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# Children with severe acute asthma admitted to Dutch PICUs: A changing landscape

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## Abstract

The number of children requiring pediatric intensive care unit (PICU) admission for severe acute asthma (SAA) around the world has increased.

**Objectives:** We investigated whether this trend in SAA PICU admissions is present in the Netherlands.

**Methods:** A multicenter retrospective cohort study across all tertiary care PICUs in the Netherlands. Inclusion criteria were children (2-18 years) hospitalized for SAA between 2003 and 2013. Data included demographic data, asthma diagnosis, treatment, and mortality.

**Results:** In the 11-year study period 590 children (660 admissions) were admitted to a PICU with a threefold increase in the number of admissions per year over time. The severity of SAA seemed unchanged, based on the first blood gas, length of stay and mortality rate (0.6%). More children received highflow nasal cannula ( $P < 0.001$ ) and fewer children needed invasive ventilation ( $P < 0.001$ ). In 58% of the patients the maximal intravenous (IV) salbutamol infusion rate during PICU admission was 1 mcg/kg/min. However, the number of patients treated with IV salbutamol in the referring hospitals increased significantly over time ( $P = 0.005$ ). The proportion of steroid-naïve patients increased from 35% to 54% ( $P = 0.004$ ), with a significant increase in both age groups (2-4 years [ $P = 0.026$ ] and 5-17 years [ $P = 0.036$ ]).

**Conclusions:** The number of children requiring PICU admission for SAA in the Netherlands has increased. We speculate that this threefold increase is explained by an increasing number of steroid-naïve children, in conjunction with a lowered threshold for PICU admission, possibly caused by earlier use of salbutamol IV in the referring hospitals.

## KEYWORDS

intensive care, pediatric asthma, severe acute asthma, status asthmaticus, steroid-naïve

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## 1 | INTRODUCTION

Asthma is the most prevalent chronic disease of childhood, with a prevalence of 5-10% in children up to 12 years in the Netherlands.<sup>1,2</sup> Acute asthma exacerbations are a significant burden to patients, their family and to public health worldwide.

Severe acute asthma (SAA) is defined as an acute asthma exacerbation that does not respond to conventional therapy with bronchodilators and systemic corticosteroids. SAA has the potential to progress to respiratory failure and can be fatal.<sup>3</sup> The 2006 national pediatric guideline for SAA in the Netherlands states that children whose asthma exacerbation does not respond in 30-60 min to conventional treatment should receive intravenous (IV) magnesium sulphate (40 mg/kg). The next step is continuous IV administration of salbutamol followed by immediate transfer to a pediatric intensive care (PICU), regardless of the dosage of salbutamol.<sup>4</sup>

A previous multicenter study on PICU admissions of children with SAA in the Netherlands showed the following risk factors that were significantly predictive for PICU admission: active or passive smoking, allergies, previous hospitalization for asthma, and non-sanitized homes.<sup>5</sup> These risk factors were congruent to studies in other countries and other populations.<sup>6-8</sup> In a recent study in the USA, treatment with inhaled corticosteroids (ICS) prior to the index hospitalization was a significant risk factor for ICU admission.<sup>9</sup> This might be due to the fact that children using ICS had more severe asthma and consequently a higher risk for SAA and PICU admission. Other relevant risk factors for PICU admission are a shorter duration of illness before being admitted to the hospital,<sup>6</sup> time since asthma diagnosis<sup>8</sup> or viral infections.<sup>10</sup>

SAA requiring PICU admission represents a major cost burden. Additionally, PICU admission itself is associated with greater psychological morbidity in children and their parents, when compared with admissions in general pediatric wards.<sup>11</sup> Unexpected admission of a child to a PICU is a stressful event and is associated with posttraumatic stress disorder (PTSD) both in children and their parents.<sup>12,13</sup>

Numbers of asthma related PICU admissions have shown a substantial increase internationally. During a 15-year period in New Jersey (USA), fewer children with SAA were admitted to a hospital, but the proportion of patients managed in the PICU more than tripled.<sup>14</sup> A study in Saudi Arabia showed a fourfold increase of PICU admissions due to SAA in children in 2013 compared to a previous cohort in 2003.<sup>15</sup> In the last decade, a substantial increase in the number of children with SAA admitted to the PICU of the Erasmus MC-Sophia was observed. To see whether this was a local or national trend we embarked on a nationwide study.

The aim of the present study was to examine the trend in prevalence of PICU admissions of children with SAA in the Netherlands and to assess patient characteristics and asthma treatment in the last decade.

## 2 | METHODS

### 2.1 | Inclusion criteria

We conducted a retrospective cohort study of children with SAA, admitted to the eight PICUs in the Netherlands. These PICUs are part of university, tertiary hospitals. Children were identified through the Pediatric Intensive Care Evaluation (PICE) database, a national database containing all children admitted to Dutch PICUs.

All children aged 2-18 years admitted to one of the eight PICUs with SAA from January 2003 to December 2013 were eligible for this study. The SAA diagnosis had to be confirmed before PICU discharge. Children <2 years of age, who are admitted at the PICU because of dyspnea generally have respiratory tract infections. In children below the age of 2 years no firm diagnosis of asthma could be made at the time of PICU discharge.<sup>16,17</sup> All admissions and re-admissions were included in the study. Because of the retrospective design of the study, the Medical Ethics Committee waived the need for informed consent.

### 2.2 | Methods

We identified our patients from the PICE database.<sup>18</sup> The PICE registry was established in 2000 as an independent national nonprofit foundation to develop and maintain a continuous registration of data relating to all children admitted to all PICUs in the Netherlands. The database contains anonymous information regarding characteristics of patients and admission, severity of illness and risk of mortality, treatment, and patient outcome.<sup>18</sup>

Two investigators retrieved all data from electronic patient records and paper chart review by using an electronic case report form created in Open Clinica. Data included demographic data, asthma diagnosis at time of admission, allergies, prescribed asthma treatment at home, SAA treatment at the referring hospital and PICU, and PICU mortality.

Inhaled or food allergies were defined as a positive radioallergo-sorbent test (RAST) or skin prick test, and/or reported by the treating physician or parents. Prescribed home asthma treatment was recorded if prescribed at least 7 days before the SAA and was categorized according to the global initiative for asthma (GINA).<sup>17</sup>

We used the following parameters to assess SAA severity: first pH and PCO<sub>2</sub> obtained at PICU admission, length of stay (LOS) on a PICU, highest infusion rate of salbutamol IV, and PICU mortality. If missing data for describing SAA severity exceeded 20%, variables were excluded from the analyses.

### 2.3 | Analyses

Data were presented as mean (and standard deviation [SD]) or as median and interquartile range (IQR) if data were not normally distributed. To assess changes in treatment over the 11-year study period, the linear-by-linear chi-square association was used for dichotomous variables, including magnesium sulphate (MgSO<sub>4</sub>) and

IV salbutamol use, invasive mechanical ventilation, and use of inhaled steroids. Outcomes and patient characteristics were compared between intubated and non-intubated children, between children with and without IV salbutamol and between age groups using the Student's *t* test for normally distributed variables, the Mann-Whitney U test for continuous variables that were not normally distributed and the Pearson chi-square for categorical variables. The Jonckheere-Terpstra test was used to determine whether the distribution of continuous variables changed with the year of admission. Continuous variables included pH and PCO<sub>2</sub> at PICU admission, LOS and highest infusion rate of salbutamol. All statistical analyses were carried out in SPSS version 21 (Chicago, IL), and a two-sided significance level of 0.05 was used.

### 3 | RESULTS

We included 590 eligible children, with a total of 660 PICU admissions. Baseline and PICU characteristics are described in Tables 1 and 2.

The number of SAA admissions per year on the PICU increased gradually over the years, from 44 children in 2003 to 138 in 2013

**TABLE 1** Baseline characteristics

Baseline characteristics (n, %)	
Sex <sup>a</sup>	
Female	233 (40)
Male	357 (60)
Age	
2-4 years	278 (42)
5-18 years	380 (58)
Ethnicity <sup>a</sup>	
White	351 (64)
Non-white	195 (36)
Medication step (GINA)	
Step 1	169 (26)
Step 2	196 (31)
Step 3	76 (12)
Step 4	41 (6)
Step 5	9 (1)
No medication	149 (23)
Allergy <sup>a</sup>	284 (50)
Type of allergy if allergic	
Inhalation allergies	164 (61)
Food allergies	45 (17)
Both	62 (23)
Diagnosed with asthma prior to PICU admission	501 (77)
Earlier PICU admission for SAA	75 (12)
Earlier NON-PICU admission for SAA	248 (40)

<sup>a</sup>For the patient specific characteristics the re-admissions were excluded, so for sex, ethnicity, and allergy *N* = 590.

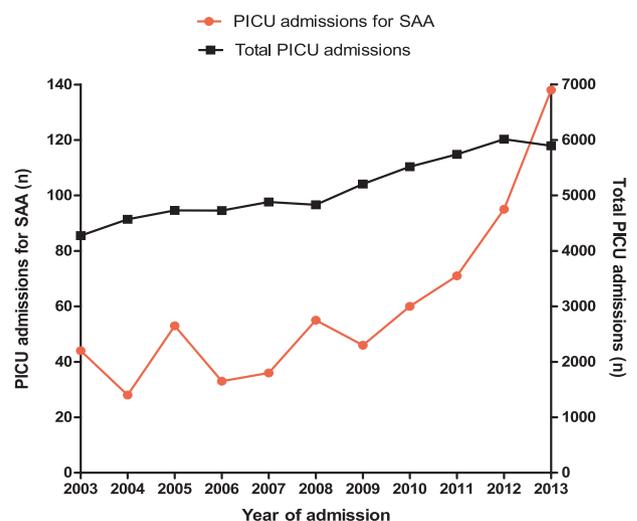
**TABLE 2** PICU characteristics

Admission characteristics	
pH at admission PICU <sup>a</sup>	7.37 (7.31-7.41)
PCO <sub>2</sub> at admission PICU, kPa <sup>a</sup>	5.0 (4.4-6.1)
Length of PICU stay in days <sup>a</sup>	3 (2-4)
MgSO <sub>4</sub> IV before admission PICU <sup>b</sup>	429 (65)
Salbutamol IV before PICU admission <sup>b</sup>	351 (54)
Salbutamol IV during PICU admission <sup>b</sup>	544 (83)
Duration salbutamol IV <sup>b</sup>	
0-6 h	23 (4)
6-12 h	50 (10)
12-24 h	101 (19)
24-48 h	168 (32)
>48 h	179 (34)
Max. dosage salbutamol IV, mcg/kg/min <sup>a</sup>	1.0 (0.4-2.0)
Invasive mechanical ventilation <sup>b</sup>	118 (19)
Mortality <sup>b</sup>	4 (0.6)

<sup>a</sup>Median (IQR).

<sup>b</sup>Number (%).

(Figure 1). In this same period the prevalence of asthma in children 2-18 years of age remained stable.<sup>19,20</sup> Reliable data of total asthma admissions in this age group in the Netherlands were not available. The total number of PICU admissions increased by 38% (from 4277 in 2003 to 5897 in 2013) (Figure 1). However, the number of SAA PICU admissions accounts only for a small increase (from 1.0% to 2.3%) of total PICU admissions. The number of PICUs remained unchanged and PICU beds increased from 107 to 109 in the Netherlands over time. The median pH and PCO<sub>2</sub> at PICU admission showed an increase and decrease over time, respectively. There was no significant difference in LOS on the PICU (*P* = 0.637) or highest infusion rate of salbutamol (*P* = 0.712, Table 3). The number of patients treated with MgSO<sub>4</sub> and



**FIGURE 1** PICU admissions

IV salbutamol in the referring hospital increased significantly over time (Table 4).

Over the years the proportion of steroid-naïve patients increased significantly ( $P = 0.004$ ) (Table 4). The proportion of patients with a diagnosis of asthma prior to admission remained stable over the years ( $P = 0.086$ ). In 118 admissions (19%) invasive mechanical ventilation was necessary due to cardiopulmonary resuscitation, secure airway and breathing for inter-hospital transport to the PICU and/or progressive respiratory failure (eg, hypoxemia, hypercapnia, apnea). The majority of the intubated patients received a dosage IV salbutamol of  $>1$  mcg/kg/min and for  $>24$  h during PICU admission. Intubated children had a significantly longer PICU LOS, lower pH and a higher  $PCO_2$  at time of PICU admission than children not intubated. The proportion of steroid-naïve children was similar in the intubated and non-intubated group (Table 5). Over the years there was a statistically significant decreasing trend of percentage of mechanically ventilated children, from 24% in 2003 to 11% in 2013 ( $P < 0.001$ ). High-flow nasal cannula was introduced in 2010, and showed an increase in the following years (Table 6).

During PICU admission 83% of the patients received IV salbutamol (Table 2). Of these patients, 33% received a highest infusion rate of 0.5 mcg/kg/min and 58% a highest infusion rate of 1.0 mcg/kg/min (Table 7). Seventeen percent (109 children) did not receive IV salbutamol during PICU admission. PICU LOS was significantly shorter in the group without IV salbutamol and more children were invasively mechanically ventilated. Other potential risk factors for IV salbutamol were not significant (Table 8).

Seven patients (1.1%) needed extracorporeal membrane oxygenation (ECMO). One patient was supported with venoarterial (VA)-ECMO after extracorporeal cardiopulmonary resuscitation (eCPR). This patient died during PICU admission (brain death). The others were supported with venovenous (VV)-ECMO, four due to refractory hypoxemia and two due to massive air leak syndrome.

Four patients died (0.6%) during the 11-year study period. Two of these patients were declared brain death following resuscitation. One patient died of respiratory failure and one of circulatory failure. All four experienced a cardiac arrest ( $n = 2$  out-of-hospital,  $n = 1$  in a general hospital, and  $n = 1$  at the PICU). All fatalities were non-white males, had doctor-diagnosed asthma and were prescribed ICS. Three were known with allergies, of whom two also had a food allergy.

Two different age groups (2-4 years and 5-17 years) were analyzed separately (Figure 2). The number of children with food or inhalation allergy, a prior diagnosis of asthma, ICS treatment before PICU admission and a viral etiology were significantly different between the two age groups. The proportion of boys, the median pH and  $PCO_2$  at time of PICU admission did not significantly differ between both age group.

## 4 | DISCUSSION

During the 11-year study period the number of children aged 2-18 years with SAA admitted to PICUs in the Netherlands increased threefold. In this same period the prevalence of asthma in this age

**TABLE 3** Severity of illness per year

Year of admission	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	P-value for trend
pH at PICU admission <sup>a</sup>	7.36 (7.31-7.40)	7.36 (7.25-7.40)	7.35 (7.24-7.39)	7.39 (7.32-7.42)	7.36 (7.30-7.40)	7.32 (7.26-7.39)	7.36 (7.30-7.39)	7.35 (7.30-7.39)	7.39 (7.33-7.42)	7.39 (7.30-7.42)	7.37 (7.33-7.42)	0.005
$PCO_2$ at PICU admission, kPa <sup>a</sup>	5.0 (4.7-5.9)	5.1 (4.5-6.6)	5.4 (4.8-6.4)	4.5 (4.1-5.5)	5.0 (4.4-6.4)	5.4 (4.5-7.4)	5.4 (4.9-6.2)	5.3 (4.5-6.8)	4.9 (4.2-5.8)	4.8 (4.3-5.8)	4.9 (4.2-5.9)	0.021
LOS PICU, days <sup>a</sup>	3 (2-4)	3 (2-4)	4 (2-5)	3 (2-3)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-5)	3 (2-4)	3 (2-4)	3 (2-4)	0.637
Maximal dosage salbutamol IV, mcg/kg/min <sup>a</sup>	0.5 (0.2-1.6)	0.8 (0.5-2.0)	1.2 (0.6-2.5)	0.9 (0.5-1.5)	1.5 (0.5-3.2)	1.0 (0.5-2.0)	1.4 (0.4-2.8)	0.9 (0.4-2.4)	1.0 (0.5-2.8)	0.7 (0.3-1.6)	0.8 (0.4-2.5)	0.712

<sup>a</sup>Median (IQR).

Non-significant values are presented in bold.

**TABLE 4** Treatment per year

Year of admission	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	P-value for trend
MgSO <sub>4</sub> <sup>a</sup>	28	16	29	37	47	65	67	72	80	86	94	<b>&lt;0.001</b>
Salbutamol IV <sup>a</sup>	46	46	52	59	43	54	46	40	58	59	66	<b>0.005</b>
MgSO <sub>4</sub> PICU	18	22	32	17	25	37	39	35	36	18	16	0.230
Salbutamol IV PICU	80	93	77	94	75	78	72	77	87	85	91	0.080
Steroid-naïve	35	41	43	44	57	47	41	47	55	59	54	<b>0.004</b>

Numbers are presented as percentages per year.

<sup>a</sup>MgSO<sub>4</sub> and salbutamol IV given in the referring hospital (at the pediatric ward or ED).

Non-significant values are presented in bold.

**TABLE 5** Invasive mechanical ventilation

	Intubated children (N = 118)	Non-intubated children (N = 542)	P-value
Age in years <sup>a</sup>	5 (3-9)	5 (3-9)	0.164
Male <sup>b</sup>	79 (67)	311 (57)	<b>0.047</b>
First SAA <sup>b</sup>	103 (87)	487 (90)	0.354
Earlier PICU admission for SAA <sup>b</sup>	17 (15)	58 (11)	0.243
Steroid-naïve before admission <sup>b</sup>	52 (46)	267 (51)	0.329
Diagnosed with asthma prior to PICU admission <sup>b</sup>	89 (76)	412 (77)	0.769
LOS PICU, days <sup>a</sup>	5 (3-7)	3 (2-4)	<b>&lt;0.001</b>
pH at PICU admission <sup>c</sup>	7.22 (0.14)	7.37 (0.07)	<b>&lt;0.001</b>
PCO <sub>2</sub> at PICU admission, kPa <sup>c</sup>	8.56 (3.85)	5.10 (1.41)	<b>&lt;0.001</b>
IV salbutamol during PICU admission <sup>b</sup>	109 (92)	435 (81)	<b>0.004</b>
IV salbutamol >24 h <sup>b</sup>	84 (83)	263 (53)	<b>&lt;0.001</b>
IV salbutamol >48 h <sup>b</sup>	67 (57)	112 (27)	<b>&lt;0.001</b>
IV salbutamol >1 mcg/kg/min <sup>b</sup>	69 (66)	196 (46)	<b>&lt;0.001</b>
Max. dosage IV salbutamol, mcg/kg/min <sup>a</sup>	1.6 (0.7-3.4)	0.8 (0.4-2.0)	<b>0.003</b>

<sup>a</sup>Median (IQR).

<sup>b</sup>Number (%).

<sup>c</sup>Mean (SD).

Non-significant values are presented in bold.

**TABLE 6** Respiratory support per year

Year of admission	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	P-value for trend
None	9	4	4	6	0	4	4	2	0	1	1	<b>0.004</b>
Nasal cannula	20	23	24	14	14	10	14	19	18	17	15	0.461
NRM <sup>a</sup>	46	27	45	61	72	54	52	57	53	58	53	0.177
HFNC <sup>b</sup>	0	0	0	0	0	0	0	2	10	13	17	<b>&lt;0.001</b>
NIV <sup>c</sup>	0	0	0	4	0	2	2	3	0	1	2	0.308
Invasive mechanical ventilation	24	46	28	14	14	31	27	17	19	10	11	<b>&lt;0.001</b>

Numbers are presented as percentages per year.

<sup>a</sup>Non-rebreathing mask.

<sup>b</sup>High-flow nasal cannula.

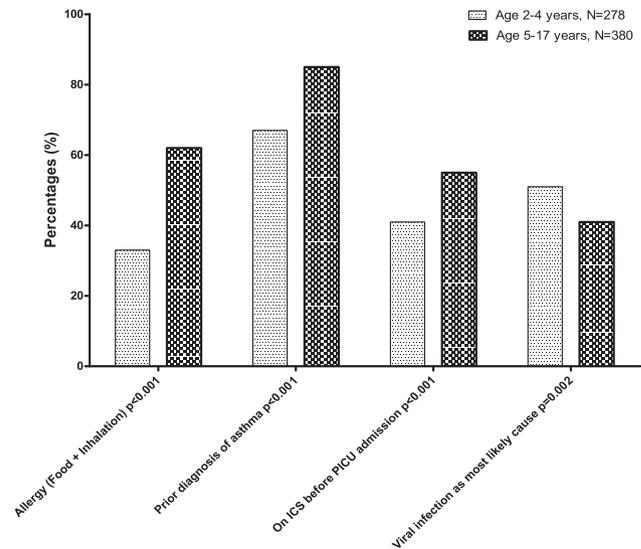
<sup>c</sup>Non-invasive ventilation.

Non-significant values are presented in bold.

**TABLE 7** Maximum dosage of salbutamol IV

Maximal dosage of salbutamol IV in mcg/kg/min	N	%
0-0.5	176	33
0.6-1.0	130	25
1.1-1.5	46	9
1.6-2.0	52	10
2.1-3.0	40	8
3.1-4.0	30	6
4.1-5.0	22	4
5.1-7.0	14	3
7.1-10.0	19	4

group remained stable,<sup>19,20</sup> and the number of PICU beds increased only marginally. The total number of PICU admissions increased by 38%, of which the number of SAA PICU admissions accounted for a rise from 1.0 to 2.3% of total admissions. The duration of PICU admission, PICU mortality, first blood gas pH and PCO<sub>2</sub> did not change over time, suggesting similar severity of SAA. Children aged 5-17 years were more likely to have an allergy, used more ICS before PICU admission and were more frequently diagnosed with asthma prior to PICU admission. A viral infection as most likely cause for SAA was recorded more frequently in children aged 2-4 years. Over the years significantly more children received MgSO<sub>4</sub> and salbutamol IV already in the referring hospital before being transported to the PICU. We observed a decrease of invasive mechanical ventilation over time together with an increased use of high-flow nasal cannulas. Intubated children had a significantly longer PICU LOS, lower pH and a higher PCO<sub>2</sub> at time of PICU admission than children not intubated. The vast majority of the intubated patients received a dosage IV salbutamol of >1 mcg/kg/min and for >24 h during PICU admission. Overall, the highest infusion rate of IV salbutamol was relatively low, with 58% receiving a maximum dosage of 1.0 mcg/kg/min. Seventeen percent of

**FIGURE 2** Preschoolers versus school-aged children

the children did not receive IV salbutamol. In these children the PICU LOS was shorter and fewer children needed invasive mechanically ventilation.

Our findings are partly consistent with previous studies. Single center retrospective studies done in Saudi Arabia (2003-2013) and Taiwan (1990-2000) also showed a significant increase in the number of children with SAA who required PICU admission, with a fivefold, respectively, twofold increase.<sup>15,21</sup> The authors suggested a lower threshold for PICU admission over time as a contributing factor to the increase in PICU admissions as well as implementation of a National Health insurance (Taiwan). One North-American study described a threefold increase in PICU admissions, without an increase in illness severity over time, comparable with our results.<sup>14</sup> That study describes the hospitalization characteristics of 28,309 children with SAA in hospitals with and without PICUs in the period 1992-2006. However,

**TABLE 8** IV salbutamol

	IV salbutamol group (N = 544)	Non IV salbutamol group (N = 109)	P-value
Age in years <sup>a</sup>	5 (3-9)	5 (3-8)	0.198
Male <sup>b</sup>	323 (59)	64 (59)	0.898
First SAA <sup>b</sup>	488 (90)	99 (91)	0.723
Earlier PICU admission for SAA <sup>b</sup>	63 (12)	10 (9)	0.459
Steroid-naïve before admission <sup>b</sup>	262 (48)	56 (52)	0.560
Diagnosed with asthma prior to PICU admission <sup>b</sup>	421 (77)	78 (72)	0.120
LOS PICU, days <sup>a</sup>	3 (3-4)	2 (2-3)	<0.001
pH at PICU admission <sup>c</sup>	7.33 (0.11)	7.38 (0.06)	<0.001
PCO <sub>2</sub> at PICU admission, kPa <sup>c</sup>	5.8 (2.63)	5.1 (1.05)	<0.001
Invasive mechanical ventilation <sup>b</sup>	109 (20)	9 (9)	<b>0.004</b>

<sup>a</sup>Median (IQR).

<sup>b</sup>Number (%).

<sup>c</sup>Mean (SD).

Non-significant values are presented in bold.

in this North-American study, 20% of patients was younger than 2 years of age and comorbidities were not an exclusion criterium. The results of this heterogeneous study group cannot be compared to our study, given the difficulty in correctly diagnosing severe wheeze or asthma in that age group such as excluding bronchiolitis and viral lower airway infections. Of the patients admitted to a PICU in that study, 10% received mechanical ventilation, with no decrease over time compared to a decrease of 25-31 to 11% over time in our study. In that population, the length of stay at the PICU and the mortality rate also remained stable during this 15-year period.<sup>14</sup> Ours and other studies show higher rates of ICU admission without a change in invasive mechanical ventilation. This might have been the result of increased monitoring and available therapies in the PICUs, that prevent deterioration and the subsequent need for mechanical ventilation and high-flow oxygen. Two other retrospective studies in Saudi Arabia (1994-2001,  $n = 56$ ) and in North-America (2000-2007,  $n = 222$ ) did not show an increase in children admitted with SAA on a PICU. Both were small single center studies.<sup>22,23</sup>

PICU mortality in children with SAA in the Netherlands is extremely low. In other countries the (in-hospital) mortality rates varied between 0.02% and 4%. In a study in the US between 2000 and 2009, the in-hospital mortality of children with SAA decreased significantly between 2000 and 2009 (0.06% in 2000 vs 0.02% in 2009).<sup>24</sup> But in another North-American study<sup>25</sup> of 261 high risk pediatric admissions with fatal and near-fatal asthma admitted to the PICU as many as 4% died (11 patients). A recent report from New South Wales in 2015 analyzed all deaths from children with asthma between 2004 and 2013.<sup>26</sup> In New South Wales asthma prevalence in children is comparable with the Netherlands and a total of 20 deaths occurred in children aged 4-17 years, with a male predominance (70%). Most of the children (80%) were at home when they were recognized to be symptomatic with asthma during their ultimately fatal attack.<sup>26</sup>

Strengths of the present study include the participation of all Dutch PICUs and the existence of a national PICU database. Approximately 5.500 patients are admitted to these PICUs each year. Furthermore, there is a national guideline for the treatment of SAA with practical treatment steps and referral guidelines, which facilitates comparison between PICUs.

There are some limitations as well. The retrospective design of this study is a disadvantage, but in this case the prospective, structured registration in a national database should overcome many disadvantages of retrospective data collection. Secondly, our study lacked a control group. Therefore we could not analyze possible changes in risk factors for PICU admission like medication adherence, exposure to cigarette smoke, air pollution and specific seasonal viruses, as these data were insufficiently available. To identify possible risk factors for PICU admission, a prospective study comparing children admitted at PICUs and children admitted at general pediatric wards would be helpful. Finally, no validated clinical asthma score was systematically used by all PICUs.

What is the clinical relevance of the present findings? An increased frequency or severity of illness is not a likely cause of the

threefold increase in PICU admissions, as the prevalence of asthma in children has remained stable in the Netherlands over these years,<sup>27,28</sup> and the first blood gas pH and  $PCO_2$ , duration of PICU admission and PICU mortality did not change over time. The number of PICU beds in the Netherlands increased by 1.9% and total PICU admissions increased with 38%, whereas the number of SAA PICU admissions increased disproportionately with a factor 3. As we have no evidence to suggest that SAA severity increased, this may indicate a lower threshold for a PICU admission over time. A possible explanation is that IV salbutamol has been administered sooner in the treatment work-up in the referring hospitals over the years. Our national SAA guideline automatically implies immediate referral to a PICU, regardless of IV salbutamol dosage. This recommendation should perhaps be reconsidered in the light of our findings.

A striking and unexpected observation was the marked increase in steroid-naïve children that were admitted with SAA over the years. The interpretation of this finding may simply reflect a first asthmatic attack of a child not previously diagnosed having asthma. As the increase was in all age groups this might also indicate a significant increase of undertreatment of known asthma. Over the 11-year study period the proportion of children with no previous diagnosis of asthma remained the same. In a previous study,<sup>5</sup> we observed that about one third of children with SAA admitted to a PICU was not known with asthma prior to that admission. Studies in Taiwan and Saudi Arabia also showed a significant number of patients not using daily ICS prior to PICU admission, respectively, 20% and 46%, compared to 50% in our study.<sup>21,22</sup>

Non-invasive respiratory support with external positive end-expiratory pressure (PEEP) can relieve airway obstruction in children with asthma,<sup>29</sup> and we observed a significant decrease of invasive mechanical ventilation together with an increased use of high-flow nasal cannulas. The decreased need for invasive mechanical ventilation could therefore have resulted from the upcoming use of high-flow nasal cannula and non-invasive mechanical ventilation, or from earlier and more frequent administration of  $MgSO_4$  and IV salbutamol in the referring hospitals over the years.

In our cohort, 10-20% of the patients did not receive any salbutamol infusion during PICU stay. Therefore, one could argue whether these children really met PICU admission criteria. It is likely that the referring clinician transferred these children to the PICU because of potential respiratory failure despite continuous nebulization and  $MgSO_4$  IV, according to the Dutch guideline.

In our study PICU mortality was 0.6%. All fatalities experienced a cardiac arrest, three of them outside of a PICU. Hence, the prevention, recognition and management of SAA at home, by general practitioners and in a regional hospital is very important. This also emphasizes the importance of proper maintenance treatment in children with asthma. Because of the already low mortality, it is not likely that more aggressive therapies will further reduce mortality.

Our national SAA guideline automatically implies immediate referral to a PICU, regardless of IV salbutamol dosage. This

recommendation should perhaps be reconsidered in the light of our findings. The high costs of PICU admission, bed availability but also risk of PTSD after PICU admission in children and their parents<sup>12,13</sup> are drawbacks of the present development toward more frequent PICU admission. It is therefore important to reduce unnecessary PICU admissions. Priority should be given to adequate diagnosis and anti-inflammatory treatment (preventing undertreatment) of children with asthma to prevent PICU admissions, to perform prospective studies into the safety of low dosage IV salbutamol, and to increase alertness of risk factors for severe SAA.

## 5 | CONCLUSION

During the last decade we observed an important, threefold increase in children with SAA admitted to a PICU in the Netherlands, while the severity of illness remained similar. Most likely reasons are earlier referral by physicians as a result of better education and implementation of national SAA guidelines and, possibly, undertreatment with ICS in children with asthma, missed diagnosis or underreporting of asthma symptoms. Our results suggest that aggressive therapy in the referring hospitals and timely referral could lead to better outcomes of SAA, and prevent deterioration and need for mechanical ventilation. On the other hand, the high costs of PICU admission and the risk of PTSD after PICU admission in children and their parents are drawbacks of the present development toward more frequent PICU admission. It is therefore important to reduce the number of PICU admissions by establishing proper diagnosis and adequate treatment of children with asthma to prevent PICU admissions, performing prospective studies into the safety of salbutamol infusion, and recognizing the children most at risk for developing SAA.

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