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Longitudinal Patterns of Medication Non-Adherence and Associated Health Care Costs

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Abstract

Background—Non-adherence to treatment recommendations is associated with poorer outcomes in inflammatory bowel disease and may increase the cost of care. We examined the longitudinal relationship between non-adherence and health care costs and hypothesized that at least three distinct trajectories of non-adherence would be observed, and that increasing non-adherence would account for significantly greater health care costs after controlling for disease activity.

Methods—Ninety-nine patients 2–21 years of age with inflammatory bowel disease were recruited into this two-year longitudinal study. Medication possession ratios were calculated from pharmacy refill data, disease activity ratings were obtained from medical charts, and hospital and physician charges associated with an ICD-9 code for ulcerative colitis or Crohn's disease were obtained from the hospital's accounting database.

Results—An average total costs $d = .68$ effect size was observed between the increasing severity and stable low severity groups, but the CIs overlap. Conversely, patients with increasing non-adherence demonstrated significantly higher health care costs than patients with stable 10%, stable 11–20% or decreasing non-adherence.

Conclusions—Medication non-adherence is related to increased health care costs after controlling for disease severity. Patients with increasing non-adherence over time demonstrate more than a 3-fold increase in costs compared to adherent patients. Additionally, patients whose adherence improves over time incur approximately the same costs as those who are consistently adherent. This suggests that, in addition to leveraging prevention efforts to keep patients from becoming more non-adherent as treatment continues, efforts aimed at modifying adherence behavior may result in significant cost savings over time.

Keywords

adherence; health care costs; inflammatory bowel disease; behavioral

In the past ten years, annual national health expenditures in the United States (U.S.) have increased by over \$1 trillion¹ and now account for over 17% of the gross domestic product.² While health expenditures per capita in the U.S. are more than twice those of many other developed nations,³ the U.S. fails to provide better quality health care or achieve better health outcomes than other countries. Recognizing this disparity and the shortcomings of our current system, the United States Department of Health and Human Services is now prioritizing efforts (i.e., alternative payment models) that incentivize high quality and low cost health care.^{4,5} In light of these changes,⁶ there is a clear and present need to identify populations that could benefit from targeted efforts to impact health care cost, quality, and outcomes.

Pediatric inflammatory bowel disease is a chronic medical condition whose economic burden deserves attention as incidence rates are consistently growing worldwide and the condition is increasingly viewed as an emerging global epidemic^{7–9}. The annual national burden of pediatric IBD from hospitalizations alone is estimated to be \$152.4 million¹⁰, and since hospitalizations make up only one-third of costs for IBD¹¹, the total annual costs for pediatric IBD may be over \$450 million. As with many chronic conditions, there is significant patient-level variability in clinical and economic outcomes^{11–13}. Specifically, per patient annual costs range from under \$100 to tens of thousands of dollars^{10,11}, and patients may be adequately maintained on mesalamine or immunomodulators, or they may progress rapidly to more costly biologic therapies and/or surgery if remission is not sustained. Given this substantial cost, it is critical that we identify modifiable predictors of health care costs to target via prevention and intervention efforts in order to reduce costs and service utilization. In addition, because lifelong patterns of disease management are established in childhood and adolescence¹⁴, efforts to identify and target predictors of health outcomes in this demographic may improve the clinical course of chronic conditions across the lifespan.

A modifiable factor that may account for differences in health outcomes and health care costs is non-adherence to treatment recommendations. Among children with a chronic medical condition, non-adherence is related to increased health care use¹⁵. In adults with IBD, patients who are non-adherent to infliximab incur significantly higher direct medical costs compared to those who are adherent^{16–19}. Non-adherence to oral medications also impacts costs, with patients who are adherent to mesalamine incurring 12.5% lower annual medical care costs, 62% lower hospital admission costs, 45% lower Emergency Department visit costs, and 13% lower outpatient visit costs compared to those who are non-adherent²⁰. This study, however, categorized patients as adherent or non-adherent using a cut point of 80% rather than measuring adherence continuously, which limits the implications of the results as the clinically meaningful cut-point at which non-adherence significantly impacts clinical outcomes and health care utilization is not established and is likely to vary across medications²¹.

Non-adherence may lead to increased health care costs via several pathways. First, patients who are non-adherent to medications are more likely to experience increased symptoms or complications that require medical attention^{22–27}. Non-adherence may also result in a poor treatment response and escalation of therapy. For example, patients with IBD may be

advanced to potentially avoidable and costly biologics or surgery without their physician having the benefit of knowing the patients' adherence to oral medication therapy. Addressing the issue of nonadherence in this scenario would have substantial cost savings as patients maintained on oral medication therapy in IBD incur approximately \$3,600 annually, those maintained on biologics incur \$25,000 to \$40,000 annually, and surgery can cost \$50,000 or more depending on several factors^{28,29}.

There is a critical need to determine the relationship between non-adherence and health care costs in pediatric IBD, because children and adolescents (i.e., < 20 years old) have more frequent hospitalizations, ED visits, and outpatient visits than adults with IBD¹², and have medical costs in the highest quartile^{11,12}, or 17–105% higher than their adult counterparts¹¹. Given their age, they are also more likely to incur significantly greater health care costs across the lifespan compared to adults. Answering this question, however, requires a statistical approach that accounts for the variability in non-adherence within and across patients over time. Using statistical techniques that compare costs across patients who demonstrate different patterns of non-adherence will help determine who cost-minimization adherence-promotion efforts should target as well as the optimal timing of such interventions. Thus, we conducted this longitudinal cohort study to advance the understanding of the complex relationship between non-adherence and health care costs, while accounting for the impact of disease activity. We accomplished this by analyzing trajectories of non-adherence (as opposed to classifications of non-adherence) over the study period along with concurrent disease status and hospital charges billed for health care services (referred to in this article as “health care costs”). We hypothesized that at least three distinct trajectories (i.e., stable, increasing, decreasing) of non-adherence would be found, and that patients in the increasing non-adherence group would account for significantly greater health care costs after controlling for the effects of disease activity.

Patients and Methods

Study Design and Sample

This was a longitudinal, retrospective, observational, cohort study of adherence, disease activity, and health care costs. Data were collected retrospectively to prevent any adherence behavior change in participants that would have resulted from being monitored prospectively. Measures of non-adherence, disease severity, and health care costs were collected for each patient at monthly intervals over the 2-year period.

Patients between 2 and 21 years of age with a diagnosis of ulcerative colitis, Crohn's disease, or indeterminate colitis were recruited from the IBD Center at Cincinnati Children's Hospital Medical Center (CCHMC). Additional eligibility criteria included: the prescription of an immunomodulator (i.e., 6-MP/azathioprine) and/or aminosalicylates; and at least one outpatient IBD Center visit per year over a contiguous 2-year period.

Measures

Non-Adherence—Monthly adherence percentage for each patient was calculated using a medication possession ratio. To create equal time intervals, we calculated approximately 26

“months” in the 2-year study period using 28 days as the proxy for one month. The monthly medication possession ratio (MPR) is calculated via the formula:

$$\left(\frac{\text{number of daily doses dispensed per 28 days}}{28} \right) * 100$$
. Values were capped so that the range was 0–100. As the duration of medication prescriptions can vary (e.g., 30–180 days), measuring monthly adherence standardizes the unit of time between outcome measures for all patients. For any cases in which more than one month supply was dispensed, non-adherence was simply carried forward. For example, if a patient is dispensed a 3 month supply, month 3 data would reveal the nonadherence from months 1 and 2 as well as 3. For patients prescribed multiple medications during a 28 day period or whose prescribed medications changed, an overall monthly MPR was created averaging all adherence values (including both immunomodulators and aminosalicylates) for that month. An overall monthly MPR was used instead of multiple adherence values as it is not possible to attribute health care charges to a specific medication. The overall monthly MPR was then subtracted from 100 to convert this value to a measure of non-adherence (e.g., MPR = 70%, non-adherence = 30%). In order to evaluate the potential impact of patients not using their home medication supply while hospitalized and, thus, appearing to be more non-adherent, we reviewed each medical chart to determine the proportion of hospitalized days for the sample during the course of the study. Over the entire sample, patients were hospitalized for only 0.34% of the total number of days in the study. Given this extremely low percentage, the potential impact is negligible and non-adherence values were not adjusted for days hospitalized.

Disease Severity—Standard care in the IBD Center includes routine assessment of disease severity via Physician Global Assessment (PGA) in which physicians rate patient disease activity as “quiescent,” “mild,” “moderate,” or “severe.” This approach correlates well with objective measures of disease severity in IBD including the PCDAI³⁰ and PUCAI³¹. Disease severity at each month was defined as the most recent previous PGA rating. Patients with missing PGA data (n = 4) were excluded from the analyses.

Health Care Charges—Health care charges were used as a proxy for the value of health care services over the 2-year period. In reference to data in this study, “health care costs” is used to describe charges. All hospital and physician charges associated with an ICD-9 code for ulcerative colitis (556.x) or Crohn’s disease (550.x) were obtained from the hospital’s accounting database for the 2-year period. Any charges for biologic therapies were excluded in order to focus analyses on oral medication adherence and charges. Monthly health care charges were calculated using a gross costing approach by summing all charges for hospital and physician services within the 28-day period at the patient-level. Monthly health care charges were then adjusted to 2014 US dollars according to the medical care component of the Consumer Price Index.³² The outcome variable, total hospital charges over the 2-year period, was then computed by summing all adjusted monthly charges for each patient.

Procedures

Disease severity, demographic, and clinical variables were obtained via medical record review. Patient pharmacy refill records were obtained from patient/family identified

pharmacies to calculate MPR and non-adherence percent. Hospital billing records were used to calculate health care charges. Approval for study procedures was obtained from the Institutional Review Board. Patients and caregivers provided informed consent/assent prior to data collection.

Data Analyses

Analyses were performed in two steps. First, latent class growth mixture modeling (LCGMM) analyses were performed using SAS (Version 9.3) PROC TRAJ to identify unobserved subgroups of patients with similar longitudinal disease severity (PGA) and medication non-adherence data. In contrast to a multiple-group longitudinal model, where an observed variable (i.e., gender, ethnicity, IV group designation, etc.) is expected to explain a portion of the response variable variance over time, LCGMM assumes that the response variable variation over time has resulted from the presence of two or more unobserved subgroups in the dataset. LCGMM classifies participants within one of the two or more subgroups based on similarities of response variable scores over time. Each of the subgroups, thus, has its own unique average response variable change trajectory.

LCGMM analyses were performed first to determine whether $k = 2$ unobserved subgroups (heterogeneity) or a single group ($k = 1$; homogeneity) generated the PGA and non-adherence sample data. The number of distinct subgroups that generated the sample data was determined by examining the following: 1.) model parameter estimation convergence, 2.) longitudinal trend component (i.e., linear slope, quadratic change, cubic change, etc.) statistical significance within the k subgroup classes, 3.) minimized repeated measures residual variance estimates (σ^2) and a minimized model fit statistic (Bayesian information criterion [BIC]) values for a given k – subgroup classes vs. $k + 1$ subgroup classes solutions, both indicative of a better fit of a k – subgroup class model vs. a $k + 1$ subgroup class model to the sample data, and 4.) posterior probabilities for a k – subgroup solution that showed greater certainty in classifying individual participants to classes compared to a $k + 1$ subgroup solution. The possibility of $k = 1$ to 5 subgroup class solutions were examined, and k – subgroup solutions in which one of the classes comprised 5% or less of the participants in the sample data were discarded. The k subgroup solutions were then cross-tabulated to determine the number of individuals in each k disease severity class present within each of the k classes of non-adherence.

Second, descriptive statistics were used to examine the hypothesis that total charges differed across PGA and non-adherence subgroups. Means, standard deviations, and 95% confidence intervals (CI) for total charges were computed for each of the k subgroups. Subgroups with non-overlapping 95% CIs were considered to have significantly different total charges at $p < .05$ by definition. Effect sizes representing the magnitude of differences between subgroups were also calculated using Cohen's d .

Results

Descriptive statistics were conducted on demographic and disease parameters to describe relevant sample characteristics including age, gender, race, specific IBD diagnosis, and type of medication. Table 1 illustrates these descriptive data.

Trajectory Analyses

LCGMM results revealed that $k = 4$ subgroups best modeled the longitudinal variation in both disease severity and non-adherence. The four disease severity subgroups are described as: 1) an increasing disease severity group ($n = 16$), 2) a stable low disease severity group ($n = 51$), 3) a decreasing disease severity group ($n = 25$), and 4) a varying disease severity group ($n = 10$). Similarly, the four non-adherence groups (see Figure 1) are described as: 1) an increasing (i.e., worsening) non-adherence group ($n = 14$), 2) a stable 10% non-adherence group ($n = 18$), 3) a decreasing (i.e., improving) non-adherence group ($n = 21$), and 4) a stable 11–20% non-adherence group ($n = 46$). Because our focus in this study was on health care costs associated with non-adherence, only non-adherence subgroup trajectories and associated cost data are depicted.

Effect sizes were calculated to determine significant differences in costs between disease severity subgroups as well as non-adherence subgroups. These analyses demonstrated that total health care costs did not differ across disease severity subgroups. An average total costs $d = .68$ effect size was observed between the increasing severity (95% CI: \$28,978.17, \$151,028.76) and stable low severity groups (95% CI: \$21,577.62, \$56,044.19), but the 95% CIs for their respective mean total costs overlap (see Table 2). Conversely, patients with increasing non-adherence, or those whose adherence worsens over time ($M[SD] = \$109,866.88[\$113,204.77]$, 95% CI: \$50,566.59, \$169,167.20) demonstrated significantly higher health care costs than patients with stable 10% ($M[SD] = \$30,136.44[\$43,589.67]$, 95% CI: \$9,999.04, \$50,273.84, $d = -.98$), stable 11–20% ($M[SD] = \$44,855.20[\$61,316.53]$, 95% CI: \$27,135.57, \$62,574.83, $d = -.85$ [although the 95% CIs overlap]) or decreasing ($M[SD] = \$32,583.92[\$33,252.16]$, 95% CI: \$18,361.74, \$46,806.10, $d = -1.02$) non-adherence (see Table 3).

Discussion

In this emerging era of accountable care, organizations will be incentivized to reduce readmissions, achieve better health outcomes, and reduce health care utilization and costs. Traditionally, practitioners exhaust medical interventions, including pharmacotherapy, to improve disease severity with the expectation that costs will consequently decrease. These interventions are done with little to no data regarding the extent to which patients are adherent to the treatment. Therefore, a significant gap in care as well as our understanding of the factors that influence health care costs persists. Data from this study demonstrate that medication non-adherence is related to significant increases in health care costs after controlling for the impact of disease severity. Specifically, patients with increasing non-adherence over time incur more than a 3-fold increase in health care costs compared to patients who are consistently adherent over time. Additionally, patients who demonstrate improvement in adherence over time incur approximately the same costs as those who are consistently adherent. This suggests that, in addition to leveraging prevention efforts to keep patients from becoming more non-adherent as treatment continues, treatment efforts aimed at modifying adherence behavior can potentially result in significant cost savings over time.

Many patient- and system-level prevention and intervention possibilities exist. Prevention efforts can focus on regular assessment of adherence and feedback to the patient and

caregivers regarding how closely the patient has adhered to a treatment regimen. Moreover, assessment of contextual factors that might contribute to non-adherence, such as socioeconomic status and psychosocial issues, can provide the opportunity for delivery of adjunctive health care services targeting issues that can have wide ranging negative health effects. With regular monitoring of adherence (e.g., via pharmacy refill, electronic monitoring, etc.), early intervention can target non-adherence and correct it prior to significant long-term health and economic costs. Clinic-based interventions can be implemented as part of regular care. These interventions must be very focused due to the limited time available in clinic and, while strictly educational interventions have not been successful^{33–38}, use of tools such as personal action plans can help to identify self-management goals for patients. Behavioral intervention delivered via separate outpatient care is promising^{39–41}; however, the number of trained professionals able to deliver these interventions is limited. With the ubiquitous use of technology by patients, options for telemedicine and mobile health applications are readily available and can increase practitioners' ability to provide inter-visit care to support better self-management. Insurance reimbursement policies and professional licensure laws need to accommodate these capabilities. Finally, system interventions have the potential to produce widespread change. Implementation of procedures such as pre-clinic planning can allow practitioners to plan the medical visit and use adherence data for self-management intervention planning. Adoption of uniform assessment procedures across subspecialties within a hospital system standardizes the approach to adherence monitoring and can destigmatize the need for self-management support. Furthermore, the current approach to health care reform itself has the potential to improve adherence through increased pressure on organizations to provide better care within a more restrictive cost structure.

In this study, we employed an objective assessment of non-adherence using pharmacy refill records to compute MPR. In addition, our use of a retrospective longitudinal design is a methodological strength with regard to adherence data as this approach precluded the likelihood of patients' social desirability response, which is common with prospective monitoring of adherence. Furthermore, our statistical approach using LCGMM provided a unique longitudinal examination of the relationship between non-adherence and health care charges data while concurrently controlling for disease activity. This allowed us to identify groups of patients with similar longitudinal non-adherence patterns, thus creating categories of patients based on long-standing non-adherence behavior rather than a cross-sectional categorization that does not capture trends in this highly variable behavior. Additional population-based research is needed to better understand the demographic and disease characteristics of patients within each of these identified trajectories to aid in intervention development.

Our assessment methodology had one notable limitation. That is, disease activity assessments were not aligned exactly with non-adherence assessments. This concern is mitigated by the fact that disease activity in this sample was predominantly mild, and rapid progression of illness is uncommon in IBD. Thus, our use of the most recent disease activity assessment was appropriate. Nevertheless, future research should examine disease activity in regular intervals aligned with assessments of non-adherence. Additionally, our aim for this study was restricted to examination of the costs associated with non-adherence to the two

most common oral medication therapies for IBD. While a smaller proportion of the sample received biologic therapy in addition to at least one of the oral medications of interest, the charges associated with biologics was not captured in our analyses. Thus, our results are specific to oral medication non-adherence and health care charges. Furthermore, our use of health care charge data carries important implications. Charges include direct institutional costs as well as indirects and profits, which often vary across hospitals. As a result, the dollar amounts presented in this manuscript may not generalize to other institutions with differing billing practices or insurance contracts. However, as “costs” are typically derived using a cost to charge ratio, the direction and magnitude of the relationship between non-adherence and costs is likely to resemble the relationship demonstrated in this study. Future economic evaluations focused on determining the dollar amount saved by improving adherence in a particular population will require inclusion of cost data.

Conclusion

This study represents an important step in documenting the problem of nonadherence and the potential impact it has on health care costs. This has important ramifications for health care reform and how practitioners approach adherence assessment and intervention in routine care. Continued research is needed to determine the long-term impact of non-adherence on health care costs in other populations. More importantly, research investigating the cost-effectiveness or cost offset of providing prevention and/or early intervention services to improve adherence in patients is a critical need. With sustained efforts to reduce non-adherence in chronic conditions, we may see concomitant reduction in health care costs.

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Figure 1.

Trajectories of medication non-adherence subgroups over two year study period.

Table 1

Clinical and Demographic Characteristics

Variable	n (%)	M (SD)	Range
Age, years		12.48 (3.87)	3.74 – 19.99
Gender, female	50 (51%)		
Racial and Ethnic Category *			
White	88 (89%)		
Black or African American	6 (6%)		
Asian	1 (1%)		
American Indian or Alaska Native	1 (1%)		
Other	2 (2%)		
Public Insurance	7 (7%)		
Diagnosis			
Crohn's Disease	69 (70%)		
Ulcerative Colitis	23 (23%)		
Indeterminate Colitis	7 (7%)		
Disease Severity (at baseline)			
Quiescent	65 (66%)		
Mild	23 (23%)		
Moderate	11 (11%)		
Severe	0 (0%)		
Medication Monitored for Adherence			
ASA	53 (54%)		
6MP and ASA	40 (40%)		
6MP	6 (6%)		
Prescribed Biologics at Baseline, yes	0 (0%)		
Prescribed Biologics During Study, yes	27 (27%)		
Underwent Surgery During Study, yes	22 (22%)		
Hospitalizations			
Number of Hospitalizations		0.42 (1.09)	0 – 6
Days Hospitalized		2.30 (7.66)	0 – 46
Clinic Visits		5.46 (3.29)	1 – 23

*
n = 1 missing

Table 2

PGA Group Differences in Health Care Charges

	M(SD) (2014 US\$)	Cohen's <i>d</i> (95% CI)		
		Increasing Severity	Stable Low Severity	Decreasing Severity
Increasing Severity	\$90,003.46 (\$112,260.12)			
Stable Low Severity	\$38,810.91 (\$62,790.96)	.68 (.06, 1.30) *		
Decreasing Severity	\$45,249.28 (\$46,440.29)	.60 (−.09, 1.28)	−.11 (−.59, .37)	
Variable Severity	\$54,756.05 (\$54,736.20)	.38 (−.46, 1.21)	−.26 (−.94, .42)	−.19 (−.92, .55)

*
CI does not include 0

Table 3

Non-Adherence Group Differences in Health Care Charges

		Cohen's <i>d</i> (95% CI)			
		Stable	10% Non-Adherence	Stable 11–20% Non-Adherence	Decreasing Non-Adherence
Stable	10% Non-Adherence				
Stable	11–20% Non-Adherence	–.26	(–.81, .29)		
Decreasing	Non-Adherence	–.06	(–.69, .57)	.23	(–.29, .75)
Increasing	Non-Adherence	–.98	(–1.73, –.23) *	–.85	(–1.46, –.23) *
					–1.02
					(–1.73, –.29) *

*
CI does not include 0