

# Risk Factors for Pediatric Intensive Care Admission in Children With Acute Asthma

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**INTRODUCTION:** Severe acute asthma in children is associated with substantial morbidity and may require pediatric ICU (PICU) admission. The aim of the study was to determine risk factors for PICU admission. **METHODS:** The study used a retrospective multicenter case-control design. The cases included children admitted to the PICU because of severe acute asthma and a history of out-patient treatment by pediatricians or pediatric pulmonologists. Controls were children with asthma without a PICU admission for severe acute asthma. The children were matched for sex, age, hospital, and time elapsed since the diagnosis of asthma. Fourteen possible risk factors were analyzed. **RESULTS:** Sixty-six cases were matched to 164 controls. In univariate analysis, all but one of the analyzed variables were significantly associated with PICU-hospitalization. After multivariate conditional logistic regression analysis, 4 risk factors remained significant. These included active or passive smoking, allergies, earlier hospitalization for asthma, and non-sanitized home. **CONCLUSIONS:** Physicians and parents should be aware of these risk factors, and efforts should be made to counteract them. *Key words:* asthma; case-control studies; intensive care; pediatrics; risk factors; status asthmaticus. [Respir Care 2012;57(9):1391–1397. © 2012 Daedalus Enterprises]

## Introduction

Asthma is the most prevalent chronic pediatric disorder, affecting approximately 6–12% of the Dutch pediatric population.<sup>1</sup> Severe acute asthma (SAA) may be life threatening, as some children fail to respond to conventional

asthma treatment (ie, administration of oral/parenteral steroids and inhaled  $\beta_2$  agonists). Severe complications may occur, such as pneumothorax, ventilator-associated pneumonia, rhabdomyolysis, circulatory failure, and even death.<sup>2,3</sup> Case series have suggested that certain characteristics, such as having divorced parents, lower socioeconomic class, poor adherence to treatment, and pre-existent severe asthma, may enhance the risk of SAA.<sup>3–11</sup>

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Most of these studies stem from outside Europe, and were published before 2005. Recent European studies on this topic are lacking. This is the first case-control study to assess risk factors for pediatric ICU (PICU) admission for pediatric SAA patients in the Netherlands. We aimed to identify characteristics that could predict the need for PICU admission for SAA among pediatric out-patients at Dutch hospitals. Early recognition could help to develop preventive strategies and improve efficacy of treatment for these children with asthma.

## Methods

### Study Population

In a retrospective case-control study, we obtained data on asthmatic children who did and did not develop SAA warranting PICU admission. Data were collected in a standardized manner in 4 out-patient pediatric clinics in the southwestern region of the Netherlands (Amphia Hospital, Breda; Maastad Hospital, Rotterdam; Erasmus Medical Center-Sophia Children's Hospital, Rotterdam; and Reinier de Graaf Hospital, Delft). As a retrospective case-control study, the medical ethics committee waived the need for informed consent. Children in this region experiencing SAA and who require intensive care treatment are transferred to the PICU of the Erasmus Medical Center-Sophia Children's Hospital. The admission criteria to the PICU were clinically predefined and did not change during the study period. They included respiratory failure and imminent exhaustion, no clinical benefit after continuous nebulization of bronchodilator drugs, and the need for intravenous administration of salbutamol (which is an indication for PICU admission according to Dutch guidelines) and/or the need for mechanical ventilation. All children with doctor-diagnosed asthma treated as out-patients by pediatricians or pediatric pulmonologists before PICU admission because of SAA from January 1994 to October 2006 were eligible as cases in this study. Children who had not been diagnosed with asthma prior to their PICU admission and presented with their first asthmatic attack were excluded from the study, because defining controls would not be feasible. Hence, this study focused on the population of children diagnosed with asthma and being treated by pediatricians or pediatric pulmonologists in out-patient clinics from 3 general hospitals and one university hospital. Controls were patients from the same participating referring hospitals, diagnosed with asthma and treated on an out-patient basis by pediatricians or pediatric pulmonologists, and who never needed PICU admission for any reason.

### Matching Criteria

Each case patient was matched to at least one control according to all the following criteria:

- Sex
- Age:  $\pm 1$  year for under 5-year-olds and  $\pm 2$  years for older children
- The same hospital, if possible; if not, the nearest hospital; however, controls for cases from a university hospital were always sought from the Erasmus Medical Center-Sophia Children's hospital.

### QUICK LOOK

#### Current knowledge

Severe acute asthma in children is associated with substantial morbidity and mortality. The most severe cases require intensive care admission. Risk factors for ICU admission include environmental exposures and previous hospitalization.

#### What this paper contributes to our knowledge

In a case-control study, risk factors for ICU admission in children with severe asthma included allergies, exposure to passive smoking, active smoking, unsanitized home(s), and a previous hospitalization for asthma. Admission for severe asthma occurred in 16% of patient without a previous asthma diagnosis.

- Period elapsed since the diagnosis of asthma, distinguished by duration of up to 1 year, 1–4 years, 4–7 years, 7–10 years, or > 10 years

### Potential Risk Factors

Table 1 shows the candidate risk factors for PICU admission, derived from previous studies.<sup>3–11</sup> All these variables were extracted from the medical records. Data from the period prior to the PICU admission were considered as the baseline values for variables that could potentially change over time (eg, smoking, pets, hay fever). This period was, on average, a few months before the admission, at a time when there were no signs or symptoms of the severe asthma exacerbation. If possible, the last documented out-patient visit before PICU admission was chosen. For variables that were not documented during the last out-patient visit, the most recent documentation prior to the PICU admission was used.

The variable “eczema” was an exception: this was scored with “yes” if it had occurred at any point prior to the PICU admission. The variable “sanitization of the home” was also an exception, because a house was scored as “sanitized” if the medical record reported that a specialized asthma nurse had visited and advised the family at any point in time before PICU admission, and specific measures for sanitization (eg, anti-dust-mite blankets applied) had been taken. A house was scored as “non-sanitized” if, for example, there were carpets, curtains, or many cuddly toys in the child's bedroom. The ethnicity of the child was based on the ethnic origins of the parents and classified as white or non-white. Social-economic status was derived from both parents' occupations at baseline. Smoking was scored as “passive” when a person who lived in the same

Table 1. Candidate Risk Factors for Pediatric ICU Admission

Patient Characteristics
Sex
Age
Ethnicity and Psychosocial Context
Ethnicity
Divorced parents
Lower social-economic status
Number of children in the family
Language barrier
Exposures and Atopy
Active or passive smoking
Exposure to pets
Sanitization of the home
Quality of the home
Allergies
Hay fever
Eczema
Severity and Treatment of Asthma
Severity of asthma
Earlier non-PICU hospitalization because of asthma
Prior PICU admission or mechanical ventilation for SAA and any complications thereof
Non-compliance with therapy
Age at first symptoms of asthma and length of symptomatic period prior to diagnosis of asthma
Undertreatment
Lack of instructions from a specialized asthma nurse
Comorbidities
Use of inhaled corticosteroids
Maintenance use of additional $\beta_2$ agonists
Chronic use of additional asthma drugs (long-acting bronchodilators, leukotriene receptor antagonists, anticholinergics or theophylline)

PICU = pediatric ICU

SAA = severe acute asthma

house as the child smoked inside the house. "Quality of the home" was a dichotomous variable, rating the house as either old or new. The variable "allergy" referred to allergies for several antigens, excluding pollen, such as allergies for dust mites, animals, and food.

These data were retrieved from the medical record based on positive radioallergosorbent tests (RAST) and/or skin allergy tests. Hay fever was extracted from the medical record and rated separately from the other allergies. Asthma severity levels were based on the amounts and types of medication at baseline. It was always scored as severe if the child had been readmitted to the PICU for asthma. The variables "non-compliance" and "undertreatment" were scored with "yes" only if the physician had specifically noted this in the medical record. "Co-morbidity" was a dichotomous variable, and included every possible medical condition besides asthma from birth till PICU admission. Asthma medication was based on the prescription at the last regular out-patient visit prior to the PICU-admis-

sion. The use of inhaled corticosteroids was determined in a dose-dependent (daily amount) and dose-independent (yes or no) fashion.

## Statistical Analysis

Variables for which no more than 30% of data were missing were compared between cases and controls using univariate and multivariate analyses. Accounting for matching, the Mantel-Haenszel statistic was used for the univariate analyses of qualitative categorical variables to identify variables associated with an SAA and the need of PICU hospitalization. For the continuous dose-dependent non-parametric variable "prescribed corticosteroids" we used the Mann-Whitney U test. For all the univariate analyses we used statistics software (SPSS 18.0, SPSS, Chicago, Illinois). The significant risk factors for SAA were identified with conditional logistic regression analysis using statistics software (SAS 9.2, SAS Institute, Cary, North Carolina). A *P* value of < .05 (2-sided) was considered statistically significant. The indices of the goodness of fit  $-2 \log$  likelihood, Akaike information criterion, and Schwarz Bayesian criterion were obtained using statistics software (SAS 9.2, SAS Institute, Cary, North Carolina).

## Results

### Study Population

From January 1994 to October 2006, a total of 139 children were admitted to the PICU because of SAA. This group had a male preponderance (61.9%). The median (range) age at PICU admission was 4.3 (0.6–16.5) years. Seventeen children were ventilated during their PICU admission, 3 of whom developed a pneumothorax.

Of these 139 PICU admissions for SAA over the study period, 78 met the inclusion criteria for our study (Figure). Twenty-two cases (16%) were excluded for not receiving asthma treatment prior to the PICU admission. Thirty-four children (24%) were excluded as they were under the care of a general physician. Three cases were excluded for incomplete data. Finally, 9 cases could not be matched with controls and thus were excluded. This resulted in a study population of 66 cases. This study population also had a male preponderance (68.2%). The median (range) age at PICU admission was 5.2 (0.6–16.5) years. Each of these cases was matched with 1 to 4 controls per case, resulting in a total of 164 controls. The case group (66 patients) did not differ from the total PICU admission group (139 patients) with respect to the patient characteristics variables represented in Table 2, except for the variable "earlier hospitalization for asthma." A possible explanation is that children who are admitted to the hospital for asthma are subsequently treated more often by a pedi-

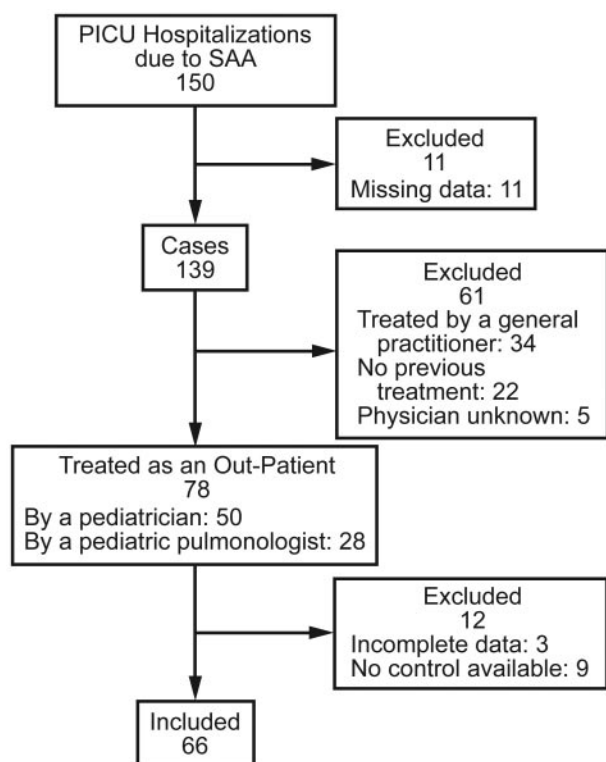


Figure. Inclusion flow-chart. PICU = pediatric ICU. SAA = severe acute asthma.

atrician or pediatric pulmonologist following their hospital admission.

### Outcomes Case-Control Study

Fourteen variables for which < 30% data were missing were analyzed in these 66 cases and 164 controls (see Table 2). The variable “comorbidity” was not further subdivided and was not a significant factor in the analysis.

### Multivariate Analysis

All but one of the variables presented in Table 2 were statistically significantly linked to PICU hospitalization. The only exception was prescribed corticosteroids in a dose-independent fashion. The conditional logistic regression analysis included all significant variables except for severe asthma. This was excluded because it was highly correlated to the dosages of inhaled corticosteroids and therefore a dependent variable. This multivariate analysis showed that only (active or passive) smoking, allergies, earlier hospitalization for asthma, and non-sanitized home proved to be significant independent risk factors (Table 3). The chi-square value was 42.09 ( $P < .001$ ). The indices of the goodness of fit ( $-2 \log$  likelihood, Akaike information criterion, and Schwarz Bayesian criterion) were without

covariates 73.69 for all of them. Including the covariates these values changed into 31.60, 39.60, and 46.83, respectively. In terms of reduction of uncertainty the percentages equal to 57.11%, 46.26%, and 36.45%, respectively, which were considered substantial.

### Discussion

This study demonstrates in a case-control fashion that non-sanitized homes, allergies, (active or passive) smoking, and earlier hospitalization for asthma were independently associated with an increased risk for PICU admissions for SAA in children (see Table 3). These characteristics have been reported by others as well.<sup>3,4,6,9</sup> An important observation was that non-sanitized homes and (active or passive) smoking were not uncommon, in spite of the fact that patients, parents, and physicians may be assumed to be aware that these constitute risk factors for worsening of asthma and for SAA.

A remarkable and unanticipated finding of this study is that 16% of children admitted for SAA had no prior diagnosis of asthma. The other 117 children developed SAA in spite of treatment by general physicians (24%) or by pediatricians (36%) and pediatric pulmonologists (20%) (see the Figure). This indicates that there is a need for the implementation of more effective preventive measures, not only in primary care but also in secondary and tertiary care.

Ethnicity (non-white origin) and a dysfunctional family system have been reported as risk factors for potentially fatal asthma,<sup>3</sup> but this was not confirmed in our study. Use of medication other than inhaled corticosteroids has also been significantly associated with PICU admission, according to the literature. This finding has also been reported in the adult literature. The systematic review by Alvarez et al<sup>12</sup> found that increased use of  $\beta_2$  agonists via inhaled or nebulized administration was associated with a greater risk of near fatal asthma and fatal asthma. The lack of association in the present study could be explained by the strong correlation between asthma severity and administration of bronchodilators such as  $\beta_2$  agonists and anticholinergic drugs. Indeed, after correction for asthma severity, these variables were no longer significant risk factors. An adult study found that the use of high dosages of inhaled  $\beta_2$  agonists was associated with a greater risk of ICU admission for asthma, even after controlling for asthma severity.<sup>13</sup>

Most patients (cases and controls) used inhaled corticosteroids, which is to be expected, according to the asthma guidelines. In our study, no difference between the use of inhaled corticosteroids between the 2 groups, measured in a dose-independent fashion, was observed (82% in cases and 81% in controls), whereas the average dose in cases

# RISK FACTORS FOR PEDIATRIC INTENSIVE CARE ADMISSION IN CHILDREN WITH ACUTE ASTHMA

Table 2. Outcomes of Univariate Analysis

Variable		Cases (%) ( <i>n</i> = 66)	Controls (%) ( <i>n</i> = 164)	Odds Ratio	<i>P</i>
Ethnicity, Psychosocial Context					
White	No	23	9	2.6	.003
	Yes	67	81		
	Unknown	11	10		
Divorced parents	No	82	95	3.0	.004
	Yes	14	4		
	Unknown	5	1		
Exposures and Atopy					
Pets	No	44	54	1.9	.03
	Yes*	39	25		
	Unknown	17	21		
Smoking	No	39	65	4.3	< .001
	Yes†	44	21		
	Unknown	17	14		
Sanitized home	No	53	16	7.3	< .001
	Yes	27	56		
	Unknown	20	28		
Eczema	No	18	51	4.0	< .001
	Yes	64	42		
	Unknown	18	7		
Hay fever	No	29	70	6.3	< .001
	Yes	42	18		
	Unknown	29	12		
Allergy	No	14	44	5.2	< .001
	Yes	74	45		
	Unknown	12	12		
Severity and Treatment of Asthma					
Severe asthma	No‡	17	70	87.3	< .001
	Yes	53	7		
	Unknown	30	24		
Prescribed corticosteroids: dose-independent	No	18	19	1.1	.75
	Yes	82	81		
	Unknown	0	0		
Prescribed corticosteroids: dose-dependent	Median (μg/d)	500	400		.038
Prescribed β <sub>2</sub> agonists	No	6	19	4.3	.002
	Yes	94	81		
	Unknown	0	0		
Prescribed anticholinergics	No	68	90	8.2	< .001
	Yes/if necessary	32	10		
	Unknown	0	0		
Earlier hospitalization for asthma (non-PICU)	No	14	49	5.2	< .001
	Yes	85	51		
	Unknown	2	0		

\* Yes: pets with hair, and/or pets with feathers.

† Yes: passive, active, or both

‡ No: intermittent, mild persisting, moderate persisting asthma.

PICU = pediatric ICU

was only slightly higher (100  $\mu\text{g}/\text{d}$ ) than in controls in the univariate analysis. This small difference in dosage lost significance in the multivariate analysis, and might imply that in some cases the average dose of inhaled corticoste-

roids was too low and that cases were therefore undertreated, receiving insufficient anti-inflammatory treatment. In the absence of reliable information on actual adherence to treatment in both groups, this explanation remains speculative.



Table 3. Significant Variables for Pediatric ICU Admission After Conditional Logistic Regression Analysis

Variable	Odds Ratio	95% CI	P
Sanitized home	17.8	2.849–111.767	.002
Allergies	5.2	1.138–23.425	.03
Passive smoking	5.9	1.019–33.702	.048
Earlier hospitalization for asthma (non-PICU)	5.4	1.336–21.449	.02

In their systematic review, Alvarez et al<sup>12</sup> reported that the use of inhaled corticosteroids measured in a dose-independent fashion did not significantly increase nor decrease the risk of near fatal asthma and fatal asthma in adults. However, they found that the use of corticosteroids in a dose-dependent fashion showed a trend toward a protective effect against fatal asthma.<sup>12</sup> Another study in adults reported that the use of inhaled corticosteroids is associated with a reduced risk of ICU admission among adults hospitalized with asthma.<sup>13</sup> These findings are in contrast to our results. Differences between the routine patient care, respective guidelines for treatment of asthma, age, and other characteristics of the patients complicate the comparisons between these studies.

In the study of Belessis et al,<sup>4</sup> the variables that include smoking, pets, hay fever, eczema, and carpets were not significant risk factors for PICU admission in children with SAA. One possible explanation may be that the cases and controls in their study were matched on prevalence of asthma, eczema, or hay fever in first-degree relatives. The study of Lyell et al<sup>7</sup> indicated that asthmatic children with near fatal asthma were more likely to have hay fever than asthmatic children admitted to the emergency department on one occasion only; passive smoking did not differ between those 2 groups. Smoking and atopy did not increase the risk of near fatal asthma and fatal asthma in studies in adults.<sup>12</sup> Earlier PICU admission due to SAA has been shown to be a risk factor for readmission because of SAA.<sup>3</sup> In our study, 8 children from the PICU admission group had been readmitted repeatedly. Because this was an exclusion criterion for controls in our study, it could not be identified as a risk factor, but previous (medium care) hospital admission was indeed recognized as a risk factor. These findings were also observed in adult studies.<sup>12</sup> Previous studies have identified male sex as a risk factor for PICU admission after acute asthma exacerbation.<sup>7</sup> Our study indeed showed a male preponderance, but this may simply reflect the higher prevalence of asthma among boys. One study suggested that asthmatic children admitted to a PICU were more likely to be older than asthmatic children who had been admitted to the emergency department on

one occasion only.<sup>7</sup> In the present study the median age at the time of PICU admission was relatively low (5.2 years); as it was a matching criterion, it was not compared between cases and controls.

A limitation of the study is that we used a retrospective study design, with information collected from the medical records. For this reason, several variables could not be analyzed reliably, such as quality of the home, psychosocial problems of the child or the family, non-compliance with therapy, (possible) undertreatment, poor inhalation technique, and instructions by a specialized asthma nurse. Data for these variables were either missing or had not been recorded in the medical record. Nevertheless, the available data provide relevant information about asthmatic children who developed severe asthmatic attacks resulting in PICU admission, in spite of treatment by general pediatricians or pediatric pulmonologists.

## Conclusions

Allergies, (active or passive) smoking, earlier hospitalization for asthma, and non-sanitized homes were significant risk factors for PICU admission for pediatric patients with SAA. These risk factors were present in spite of treatment by pediatricians or pediatric pulmonologists. Thus, there is room to improve current strategies to prevent SAA. Physicians, parents, and patients should be aware of these risk factors, which are preventable to some extent. Earlier identification of children at risk for PICU admission may result in better asthma management and thus in a reduction of PICU admission for SAA. Future prospective standardized studies are needed to validate these results and especially to determine the role of non-adherence.

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