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Multidisciplinary Treatment in Children With Problematic Severe Asthma: A Prospective Evaluation

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Summary. Objective: For children with problematic severe asthma, achieving adequate control of asthma is difficult. The aim of this prospective observational study was to evaluate the effects of intensive multidisciplinary inpatient treatment on multiple outcome variables in children with problematic severe asthma. Methods: Participants were 89 children with problematic severe asthma (mean age 13.6 ± 2.5 years) treated in tertiary care clinics at high altitude (Switzerland) or sea level (Netherlands) and their parents (85 mothers, 55 fathers). The primary outcome variable was the Childhood Asthma Control Test (C-ACT). Other outcome variables were forced expiratory volume in 1 sec (FEV_1), fractional concentration of exhaled nitric oxide (FeNO), quality of life [PAQLQ(S)], children's coping (UCL-A), parents' report of behavioral problems (CBCL), and parenting stress (PSI/NOSI). Evaluations were taken pre-treatment, post-treatment, and 3–6 months follow-up. Median [P25;P75] treatment duration 74 [56;80] days; Median follow-up interval 131 [103;177] days. Results: The percentages of children showing controlled asthma (C-ACT) were 18% (pre-treatment), 69% (post-treatment), and 44% (follow-up). The vast majority of the children (80%) showed an improvement on C-ACT with 4% showing a deterioration. On C-ACT, FeNO, quality of life, and behavioral problems, improvements at post-treatment were highly significant. Improvements generally remained at a functional level at follow-up. Children's coping and parenting stress in parents did not change. Conclusions: The improvement in asthma control and other outcome variables suggests that multidisciplinary inpatient treatment is an effective approach for a heterogeneous group of children with asthma that remained uncontrolled in secondary care. **Pediatr Pulmonol. 2017;52:588–597.** © 2016 Wiley Periodicals, Inc.

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INTRODUCTION

Asthma, a chronic inflammatory disease of the airways, is common in children with a reported prevalence ranging from 5% to 15%.[1] Most children respond well to safe and evidence-based pharmacological treatment. In the Netherlands, pediatric asthma patients that do not show an adequate response to standard care with medication and treatment in usual secondary care can be referred to specialized tertiary care.

It is not always clear whether treatment of asthma is difficult because the asthma is therapy-resistant or because of other reasons such as living in a house with detrimental environmental conditions for the asthma. Psychological factors may also obstruct treatment effects, but it is unclear whether psychological problems are a cause or consequence of asthma.[2–5] Some studies suggest that poor adherence and disease management are an explanation for poor asthma control,[6–8] while others underline that stress should be addressed in treatment.[9–11] Several models of pediatric asthma specify mutually causal interrelations between biological variables, psychological variables such as behavioral problems and inadequate coping, and social variables such as parenting stress.[12] This biopsychosocial

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model suggests that all these variables may potentially improve after successful treatment.

Given the alleged multiple factors that may play a role in persistence of asthma symptoms, multidisciplinary inpatient treatment is a treatment option to improve asthma control. Studies evaluating a small set of outcome variables in children treated in tertiary care clinics-mainly regarding treatment at high altitude-indicated an improvement of quality of life and control of asthma as measured with questionnaires.[10,13–15] Lung function parameters such as forced expiratory volume in 1 sec (FEV_1) yielded equivocal results; some studies showed no significant improvement in FEV_1 during inpatient treatment,[10,13,15] but in other studies FEV_1 improved.[14,16] As yet, an encompassing evaluation of multidisciplinary inpatient treatment including biological, psychological, and social variables is missing.

Our current prospective observational study offers an evaluation of the effects of multidisciplinary inpatient treatment on multiple outcome variables in children with problematic severe asthma. We hypothesized that asthma control and the associated psychosocial outcomes improve after treatment.

METHODS

Participants

Our prospective study examined children with asthma before and after inpatient treatment in a high altitude asthma clinic with a hypo-allergenic environment in Switzerland, the Merem Netherlands Asthma Center Davos (NAD), and an asthma clinic at sea level in the Netherlands, the Merem Asthma Center Heideheuvel (ACH). Referral to one of the clinics was made by a pediatric pulmonologist or pediatrician with expertise in asthma, and based on persistent lack of disease control, co-existence of multiple asthma-related problems, and the need for an intensive multidisciplinary approach to therapeutically target these problems. Patients were admitted according to the guidelines (PSA) of the Dutch Pediatric Respiratory Society.[17] All children had troublesome asthma with lack of control in regular care and needed intensive multidisciplinary treatment according to the Dutch guidelines. About 70% of the patients fulfilled the strict criterion of persistent symptoms despite treatment in step three according to Global Initiative for Asthma 2012 criteria (double dose of inhaled steroids and/or need for additional long acting β2-adrenergic agonists or leukotriene receptor antagonist) or higher.[18] The majority of patients presented with several components of atopic disease.[19]

From 2010 to 2012, all children aged 7–18 years who were referred to one of the two clinics were invited to participate in the study. The medical ethics committee of the Amsterdam Medical Center (AMC), Amsterdam, the Netherlands, approved the study. All parents and children aged 12 and older provided written consent, children younger than 12 provided oral assent.

Treatment

Treatment in both clinics consists of an intensive inpatient pulmonary multidisciplinary rehabilitation program. Treatment is personalized by using a modular approach with standardized treatment modules in both centers. A standardized diagnostic program is performed at admission with somatic and psychosocial assessments. All children follow the basic psycho-educational asthma program to increase knowledge, technical skills (inhalation technique), self-management, and coping strategies. Other modules consist of optimizing asthma medication, improving physical fitness, food and diet, school, family and system interactions, and personalized psychological and social support. Parents participate in a tailored educational program. Treatment is comparable at both locations with exception of the high altitude of NAD. Moreover, children at ACH go home in the weekends. The duration of the inpatient rehabilitation program varies from 1 to 3 months. Discharge criteria are: Individual treatment goals of the child are reached or child/parents discontinue treatment.

Procedure

Two weeks before the start of inpatient treatment in one of the specialized asthma clinics, the patients and parents received questionnaires on asthma control, health-related quality of life, coping, behavioral problems, and parenting stress at their homes. At discharge and at follow-up (3–6 months after discharge), the same self-report questionnaires were administered to the children. Moreover, before therapy and at discharge assessments of lung function and airway inflammation were taken.

Medical history and physical examination were performed on the day of arrival by the pediatrician. Medical history included atopic symptoms, exercise intolerance, medication, reliever therapy, and adherence as derived from the clinical interview.

Instruments

Descriptive Variables

The following characteristics of children were assessed: gender, age, length of stay, sensitization to inhaled allergens, ICU admission in history, medication including history, exacerbations with need for oral prednisolone in the past year, and school absence in the past year.

Outcome Variables

The primary outcome was asthma control, assessed with the Childhood Asthma Control Test (C-ACT).[20–22] The C-ACT was chosen for children as well as adolescents because we wanted a uniform measure that was scored by children and parents in this study. This 7-item checklist

assesses control of asthma reported by the child (four questions) and their caregivers (three questions) using a 4-point Likert response scale. The questionnaire has been validated for children from 4 to 12 years with relatively mild, controlled asthma.[21] A cut-off $\leq$19 indicates uncontrolled asthma.[22] A minimal important difference (MID) of two points has been recommended.[23]

Pulmonary function testing (PFT) was performed using the Masterscreen PFT (Jaeger Viasys, Germany) using a standardized protocol for spirometry according to the ATS and ERS guidelines.[24] Short and long acting β_2-adrenergic agonists were stopped at least 12 hr before PFT. Forced expiratory volume in 1 sec (FEV_1) before β_2-agonists was obtained. Even in children with severe asthma, FEV_1 is in between asthma attacks often within a normal range of 80–120% predicted. We considered a FEV_1 of <80% predicted as deviating from normal.

Airway inflammation was measured with the Niox Flex (Aerocrine, Sweden) using the fractional concentration of exhaled nitric oxide (FeNO) according to the ATS guideline.[24] Normal values in children range from 10 to 25 parts per billion. We used a cut-off score of >35 for problematic airway inflammation in these children.[25]

The Pediatric Asthma Quality of Life Questionnaire, PAQLQ(S), is a widely used disease-specific health-related quality of life self-report measure for children aged 7–17 years.[26] The questionnaire assesses three domains: symptoms (ten items), activity limitations (five items), and emotional function (eight items). A score $\geq$5.87 on total quality of life was considered to reflect adequate quality of life.[27] The cut-off score was based on a Dutch reference group comprising a subgroup with many respiratory symptoms in the past 7 days and a subgroup with few respiratory symptoms. The cut-off score was calculated as the mean of one standard deviation (SD) above the mean of the subgroup with many symptoms and 1 SD below the mean of the group with few symptoms[27] according to the method recommended by Jacobson and Truax.[28] A change in PAQLQ(S) score of 0.5 has been defined a MID on group level.[23,29]

The Utrecht Coping List for Adolescents (UCL-A) questionnaire measures coping in adolescents.[30,31] The 47 items constitute seven domains: confrontation, palliative reaction, avoidance, seeking social support, passive reaction pattern, expression of emotions, and reassuring thoughts. For most people, the domains "confrontation" and "seeking social support" are considered more adequate coping strategies than the other five coping strategies.[31] This questionnaire does neither have a cut-off score differentiating dysfunctional and functional coping nor a score for minimal important or clinically relevant change.

The Child Behavior Checklist (CBCL) is a standardized questionnaire that uses ratings by parents to assess emotional and behavioral problems of children and adolescents.[32] The CBCL consists of 120 items with a 3-point Likert scale response format. A global score and scores on the domains internalizing and externalizing behavioral problems are used (T-scores). A T-score of $\geq$63 (90th percentile in the norm population) indicates that a child has clinically relevant symptoms and might need professional help. No criteria for minimal important or clinically relevant change have been defined.

The Parenting Stress Index [Dutch: "Nijmeegse Ouderlijke Stress Index"] (PSI/NOSI) assesses the multiple dimensions of parenting stress.[33,34] The 123 items comprise two major domains: The "parent domain" (perceived stress regarding family factors) and the "child domain" (stress evoked by their child's behavior and emotions). Items are scored on a 6-point Likert-scale; a higher score reflects more stress. The cut-off criterion for more than average total parenting stress in mothers is $\geq$293 and in father $\geq$271.[34] No criteria for minimal important or clinically relevant change have been defined.

Statistical Analysis

Statistical analyses were performed with SPSS 23. *P* values <0.05 (two-sided) were considered statistically significant. Attrition analyses using independent *t*-tests or Mann–Whitney *U* tests compared the scores at baseline between the children with complete and incomplete records. Scores at baseline were compared with norm reference scores using descriptive statistics (C-ACT, FEV_1, FeNO) or one sample *t*-tests (PAQLQ-(S), UCL-A, CBCL, PSI/NOSI). To address concerns of type I error due to multiple tests, the Holm's sequential Bonferroni correction of the significance level was applied.[35,36] Group changes over time were evaluated by one-way repeated measures analysis of variance (ANOVA) and Bonferroni posttest for the outcome measures that were assessed at baseline, post-intervention, and follow-up. Outcome measures that were only assessed at baseline and post-intervention (FEV_1, FeNO, and CBCL) were compared with paired samples *t*-tests or Wilcoxon signed rank tests depending on data characteristics. To quantify the number of children with scores below and above a clinically relevant cut-off, established criteria were used.

RESULTS

Sample Characteristics

In the study period, 45 children were admitted to NAD of whom 37 (82%) were included; one child did not provide informed consent, seven did not return the questionnaires. Of the 60 children admitted to ACH, 52 children were included (87%); two children did not provide informed consent and six did not return the

TABLE 1— Characteristics and Asthma Outcome Variables of the 89 Children at Baseline

Female, number (%)	46 (52%)
Age of child, mean (SD), range years	13.6 (2.5), 7–18
Length of stay, median [P25;P75] days	74 [56;80]
Lung function measures	
FEV_1, mean (SD) (n = 89)	100.5 (15.6)
FeNO, median (interquartile range) (n = 88)	19.5 (23.8)
Control of asthma (C-ACT) total score, mean (SD) (n = 82)	14.2 (5.8)
Allergy (sensitization), number (%)	
House dust mite (n = 81)	60 (74%)
Pollen (n = 82)	52 (63%)
Animals (n = 82)	56 (68%)
Non-allergic (n = 81)	10 (12%)
Medication	
Daily inhaled budesonide-equivalent, mean (SD) μg, (n = 88)	1,037 (666)
Daily use of LABA, number (%)	79 (89%)
Daily use of LTRA, number (%) (n = 76)	63 (83%)
Omalizumab, number (%)	9 (10%)
Intensive care unit admission in history, number (%)	8 (9%)
Exacerbations with need for oral prednisolone ≥2 per year, number (%) (n = 77)	53 (69%)
School absence in past year ≥4 weeks, number (%) (n = 80)	43 (54%)

FEV_1 (forced expiratory volume in 1 sec) is expressed as percent of predicted (% pred).
FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb; normal range 10–25 ppb; a higher value corresponds with more eosinophilic inflammation).
C-ACT, Childhood Asthma Control Test (total score range 0–27; a higher score reflects better control); LABA, long acting β_2-agonists; LTRA, leukotriene receptor antagonist.

questionnaires. Eighty-five mothers (35 NAD, 50 ACH) and 55 fathers (21 NAD, 34 ACH) of the 89 children completed the PSI/NOSI-questionnaire.

The median [P25;P75] duration of the pre-to-post treatment interval was 74 [56;80] days. The median [P25;P75] follow-up duration post-treatment was 131 [103;177] days. No post-treatment or follow-up measurements were received from 24 to 37 children and their parents (Table 3 shows the exact numbers).

Attrition Analyses

Attrition analyses comparing the scores at baseline revealed no differences between the participating children with complete post-treatment records and the children with incomplete records with respect to FEV_1, FeNO, C-ACT, PAQLQ, CBCL, and PSI/NOSI-scores (all P values >0.05). On the UCL-A, most domains did not show difference with two exceptions. The attrition group scored lower on "confrontation" (mean 13.2 ± 3.3, n = 28 vs. mean 16.0 ± 3.5, n = 55, $P = 0.001$), and "reassuring thoughts" (mean 9.8 ± 2.8, n = 28 vs. mean 12.0 ± 2.8, n = 55, $P = 0.001$).

Asthma Control

Table 1 shows the asthma outcome variables at baseline of the 89 children. The mean total C-ACT-score of 14.2 reflects poor control of asthma (≤19) despite previous intensive treatment with medication. All but 10 children had sensitization to inhaled allergens.

Quality of Life

Table 2 shows the baseline values of psychological and social variables. One-sample t-tests showed that mean PAQLQ-scores in our study sample on all domains were lower than mean scores from the reference population with many respiratory symptoms.[27]

Psychological Variables

On most domains, UCL-A-scores did not show deviations from the mean of the Dutch reference group,[31] except for the higher scores of our group on the domains "palliative reaction" and "avoidance."

The CBCL total and internalizing T-scores were higher than the means of the norm reference population[32] indicating more behavioral problems. For this sample of children with asthma, 24% scored in the clinical significant range on the total problem score (T-score ≥63; 90th percentile in the norm reference population); which is an indication that a child has clinically relevant symptoms and might need professional help.

Parenting Stress

Compared to the means from a non-clinical Dutch reference population,[34] parenting stress scores (PSI/NOSI) were low on all domains in mothers and fathers. Compared to the Dutch reference scores at the PSI/NOSI of a clinical sample, deviations were even larger than the deviation from reference scores of the non-clinical population.

TABLE 2— Psychological and Social Variables of Children With Asthma (n = 89) and Their Parents (85 Mothers, 55 Fathers) at Baseline

	Mean	SD	Deviation from norm	95% CI	n (%) children with scores below the norm	*P*-value[1]
Children reports						
Quality of life [PAQLQ(S)] (n = 86)						
Total score, mean (SD)	4.8	(1.2)	−0.54	−0.79 to −0.29	68 (79%)	<0.010
Symptoms, mean (SD)	4.4	(1.4)	−0.61	−0.91 to −0.31		<0.010
Activities, mean (SD)	4.2	(1.5)	−0.38	−0.69 to −0.06		0.140
Emotions, mean (SD)	5.7	(1.3)	−0.54	−0.81 to −0.26		<0.010
Coping (UCL-A), mean (SD) (n = 83)						
Confrontation	15.1	(3.6)	−0.25	−1.04 to 0.54		1.000
Palliative reaction	19.5	(3.6)	0.98	0.21 to 1.76		0.112
Avoidance	16.8	(3.4)	2.07	1.34 to 2.80		<0.010
Seeking social support	13.1	(4.0)	0.55	−0.32 to 1.41		0.848
Passive reaction pattern	11.2	(3.5)	−0.65	−1.42 to 0.11		0.540
Expression of emotions	6.2	(2.1)	−0.22	−0.69 to 0.25		1.000
Reassuring thoughts	11.2	(3.0)	−0.07	−0.72 to 0.58		1.000
Behavioral problems (CBCL), mean (SD) (n = 87)						
Total score	53.9	(9.8)	4.14	2.06 to 6.23	21 (24%)	<0.010
Internalizing	57.3	(9.7)	7.12	5.05 to 9.19		<0.010
Externalizing	48.7	(10.3)	−1.43	−3.62 to 0.75		0.950
Parent reports						
Parenting stress (PSI/NOSI)						
Mothers (n = 85) total score, mean (SD)	225.7	(67.3)	−40.83	−55.35 to −26.30	12 (14%)	<0.010
Parent domain, mean (SD)	98.5	(31.0)	−22.49	−29.17 to −15.81		<0.010
Child domain, mean (SD)	127.2	(41.1)	−18.14	−27.00 to −9.27		<0.010
Fathers (n = 55) total score, median (interquartile range)	207	(100)	−38.88	−56.23 to −21.53	10 (18%)	<0.010
Parent domain, median (interquartile range)	84.0	(45.7)	−16.31	−24.20 to −8.42		<0.010
Child domain, mean (SD)	119.7	(38.2)	−22.48	−32.81 to −12.14		<0.010

PAQLQ(S), Pediatric Asthma Quality of Life Questionnaire (range 1–7; a higher score reflects better quality of life); UCL-A, Utrecht Coping List for Adolescents (range confrontation 7–28, palliative reaction 8–32, avoidance 8–32, seeking social support 6–24, passive reaction pattern 7–28, expression of emotions 3–12, reassuring thoughts 5–20); CBCL, Child Behavior Checklist: a higher score reflects more problems (T-score ≥60 borderline clinical significant, T-score ≥63 clinical significant); PSI/NOSI, Parenting Stress Index (total scores in the non-clinical norm reference population range from 123 to 738; parent domain 58–348, child domain 65–390).
[1]One sample *t*-tests, *P*-values following correction for multiple comparisons (Holm's sequential Bonferroni method) are given.

Primary Outcome

Asthma Control

Figure 1 shows the score of each individual child (n = 49) with available scores on the primary outcome C-ACT at pre- and post-treatment. The scores of 34 (69%) children that provided post-therapy assessments were >19. Using the MID criterion of two points[23] on the C-ACT, 80% of the children showed an improvement from admission to discharge, 4% showed a deterioration, and 16% did not reach this MID. At follow-up, compared to pre-treatment scores, 39 (66%) of the children showed an improvement and 12 (20%) showed a deterioration.

The top of Figure 2 shows the percentages of children scoring higher than the cut-off criterion of 19 at the C-ACT at pre-therapy, post-therapy, and follow-up. More children showed a poor C-ACT score at baseline than at discharge or follow-up (Fig. 2). Repeated measures ANOVA showed that asthma control improved significantly post-treatment. The improvement was maintained at follow-up (Table 3).

Secondary Outcomes

Lung Function

Before therapy, FeNO scores of 66 of 88 children were below the cut-off criterion of 35 ppb for problematic airway inflammation. After therapy, this held for 61 of 63 children (Fig. 2). The median observed change in FeNO of −7 ppb [IQR −16.3 to −1] was highly significant ($P < 0.001$).

The mean FEV_1 percentage predicted was in the normal range for most of the children at baseline (Fig. 2). Nevertheless, a significant improvement of 2.8 (SE 1.1) % after treatment was found (mean from 100.8 SD to 16.2–103.7 SD 15.8, $P = 0.02$).

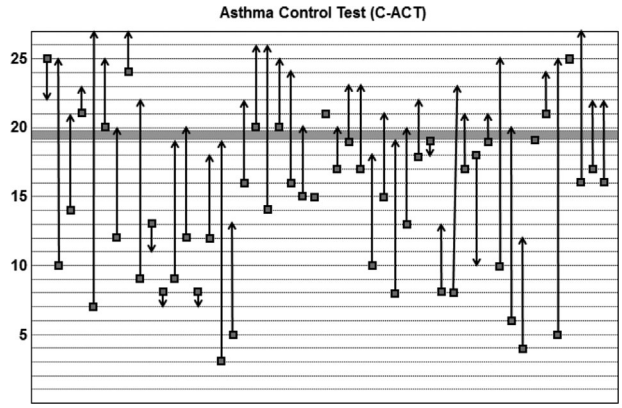

Fig. 1. Arrows showing the pre-to-post-treatment change (median [P25;P75] treatment duration 74 [56;80] days) on the Asthma Control Test (C-ACT) for each individual child with available pre- and post-treatment assessments, n = 49. A score ≤19 is considered uncontrolled asthma.

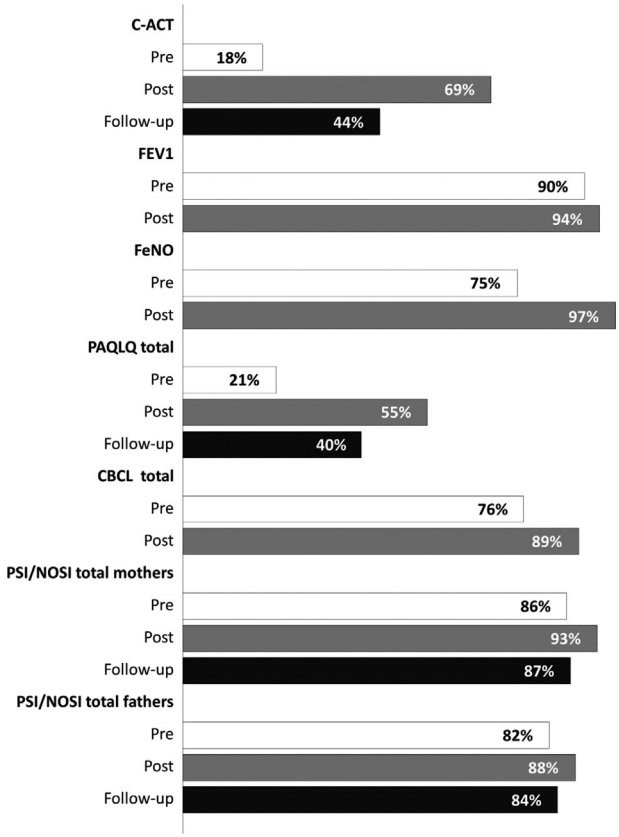

Fig. 2. Percentage of children from total number (n = see Table 3) of children having an acceptable score at pre-treatment, post-treatment (median treatment duration 74 days), and follow-up (median duration 131 days after the end of treatment). C-ACT, Childhood Asthma Control Test. FEV_1 (forced expiratory volume in 1 sec) is expressed as percent of predicted (% pred). FeNO (fractional concentration of exhaled nitric oxide) expressed as parts per billion (ppb); PAQLQ(S), Pediatric Asthma Quality of Life Questionnaire (Self-Report); CBCL, Child Behavior Checklist; PSI/NOSI, Parenting Stress Index. Cut-off scores were: C-ACT: >19, FEV_1: ≥80% pred, FeNO: <35 ppb, PAQLQ total: ≥5.87, CBCL total: <63, PSI/NOSI total mothers: <293, and PSI/NOSI total fathers: <271.

Quality of Life

On the PAQLQ total score, before therapy, 18 of 86 children were above the cut-off criterion of 5.87,[27] after therapy 32 of 56 children, and at follow-up 26 of 63 children (Fig. 2). After therapy, 33 children (60%) showed an improvement according to a MID score >0.5[23,29] while 5 (9%) showed a deterioration. At follow-up, 35 children (57%) showed an improvement compared to pre-treatment while 13 (21%) showed a deterioration.

Repeated measures ANOVA showed that PAQLQ total and domain scores improved over time; post hoc tests with Bonferroni correction showed that post-treatment PAQLQ scores as well as follow-up scores were significantly higher than pre-treatment scores (Table 3).

Psychological Outcomes

None of the coping domains showed a significant change after treatment. At the CBCL, 58 of 65 children scored in the healthy range after therapy using the 90th percentile criterion (Fig. 2). The mean observed improvement of the CBCL total score (4.6) was highly significant ($P < 0.001$) as well as the improvement (5.7) at the domain internalizing behavioral problems (Table 3).

Parenting Stress

Regarding the PSI/NOSI total score, most mothers and fathers scored below the cut-off criterion (i.e., no parenting stress)[34] before and after treatment, and at follow-up (Fig. 2). Neither the scores of mothers nor fathers showed a significant change over time (Table 3).

DISCUSSION

This prospective observational study evaluated the effects of multidisciplinary inpatient treatment in children with problematic severe asthma in whom adequate control of asthma could not be achieved in secondary care. Overall, the population admitted for this treatment showed low control of asthma, low quality of life, and a coping style characterized by palliative reaction and avoidance in combination with internalizing behavioral problems. After the intervention, the vast majority of children improved on several aspects of asthma control. Moreover, clinically relevant improvement of ACT, and highly significant improvements of quality of life, airway inflammation, and behavioral problems were established.

While the emphasis in asthma management in general has been shifted to achieving full control of asthma,[6] in a subgroup of children with asthma this target appears very hard to achieve. Nevertheless, our study demonstrated that an improvement on C-ACT and FeNO from pre- to post-treatment in a large part of our group is possible with intensive treatment in a clinical and multidisciplinary

TABLE 3— Questionnaire Outcomes Before Treatment, at Post-Treatment (on Average 74 Days After the Start of Treatment) and at Follow-Up (on Average 131 Days After the End of Treatment)

	Mean (SD) scores						Estimated mean differences between the time points				
	Pre-treatment		Post-treatment		Follow-up		Overall	Pre- to post-treatment		Pre-treatment versus follow-up	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	*P*-value	Mean dif (95% CI)	*P*-value	Mean dif (95% CI)	*P*-value
C-ACT total	14.2 (5.8)	82	20.4 (4.9)	52	18.2 (5.4)	62	<0.001	6.1 (8.2 to 4.0)	<0.001	4.2 (6.7 to 1.7)	<0.001
PAQLQ total	4.8 (1.2)	86	5.8 (1.0)	56	5.4 (1.2)	63	<0.001	0.94 (1.37 to 0.51)	<0.001	0.58 (1.03 to 0.13)	0.008
Symptoms	4.4 (1.4)	86	5.4 (1.3)	56	5.0 (1.4)	63	<0.001	1.02 (1.57 to 0.47)	<0.001	0.65 (1.25 to 0.04)	0.033
Activities	4.2 (1.5)	86	5.4 (1.4)	56	5.0 (1.4)	63	<0.001	1.06 (1.61 to 0.50)	<0.001	0.76 (1.36 to 0.16)	0.009
Emotions	5.7 (1.3)	86	6.5 (0.7)	56	6.1 (1.2)	63	<0.001	0.73 (1.12 to 0.33)	<0.001	0.39 (0.74 to 0.05)	0.022
CBCL total	53.9 (9.8)	87	48.9 (11.3)	65	n.a.	n.a.	n.a.	−4.6 (−6.6 to −2.5)	<0.001		
Internalizing	57.3 (9.7)	87	52.0 (12.6)	65	n.a.	n.a.	n.a.	−5.7 (−8.3 to −3.1)	<0.001		
Externalizing	48.7 (10.3)	87	45.5 (9.9)	65	n.a.	n.a.		−2.2 (−4.2 to −0.1)	0.041		
PSI/NOSI mothers total	225.7 (67.3)	85	21 1.6 (59.6)	56	213.9 (69.8)	62	0.349	1.5 (−15.1 to 18.12)	1.000	9.9 (−13.7 to 33.5)	0.876
Parent	98.5 (31.0)	85	92.4 (29.5)	56	93.4 (35.3)	62	0.550	0.66 (−9.6 to 8.3)	1.000	3.1 (−8.7 to 14.9)	1.000
Child	127.2 (41.1)	85	119.2 (33.5)	56	120.5 (38.6)	62	0.270	2.2 (−7.2 to 11.6)	1.000	6.8 (−6.6 to 20.2)	0.609
PSI/NOSI fathers total	207 (100)	55	194.2 (62.4)	35	200.7 (70.0)	38	0.240	6.9 (−6.4 to 20.2)	0.585	0.61 (−9.8 to 11.1)	1.000
Parent	84.0 (45.7)	55	84.5 (29.1)	35	88.1 (36.3)	38	0.500	2.4 (−4.6 to 9.5)	1.000	0.12 (−5.6 to 5.8)	1.000
Child	119.7 (38.2)	55	109.7 (35.6)	35	112.6 (37.2)	38	0.254	4.5 (−3.7 to 12.6)	0.524	0.49 (−6.5 to 7.5)	1.000

Significance levels of repeated measures analysis of variance (overall *P*-value) and Bonferroni corrected posttests (pre- to post-treatment and pre-treatment vs. follow-up).
C-ACT, Childhood Asthma Control Test (total score range 0–27; a higher score reflects better control); PAQLQ(S), Pediatric Asthma Quality of Life Questionnaire (range 1–7; a higher score reflects better quality of life); CBCL, Child Behavior Checklist, a higher score reflects more problems (T-score ≥60 borderline clinical significant, T-score ≥63 clinical significant); PSI/NOSI, Parenting Stress Index (total score ranges from 123 to 738; parent domain 58–348, child domain 65–390); Ci, confidence interval; n.a., not assessed.

setting. FEV_1 was in most children already in the normal range at pre-treatment, but nevertheless showed a small but significant improvement at post-treatment. This is in agreement with sparse and small previous studies.[10,13–15,37–39] Compared to previous studies, our study is unique regarding three characteristics: it was done in a large cohort of children, the design was prospective, and the effect of treatment on multiple outcomes was examined.

Considering the positive C-ACT changes in many children, the improvement in quality of life—though highly significant—was relatively disappointing because a high percentage of the group did still not meet the cut-off criterion for normal scores. The mean total quality of life score of our group after the intervention (5.8) was about similar to the mean score of a group with uncontrolled asthma (5.9) that was described previously.[23] The somewhat less positive outcome for quality of life scores as compared to asthma control test scores could reflect that improvement of quality of life has a longer latency time than improvement of asthma control, which would imply that continuing attention in aftercare to the quality of life burden might be needed for some children. Tentatively, it is possible that a further focus on cognitive-behavioral mechanisms is needed to bring about enduring changes in lifestyle, self-regulation, and other determinants of quality of life.[40,41] However, it is also possible that somewhat lower increase in quality of life is explained by the chosen cut-off criterion of quality of life being too high for the children with problematic severe asthma who are commonly included in the inpatient treatment that was evaluated in the current study. This is a topic for future research.

With respect to psychosocial outcomes, consistent with the biopsychosocial model and previous studies,[42–44] our study confirmed that children with asthma are at risk of having internalizing behavioral problems. After treatment, the percentage of children with clinically relevant behavioral problems was comparable to the percentage in the general population. The improvement was less clear in other psychosocial variables. Although also the coping domains palliative reactions and avoidance behavior at treatment entrance reflected internalizing problems, they did not significantly change during therapy. A possible reason is that the profile of coping styles was too heterogeneous with many children having an adequate score already at the start of treatment. Also parenting stress did not change. Our previous study in this group showed that parenting stress was low but associated with more airway inflammation and greater child behavioral problems at pre-treatment.[45] According to the stress-appraisal model, parenting stress is not only determined by the severity of stressors but also by one's capability to deal with stressors.[46] In general, this group of parents may have learned to cope well with the disease of their child and have grown accustomed to their way of living and caring for their child. This observation as well as the observation that parenting stress levels did not change after therapy, suggests that in the overall group parenting stress is not an important issue. This does not exclude that parenting stress might be an important target of treatment in selected cases.

The C-ACT was chosen as primary endpoint in our study, because the problematic severe asthma of virtually all children would be reflected in low asthma control scores. All other variables were secondary endpoints, because it was known in advance that children would differ widely across these measures. Inherent to problematic severe asthma, it is impossible to include a single variable that would adequately reflect the complex and heterogeneous nature of the asthma for an individual child. Instead, we used separate measures of biological aspects of asthma as recommended[47] and several measures of psychosocial aspects. It was also not valid to make a composite score because for the one child a physiological measure like FEV_1, FeNO, or still another measure might be relevant, while for another child behavioral problems that are associated with poor adherence or a traumatic reaction to respiration problems are the core problem. Therefore, we evaluated the number of individual children that showed improvements at a broad set of biopsychological variables that are relevant for a restricted proportion of children with problematic severe asthma.

Our study has several limitations. The missing assessments at post-therapy and follow-up were a limitation; however, attrition analyses generally revealed no differences at baseline between the children with and without post-treatment assessments. A comprehensive long-term follow-up was lacking in our study. After the inpatient treatment, children returned to their pediatric pulmonologist or pediatrician for follow up in secondary care settings. For the present study, only data from questionnaires administered to the children could be obtained. Data on medication use, exacerbations, and hospitalizations from the medical records in secondary care covering follow-up were not available. A final limitation of this study is its observational design. Although improvement is indicated by the analyses, a randomized controlled trial is needed in order to verify that this treatment is superior to treatment as usual in secondary care.

Patients are heterogeneous in the sense that different pathological processes maintain the asthma and that different psychological, environmental, and social processes may play a crucial role in maintaining uncontrolled asthma. Therefore, treatment customized to the individual patient is of great importance. Overall, the observed improvements in asthma control, airway inflammation, quality of life, and behavioral problems

suggest that multidisciplinary inpatient treatment is a useful approach for a heterogeneous group of children with asthma that remained uncontrolled in secondary care.

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