MANAGEMENT OF PATIENTS WITH CUSHING'S DISEASE: A CANADIAN COST OF ILLNESS ANALYSIS

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ABSTRACT

Background
Cushing's disease (CD) is a rare disorder caused by increased pituitary secretion of adrenocorticotropic hormone (ACTH) resulting in elevated production of cortisol. It is associated with multiple adverse cardiovascular, metabolic, musculoskeletal and mental consequences. Patients with CD require substantial health care resources both in terms of treatments with a curative intent and control of disease related co-morbidities. In this study, a cost of illness analysis was conducted to estimate the direct cost of CD care in Canada.

Methods
This was a retrospective cohort study of 86 CD patients. Data collection included patient demographic and disease related information, existing comorbidities, treatments received and all clinical outcomes. In addition, healthcare resource utilization to manage CD was also collected. Once the mean cost per patient was determined, the overall disease prevalence was used to estimate the total direct cost of illness in Canada.

Results
The sample included 86 CD patients, with a mean age of 43 years at diagnosis, 72% were female. All received a first line intervention consisting of transsphenoidal pituitary surgery (78%), bilateral adrenalectomy (5%), radiation therapy (5%) or medical therapy ± radiation (13%). In addition, 18 and 14 patients subsequently received a second and third line intervention, respectively. The mean cost was $85,946 per patient over the first three lines of therapy. Combining this estimate with the reported disease prevalence (5.5 patients per 100,000 [95%CI: 4.2 to 6.8]), the total direct cost of CD in Canada was estimated to be approximately $80.6 million (95%CI: $61.5 to $99.6 million) over the first 3 lines of therapy.

Conclusions
CD is a debilitating condition that is associated with substantial health care costs. Strategies that provide clinical cure or long term disease control need to be identified to reduce patient morbidity and to save health care costs in patients who remain uncontrolled.

Key Words: *Cushing's disease, pituitary surgery, second-line therapies, cost-analysis*

Cushing's disease (CD) is a chronic condition whose signs and symptoms are secondary to prolonged exposure to abnormally high cortisol levels.[1] The disease was first described by Harvey Cushing in 1932 and is characterized by weight gain, especially around the face, trunk and abdomen, thinning of the skin, purple skin striae and proximal muscle weakness.[1,2] Elevated steroid levels can also cause systemic effects such as insomnia, cognitive impairment, depression,

reduced libido and impotence in males as well as infertility and hirsutism in women. Long term effects include insulin resistance and diabetes, osteoporosis, increased lipid levels and hypertension, which elevate the risk of cardiovascular events.[2,3,4] Left untreated, CD is also associated with an increased risk of early mortality.[5] Therefore, immediate and effective medical interventions are required to correct hypercortisolism and avoid or limit the impact of these complications.

Approximately 70 to 80% of all cases of Cushing's syndrome (CS) are secondary to excess adrenocorticotrophic hormone (ACTH) secretion by a benign corticotrophic pituitary adenoma or more rarely by extrapituitary benign or malignant tumors (ectopic ACTH syndrome). In 15-20% of cases, CS results from ACTH-independent cortisol excess caused by unilateral adrenocortical tumors or by bilateral adrenal hyperplasia or dysplasia.[1,3] In cases of CD where a pituitary corticotrophic adenoma is confirmed by pituitary MRI and/or gradient of ACTH levels documented by bilateral inferior petrosal sinus sampling (BIPSS), the initial treatment of choice is surgical selective removal of the pituitary tumor (transsphenoidal surgery [TSS]).[6,7]

The results of pituitary surgery are largely dependent on the neurosurgeon's expertise and it is effective in maintaining long term remissions in approximately 50-60% of patients after 10-20 years of follow-up.[6,7] When pituitary surgery is contraindicated or has failed, or when the patient refuses surgery, the hypercortisolism has been treated with second-line therapies such as radiotherapy, medical therapy or bilateral adrenalectomy (BLA). Radiotherapy may take several months to achieve normalization of cortisol secretion, and in approximately 50% of cases, results in new onset hypopituitarism over the long-term.[7,8] As an alternative to surgery or radiation, drug therapy with agents such as ketoconazole, metyrapone, mitotane, cabergoline, pasireotide, and mifepristone have also demonstrated clinical benefit.[6,7]

However, several medical therapies are prescribed off-label, require close medical monitoring, are not effective in all patients and each agent has its own risk of toxicities.[6,7]

The mean age of CD diagnosis is usually in the fourth decade of life.[1,3] Combined with the long term care required for all patients, CD can have a major socioeconomic impact on individuals and society both in terms of direct health care costs and indirect costs such as lost productivity. In one retrospective cohort study from the United States, Swearingen et al., used insurance claims data reported over 4 years (from 2004 to 2008) to identify a sample of 877 CD patients.[9] Each CD patient was then matched based on age and gender to 4 patients with nonfunctional pituitary adenomas and 10 control subjects from the population. Compared to the two reference groups, CD patients required significantly more health care resources such as visits to their physician's office and emergency department, use of supportive medication and hospital admissions. For every calendar year, the mean direct cost for CD patients was $26,444, compared to $13,708 and $5,954 in patients with nonfunctional pituitary adenomas and subjects from the general population, respectively.[9] It was also interesting to note that CD patients who successfully responded to treatment were less costly to manage than those who did not. The investigators concluded CD has a significant impact on health care resource use and effective interventions can reduce the prevalence of the associated comorbidities, thereby saving health care costs.[9]

Upon review of the health economic literature, there is no published data on the burden of CD on the Canadian health care system. Such data would be of value to health policy decision makers and health economists because it could provide initial data for quantifying the impact of new therapies for CD. In this study, data was collected from patients treated in Southwestern Ontario and was used to estimate overall health care resource use and the direct cost of care for CD in Canada.

METHODS

Study Design

The Southwestern Ontario (SWO) database consists of family practice level patient data on the clinical diagnoses of each visit, symptoms

corroborating the diagnoses, clinical data (e.g. HbA1C, blood pressure, lipid values, hormonal levels, smoking status, height, weight, fitness level), prescribed treatments and medications, hospitalizations, diagnostic/laboratory test results and procedures allowing for the conduct of patient level analyses. The database includes patients residing from Windsor to Woodstock, to Owen Sound, with an estimated coverage of 2.5 million people. Data from 53 primary care practices participating in the SWO database cohort have been routinely updated on a quarterly basis since 2000, with a total of 523,718 charts included in the database. To create the database, the data abstraction is done from physician notes, laboratory reports and discharge summaries. The abstractor retrieves the patient chart quarterly if there has been clinical activity, as signaled by a billable action within that quarter.

This was a multicenter retrospective cohort study consisting of patients with CD who were receiving treatment in Southwestern Ontario over a 12 year period (from 2001 to June 2013). To be eligible, patients had to be adults with a diagnosis of CD, under a physician's own care for at least 12 months; the reporting physician was the individual primarily responsible for management and follow up and at least two urinary free cortisol (UFC) readings (range: 2-6 readings) must have been available.

Data Collection and Economic Analysis

Patient enrolled in the Southwestern Ontario database were reviewed for eligibility and selected consecutively. For patients meeting the inclusion criteria, clinical and resource utilization information was extracted. The data collection included patient demographic, laboratory/monitoring tests, UFC values, existing comorbidities, treatments received and all clinical outcomes. In addition to the clinical information, healthcare resource used to manage CD was also collected. This consisted of visits to medical specialists and the emergency department (ED), hospital admissions, diagnostic and biochemistry tests, concomitant medication to manage the CD related comorbidities and radiation therapy for disease control.

Complications were reported within 7 days post-surgery for either TSS or BLA. Ontario Case Costing Initiative (OCCI) inpatient costs (F2010/2011) were then applied to derive the estimated costs of complications. The frequency of co-morbidities was available during the study period. Assessments over 1 year or 2 years post intervention demonstrated minimal changes in frequency; as such, an overall percentage was used. Since dosing schedule was not reported, the dose of each medication was retrieved from product monographs and applied to the associated unit costs.

Resource use items were then converted into costs to estimate the mean cost per patient with CD. Unit costs for procedures and hospitalization were obtained from the OCCI.[10] Unit costs for diagnostic procedures and biochemistry tests were obtained from the Ontario Schedule of Benefits for Laboratory Fees. Physician fees for service were obtained from the Schedule of Benefits: Physician Services under the Health Insurance Act, Ontario Ministry of Health, 2011. Unit costs of medications were retrieved from IMS/Brogan Inc. Unit costs were also supplemented from literature sources when necessary. A one way sensitivity analysis was also done to evaluate the impact of variations in key cost drivers. All costs were reported in 2011 Canadian dollars.

Data Analysis

The study was designed to measure overall resource use and the total cost of a CD patient over the first three lines of therapy. To meet the primary objective, the final sample for this cohort study consisted of 86 patients representing all patients identified with CD from the entire dataset of 523,718 charts. Urinary free cortisol test, ACTH tests, dexamethasone tests and imaging confirmed the diagnosis of CD for all patients. In addition, tests such as desmopressin and BIPSS, were rarely used for diagnoses. With 86 patients, the overall cost of CD was measured with a precision that extended to ±$1,000, with a 95% probability. Patient, clinical and economic data were presented descriptively as means, medians, or proportions. The population prevalence, which has been estimated based on a population study in Liège, Belgium to be 5.5 per 100,000 (95%CI: 4.2

to 6.8), was then used to estimate to total direct economic burden of CD in Canada.[11]

RESULTS

The sample of 86 patients who met the eligibility criteria had a mean age of 43 years (range: 18-71) at diagnosis and 72% were female. Approximately three-quarters were diagnosed with micro-adenomas (77%) while the remainder had macro-adenomas or non-visible tumours (Table 1). Patients had a mean CD duration of 13 years and were followed by their primary physician for approximately 6.5 years. The main comorbidities consisted of hypertension (67%), dyslipidemia (24%), type II diabetes (23%), depression (17%) and osteoporosis (12%) - (Table 1).

TABLE 1 Demographic and clinical characteristics of CD patients

Parameter (SD)[1]	**CD Patients (n=86)**
Mean age at diagnosis	43 (Range: 18-71)
Female gender	72%
Disease pathology	
Macro-adenomas	12%
Micro-adenomas	77%
Non-visible tumours	11%
Mean duration of disease in yrs (range)	13 (1 to 18)
Mean duration of follow up in yrs	6.5
BMI (mean)	31 (14)
UFC prior to initial treatment (mean, nmol/24h)	277 (39)
Existing comorbidities	
Hypertension	67%
Dyslipidemia	24%
Type II diabetes	23%
Osteoporosis	17%
Depression	12%
Prior MI	7%
Sleep apnea	6%
Prior stroke	3%
Prior CHF	3%

Abbreviations: SD = standard deviation, BMI = body mass index, MI = myocardial infarction; CHF = congestive heart failure, UFC = urinary free cortisol (Normal range: < 110nmol/24hr); [1]Estimates may not add up to 100% because of rounding errors.

Among the 86 patients, all received a first line intervention consisting of surgery (TSS, 78%, BLA, 5%), radiation therapy (5%) or medical therapy (± radiation) (13%). Consistent with treatment recommendations, TSS was the most commonly used first line intervention.[6,7] However, 18 of 86 (21%) patients failed to achieve a durable disease response and required a second intervention (Table 2). Medical therapy was the most commonly used second-line of therapy followed by TSS and BA (n = 7 of 18). The long term data also revealed that the majority of patients unresponsive to the initial therapy remained treatment refractory. Of the 18 patients who required second line therapy, 14 went on to receive a third intervention, consisting primarily of medical therapy (Table 2).

TABLE 2 Summary of interventions to manage CD

Parameter[1]	CD Patients (%, n)
First line therapy (n=86)	
Transsphenoidal surgery	78% (67)
Medical therapy (± radiation)	13% (11)
Bilateral laparoscopic adrenalectomy	5% (4)
Radiosurgery	5% (4)
Proportion receiving 2nd line therapy	18 of 86 (21%)
Second line therapy (n=18 of 86; 20.9%)	
Medical therapy (± radiation)	39% (7)
Transsphenoidal surgery	22% (4)
Bilateral laparoscopic adrenalectomy	22% (4)
Radiosurgery	17% (3)
Proportion receiving 3rd line therapy	14 of 86 (16%)
Third line therapy (n=14 of 86; 16.3%)	
Medical therapy (± radiation)	71% (10)
Radiosurgery	21% (3)
Transsphenoidal surgery	7% (1)
Bilateral laparoscopic adrenalectomy	0% (0)

Abbreviations: SD = standard deviation; [1]Estimates may not add up to 100% because of rounding errors.

Overall health care resource use by line of therapy was then quantified in the sample of 86 patients. Total health care resource consumption was highest during first line therapy, and this consisted of a mean of 5 ED visits, 17 specialist visits and 0.3 hospital admissions for approximately 7 days (Table 3). The 18 patients who received a second line therapy required additional health care resources for poorly controlled disease. In addition, it was also interesting to note that the mean number of hospital admissions increased compared to the first line setting (mean = 0.5 vs. 0.3), as was the length of hospital stay (Table 3). The same trend was identified in the 14 patients who subsequently received a third line intervention. Overall hospitalization and length of stay was also elevated in these latter patients. In addition, all patients were receiving concomitant medication for control of their existing comorbidities.

Cost of Patient Care for the First Three Lines of Therapy

The next phase of the study was to estimate the overall cost impact of CD over the first three lines of therapy. When healthcare resources, such as specialist or ED visits, hospitalization and supportive care, were quantified, the mean cost was estimated to be approximately $86,946 per patient (Table 4). It was also interesting to note that the cost increased by line of therapy (Table 5). Therefore, the successful initial management of CD will have major economic implications to the health care system.

TABLE 3 Health care resource use by line of therapy

Parameter (mean, SD)[1]	CD Patients (n=86)
First line therapy	
ED visits	4 (5)
Specialist visits	17 (16)
Hospital admissions	0.3 (0.5)
Length of hospital stay (days)	7 (3)
Proportion receiving 2nd line therapy	18 of 86 (21%)
Second line therapy	
ED visits	6 (3)
Specialist visits	15 (10)
Hospital admissions	0.5 (0.1)
Length of hospital stay	10 (6)
Proportion receiving 3rd line therapy	14 of 18 (78%)
Third line therapy	
ED visits	5 (3)
Specialist visits	13 (9)
Hospital admissions	0.7 (0.7)
Length of hospital stay (days)	12 (7)
Concomitant medication (%)	
Antihypertensives	
Ramipril	56%
Metoprolol	38%
Hydrochlorothiazide	86%
Amlodipine	54%
Telmisartan	37%
Antidiabetics	
Metformin	97%
Sulfonylurea	67%
Rosiglitazone maleate	79%
Exenatide/Liraglutide	81%
Sitagliptin/saxagliptin	93%
Lipid lowering agents	
Atorvastatin	83%
Gemfibrozil	73%
Antidepressants: Paroxetine	21%
Laboratory/monitoring tests (range)	
UFC	2 (2 to 6)
ACTH	1.3 (1 to 3)
Dexamethasone suppression tests	1.0 (0 to 2)
BIPSS	0.1 (0 to 1)
Desmopressin tests	0.13 (0 to 1)
Imaging studies	1.1 (0 to 2)

Abbreviations: SD = standard deviation, ED = emergency department, UFC = urinary free cortisol, ACTH = cosyntropin test, BIPSS = Bilateral inferior petrosal sinus sampling test; [1]Estimates may not add up to 100% because of rounding errors.

TABLE 4 Overall cost of care over the first three line of therapy

Parameter (mean)	Cost per CD patient
Surgical interventions	$21,868
Radiation therapy	$7,797
Medical therapy	$29,984
Concomitant medication	$13,280
Hospitalization, clinic and emergency visits	$14,017
Total cost per patient[a]	**$86,946**
Cost of illness	**$80.6 million**
Canada (95%CI)[b]	**($61.5 to $99.6 million)**

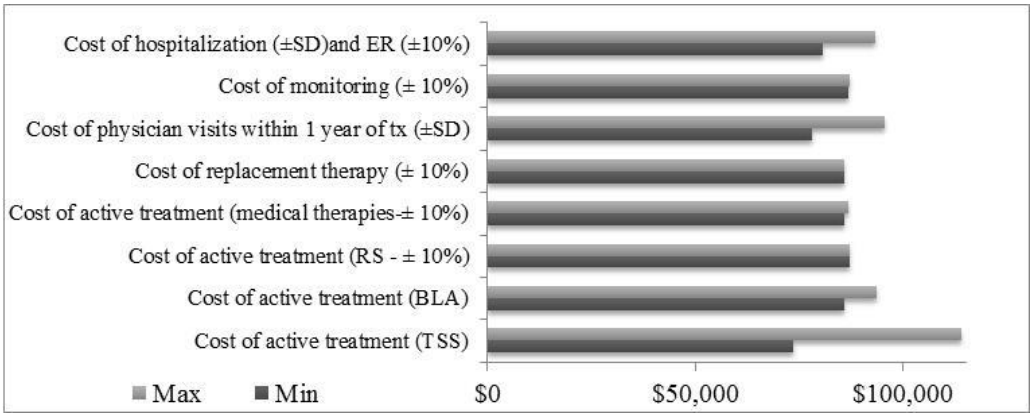
Abbreviations: SD = standard deviation; [a]total costs of interventions, medical therapy, concomitant medication, hospitalization, clinic and ER divided by total number of patients; [b]The 95% CI was calculated based on the variability of the population prevalence, which was estimated to be 5.5 per 100,000 (95%CI: 4.2 to 6.8)[10]; This estimate reflects the cost of illness of the first three lines of therapy, which in the current study, spanned a 12 year period.

TABLE 5 Cost per line of therapy

	1st			2nd			3rd		
	Surgery	**RS**	**MT**	**Surgery**	**RS**	**MT**	**Surgery**	**RS**	**MT**
Number of patients	**71.0**	**4.0**	**11.0**	**9.0**	**3.0**	**7.0**	**1.0**	**3.0**	**10.0**
Total costs	$1,829,978	$34,755	$360,152	$254,333	$44,247	$234,854	$25,080	$49,736	$383,002
Total cost per patient	$25,774	$8,689	$32,741	$28,259	$14,749	$33,551	$25,080	$16,579	$38,300
Total cost per patient per line of treatment	**$25,871**			**$28,075**			**$32,701**		

RS: Radiosurgery, MT: medical therapy; Surgery: includes transsphenoidal surgery and bilateral adrenalectomy.

FIG. 1 One way sensitivity analyses on the key cost drivers



A one way sensitivity analysis was then performed to evaluate the impact of variations on key economic parameters (Figure 1). This included variations (either by the SD or ±10% where indicated) in the cost for TSS, BLA and replacement therapy, hospitalizations and ER, physician visits as well as cost of medical therapies. The findings of the sensitivity analysis revealed that the single most important economic driver was the cost of TSS in the first line setting. Variations in the cost of this parameter changed the mean cost per patient from a low of $73,325 to an upper range of $113,852. In contrast, variations in the cost of hospitalization, physician and ER visits as well as medical management did not have a major impact on the mean cost per patient (Figure 1).

Burden of Illness Analysis

The final phase of the analysis was to estimate the total cost of CD to the Canadian health care system. The population in Canada at the end of September 2013 was reported to be 35.6 million.[12] Using the CD population prevalence, which has been estimated to be 5.5 per 100,000 (95%CI: 4.2 to 6.8), and the mean cost per patient estimate from the current data, the total burden of CD over the first three lines of therapy incurred by the Canadian health care system was estimated to be approximately $80.6 million (95%CI: $61.5 to $99.6 million) (Table 4).

DISCUSSION

CD is a relatively uncommon medical condition with a population prevalence estimated to be 5.5 per 100,000 (95%CI: 4.2 to 6.8).[11] Hence in Canada, there would be approximately 1934 active cases (95%CI: 1495 to 2421). In addition to its significant morbidity and mortality, the long term course of CD and its associated comorbidities have made it costly to manage. CD is also most commonly diagnosed in the fourth decade of life.[1,3] As a result, it would also be associated with substantial indirect costs such as lost productivity. Lastly, there would be considerable social stigma associated with the neuro-psychological and physical co-morbidities characteristic of the condition when poorly controlled. As a result, clinical interventions that are rapidly effective and provide long term CD control need to be identified.

Upon review of the health economic literature, there were no published Canadian studies that have measured the direct and indirect costs associated with the management of CD. Therefore, we sought to partly address this gap in the literature by measuring the direct cost of care in a sample of 86 CD patients that were treated in

the province of Ontario, Canada. The results of the current investigation determined that CD is a resource intensive condition with hospitalization, including surgical interventions and supportive care, responsible for up to 40% of total cost. To adequately control the elevated cortisol levels and the associated comorbidities, patients required multiple treatments and costly laboratory or diagnostic investigations. Despite these interventions, patients in our cohort still required multiple hospital admissions over the course of their disease. When the health care resources were quantified, the mean cost was approximately $86,946 per patient for the first three lines of therapy. When applied over the estimated number of active cases in Canada, the total direct health care cost of CD was estimated to be approximately $80.6 million, with the upper 95%CI reaching 99.6 million. Despite the rarity of this disease, the direct burden of illness is substantial. Given these findings, health policy decision makers and clinicians need to focus on effective early intervention strategies.

There are a number of limitations in the current cost of illness analysis that have to be acknowledged. The study was retrospective which sometimes created challenges in cases where gaps in the data existed. In addition, indirect costs could not be quantified from the patient medical records. The total sample size was small (n=86) and selected from only one region of Canada, mainly from general practices, as such, more severe patients who have been referred to specialized centers, may not have been included in this analysis. This could compromise the generalizability of the results to other jurisdictions; extrapolation of costs is based on epidemiological data reported in Europe. Only adult patients with CD were considered. Therefore, the findings cannot be extended to children with CD or to exogenous causes of elevated cortisol levels. Patients were followed for only three lines of therapy and not until full clinical cure or death. Therefore, the cost estimates are certainly underestimated.

CONCLUSION

In conclusion, the findings of the cost of illness analysis revealed that CD is a debilitating and costly medical condition. Poorly controlled cortisol levels in CD patients can also be severe enough to require multiple hospitalizations.

Therefore, clinically effective and cost effective early intervention strategies for CD patients are required to avoid downstream health care costs and to reduce overall patient morbidity and mortality.

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