

TITLE PAGE

Title

Predictors of treatment success in children with difficult to treat atopic dermatitis using a personalized integrative multidisciplinary treatment program (PIM)

Running head

A personalized integrative multidisciplinary treatment program (PIM): who benefits?

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PIM was used as a treatment approach in the DAVOS trial, a pragmatic trial that aims to investigate the long-term effectiveness of inpatient treatment in the alpine climate compared to outpatient treatment in moderate maritime climate. The DAVOS trial was supported by unrestricted grants from the European Allergy and Asthma Center Davos, the patient support group "Vereniging Nederland Davos", and Merem Dutch Asthma Center Davos.

Conflict of interest

The authors report no conflict of interest.

ABSTRACT

Background: A 6 week personalized integrative multidisciplinary treatment program (PIM) was developed for children with difficult to treat AD who appeared unresponsive to treatment according to current guidelines.

Objective: The aim of the present study was to identify clinical and psychosocial characteristics that predict long-term treatment success after PIM.

Methods: Treatment was considered successful when there was a 75% reduction on the Self-Administered Eczema Area and Severity Index and/or little impact of AD on daily life, measured with the Children's Dermatology Life Quality Index (score ≤ 6), six months after the end of PIM. PIM is a personalized, integrative, multidisciplinary treatment program with clearly defined goals and strategies, addressing atopic, pediatric, mental health comorbidities, and general well-being, for

children and adolescents aged 8 to 18 years. Multivariate logistic regression models were constructed using a backward selection procedure. Questionnaires were used to assess psychosocial characteristics, clinical data was extracted from medical records.

Results: In total, 79 children / adolescents with difficult to treat AD completed PIM and long-term treatment results were available for 74 children / adolescents. The majority (77%) of children / adolescents demonstrated long-term treatment success with PIM. Predictors of long-term treatment success (adjusted ORs) included maternal disease acceptance OR (95%CI) 1.84 (1.15 – 2.94). A group (23%) of mostly females OR (95%CI) 0.10 (0.02 – 0.54) with multiple somatic complaints OR (95%CI) 0.88(0.80 – 0.97), from families where the mother has anxiety for the use of topical corticosteroids OR (95%CI) 0.62(0.40 – 0.94), is less likely to obtain long-term treatment success.

Conclusion: Most children and adolescents with difficult to treat AD, seemingly unresponsive to conventional treatment according to current guidelines, are able to improve with PIM. Psychosocial and family but not clinical variables, predicted long-term treatment success after participating in PIM.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Its prevalence has been increasing in recent decades, currently affecting 10% to 20% of children in Western Europe.¹ AD has a significant negative effect on the quality of life of affected children and their parents, with increasing disease severity further reducing reported quality of life.^{2,3} AD treatment is mainly aimed at controlling inflammation and optimizing the skin barrier function with topical treatment. AD is often accompanied by other atopic comorbidities, especially when there is more severe disease.⁴ Being diagnosed with multiple atopic comorbidities increases the burden on the child and family and may negatively affect adherence to treatment. Furthermore, children with AD experience significant psychosocial problems compared to their peers, and an association between AD and the development of mental health disorders such as ADHD and depression has been suggested.⁵⁻⁷

For most children conventional treatment according to current guidelines results in acceptable disease control. Nevertheless, approximately 3% of all affected children do not respond well to regular treatment and may be considered difficult to treat.⁸ For these children, most of them under the age of 4 years old, additional treatment approaches have been developed, such as therapeutic education programs and multidisciplinary programs to help them successfully manage and cope with AD.⁹⁻¹³ However, there are only few treatment possibilities specifically for older children and adolescents.^{11, 12}

We developed a personalized integrative multidisciplinary treatment program (PIM) for children (in- or outpatient) aged 8 to 18 years with difficult to treat AD. PIM includes assessment of other atopic, pediatric, mental health comorbidities, and general well-being. It is a resource and time intensive program. Therefore, it is important to identify children who will or will not benefit from the program. The aim of this study was to identify clinical and psychosocial characteristics of children and their parents that predict long-term treatment success after treatment with PIM.

MATERIALS AND METHODS

Patients

Children (8-18 years) with difficult to treat AD were referred to our academic national tertiary referral center to participate in PIM. We defined difficult to treat AD as moderate to severe AD seemingly unresponsive to conventional treatment according to current guidelines. More specifically, children who were dependent on use of at least a moderate potency topical corticosteroid and were not able to step down; or with a history or current use of systemic immunosuppressive treatment; or who were treated repeatedly with high potency topical corticosteroids or systemic immunosuppressive treatment; or who experienced a significant impact of AD on the child's or the families quality of life were eligible to participate in PIM. We included 74 children who were treated with PIM during the DAVOS trial and completed the 6 month follow-up period.¹⁴

Study design

PIM was used as a treatment approach in both arms of the DAVOS trial, a pragmatic trial that aims to investigate the long-term effectiveness of alpine climate treatment carried out from 2010 to 2014.¹⁵ The trial is registered at Current Controlled Trials ISRCTN88136485. All children and when appropriate their parents provided written informed consent to participate in the trial. Study procedures were reviewed and approved by the institutional review board of the University Medical Center Utrecht, the Netherlands (09-192/K).

Description of PIM

PIM is a personalized, integrative multidisciplinary treatment program with clearly defined goals and strategies, based on the perspective of the child and parents. It is suitable for children and adolescents. During PIM, AD as well as other atopic, pediatric and mental health comorbidities, and general well-being are addressed. PIM is a six week program followed by an easy access phase of six months. The dermatologist and dermatology nurse assess eligibility for participation in PIM. A more detailed description of PIM can be found in PIM Supplementary Table 1: a detailed description of PIM. A roadmap describing the most important elements of PIM is shown in Table 1.

At the day of the initial visit, child and parents were consecutively seen by the case manager, dermatologist, dermatology nurse, pediatrician, allergist, and pediatric psychologist. The child and his parents explicitly specified the current problems and verbalized treatment goals, which is part of the patient-centered treatment approach. Examples of the problems children and parents may experience are described in PIM Supplementary 2. At the end of the day of the first visit, the multidisciplinary treatment team discussed and prioritized the problems, regardless of the nature of the problems (i.e. medical problems were not necessarily addressed first). A structured treatment plan was created using a goal-oriented approach based on the child and parents' perspective. Examples of treatment goals and the corresponding strategies can be found in PIM Supplementary Table 3.

During the six week intervention period, the children were seen almost on a weekly basis in the outpatient clinic in the Netherlands or spent the intervention period in the clinic in Switzerland. In this period, children had 5 consultations with the dermatologist (30 minutes) and the dermatology

nurse (30 minutes), 4 consultations with the pediatrician-allergist (30 minutes), and 3 consultations with the psychologist (45 minutes). During the six week intervention period, strategies were already developed for the period after the end of PIM. This concerned treatment goals that were addressed during the intervention period but also treatment goals that could not be completed within this period. At the end of the intervention period, an evaluation of the treatment goals with child and parents was conducted by each health professional. The child, parents and health professionals specifically discussed what was needed to succeed in sustaining the treatment goals during the period after PIM has ended.

All children and parents were offered the possibility for easy-access contact with the multidisciplinary team via the nurse during the following six month period using a digital platform for AD.¹⁶ Some children and parents were also referred to health care specialists closer to their home to address ongoing problems (for example diagnostics and treatment of ADHD or autism, help to overcome obesity, help to improve family relations).

Responders / non responders

Treatment was considered effective, when clinically relevant improvement was observed on disease activity (SA-EASI scored by the parents) or quality of life (CDLQI) experienced by the child after six months.^{17, 18} A relative improvement of 75% on the SAEASI was considered a clinically relevant improvement. We used severity banding to interpret CDLQI scores.¹⁹ A score ≤ 6 corresponds to a small effect on the child's life. To define long-term responders, we used data from study inclusion or baseline, and the last follow-up assessment. Six months after the end of PIM, long term responders demonstrated a reduction of at least 75% on the SAEASI and/or scored 6 or less on the CDLQI. Children were characterized as "responders" or "non-responders" in subsequent data analysis.

Predictors

Both children and parents completed questionnaires before the start of PIM and six months after the end of PIM.¹⁵ Demographic and social characteristics were assessed with standard questionnaires. Clinical parameters were extracted from the digital patient file. Behavioral and emotional problems were assessed with the parent-completed Child Behavior Checklist, which includes the internalizing syndrome scales anxious/depressed, withdrawn/depressed, somatic

complaints, social problems, thought problems, attention problems, and the externalizing syndrome scales rule-breaking behavior, and aggressive behavior.²⁰ Children's itching cognitions and AD specific coping were measured with the Dutch translation of the German coping with disease (COPEKI/JU) and itching cognitions (JUCKKI/JU) questionnaires.²¹ Age specific versions of the questionnaires were used for children and adolescents, when available. Both child and parents completed the Dutch version of the State-Trait Anxiety Inventory.^{22, 23} For parents, state anxiety concerned the use of topical corticosteroids whilst for children, state anxiety referred to how they felt at the moment they completed the questionnaire. Parental quality of life was assessed with a German disease-specific quality of life questionnaire translated into Dutch.²⁴ The questionnaire consists of 26 items measuring five domains: psychosomatic well-being, effects of the disease on social life, confidence in medical treatment, emotional coping, and acceptance of the disease.

Statistical analyses

Candidate predictors were based on literature and clinical experience. Univariate logistic analyses were done to identify predictors associated with responder status. Multivariate logistic regression models were used to explore the contribution of the candidate predictors on responder status using a backward selection procedure. Data was analyzed using IBM SPSS Statistics for Windows version 22.

RESULTS

In total, 79 children with difficult to treat AD participated in PIM and long-term treatment results were available for 74 children.¹⁴ There were no differences in baseline characteristics between the children who did and did not complete long-term study assessments (data not shown).

Six months after the end of PIM, the majority of children (77%, n=57) showed a 75% reduction of disease activity according to a clinical scoring system and/or indicated little impact on their quality of life and were characterized as responder. Table 2 describes the baseline characteristics of responders and non-responders, additional characteristics are presented in Supplementary Table 1.

All children had moderate to severe AD according to a clinical scoring system and indicated a moderate to large impact on their quality of life. The mean age was 12 to 13 years. Most children (86% of responders and 82% of non-responders) experienced an AD onset in the first 6 months of

life. Most children were currently using potent or very potent topical corticosteroids (95% of responders, 88% of non-responders) and a majority of children used systemic immunosuppressives in the past (60% of responders, 71% of non-responders). Besides AD, most children were diagnosed with other atopic comorbidities such as asthma (84% of responders, 88% of non-responders), rhinitis (86% of responders, 94% of non-responders) or food allergy (68% of responders, 65% of non-responders). Females were overrepresented in the group of non-responders (71% versus 40% in the responder group) and there were statistically significant more somatic complaints in this group ($P=0.020$).

There were 53%, $n=30/57$ children who demonstrated both improved disease activity and quality of life, 10%, $n=6/57$ children who demonstrated improved disease activity but not quality of life, and 37%, $n=21/57$ children who experienced little impact on quality of life but demonstrated less than 75% reduced disease activity. We could not identify demographic, clinical or psychosocial characteristics that differed between these children (data not shown). The majority of the long-term non-responders (70%, $n=12/17$) demonstrated a 75% reduction of disease activity according to a clinical scoring system and/or indicated little impact on their quality of life immediately after the end of PIM.

Parental baseline characteristics are described in Table 3. Mothers of responders indicated a higher psychosomatic wellbeing ($P=0.016$) and better disease acceptance ($P=0.007$). Furthermore they indicated a significantly lower general anxiety ($P=0.045$) and specific anxiety for the use of topical corticosteroids ($P=0.038$). There were no statistically significant differences between the responders and non-responders concerning paternal quality of life and anxiety.

Univariate analysis demonstrated no statistically significant influence of clinical parameters on responder status. In the final multivariate model, sex (being female OR (95%CI 0.10 (0.02 – 0.54)) and somatic complaints of the child (OR (95%CI) 0.88(0.80 – 0.97)), as well as maternal fear of using topical corticosteroids (OR (95%CI) 0.62(0.40 – 0.94)), and maternal disease acceptance (OR (95%CI) 1.84 (1.15 – 2.94)) were significantly associated with being a long-term responder (Table 4).

DISCUSSION

We provided a personalized integrative multidisciplinary treatment program (PIM) for children and adolescents with difficult to treat AD. The program offered a structured treatment approach with clearly defined goals and strategies, addressing AD as well as other atopic, pediatric and mental health comorbidities. Six months after participating in PIM, the majority of our study population (77%) demonstrated at least a 75% reduction in disease activity and/or indicated little impact of AD on their daily life. Psychosocial and family variables, but not clinical variables, predicted long-term treatment success after participating in PIM.

The majority (77%, n=57) of our study population demonstrated substantial long-term improvement in disease activity and quality of life after participating in PIM. Children who participated in PIM appeared to be unresponsive to conventional treatment according to current guidelines.

Apparently, PIM is an effective treatment option for these children. Multidisciplinary eczema interventions may lead to improvements in disease severity and quality of life.¹³ However, little is known about the effective elements of a multidisciplinary approach. In most patients, we observed an accumulation of medical, psychological and social problems that needed tailored treatment. Studies concerning children with asthma and diabetes have shown that engagement with children's expertise about their own lives, exploring children's understandings and preferences, and avoiding age-based assumptions about children's contributions to their care are important factors for successful patient centered care.²⁵ During PIM, the children and their families were actively involved in the design of the treatment goals and treatment strategies. Input from the child and parents was combined with an integrative multidisciplinary approach by the involved health professionals. Actively involving the parents may also contribute to the successful treatment results, because of the relationship between parental treatment competence and self-efficacy and child behavior.²⁶ Integrating knowledge by means of multidisciplinary team work and clearly defining and making use of the specific role of each team member was demonstrated important in the care for adolescents with type 1 diabetes.²⁷ During PIM, each health professional contributed to the treatment goals and other atopic, mental health, pediatric comorbidities, and general well-being were explicitly addressed. Because the child psychologist was a member of the treatment team, children and parents were more inclined to accept and understand the need for psychological treatment. Addressing all the relevant aspects structurally and simultaneously is a unique and probably effective aspect of PIM compared to other treatment programs.

Some children (23%, n=17) were characterized as long-term non-responders. During PIM, professionals and children developed strategies that could help them to retain treatment effects. Despite these efforts, in some families practical and psychosocial problems seem to prevent long-term treatment success. The identified non-responders were characterized by female sex, multiple somatic complaints according to the CBCL, maternal anxiety for topical corticosteroids and maternal difficulties with disease acceptance. This pattern of child and family characteristics might resemble that of children with functional somatic symptoms. These are physical symptoms that are insufficiently explained by a medical condition after adequate examination and investigation.²⁸ Functional somatic symptoms are often characterized by a disproportionate burden of disease compared to the severity of the complaints. They are more common in females and more common with increasing age, ranging from 4 times more problems in adolescents to 2-9 times more problems in adulthood.^{29, 30} Furthermore, functional somatic symptoms seem to have an intergenerational character, with mothers often experiencing functional symptoms themselves, as well as anxiety and depression.^{31, 32} Therefore actively involving the parents when treating a child with difficult to treat AD, also in the case of adolescents, seems essential when functional somatic symptoms might be suspected. Furthermore, other treatment methods may be used for these children during intervention, such as hypnotherapy or cognitive behavioral therapy which has been shown to be effective in the treatment of functional abdominal pain.^{33, 34} However, the majority of long-term non-responders (12 out of 17) demonstrated a positive response to PIM immediately after the program.

Children from families that are unlikely to achieve long-term treatment success according to the predictors that we identified, may also benefit from a more intensive follow-up period to sustain the treatment effect in the long term, for example with more intensive support to the whole family and guidance or more frequent booster visits.³⁵ This would be in line with the current conventional treatment for functional somatic symptoms, which consists of simultaneous and often prolonged simultaneous medical and psychological treatment.³⁶

A strength of our study is that we chose stringent criteria for the definition of responders and non-responders. We expected at least 75% improvement using a clinical scoring system and/or a quality of life score corresponding with little impact of AD on the child's life. Both disease control and the impact of AD on daily life are regarded important outcomes for AD.³⁷ Because we used AD severity based on a clinical scoring system and quality of life for our definition of treatment success, these variables could not be used as predictors in the statistical model. We used the SAEASI to assess AD

severity, which is a validated instrument for patient assessment of disease severity. Within the study sample, SAEASI and EASI scores by a professional demonstrated a correlation coefficient of 0.64, supporting the use of this instrument. The generalizability of our study is limited. In this study, PIM was provided to children who were considered difficult to treat, which we broadly defined as children with insufficient disease control despite conventional treatment strategies according to current treatment guidelines. The sample size of our study reflects the relatively small group of children with difficult to treat AD. Furthermore, children and adolescents aged 8 to 18 years were treated with PIM. Although it is possible that younger children with difficult to treat AD also profit from PIM, this was not investigated in this study.

Identifying children and families who may benefit from certain interventions is important to increase effectiveness in health care, resulting in less overtreatment or undertreatment and a selective application of expensive treatments. PIM is indicated for a subpopulation of children with AD. This study had an observational design and is based on data from a randomized trial.¹⁴ Future randomized studies are needed to confirm and validate our findings, for example by directly comparing PIM with regular treatment to confirm our findings, and to further characterize the heterogeneous population of children with difficult to treat AD and to provide earlier identification of children with difficult to treat AD.

Clinical implications

In current practice, when a child presents with difficult to treat AD, other atopic diseases, psychosocial, parent or family factors are not necessarily addressed. Our study demonstrates that treatment with an integrative program addressing AD simultaneously with other atopic, pediatric and mental health comorbidities, and general well-being, results in sustained improvement on disease activity and /or quality of life for the majority of children. Structural involvement of a pediatric psychologist within the team and attention for psychosocial problems throughout PIM was valuable. It has been reported before that the diagnosis of underlying psychological factors is essential to determine an effective AD treatment plan.^{10, 38} A small subgroup of children from families with characteristics resembling functional somatic symptoms does not respond sufficiently in the long term. Specifically addressing parental disease acceptance and parental fear of using topical corticosteroids could be helpful. A clinical approach that overemphasizes the somatic and ignores psychosocial factors including the parents is a pitfall in the treatment of functional somatic

symptoms.^{36, 39} An important risk that dermatologists and pediatricians should be aware of in this group is overtreatment. Due to a lack of treatment response physicians tend to intensify treatment according to the guidelines.⁴⁰ In children with functional symptoms this is usually not effective. Physicians can support these children and their parents by continuously emphasizing the inextricable link between body, brain and mind and the importance to address all in treatment.^{36, 38}

CONCLUSION

The majority (77%) of children with difficult to treat AD, seemingly unresponsive to conventional treatment according to current guidelines, are able to improve with PIM. Identifying children based on psychosocial and family but not clinical variables, predicted long-term treatment success after participating in PIM. Attention should be paid to a small group of children, mostly females with multiple somatic complaints, from families where the mother has anxiety for the use of topical corticosteroids and difficulties with disease acceptance.

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Table 1 - PIM Roadmap

1: Multidisciplinary treatment team	Dermatologist, dermatology nurse, pediatrician-allergist, pediatric psychologist and physiotherapist, supported by a case manager
2: Evaluation of problems	Based on the perspective of the child and parents Systematic evaluation of all possibly relevant factors Start the evaluation with a blank history, repeating previous evaluations and re-evaluate current treatment strategies
	Include assessment of AD, other atopic and pediatric comorbidities, mental health comorbidities and general well-being (school absence, physical fitness, knowledge of treatment)
3: Development of the treatment plan	Use a positive, goal-oriented approach (I want to.....) Make sure treatment goals match the problems defined by the child and parents Agree on treatment goals with child, parent and treatment team Prioritize regardless of the nature of the problems Create personalized intervention strategies, adapted to emotional and cognitive development of child and parental capabilities
4: Intervention period	Make sure to address all relevant domains: AD / other atopic comorbidities / mental health / other pediatric comorbidities / adherence Simultaneously address different domains of the same problem Develop strategies for the period after the end of PIM Systematic evaluation during PIM with child and parents
5: Results	Evaluate the treatment goals and celebrate the result of PIM Decide on what is needed to sustain the treatment goals
6: Support	Weekly multidisciplinary team meetings Case manager Digital resources to support the program Synergy within the treatment team
7: Pitfalls	Communication Sharing relevant observations and results Trust the leadership of other health professionals

Table 2 - Baseline demographic and clinical characteristics of responders and non-responders. Data is described as mean(SD), median (IQR) or n(%)

	Responder n=57	Non-responder n=17	p-value
Age (years)	12.4 (2.6)	13.2 (2.0)	0.206
Females	23 (40%)	12 (71%)	0.051
SAEASI	39 (18.5)	34.5 (16)	0.361
CDLQI	7.9 (4.4)	10.5 (5.3)	0.074
AD onset in first 6 months of life	49 (86%)	14 (82%)	0.707
Asthma diagnosis	48 (84%)	15 (88%)	1.000
Rhinitis diagnosis	49 (86%)	16 (94%)	0.675
Food allergy diagnosis	39 (68%)	11 (65%)	0.775
Psychiatric diagnosis (DSM-V)	5 (9%)	3 (18%)	0.340
CBCL somatic complaints t-score ^a	63.0 (7.7)	68.0 (7.7)	0.020
Itching cognitions – coping	1.8 (0.8)	1.9 (0.5)	0.688
Current use of potent or very potent TCS	54 (95%)	15 (88%)	0.323
Current use of systemic immunosuppressives	8 (14%)	1 (6%)	0.640
History of use of systemic immunosuppressives	34 (60%)	12 (71%)	0.353
TARC (pg/ml)median IQR	1085 (1560)	1119 (1300)	0.772

^aThe CBCL subscales can be seen in Supplementary Table 1.

Table 3 - Parental characteristics of responders and non-responders

	Responder n=57	Non-responder n=17	p-value
Parental quality of life			
QoL mother psychosomatic wellbeing	33.1 (4.9)	29.8 (4.4)	0.016
QoL mother effects on social life	24.5 (4.4)	22.3 (4.0)	0.075
QoL mother satisfaction with medical care	19.0 (3.0)	18.1 (2.1)	0.248
QoL mother emotional coping with disease	14.3 (3.0)	12.9 (2.2)	0.080
QoL mother acceptance of disease	8.1 (1.6)	6.9 (1.3)	0.007
QoL father psychosomatic wellbeing	35.3 (4.6)	33.6 (5.8)	0.266
QoL father effects on social life	25.7 (3.1)	25.2 (4.4)	0.593
QoL father satisfaction with medical care	18.4 (2.6)	18.1 (3.2)	0.710
QoL father emotional coping with disease	14.9 (2.7)	13.5 (3.1)	0.128
QoL father acceptance of disease	7.7 (1.6)	6.8 (1.9)	0.075
State / trait anxiety			
STAI mother trait anxiety	4.3 (2.5)	5.7 (2.3)	0.045
STAI mother state anxiety topical steroids	5.7 (2.3)	6.9 (1.9)	0.038
STAI father trait anxiety	4.2 (2.5)	5.3 (2.7)	0.175
STAI father state anxiety topical steroids	5.7 (2.6)	6.5 (3.1)	0.338

Table 4 - Logistic regression analysis for long-term responders

Predictor	Univariate analysis OR(95%CI)	Multivariate analysis (reduced model) OR (95%CI)	P value
Age	0.86 (0.68 – 1.09)		
Females	0.28 (0.09 – 0.91)	0.10 (0.02 – 0.54)	0.007
Potency of currently used TCS	1.9 (0.63 – 5.76)		
History of use of systemic immunosuppressives	0.43 (0.11 – 1.69)		
Itching cognitions – catastrophizing	0.47 (0.22 – 0.99)		
CBCL Somatic complaints	0.92 (0.86 – 0.99)	0.88 (0.80 – 0.97)	0.012
QoL Maternal disease acceptance	1.58 (1.10 – 2.28)	1.84 (1.15 – 2.94)	0.011
QoL Maternal psychosomatic wellbeing	0.86 (0.76 – 0.98)		
STAI Maternal trait anxiety	1.25 (1.0 – 1.55)		
STAI Maternal fear of topical corticosteroids	0.76 (0.59 – 0.99)	0.62 (0.40 – 0.94)	0.025

1 Supplementary Table 1 – CBCL and COPEKI / COPEJU subscales

	Responder n=57	Non-responder n=17	p-value
CBCL social problems t-score	55.8 (7.6)	53.8 (4.4)	0.302
CBCL thought problems t-score	59.9 (7.7)	60.8 (7.8)	0.672
CBCL attention problems t-score	56.5 (5.6)	57.5 (5.1)	0.529
Internalizing behavior			
CBCL anxious/depressed t-score	56.2 (7.8)	56.1 (5.8)	0.934
CBCL withdrawn t-score	57.5 (8.0)	56.4 (6.6)	0.614
CBCL somatic complaints t-score ^a	63.0 (7.7)	68.0 (7.7)	0.020
Nightmares	12 (21%)	5 (29%)	0.472
Constipated	7 (12%)	5 (29%)	0.093
Dizzy	8 (14%)	4 (24%)	0.351
Overtired	15 (26%)	10 (59%)	0.013
Aches	10 (18%)	5 (29%)	0.285
Headaches	20 (35%)	10 (59%)	0.080
Nausea	13 (23%)	4 (24%)	0.950
Eye problems	4 (7%)	3 (18%)	0.189
Skin problems	50 (88%)	14 (82%)	0.570
Stomach aches	21 (37%)	11 (65%)	0.042
Vomiting	8 (14%)	3 (18%)	0.713
Externalizing behavior			
CBCL rule breaking behavior t-score	52.7 (4.0)	52.7 (3.4)	0.933
CBCL aggressive behavior t-score	55.1 (6.1)	53.1 (4.1)	0.228
Coping with itch – children	(n=28)	(n=6)	

COPEJU social anxiety	1.3 (1.1)	2.6 (0.8)	0.001
COPEJU stress	1.6 (0.8)	2.4 (0.7)	0.005
Coping with itch – adolescents	(n=25)	(n=11)	
COPEKI social anxiety/depressive moods	1.3 (0.7)	1.3 (1.1)	0.918
COPEKI itching-scratching circle/stress	2.2 (0.7)	2.4 (0.7)	0.553
COPEJU depressive moods/ itching-scratching circle	1.9 (0.8)	2.8 (0.5)	0.002

^aThe answer categories 'somewhat or sometimes true' and 'very true or often true' are collapsed into one.

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PIM SUPPLEMENTARY 1: Detailed description of PIM

PIM: Evaluation of problems (case is an example)

Jonathan is a 14-year old boy, suffering from atopic dermatitis (AD), allergic rhinitis, asthma and food allergy. Jonathan sleeps badly mainly because of continuous itch. During the day he is tired, irritable and feels depressed. Jonathan's mother has become desperate. Jonathan's late sleep onset and frequent nightly awakenings affect her sleep and Jonathan's school performance and attendance. She is fed up with the constant fighting about his AD treatment. Jonathan is referred to PIM (a 6 week personalized integrative multidisciplinary treatment program) by his dermatologist. Before visiting our center, Jonathan and his mother completed a digital questionnaire about symptoms of AD, asthma, rhino conjunctivitis, food allergy, and the impact of these diseases on family life as well as general wellbeing. The dermatologist and dermatology nurse assessed eligibility for participation in PIM.

PIM: Development of the treatment plan

Standardized questionnaires (available online through publishers) are used to identify problems or other aspects that may need additional attention during the intervention. At the day of the first visit Jonathan and his mother are consecutively seen by the case manager, dermatologist, dermatology nurse, pediatrician-allergist (within PIM a pediatrician trained as an allergist), pediatric psychologist and physiotherapist for an extensive assessment. This involves the skin and other atopic, pediatric and mental health comorbidities, but also general wellbeing, including school absence, physical fitness, and knowledge of treatment guidelines. Jonathan indicates which problems he experiences and what he would like to be different at the end of PIM. A detailed description of the problems Jonathan described to each health professional can be found in PIM Supplementary 2.

At the end of the day of the first visit, the identified problems from the perspective of the child and/or the parents, and the professionals are discussed among the members of the multidisciplinary team. The professionals plan a stepped integrated intervention strategy and create a structured treatment plan using a goal-oriented approach. The treatment goals are then discussed and prioritized regardless of the nature of the problems (i.e. medical problems are not necessarily addressed first) together with Jonathan, his mother, and the members of the multidisciplinary team. Jonathan's treatment plan consists of the following goals:

- I want to get up in the morning and do my treatment without having discussions about this with my mother

- I want to sleep better and have a normal school schedule
- I want to have a better looking skin and be slimmer
- I want to have more control about my itch
- I would love to play soccer again and see my friends
- I would like to be more cheerful (less depressive)

The treatment goals and corresponding intervention strategies are evaluated continuously during and after the intervention in the team. Examples of treatment goals and strategies are shown in PIM Supplementary 3. The dermatologist has the final responsibility for the total treatment plan.

PIM: the intervention period

1. Atopic dermatitis

The dermatologist evaluates the medical history and explains the course of AD; that it is characterized by exacerbations and remissions; that it is essential to monitor the skin regularly (this can be done by Jonathan or his mother) and that appropriate action should be taken when needed. The dermatologist gives an overview of the currently available AD treatment, with careful explanation of its use and occurrence of side effects. In order to reduce the severe AD and itch, the dermatologist adjusts treatment with more potent topical corticosteroids and provides specific instructions how to use it. The fingertip unit is explained. A personal action plan is provided which indicates how to phase out or step up treatment depending on AD severity using a traffic light approach. Within this approach, red is used for exacerbations, orange when the skin lesions improve after an exacerbation and green for the controlled phase where topical treatment continues in a lower frequency and potency. The dermatology nurse takes Jonathan's intelligence profile into account while designing his personal action plan and adds pictures of his skin to the traffic light colors to help him decide in which phase his skin is. The dermatology nurse provides a try-out of different emollients and prescribes one that has been chosen by Jonathan himself.

2. Other atopic comorbidities.

Because of the severity of AD symptoms and the focus on AD related problems, other atopic disorders might be viewed as secondary by both the children, parents as well as health care professionals. The pediatrician-allergist systematically assessed symptoms of allergic asthma, rhinitis and food allergy. The pediatrician-allergist took a detailed medical history, physical examination and additional tests

(spirometry, metacholine challenge, total IgE, specific IgE for aeroallergens and food allergens, DBPCFCs for children suspected of food allergy).

Some children with severe asthma did not even notice they had difficulty breathing because of the predominant symptoms of itch. Jonathan had to quit soccer, but his mother was surprised by the bad results of the lung function test and the subsequent diagnosis of asthma. The pediatrician-allergist initiated or optimized asthma and allergic rhinitis treatment and advised to start playing soccer again. The diet was reevaluated and adjusted: milk and some fruits were reintroduced successfully in Jonathan's diet with the help of a dietician. The elimination diet for nuts and peanuts was continued, based on a positive DBPCFC.

3. Mental health comorbidities.

As a consequence of AD most patients have to cope with relapses, itch, sleeping problems and intensive treatment. This requires appropriate management skills of patients and families. Meanwhile AD can be related to psychological complaints of depression and concentration. The pediatric psychologist assesses disease management abilities, cognitive abilities, and mental health and instructs patients about therapeutic techniques. Habit reversal is used to teach Jonathan how he can control his scratching behavior. He develops an active coping strategy instead of retiring to his room. Cognitive behavioral therapy focused on coping with itch and worries about his AD, but also addressed the negative thoughts about the relation with his father and his depressive feelings.

Together with the school mentor, a plan is made to optimize school presence gradually in the next weeks. Every week school presence is increased with one hour until optimal school attendance is obtained. Meanwhile the psychologist discusses sleep hygiene advice (about regularity, doing sports/being outside, screen time, food and drinks) for better sleep, especially earlier sleep onset. She also teaches him relaxation techniques: a combination of muscle relaxation and hypnotherapy. Hypnotic suggestions of a cool environment or a fresh breeze helped Jonathan to relax and to experience less itch before going to sleep.

4. Other pediatric comorbidities.

The pediatrician-allergist assesses the amount and side-effects of the total used medication (together with the dermatologist) and general health status, including physical activity and obesity. The chronic inflammation and the chronic use of potent topical steroids or systemic immunosuppressive drugs indicates growth monitoring of the child or the assessment of other symptoms that are related to a hypothalamic-pituitary-adrenal axis alteration. The pediatrician-allergist concludes normal growth and

no other potential side-effects of steroids used and a good general health. However Jonathan is a little overweight, probably as a consequence of quitting sports. During PIM, all children are encouraged to exercise on a regular basis using the personalized action plan of the physiotherapist, when needed under supervision of a physiotherapist near home or with special programs for children with chronic disease.

5. Adherence to treatment.

Adherence to treatment is an important treatment goal that occurred in almost every treatment plan. The dermatologist and pediatrician-allergist prescribe treatment, but the nurse helps with the organization of treatment regimens taking into account family and school life, whereas the pediatric psychologist guides the process of autonomy development. Younger children are dependent on their parents for their daily AD treatment and the correct treatment regimen, but a shared routine (for example child does front and parents do the back) gradually leads to independence where the child is responsible for his or her own treatment. The nurse made a daily therapy schedule together with Jonathan in which all medicines and activities are noted, including medication for asthma and allergic rhinitis. Jonathan was asked to keep a medication diary to give him insight into his adherence to treatment.

PIM SUPPLEMENTARY 2: Description of the problems Jonathan experiences

Dermatologist: Jonathan says that the itch drives him crazy. He wants his skin to look normal and he wants the itching to stop. He further mentions he feels sad about his disease and himself. Jonathan's mother mentions that the topical treatment that Jonathan received until now has not been effective. Jonathan's medication has been prescribed by the dermatologist in the past. Both the general practitioner and the pharmacist warned Jonathan's mother for the consequences of frequent use of topical corticosteroids. She tells the dermatologist that she is confused by the conflicting advice. The answers to the AD treatment management questionnaire confirm a lack of knowledge on frequency of TCS application during a flare, amount of TCS to be used and potency of the currently prescribed TCS.

Dermatology nurse: Jonathan explains that he tries to treat his skin twice a day, but it takes a lot of time. He finds it difficult to be compliant and thinks treatment will not be effective anyway. Furthermore it can be painful to apply the ointment to the skin. When the dermatology nurse asks Jonathan and his mother to assess Jonathan's skin, she notices that they recognize the severe AD spots but not the lesions with mild AD and the lesions that are lichenified. The same is seen when the nurse asks which lesions are treated. The SAEASI by Jonathan demonstrates a lower score compared to the nurse suggesting that Jonathan underestimates his AD.

Psychologist: Jonathan says that he hopes to sleep and feel better and to experience less itch. Jonathan says he is going crazy because of his itch and sometimes wishes to be dead. His mother hopes that Jonathan will be happier; Jonathan withdraws to his bedroom many times because he feels so miserable. She also hopes that he feels more responsible for his own treatment. Jonathan is asked to imagine this situation after the end of PIM and to make a drawing of it. The questionnaire confirms Jonathan's feelings of depression. Regarding the family situation, Jonathan says that he lives with his mother. He is not in contact with his father. Jonathan is in the second class of high school and he has a few friends. Because of his sleeping problems, Jonathan usually arrives at school at 11 o'clock. If the absence does not change, Jonathan will not move to the next class, despite his average intelligence level (confirmed with an intelligence test).

Pediatrician-allergist: Jonathan says that he has quit playing soccer because of complaints of fatigue and breathlessness. His runny nose also bothers him. He doesn't consume milk, peanut, nuts and fruit products; a diet started at a very young age and was advised at that time as AD treatment.

Physiotherapist: the maximal cycle ergometer test confirms Jonathan's low physical fitness.

PIM SUPPLEMENTARY 3: Examples of treatment goals addressed within PIM and corresponding intervention strategies by the professional

Treatment goal from patient perspective	Description of intervention	Health professional
I want to...		
Look better and have less itch	Optimize treatment	Dermatologist
	Discuss effects and side effects	Dermatologist
	Demonstration of topical treatment	Dermatology nurse
	Lifestyle advise (e.g. shower behavior)	Dermatology nurse
	Controlling scratching by habit reversal	Pediatric psychologist
	Relaxation techniques	Pediatric psychologist
	Strategies to improve adherence, e.g. patient education about itching-scratching circle, traffic light approach, implementation of therapy in daily schedule and general coaching	All health professionals
Stop my running nose and itchy eyes	Recognize symptoms of asthma, rhinitis	Pediatrician-allergist
	Optimize treatment of asthma, rhinitis	Pediatrician-allergist
Know what I can and cannot eat	Dietary assessment and food reintroduction	Pediatrician-allergist / Dietician
	Assessment of food allergies	Pediatrician-allergist
	Knowing how to handle in case of adverse reaction	Pediatrician-allergist
	Relation between food and AD	Dermatologist
	Treatment of fear of certain foods/ fear of adrenaline auto-injector	Pediatric psychologist
Be fit and sleep better, reduce school	Analysis of sleep problems	Pediatrician-allergist / Pediatric psychologist

absence		
	Medication for earlier sleep onset (melatonin) and rhinitis (anti-histamines)	Pediatrician-allergist
	Psycho-education about sleep and advices on sleep hygiene	Pediatric psychologist
	Hypnotherapy and relaxation techniques to improve sleep	Pediatric psychologist
	Assess physical fitness	Pediatrician-allergist / Physiotherapist
	Evaluate asthma, rhinitis, food allergy, condition, weight and growth	Pediatrician-allergist
	Patient education: importance of sports	All professionals
	Individual sporting advice	Physiotherapist
	Optimize all atopic comorbidities	Dermatologist / Pediatrician-allergist
	Make a daily schedule of regularity and set times for sleeping, school presence, homework etc.	Pediatric psychologist / Dermatology nurse
	Contact school and make a stepped plan for extension of school presence	Pediatric psychologist
Concentrate better	Neuropsychological /cognitive evaluation	Pediatric psychologist
	School and learning advices including planning of homework	Pediatric psychologist
	Advice about balancing mental efforts and physical/relaxing activities	Pediatric psychologist
Reduce tension about the atopic treatment with my parents	Consistent integrated treatment advice from all involved health professionals	All health professionals
	Parenting advise including autonomy of the child in his treatment	Pediatric psychologist

	Personalized daily treatment plan and lifestyle advice	Dermatology nurse
	Improve coping with disease	Pediatric psychologist
	Self-assessment with patient-oriented severity assessment tool to recognize flares	Dermatologist / dermatology nurse
Feel happy and optimistic	Reach above treatment goals	Child / parents and all health professionals
	Discuss what is needed to help the child sustain his goals	Child / parents and all health professionals