

ORIGINAL ARTICLE

Behavioral functioning and treatment adherence in pediatric eosinophilic gastrointestinal disorders

Kevin A. Hommel^{1,2,3,4}, James P. Franciosi^{1,2,5}, Wendy N. Gray^{1,3,4}, Elizabeth A. Hente^{1,3,4}, Annette Ahrens^{1,6} & Marc E. Rothenberg^{1,2,6}

¹Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; ²University of Cincinnati College of Medicine, Cincinnati, OH, USA;

³Center for the Promotion of Treatment Adherence and Self-Management, Cincinnati, OH, USA; ⁴Division of Behavioral Medicine and Clinical Psychology, Cincinnati, OH, USA; ⁵Division of Gastroenterology, Hepatology, and Nutrition, Cincinnati, OH, USA; ⁶Division of Allergy and Immunology, Cincinnati, OH, USA

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Correspondence

Kevin A. Hommel, Center for the Promotion of Treatment Adherence and Self-Management, Division of Behavioral Medicine and Clinical Psychology, MLC-7039, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA.

Tel.: 513 803 0407

Fax: 513 803 0415

E-mail: kevin.hommel@cchmc.org

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Abstract

Objective: To examine behavioral predictors of treatment adherence in patients with eosinophilic gastrointestinal disorders (EGID).

Methods: Participants were 96 patients 2.5–18 yr of age with eosinophilic esophagitis or eosinophilic gastroenteritis and their caregivers (mother, father). We assessed maternal and paternal report of child/adolescent internalizing symptoms (e.g., anxiety, depression) and externalizing symptoms (e.g., aggression, anger) using the Behavior Assessment System for Children, 2nd edition (BASC-2). A multi-informant adherence assessment approach and an 80% cut point were used to classify patients as adherent or non-adherent.

Results: Sociodemographic predictors did not distinguish between adherent and non-adherent patients. Maternal report of internalizing symptoms significantly correlated with non-adherence ($p < 0.001$). Post hoc probing revealed a significant contribution of depression, with depressed patients being more likely ($OR = 7.27$; $p < 0.05$) to be non-adherent than non-depressed patients. Paternal report of internalizing and externalizing symptoms was not associated with non-adherence.

Conclusions: Maternal report of patient internalizing behavioral symptoms, particularly depression, is significantly associated with non-adherence in patients with EGID. These symptoms are potential risk factors and should be considered when assessing and treating non-adherence. Clinical care of patients with EGID should include routine screening for depression.

Eosinophilic gastrointestinal disorders (EGID) are a collection of chronic medical conditions in which an excessive accumulation of eosinophils in the gastrointestinal tract causes site-specific inflammation and damage (1). The pathogenesis involves allergen-induced inflammatory responses associated with a conserved gene expression pattern (2, 3). While eosinophilic inflammation can occur anywhere in the gastrointestinal tract, it is often concentrated in the esophagus (eosinophilic esophagitis [EoE]) or the stomach and small intestine [eosinophilic gastroenteritis (EGE)]. Patients with EGID may experience a range of undesirable disease symptoms including, but not limited to, failure to thrive, abdominal pain, vomiting, diarrhea, gastric dysmotility, and dysphagia (4). Prevalence of EoE, the most common EGID,

has been estimated at ~1:1000 and, along with other types of EGID, is rising to levels that may be more than well-known gastrointestinal diseases such as pediatric inflammatory bowel disease (IBD) (1, 2, 5).

Management of EGID is comprehensive and may involve routine endoscopies with biopsies, severe dietary modifications, and long-term oral medications. It is not uncommon for patients to be put on an elimination diet in an attempt to remove suspected pathogenic foods from the diet. In severe cases, amino acid-based elemental formulas may serve as the sole source of nutrition (6). With regard to oral medication, swallowed glucocorticosteroids using formulations originally produced for asthma (such as metered-dose inhalers and liquids designed for nebulization) are commonly prescribed.

However, use of these medications is unpleasant because of their taste and perceived association with the side effects of systemic glucocorticoids (e.g., hirsutism, acne, impaired growth, cushingoid appearance, and mood problems). Additionally, a small subset of patients may develop local *Candida* esophagitis as a result of EGID treatment.

Non-adherence is a major concern for all patients with chronic illness, with non-adherence prevalence rates averaging ~50% in children (7) and up to 88% in adolescents (8). Problematic adherence rates have also been observed in both IBD and celiac disease, two gastrointestinal disorders whose treatment is greatly similar to that of EGID. For IBD, medication non-adherence prevalence rates range as low as 16% (9) up to an alarming 88% (8). In celiac disease, non-adherence to a gluten-free diet varies widely, from 5% to 70% (10, 11). Little is known regarding adherence rates in the pediatric EGID population. We previously reported high variability in adherence to medication, dietary modifications, and tube feedings in pediatric patients with EGID (12). In this report, adherence to prescribed medications was the most problematic aspect of EGID treatment, with an overall medication non-adherence prevalence rate of 30%. Non-adherence in EGID is a significant concern as eosinophilic inflammation may result in increased morbidity, progressive scarring, and gastrointestinal dysfunction (5); yet, the factors that predict non-adherence are unknown.

Identifying contributing factors to poor adherence among patients with EGID is paramount given the documented rates of non-adherence and the associated health consequences. However, the available literature provides little guidance as to what factors may be most influential in pediatric adherence to EGID treatment. For other chronic pediatric diseases [asthma (13), diabetes (14, 15), renal transplant (16), HIV (17, 18), and IBD (19)], behavioral problems, such as externalizing symptoms (e.g., attention problems, hyperactivity, oppositional behavior) and internalizing symptoms (e.g., anxiety and depression), are related to poor adherence. Whether a similar relationship exists for patients with EGID is unknown, yet critically important for improving treatment adherence.

Though limited, studies in patients with EGID suggest that they may be at particular risk for problematic psychosocial functioning. Compared to patients with cystic fibrosis, IBD, epilepsy, type 1 diabetes, and renal transplant, patients with EGID have significantly lower emotional health-related quality of life (HRQOL) and the lowest overall HRQOL (20). They are also at risk for higher internalizing and externalizing symptoms. In a recent study, 45% of patients with EGID demonstrated clinically elevated levels of internalizing symptoms, whereas only 2% of controls were in the clinical range (21). Higher overall rates of depressive symptoms were also reported in this study. Given the high prevalence of medication non-adherence and psychosocial difficulties in patients with EGID, examination of the relationship between behavioral factors and adherence in this population is likely to inform the development of effective adherence intervention protocols aimed at improving patient health outcomes.

We designed this cross-sectional study to examine behavioral predictors of medication non-adherence in patients with

EGID. Using a multi-informant assessment approach, internalizing and externalizing symptoms were examined as individual predictors of non-adherence to oral medication. On the basis of prior literature in other pediatric populations, we hypothesized that caregiver reports of patient internalizing and externalizing symptoms would predict poor adherence to oral medications in patients with EGID, with internalizing symptoms accounting for the majority of variance in medication adherence.

Methods

Participants

The institutional review board at Cincinnati Children's Hospital Medical Center (CCHMC) approved this study. Patients diagnosed with EoE and EGE, collectively EGID, were recruited from the Cincinnati Center for Eosinophilic Disorders (CCED). Inclusion criteria for eligibility included (i) patient age between 2.5 and 18 yr and (ii) primary diagnosis of EGID. Patients were excluded from the study for a diagnosis of (i) severe developmental delay as determined by medical chart review or (ii) a comorbid chronic condition as determined by medical chart review. Participants were (i) new patients, both local and referral, seen in the CCED and (ii) existing patients followed in outpatient gastroenterology and their caregivers (i.e., mothers and/or fathers). A total of 116 patients were contacted for the study. Nine declined participation (5 – time constraints, 2 – not interested in research, and 2 – family overwhelmed with clinic visit), one withdrew from participation (did not complete questionnaires), one was diagnosed with reflux, one was excluded from analyses because of procedural error, and eight did not return complete data sets. This produced a final sample of 96 participants with EGID and their caregivers.

Study design and procedures

Participants for this cross-sectional study were systematically identified via medical chart review by study coordinators and were approached during clinic or endoscopy appointments or while attending an educational conference. Participants provided informed consent/assent, and self-identified primary caregivers completed caregiver-report, patient age-specific assessments during the study visit. Study visit procedures differed slightly by appointment type (i.e., clinic appointment, outpatient surgery, or conference meeting). To best accommodate families, prepaid, addressed envelopes were available for those who did not have ample time in clinic to complete the study. Families then returned completed forms by mail. Study staff reviewed forms upon receipt and conducted follow-up phone calls to collect any missing data.

Measures

Caregivers provided demographic data including caregiver ages, education, marital status, employment status, and household income.

Behavior Assessment System for Children, 2nd edition (BASC-2) The BASC-2 Parent Rating Scales [child aged 2–18 yr; separate forms for developmentally appropriate assessments – preschool (ages 2–5 yr), child (ages 6–11 yr), and adolescent (ages 12–21 yr)] were used as a caregiver report to measure patients' emotional and behavioral functioning. Domains include externalizing, internalizing, school problems, adaptive skills, and other problems, and each domain is comprised of several subscales (22). For each question, caregiver respondents were given a specific behavior and asked to rate the frequency with which their child displays that behavior using a four-point scale (never, sometimes, often, and almost always). Responses were scored using a computerized scoring program according to age- and gender-normed data resulting in *t*-scores for all domains and subscales. *T*-scores above 69 indicate the presence of 'clinically significant' symptoms. The BASC-2 is a well-validated measure demonstrating adequate internal consistency ($\alpha = 0.90$ – 0.94) and test–retest reliability ($r = 0.84$ – 0.90) (23).

EGID Treatment Adherence Questionnaire (TAQ)

The TAQ was specifically developed for use in this study to assess adherence and adherence-related factors involved with EGID treatment regimens. This 12-item parent-report questionnaire measures pediatric patients' adherence to medication and dietary restriction regimens. For the purpose of this study, only medication adherence was analyzed. This decision was based on prior research indicating that adherence to prescription medications is most problematic in patients with EGID (12). A medication non-adherence percentage was calculated using this equation: number of doses missed over past 14 days/number of doses prescribed over past 14 days $\times$ 100. The number of missed doses was determined by asking the following: 'Children and adolescents also often have difficulty taking medications. They may forget, have activities that conflict with taking medicine, or just decide not to take a dose of medication. There may be other reasons too. All of these reasons are completely understandable. Please tell us the number of medication doses your child/adolescent has missed in the past 2 wks: _____'.

Data analyses

Raw data were entered into a secure electronic database, and data quality analyses were conducted. All descriptive and inferential data analyses were conducted in PASW 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were conducted for demographic, adherence, and behavioral functioning data. A multivariate analysis of variance (MANOVA) test was conducted to examine potential differences in adherence across patient diagnostic, ethnic, gender, age, and recruitment source (i.e., CCED, gastroenterology clinic, conference) categories. Age was categorized as toddler (age, 2–4 yr; $N = 26$), young child (aged 5–7 yr; $N = 25$), child (aged 8–12 yr; $N = 28$), and adolescent (aged 13–18 yr; $N = 17$), consistent with prior studies in pediatric populations (24). Linear regression analyses were performed to examine the contribution of internalizing and externalizing

behavioral problems to both maternal and paternal report of medication adherence. Planned post hoc analyses included linear regression analysis to determine specific subscales of domains that significantly predicted medication adherence as well as chi-square analysis to examine the risk of medication non-adherence based on behavioral problem scales. For linear regression analyses, adherence data were analyzed as a continuous variable. For chi-square analysis, adherence data were dichotomized into non-adherent vs. adherent. Per convention in the adherence literature, an 80% cut point for non-adherence was utilized for this study. All tests were considered significant at the $p < 0.05$ level.

Results

Patient demographics

Descriptive data for the demographic and disease parameters of this study (i.e., patient age, gender, ethnicity, diagnosis, primary and secondary caregiver age, relation to patient, marital status, employment status, education level, and annual family income) are shown in Table 1. A large percentage of primary caregivers were married (89.6%), had at least some level of post-secondary education (94.8%), and had a high annual family income (median, \$100,001–125,000). Non-adherence and behavioral functioning data are illustrated in Table 2. Using an 80% cut point for adherence, non-adherence prevalence rates ranged from 3.1% (father-reported) to 10.4% (mother-reported).

Demographic predictors of adherence

Preliminary analyses consisted of examining potential differences in adherence across several key variables included in the study. A MANOVA revealed no significant differences in mother-reported non-adherence based on recruitment source ($F = 0.35$, $p > 0.05$), diagnosis ($F = 0.27$, $p > 0.05$), ethnicity ($F = 1.87$, $p > 0.05$), patient gender ($F = 0.31$, $p > 0.05$), or age category ($F = 0.18$, $p > 0.05$). No significant differences were observed in father-reported non-adherence based on recruitment source ($F = 0.15$, $p > 0.05$), diagnosis ($F = 1.17$, $p > 0.05$), ethnicity ($F = 0.56$, $p > 0.05$), patient gender ($F = 2.73$, $p > 0.05$), or age category ($F = 0.54$, $p > 0.05$).

Relationship between internalizing and externalizing symptoms and adherence

We conducted multiple linear regression analyses to examine the contribution of patient internalizing and externalizing behavioral problems to parent-reported non-adherence. For each equation, internalizing and externalizing domain *t*-scores were entered simultaneously with parent-reported non-adherence serving as the dependent variable (see Table 3). Father-reported internalizing ($p > 0.05$) and externalizing ($p = 0.07$) behavioral problems did not significantly contribute to father-reported non-adherence. In contrast, mother-reported internalizing behavioral problems contributed significant

Table 1 Demographic and disease-related descriptive data

<i>N</i>	96
Patient age (yr $\pm$ s.d.)	8.31 $\pm$ 4.32
Patient gender (% male)	77.1%
Ethnicity (% White, not Hispanic origin)	84.4%
Primary caregiver relation to patient (% biological mothers)	95.8%
Primary caregiver age (yr $\pm$ s.d.)	39.70 $\pm$ 5.82
Primary caregiver marital status (% married)	89.6%
Primary caregiver education level (% with at least some college education)	94.8%
Primary caregiver employment status (%)	
Employed part-time	27.1%
Employed full-time	32.3%
Secondary caregiver relation to patient (% biological fathers)	89.8%
Secondary caregiver age (yr $\pm$ s.d.)	42.14 $\pm$ 6.85
Secondary caregiver marital status (% married)	95.5%
Secondary caregiver education level (% with at least some college education)	85.4%
Secondary caregiver employment status (%)	
Employed part-time	1.1%
Employed full-time	93.2%
EGID diagnosis (%)	
Eosinophilic esophagitis	85.4%
Eosinophilic gastroenteritis	14.6%
Median annual family income	\$100,001–125,000

EGID, Eosinophilic gastrointestinal disorder.

variance to mother-reported non-adherence ($t = 4.14$, $p < 0.001$); externalizing problems did not significantly contribute ($p > 0.05$).

Post hoc probing of significant relationship between internalizing problems and adherence

Post hoc probing of the significant mother-reported internalizing behavioral problems–non-adherence relationship was conducted to examine which specific subscales of the internalizing domain accounted for this relationship. A linear regression was conducted in which the anxiety, depression, and somatization subscales were entered simultaneously with mother-reported non-adherence serving as the dependent variable. This analysis revealed that both anxiety and somatization did not contribute significant variance to non-adherence, whereas depression was a significant predictor ($t = 3.10$, $p < 0.01$). Additionally, a chi-square analysis was conducted to examine the risk of medication non-adherence based on the behavioral problem symptoms. This analysis revealed that patients who demonstrated clinically significant depression symptoms were more likely ($OR = 7.27$) to demonstrate

Table 2 Non-adherence and behavioral functioning data

<i>N</i>	96
Mother-reported:	Mean $\pm$ s.d.
Adherence	91% $\pm$ 14%
Externalizing Behavior Problems	48.98 $\pm$ 9.17
Internalizing Behavior Problems	52.06 $\pm$ 12.69
Anxiety	49.13 $\pm$ 10.32
Depression	49.55 $\pm$ 10.48
Somatization	56.40 $\pm$ 15.96
Father-reported:	
Adherence	95% $\pm$ 6%
Externalizing Behavior Problems	51.34 $\pm$ 8.36
Internalizing Behavior Problems	56.86 $\pm$ 10.00
Anxiety	51.95 $\pm$ 9.02
Depression	52.09 $\pm$ 8.85
Somatization	62.23 $\pm$ 12.30

medication non-adherence ($\chi^2 = 6.72$, $p < 0.05$) than non-depressed patients.

Discussion

This study is the first to examine caregiver-reported behavioral predictors of medication non-adherence in pediatric patients with EGID. Results revealed that father-reported externalizing and internalizing and mother-reported externalizing behavioral problems did not significantly contribute to medication non-adherence, whereas mother-reported internalizing behavioral problems emerged as a significant predictor of medication non-adherence. Moreover, depressive symptomatology significantly predicted non-adherence after statistically controlling for the influence of anxiety and somatization. Patients who exhibited clinically significant depression had a sevenfold greater risk of being non-adherent compared to non-depressed patients. It is plausible that patients who develop depressive symptoms might become non-adherent, as has been reported in prior research in other health conditions (25–27). Certainly, patients with EGID, who experience abrupt and significant changes in diet, medication regimen, and lifestyle, are likely to be prone to affective comorbidity such as depression. This may in turn lead to decreased motivation to adhere to treatment regimens or work through issues/barriers that result in non-adherence. Alternatively, internalizing problems such as depression might work in a bidirectional manner with treatment adherence: decreased motivation owing to depression may result in non-adherence, and increased non-adherence leads to poorer health and overall functioning, which further exacerbates depressive symptoms. Unfortunately, the cross-sectional nature of this study precludes testing of these conceptual models. Prospective longitudinal studies are urgently needed to further characterize risk factors for medication non-adherence and depression in patients with EGID, as these results would impact treatment considerations for patients.

Table 3 Multiple regression model of internalizing and externalizing behavioral symptoms predicting adherence

Variables	β	t	R^2	Partial correlation	F
Equation 1 (DV = mother-reported non-adherence)					
Step			0.20		9.71**
Mother-reported BASC-2 internalizing problems	0.45**	4.14		0.42	
Mother-reported BASC-2 externalizing problems	-0.02	-0.20		-0.02	
Equation 2 (DV = father-reported non-adherence)					
Step			0.09		1.74
Father-reported BASC-2 internalizing problems	-0.13	-0.77		-0.13	
Father-reported BASC-2 externalizing problems	0.32	1.86		0.29	
Equation 3 (post hoc; DV = mother-reported non-adherence)					
Step			0.25		8.86**
Mother-reported BASC-2 anxiety	0.18	1.35		0.15	
Mother-reported BASC-2 depression	0.38*	3.10		0.33	
Mother-reported BASC-2 somatization	-0.00	-0.03		-0.00	

* $p < 0.01$; ** $p < 0.001$. BASC-2, Behavior Assessment System for Children, 2nd edition; DV, dependent variable.

Notably, we found significant association between internalizing behavioral problems and non-adherence for mother-reported variables but not father-reported variables. This difference may have resulted from greater involvement by mothers (than by fathers) in patient care, leaving mothers more attuned to their children's behavioral and emotional functioning as well as their adherence to recommended therapies. Fathers, while probably knowledgeable of the disease and its recommended treatments, may be less familiar with these behavioral nuances.

The findings of this study have two important clinical implications. First, because internalizing problems may go undetected or misinterpreted (e.g., depression masked by anxiety symptoms), it would be optimal to conduct routine clinical assessment of critical internalizing symptoms, particularly depression. Depression screeners, such as the Children's Depression Inventory Short Form (28), can be completed within 2–5 min and could be administered either in a waiting room or in the exam room. When a clinical level of depression is identified, the patient should be referred to a mental health provider such as a clinical psychologist. Second, the findings suggest that behavioral interventions that focus on improving adherence to medication should also focus on the treatment of depression. As only a subgroup of patients will require this additional treatment, it could be accomplished in modular format, with most patients receiving treatment for non-adherence and some patients receiving the additional adjunctive treatment for depression.

Employing a widely used, comprehensive, validated, and developmentally appropriate measure of behavioral functioning allowed us to examine both broad and specific behavioral factors that influence the medication adherence of these patients. The multi-informant approach to adherence assessment allowed us to examine differential ratings and their association with behavioral functioning. The sample size was fairly large considering the prevalence of these

disorders, and we recruited both local and referral patients. Nevertheless, our findings should be interpreted within the context of a few limitations. First, our sample, while representative of the population, was primarily men and Caucasian. Thus, these findings might not generalize well to underrepresented groups within EGID. Second, our measure of adherence was parent-report and was developed for the purpose of this study. However, the construction of this measure was guided by the recommendations of Rapoff (29) and Mackner and Crandall (30) to improve the validity of self/parent-report measures of adherence. As per their recommendations, our measure of adherence was phrased in a non-judgmental manner, and non-adherence was normalized to minimize bias (e.g., social desirability) in reporting. Third, the cross-sectional study design limits any inferences of causality between non-adherence and internalizing behavioral problems and precludes examination of trajectories of behavioral change in these variables over time. However, cross-sectional studies are useful in exploring potential cause-effect relationships that should be further demonstrated in longitudinal studies.

Further research is needed in several areas. Longitudinal assessment of self-management behavior and related psychosocial factors will help to identify the stability of associations between these variables as well as the design and optimal timing of behavioral interventions to treat non-adherence and behavioral problems that may contribute to poor self-management. Additionally, the degree to which adherence and self-management impact health outcomes, such as disease severity and eosinophil count, will be important for understanding the need to address non-adherence. Using objective measures of medication adherence will help to further define the prevalence and frequency of non-adherence by providing an unbiased assessment of adherence. Finally, assessment of additional self-management behaviors, such as dietary habits, will provide a clearer picture of contributors to health outcomes in the pediatric EGID population.

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