern Europe. Furthermore, of patients with CD who had an MRI, in Western Europe, 27 (7%) also had a computerized tomography and 7 (2%) a capsule endoscopy, whereas in Eastern Europe, 8 (8%) patients had a capsule endoscopy. No patients with UC had additional investigations to MRI performed.

DISCUSSION

In this population-based inception cohort of unselected IBD patients, we have found high health care costs across Europe, with 1367 patients accumulating expenses exceeding 5 million Euros in their first year of follow-up after initial presentation and diagnosis. The majority of expenses were caused by diagnostic procedures and surgical treatment, but already at this early time

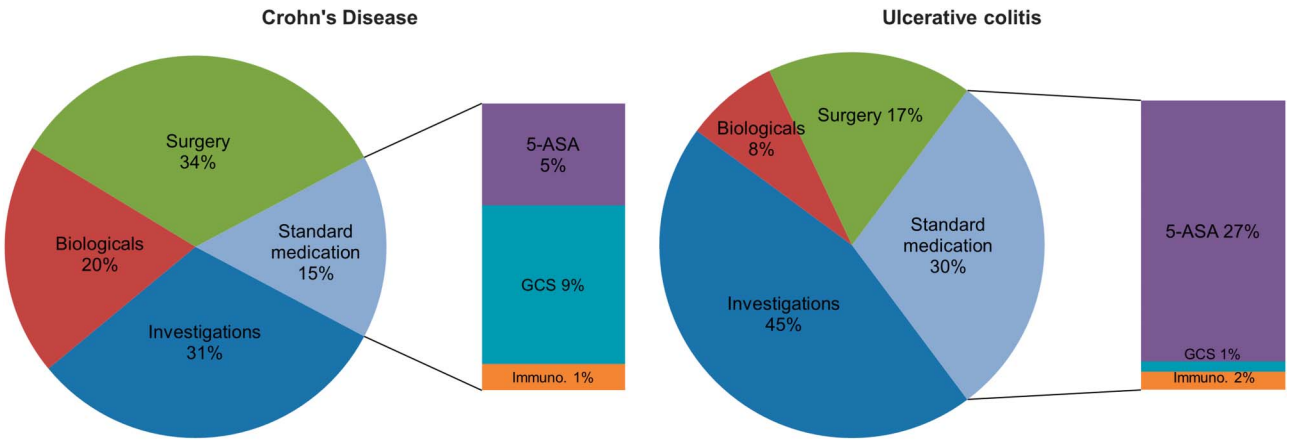

FIGURE 2. Proportion of total expenditures for patients with CD (€2,523,939) and UC (€1,590,162) spent on investigations and medical and surgical therapies during the first year of disease in a European inception cohort. GCS, glucocorticosteroids. Investigations: diagnostic procedures and investigations during the first year from diagnosis.

point in disease course, biological therapy was used in a large proportion of patients accounting for 20% of costs for patients with CD. A diagnosis of CD, a young age at diagnosis, CD patients with ileal location or stricturing or penetrating disease behavior, and UC patients with more severe disease extent carried the greatest expenditures.

IBDs are expensive diseases, with onset in young persons and lifelong chronicity[7,18–20] that are grouped with such illnesses as juvenile diabetes and rheumatoid arthritis for prolonged course and attendant expenses. Moreover, the potential for malignancy requires lifelong follow-up even in quiescent patients.[21] In fact, per capita costs of patients with IBD during this initial year of disease after diagnosis in this study exceeded that of other chronic disorders, i.e., type 1 diabetes, psoriasis, and obesity.[22–24] However, it must be kept in mind that this is a first-year cohort, where increased costs due to extensive diagnostic procedures are found.[5] Indeed, in our patients, the outlay on diagnostics was as high as 38%.

Accurate determination of health care costs in IBD is important to inform those who determine the allocation of medical resources in European countries. The costs of health care for IBD are best evaluated in unselected patient samples captured simultaneously from regions in many countries with advanced medical services and prospectively incepted within a relatively short time frame, using uniform diagnostic criteria, as in the present cohort. Several measures including standardizing diagnostic criteria, case ascertainment methods, and intervals of follow-up visits and recorded data, thereby making patients comparable, ensured that all centers performed a population-based cohort study and collected accurate and valid clinical data. Thus, bias arising from analysis of patients with chronic and severe disease referred to tertiary health care centers is avoided.

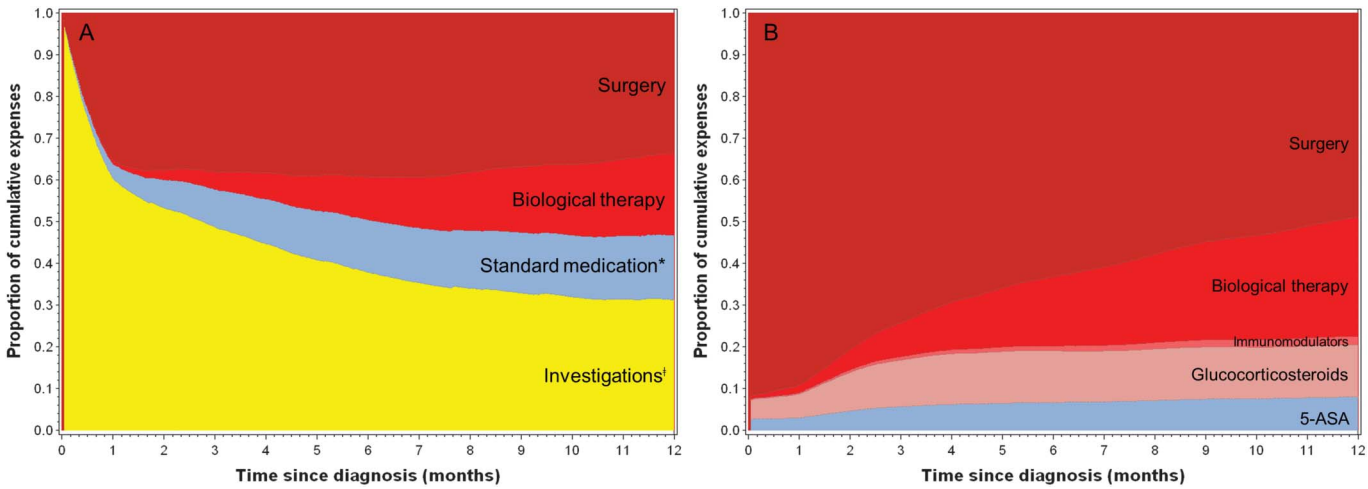

FIGURE 3. Distribution of cumulative expenses for CD patients regarding (A) treatment and investigations and (B) treatment choices during the first year from diagnosis in a European inception cohort. *Standard medication: 5-ASA, glucocorticosteroids, and immunomodulators. ‡Investigations: diagnostic procedures and investigations during the first year from diagnosis.

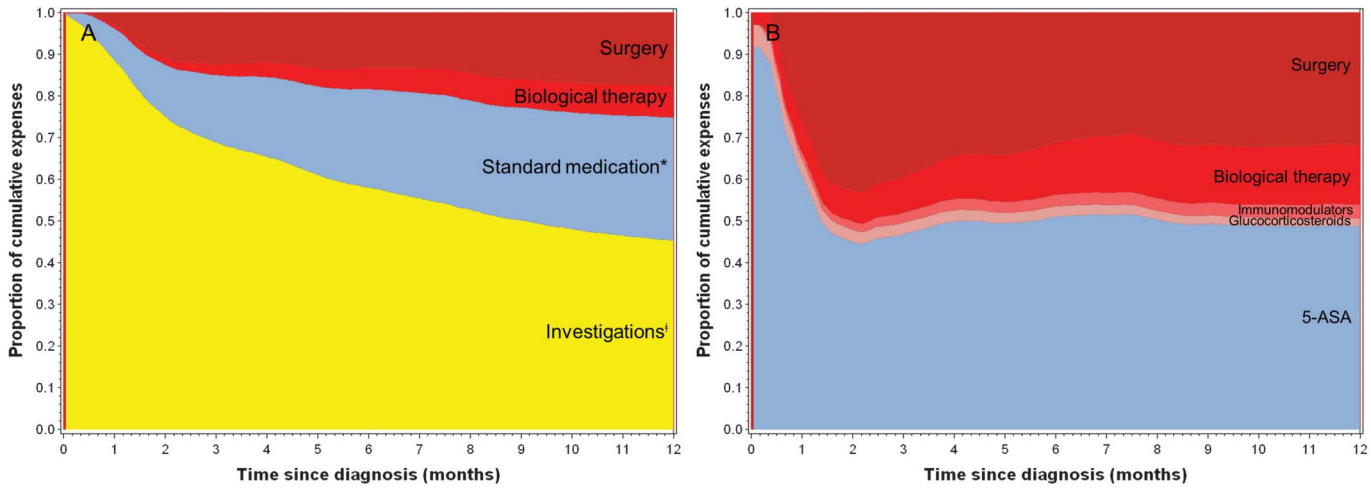

FIGURE 4. Distribution of cumulative expenses for UC patients regarding (A) treatment and investigations and (B) treatment choices during the first year from diagnosis in a European inception cohort. *Standard medication: 5-ASA, glucocorticosteroids, and immunomodulators. ‡Investigations: diagnostic procedures, and investigations during the first year from diagnosis.

TABLE 4. Resource Costs (in euros) Per Patient in the First Year of Follow-up of 1367 Incident Patients with IBD

	All Centers				Western Europe				Eastern Europe			
	IBD	CD	UC	IBDU	IBD	CD	UC	IBDU	IBD	CD	UC	IBDU
Investigations	1495	1857	1248	1432	1434	1790	1176	1440	1753	2119	1518	1230
5-ASA	567	328	734	584	549	268	743	585	641	562	700	545
Glucocorticosteroids	217	509	29	112	241	584	26	116	110	218	37	27
Immunomodulators	63	85	51	46	69	97	54	47	38	37	41	11
Biologicals	571	1168	216	222	667	1366	273	231	161	399	0	0
Surgery	1044	1995	476	503	1126	2128	557	524	692	1478	168	0
Total	3956	5942	2753	2898	4087	6232	2829	2944	3395	4812	2464	1814

TABLE 5. Predictors of Higher Total Expenses During the First Year After Diagnosis in an IBD Inception Cohort

	All Centers			Western Europe			Eastern Europe		
	IBD	CD	UC	IBD	CD	UC	IBD	CD	UC
Region (East versus West)	0.89	0.10	0.51	—	—	—	—	—	—
Gender	0.63	0.39	0.75	0.32	0.76	0.52	0.43	0.31	0.41
Diagnosis[a]	<0.01[b]	—	—	<0.01[b]	—	—	<0.01[b]	—	—
Young age at diagnosis	<0.01[b]	0.03[b]	0.01[b]	<0.01[b]	0.02[b]	<0.01[b]	0.99	0.88	0.83
Diagnostic delay	0.51	0.74	0.17	0.40	0.56	0.04[b]	0.5505	0.53	0.57
Behavior (CD)[c]	—	<0.01[b]	—	—	<0.01[b]	—	—	<0.01[b]	—
Location (CD)[d]	—	0.02[b]	—	—	0.02[b]	—	—	0.50	—
Disease extent (UC)[e]	—	—	<0.01[b]	—	—	<0.01[b]	—	—	0.08

P values in multilevel regression model.
[a]CD > UC.
[b]$P < 0.05$.
[c]B3 > B2 > B1.
[d]L1/L4 > L2/L3.
[e]E3 > E2 > E1.

TABLE 6. Predictors of Higher Costs for Examinations and Treatment During the First Year After Diagnosis in an IBD Inception Cohort

	Examinations	5-ASA	GCS	Immunomodulators	Biologicals	Surgery
CD						
Region (East versus West)	0.17	0.06	0.07	0.82	0.90	0.22
Gender	0.88	0.58	0.89	0.78	0.07	0.57
Age	0.08	0.23	0.90	0.78	0.70	0.78
Diagnostic delay	0.08	0.56	0.16	0.04[a]	<0.01[a]	0.43
Behavior[b]	0.03[a]	0.52	0.58	0.82	0.78	0.54
Location[c]	<0.01[a]	0.50	<0.01[a]	0.30	0.33	0.13
UC						
Region (East versus West)	<0.01[a]	0.77	0.24	0.29	—	0.21
Gender	0.81	0.93	0.43	0.81	0.53	0.36
Age	0.80	0.04[a]	0.54	0.07	0.44	0.21
Diagnostic delay	0.97	0.15	0.66	1.00	0.34	0.07
Disease extent[d]	0.02[a]	0.02[a]	0.35	0.65	0.44	0.94

P values in Multilevel Regression Model.
[a]$P < 0.05$.
[b]B3 > B2 > B1.
[c]L1/L4 > L2/L3.
[d]E3 > E2 > E1.
5-ASA, 5-aminosalicylates; GCS, glucocorticosteroids.

Notably, our entire cohort was community-based, so that any high costs in certain study sites could not be the result of any referral of complicated patients to a specialized referral center. Thus, the cohort presented here reflects all levels of disease severity.

We noted East-West differences in several modalities, including use of biologicals and cost. This has not been documented previously. Interestingly, Eastern European CD patients had higher mean costs for biological therapy due to a higher number of infusions. Because of the short follow-up period, it needs to be confirmed during long-term follow-up if this difference in fact is caused by differences in management. Although access to some diagnostic procedures such as colonoscopy, capsule endoscopy, or MRI may vary within geographical regions or countries, the diagnostic approach for obtaining an IBD diagnosis overall was very similar across the European centers, in accordance with the European Collaborative study group on Inflammatory Bowel Disease study.[25] In this study, the participating centers overall acted in accordance with international guidelines,[26–30] although the adherence to

TABLE 7. Frequency of Diagnostic Procedures Performed in a European Inception Cohort

	Western European Centers			Eastern European Centers		
Procedures	CD	UC	IBDU	CD	UC	IBDU
None	5 (1%)[a]	0 (0%)	1 (1%)	2 (2%)[a]	0 (0%)	0 (0%)
Upper GI endoscopy	37 (9%)[b]	18 (3%)[b]	4 (3%)	36 (35%)	15 (10%)	0 (0%)
Colonoscopy	378 (93%)	454 (81%)[b]	104 (73%)	100 (96%)	133 (90%)	6 (100%)
Proctoscopy/sigmoidoscopy	23 (6%)	144 (26%)	53 (37%)	4 (4%)	35 (24%)	1 (17%)
Capsule endoscopy	42 (10%)	1 (0%)	6 (4%)	15 (14%)	0 (0%)	0 (0%)
Trans rectal ultrasound	2 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
MRI	73 (18%)	6 (1%)	5 (4%)	11 (11%)	3 (2%)	0 (0%)
CT scan	142 (35%)	24 (4%)	13 (9%)	26 (25%)	2 (1%)	1 (17%)
Bowel x-ray	43 (11%)	13 (2%)[b]	5 (4%)	16 (15%)	19 (13%)	1 (17%)

[a]Patients diagnosed after surgery.
[b]Difference between Eastern and Western European centers, $P < 0.05$.
CT, computerized tomography; GI, gastrointestinal.

international guidelines is influenced by differences in practice across Europe and by socioeconomic considerations. Surprisingly, however, significant differences were found regarding diagnostic procedures in patients with UC caused by a higher frequency of upper endoscopy, colonoscopy, and bowel x-ray in Eastern Europe, and an apparent underutilization of i.e. colonoscopy in Western European centers. Also, more patients in Eastern Europe had "unnecessary" procedures performed (e.g., starting with a sigmoidoscopy followed by colonoscopy if findings were positive for IBD).

UC and CD do not demonstrate differences of disease behavior in different countries,[10,25] and we are not aware of any major clinical differences in the patients in our cohort.[11] Therefore, the question arises as to whether the cost disparities demonstrated could be caused by differences in medical decision-making, as when to give biological treatment or opt for surgery or to economic considerations engendered by the enormous diversity throughout Europe regarding reimbursement rules for treatment and procedures, budgetary restrictions, and national economic guidelines because choices regarding medical and surgical treatment are strongly linked to extramedical considerations. Because we used the Danish diagnosis-related group price index for all countries and did not match prices in individual countries with gross national product, we cannot answer this question. Furthermore, the patient number in Eastern Europe is smaller, which could skew the data and result in higher mean costs. However, these limitations should not distract from the value of our findings.

Establishing guidelines such as those of ECCO[26,27] to change inadequate practice and guide clinicians where evidence is limited has a fundamental role in driving specific improvements in the quality and management of IBD care across Europe. The findings of the current cohort are overall encouraging as the majority of patients received care according to guidelines despite differences found regarding treatment (i.e., the use of biologics) and utilization of diagnostic procedures. Whether these differences influence on long-term outcome and health-related quality of life remains to be shown. In the present cohort, however, short-term outcomes did not differ between the 2 geographic regions.[11,31]

Several studies have examined the cost of IBD. Published cost estimates of resources have differed considerably by author and country, primarily because of the high prices in private medical practice in some countries and the confounding methods of estimating expenses.[32] Because most, if not all, patients in our cohort were treated in countries with a public health system,[1] as is typical of European countries, the former bias was avoided. Therefore, we show here costs that are typical of European medicine and thus are likely transferable to similar health care settings outside of Europe. However, despite all centers performing a population-based inception cohort study, such an extrapolation of the findings of this cohort to the whole of Eastern and Western Europe should be done with caution. Our method of collecting data did not allow for adding charges for hospital admissions for other medical indications; we cannot know whether our IBD cases were subject to more comorbidities than the non-IBD population, and our estimates of costs could have been lowered because of this omission. All costs for surgery include hospital hotel charges, and these were the majority of all admissions. Similarly, day-care hospital charges for the administration of infliximab are included in the cost of biological therapy. In a cost model before the introduction of biological therapy in IBD treatment, surgery in CD was the most relapse preventing entity to treat with.[3] Long-term follow-up of our cohort will in due time be able to tell whether immunomodulators combined with biologicals have similar effect on disease and on cost.[11]

It is expected that the mean annual cost of caring for our patients with IBD will drop when the follow-up extends beyond 1 year, as we have shown for an earlier European cohort.[5] However, this is unknown since the cost of treating IBD now includes expensive biological therapy often given throughout life. Of note, the proportion of patients receiving immunomodulators or biological therapy is higher than reported in previous population-based cohorts from the biological era,[11,18,33] and already during the first year of disease, where diagnostic procedures still take up a large proportion of costs, biologicals accounted for 20% and 8% of costs in CD and UC patients, respectively. To date, no study has shown that biological therapy reduces overall costs in patients with IBD. In a Markov model of real IBD patients selected from the European Collaborative study group on Inflammatory Bowel Disease cohort,[5] we have previously shown that infliximab therapy remains very expensive in a projected horizon of 10 years of follow-up even at a 50% reduction in acquisition price.[34,35] In retrospective cohort studies, it was clearly shown that infliximab therapy raised the expenditure in CD despite clinical gain.[36,37]

In conclusion, we have reported that there is substantial expense in diagnosing and treating IBD in our pan-European inception cohort of unselected IBD patients and demonstrated differences in practice and in expense outlay in Eastern and Western European countries. Further study is required of this cohort on long-term follow-up to determine costs over time and whether extended and aggressive treatment in the first year with immunomodulators and biological agents eventually will produce a drop in cost. Furthermore, the cross-continent disparities require more investigation.

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