THE ROLE OF TRANSITION AMONG PEDIATRIC-ONSET INFLAMMATORY BOWEL DISEASE PATIENTS

Ph.D. Thesis

Dr. Luca Tóbi

Doctoral School of Károly Rácz Clinical Medicine

Semmelweis University

Supervisor: Áron Cseh, MD, Ph.D

Official Reviewers: Petra Golovics, MD, Ph.D.

Árpád Patai, MD, Ph.D.

Head of the Complex Examination Committee: András Szabó, Prof., D.Sc.

Members of the Complex Examination Committee: Tibor Ertl, Prof., D.Sc.

András Tislér, MD, Ph.D.

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INTRODUCTION

Over the past 250 years, IBD emerged from sporadic cases to a global entity, impacting millions worldwide [1]. Approximately 10% of all IBD patients have a **pediatric-onset** disease (PIBD), of whom 6% are diagnosed before 6 years of age, categorized as very early onset, and 1% diagnosed within their first year of life [21-23]. PIBD is thought to be more complex and extensive compared to the adult-onset form, often exhibiting a more severe phenotype and rapid progression [46].

Ensuring an uninterrupted, comprehensive, and accessible healthcare throughout adolescence is essential in achieving the best possible disease course and outcome for PIBD patients, underscoring the significance of transition in their care [116]. **Transition** was first defined by Blum et al. in 1993 as a purposeful, planned movement of adolescents or young adults with chronic conditions from the pediatric to the adult healthcare system, including the gradual shift of the healthcare- and disease-related responsibilities from the caregivers and the parents to the patients [117]. In contrast, **transfer** refers solely to the point of handover of care between pediatric and adult healthcare-providing teams [116, 118, 119]. Transitional care has gained increasing attention over the past decade, especially considering the rising incidence of pediatric-onset IBD cases. Despite the emerging need, based on the lack of data from primary research to guide the recommendations, there are currently **no official consensus guidelines and standardized transitional practices** regarding IBD patients**.**

OBJECTIVES

We aimed our research to examine three main questions:

(1) What are the determinants of a successful transitioning process?

(2) What are the short- and long-term effects of the changing process to adult care, including the comparison between transition and self-transfer on the disease activity, course, and patient compliance?

(3) What are the unique characteristics of PIBD patients that require special attention in adult care?

METHODS

Our longitudinal, follow-up, controlled observational study incorporated a retrospective and a prospective data collection period, with the aim to analyse the effects of the changing period to adult care, including the comparison of a structured transitional program with self-transfer on the disease course, activity, and compliance of the patients. Furthermore, we examined the determinants of a successful transfer and the special characteristics of the PIBD patients, that require special attention in adult care. The project was carried out in the *Pediatric Center of Semmelweis University* (Budapest, Hungary), in cooperation with the *Department of Surgery, Transplantation, and Gastroenterology* and the *Department of Internal Medicine and Oncology of Semmelweis University*.
The study was performed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

1. Study period: The study period was 20.5 years, between 01.09.2001 and 01.03.2022.

2. Data collection: We collected data from the medical systems of the participating Clinics and the *eHealth Infrastructure of Hungary*. The data was reviewed retrospectively until 2018, thenceforth prospectively.

3. Inclusion and exclusion process

Inclusion criteria: All 382 PIBD patients (including CD, UC, and IBD-U) treated partially or entirely in our Pediatric Center during the examination period were available for the initial inclusion process in the study.

Exclusion criteria: Due to inaccessible medical data from the study period 31 patients were excluded, resulting in 351 patients being enrolled in our research.

Transition and self-transfer: Of the included 351 patients, 152 were moved to adult care during the examination period, of whom 73 were enrolled in our transitional program, whereas 79 adolescents self-transferred to adult care and served as our control group. There was no significant difference between the two groups considering either of the examined patient-, disease-, or treatment-related variables noted in the data collection section. Both self-transfer and transition were initiated in 2015. Until 2018 the transitional meetings were held irregularly, thereafter monthly.

4. Study design: Our transitional program consisted of an integrated *educational (mentor) program* and a *joint transitional meeting* with a written *handout summary*.

Mentor program: From the age of twelve, patients had the opportunity to be enrolled in our age-appropriate, personalized educational program.

Last year before moving to adult care: A year before the planned transfer to adult care, we actively started to prepare all of our patients, regardless of their participation in the mentor program.

Timing of the transfer: We aimed the transfer after finishing high school, around 18 to 19 years of age, with a disease in stable remission. Special requests from the patients considering the timing of their transfer were also taken into consideration.

Joint transitional meeting, adult healthcare providers: The joint transitional meetings were held in our Pediatric Center, with the attendance of the former pediatric and the future adult care provider, the transitional coordinator, and the patient.

A detailed *handout summary* was prepared for the meeting, which summarised the most important information about the medical history of the patient, as well as the former disease course, treatments, hospitalizations, surgeries, and diagnostic results regarding their inflammatory bowel disease.

5. *Statistical analysis:* $P < 0.05$ was considered significant. We employed Fisher's exact test to assess the association between categorical variables. To examine the differences between continuous variables, Welch's test was used, and in the case of non-normal distributions, the Mann-Whitney test was employed. The Cox proportional hazard model was applied to evaluate the impact of various variables on the occurrence of the outcome variable. For Kaplan-Meier curves, cumulative events were plotted, and the curves were compared using the log-rank test.

Ethical considerations: The Semmelweis University Clinical Research Committee accepted our study design and we were informed that no further ethical allowance is required.

RESULTS

1. Transition and self-transfer to adult care

During the examination period, **43.3% (n = 152) of all patients got moved to adult care, of whom 73 (48%) enrolled in our transitional program and 79 (52%) self-transferred to adult care**. A significantly **higher proportion of the transitioned patients had their disease in remission at the time of transfer** to adult care than the self-transferred patients (91.04% vs. 68.16%, *p = 0.0012*; OR 0.2101 [95% CI: 0.08115 - 0.5472]). **The mean time elapsed between the last pediatric and the first adult care visit was significantly higher in the self-transferred group than in the transitional group** (361.95 ± 476.01 days vs. 141.44 ± 158.43 days, *p = 0.0002)*.

2. Lost-to-follow-up patients

During the study period, 49 patients discontinued their medical care, accounting for 13.96% of all patients. The 5.13% **lost-to-follow-up rate reported in pediatric care significantly increased after being transferred to adult care**, affecting every fifth patient (20.4%, *p ‹ 0.0001*, OR 5.331 [95% CI: 2.900 to 9.798]). **The rate of discontinuation of care was the highest during the changing period from the pediatric to the adult health care system**, reaching 12.66% of all patients, accounting for 8.22% of the transitioned and 10.53% of the self-transferred patients (*p = 0.4540*; OR 0.6179 [95% CI: 0.2109 - 1.6650]).

Transition showed to be a significant protective factor for continuing care, as after the initiation of the healthcare provider changes 13.7% (n = 10) of the transitioned and 26.58% (n = 21) of the self-transferred patients discontinued their medical care (*p = 0.0367*; OR 0.4384 [95% CI: 0.193 - 1.018]. With Kaplan-Meier analysis, compared to the transitioned group the **self-transferred patients were shown to be at a 1.59-fold higher risk of discontinuing their medical care after leaving pediatric care**, including both the changing and the adult healthcare period (*p = 0.0489*).

The mean time elapsed since loss of care (last attended visit) was significantly higher among the self-transferred patients compared to the ones enrolled in our transitional program (2.71 ± 1.48 years vs. 1.65 ± 0.90 years, *p = 0.0490*).

After performing multiple univariate and multivariate logistic regressions examining the risk factor for discontinuation of medical care, the **higher number of days being hospitalized yearly showed to be a risk factor during pediatric care** (17.85 ± 23.1 days vs. 9.27 ± 10.2 days, *p = 0.014*; OR 1.036 [95% CI: 0.010 - 0.062]). **Female gender was a risk factor during the changing period between the two healthcare systems**, with 87.5% (n = 14) of the lost patients being female (*p = 0.010*). This accounts for 17.95% of all female patients being moved to adult care compared to 2.7% of the male patients being lost (*p = 0.0027*; OR 7.875 [95% CI: 1.946 - 35.61]). **The only significant protective factor for continuing care in the adult system was the enrollment in our transitional program** (*p = 0.0007*), with a lost-to-follow-up-rate of 5.97% (n =

4) vs. 15.94% (n = 11) among the transitioned and self-transferred patients.

3. Disease activity

After being moved to adult care, **48.53% (n = 66) of the patients experienced a relapse during the follow-up period**, accounting for **significantly more patients of the self-transferred group than of the transitioned patients** (59.42% vs. 37.31%, *p = 0.0108*; OR 2.460 [1.258 - 4.993]). With Kaplan-Meier curve analysis (**Figure 11.**) this difference was also shown to be significant, resulting in a **1.88-fold increased risk of relapse among the self-transferred patients** compared to the transitioned group during the same timeframe in adult care (95% CI 1.13 - 3.09, *p = 0.013*).

The transitioned patients spent a significantly higher proportion of time with a disease in remission in adult care compared to the self-transferred patients (83.63% ± 28.5% vs. 77.47% ± 29.65%, *p = 0.0339*; OR 0.7703 [0.7448 - 0.7967]). Additionally, **the time while the disease of the self-transferred patients had severe disease activity was significantly higher** compared to the transitioned patients (1.66% ± 4.88% vs. 1.15% ± 5.27%, *p = 0.0204*). To exclude that the baseline disease activity was already higher among the self-transferred patients, we also compared the disease activity of the 2 groups during pediatric care. There was no significant difference either between the proportion of time spent in remission (*p = 0.1337*) or with severe disease activity (*p = 0.5390*) in pediatric care, therefore in our study **transition was shown to be a**

protective factor against serious disease activity, as well as a significant determinant of disease remission in adult care.

4. Patient compliance

Compliance problems were reported in 69.52% (n = 244) of all patients, with a mean of 3.03 ± 2.57 occasions per person. **The non-compliance rate was increasing with both age and disease duration**, exceeding 50% non-compliance rate by the time of transferring to adult care.

After being moved to adult care the compliance of all patients significantly decreased (38.46% vs. 28.95%, *p = 0.0002*; OR 0.4148 [0.2591 - 0.6666]). The non-compliance rate was 77.5% among the self-transferred and 63.01% among the transitioned patients (*p = 0.0534*), resulting in a **significantly higher adherence to medications among the transitioned group compared to the self-transferred patients** (31.88% vs. 16.42% non-adherence rate, *p = 0.0455*; OR 2.383 [CI 95%: 1.042 - 5.156]). **During the changing period to adult care, 8.89% of all patients discontinued their medications**, accounting for 10.94% of the self-transferred and 7.04% of the transitioned patients (*p = 0.2900*).

5. Healthcare providers

The transitioned patients continued their medical care during the majority (96.06%) of the follow-up period in IBD Centers, classified as healthcare providers specialized in the treatment of IBD patients, which rate was significantly lower among the self-

transferred patients (36.7%, *p ‹ 0.0001*; OR 0.0238 [0.0218 - 0.0261]).

6. Surgical interventions

During pediatric care, **15.01% of our patients required surgery** (n = 53), a mean of 1.89 times per person, with 25.74% of these procedures being emergency interventions. **During the follow-up period in adult care, 12.5% of the patients required surgical intervention,** accounting for 13.04% of the self-transferred and 11.94% of the transitioned patients (*p = 1.0*), resulting in a mean of 1.82 surgery per person. 22.58% of these procedures were emergency interventions.

7. IBD-related complications

IBD-related complications were reported in 23.36% of all patients (n = 218), with a mean of 3.02 ± 3.59 complications per person. The mean age at the time of the appearance of complications was 15.64 ± 4.5 years, with a mean disease duration of 4.83 ± 4.13 years. **A severe disease course resulted in complications in 77.49% of the cases**, followed by 10.49% due to treatment, and in 11.69% both played a role. **Hospitalization was necessary in 51.24% of the cases, with a significantly higher surgical rate in adult care compared to pediatric care** (30% vs. 12%; *p = 0.0255*; OR 0.3475 [0.151 - 0.8323]).

Bone density was decreasing with both age and longer disease duration, with most patients being at high risk for low bone density at the time of transfer. The mean age of patients with

osteopenia was 15.52 ± 3.32 years with a mean disease duration of 3.69 ± 2.98 years and 16.44 ± 2.27 years of age and 6.10 ± 4.37 years disease duration for **osteoporosis**.

8. Anthropometry

CD patients were prone to malnutrition during the examination period, with 11.94% of their weight measurements being at the severely low range, and a significantly lower proportion of their measurements being in the normal range (69.14%), compared to either the IBD-U or the UC patients (81.57% and 78.27%, $p < 0.0001$). The proportion of patients with severely high weight percentile was significantly higher after 5 years of disease duration (1.15% vs. 4.65%, $p = 0.0158$; OR 0.1530 [95% CI: 0.03117 - 0.6379])

IBD-U patients were shown to be at high risk of inadequate growth, as 9.23% of all their height measurements were at the severely low range (< 3 pc), compared to the 4.62% reported among the CD and 0.26% of the UC patients ($p = 0.0089$ and $p < 0.0001$; OR 0.4767 [0.2884 - 0.8179].

The proportion of the patients being in the normal BMI percentile range significantly decreased for all disease subtypes after 5 years of disease duration, resulting in a high risk for non-adequate nutrition and/or growth by the time of transfer to adult care ($p < 0.0001$ for CD and UC and all patients, $p = 0.0116$ for IBD-U; OR 149.1 [9.012 - 2468]). **CD patients had a low BMI percentile in 13.55% of the measurements**, which was significantly higher

than the proportion of either the IBD-U or the UC patients ($p = 0.0054$ and $p = 0.0093$).

9. Medications and side effects

In adult care, 63.97% (n = 87) of all patients required a therapy change, without a significant difference between the self-transferred (62.32%, n = 43) and the transitioned (65.67%, n = 44) group ($p = 0.7233$). **Therapy escalations accounted for 62.5% of all these treatment modifications, of which 5% were the reinduction of the self-discontinued medications**. **Side effects of IBD medications were reported in 34.76% of all patients**, accounting for 39.8% of CD, 33.3% of the IBD-U, and 25.26% of UC patients. Evaluating the frequency of appearance of side effects, there was an event reported every 1069.63 days during methotrexate treatment, every 1252.05 days during steroid, every 1300.23 days during infliximab, every 4969 days during adalimumab and every 5043.76 days during azathioprine therapy.

CONCLUSIONS

We found a positive association between a structured transitional program and lower disease activity, fewer relapses, and better adherence to medications as opposed to self-transfer. Furthermore, enrollment in transition was shown to be the only significant protective factor for continuing medical care after transfer. The changing process to adult care was linked to a deterioration in medication adherence and in overall compliance of the patients, with a high lost-to-follow-up rate between the healthcare systems regardless of enrollment in a structured transition, in which female gender was a risk factor. The PIBD patients had an extensive and medically complex disease upon arriving at adult care, with a history of former surgeries and IBD-related complications, high rates of malnutrition, growth impairment, and poor bone health, and with their compliance worsening with both higher age and longer disease duration.

Based on our results and the corresponding reports of the current literature, the conduction of numerous, multi-centric transitional studies is advised in the future, as structured transitional programs seem to have a key role in ensuring the best possible disease outcome for PIBD patients. These studies could guide future recommendations, and help the establishment of a gold-stand transitional and educational method.

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Doi: 10.1556/650.2025.33249

Impact factor: 0.8

Date: accepted for publication: 26.01.2025

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