Asthma medication use in infancy: determinants related to prescription of drug therapy
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Background. Little is known about factors that determine prescribing of asthma therapy in infancy.

Objective. To describe factors related to the initiation and refill of asthma therapy in infancy.

Methods. This study included 1202 infants who participated in a prospective birth cohort study: the ‘Wheezing Illnesses Study Leidsche Rijn (WHISTLER)’. Outcomes, asthma therapy initiation and refill, were assessed using prescription data. Logistic regression analysis was used to study determinants of therapy initiation in two groups: total population and infants with a respiratory system symptom diagnosis. In addition, determinants of refilling prescriptions were studied in infants who started therapy in their first year of life.

Results. Fifteen per cent of all infants started asthma therapy in their first year of life. Respiratory symptoms were an important driver of both initiation and refill of prescriptions. In the total population, therapy initiation was associated with male gender [odds ratio (OR): 1.6, 95% confidence interval (CI): 1.1–2.6], day-care attendance (OR: 1.6, 95% CI: 1.0–2.5) and breastfeeding (OR: 0.6, 95% CI: 0.3–1.0). For infants with a respiratory system symptom diagnosis, day-care attendance was associated with an increased chance of therapy initiation (OR: 5.3, 95% CI: 1.8–16.2) and breastfeeding was associated with a lower chance of starting therapy (OR: 0.4, 95% CI: 0.1–1.1). Dutch children had a higher chance of refilling prescriptions in infancy (OR: 5.3, 95% CI: 1.1–26.8).

Conclusions. Apart from other factors involved, the principal reason for initiation and refill of asthma therapy in infancy was the presence of respiratory symptoms. This appeared the only reason to prescribe medication and physicians are not distracted by other factors.

Keywords. Asthma medication, drug prescription behaviour, infancy, respiratory symptoms.

Introduction

Respiratory symptoms are common in infancy and result in high health care utilization. Physical signs are most often not present and parents find it difficult to differentiate between normal symptoms and abnormal respiratory symptoms, such as wheeze and chronic cough. Therefore, distinguishing asthma from other respiratory disorders is difficult which also hampers treatment in infancy.

In contrast to studies that describe determinants of asthma or wheeze, little is known about factors that determine asthma medication use in infancy. De Jong et al. showed that besides the severity of symptoms, child, physician and maternal characteristics influence prescription behaviour. It is very difficult, if not impossible to diagnose asthma in infancy, because most respiratory symptoms early in life are transient and objective diagnostic tools are lacking at this age. It is expected that the lack of a clear diagnosis in infancy leads to variability in GP’s prescription behaviour.

Guidelines on asthma treatment in young children state that inhaled therapy constitutes the cornerstone of asthma treatment in children aged <5 years. Short-acting beta-agonists (SABA) are the preferred
reliever treatment and inhaled corticosteroids (ICS) should be prescribed for persistent symptoms. However, ICS are registered for use from the age of 1 year on17 and prolonged use of inhaled or systemic corticosteroids should be avoided in very young children. Studies performed in children aged <5 years suggest that clinically effective doses of ICS are safe and potential risk are well balanced by clinical benefits.18,19 However, many children start using asthma medication at very young age which is not always advised by treatment guidelines. Therefore, treatment of infants with respiratory symptoms is very difficult for GPs and non-symptom-related factors are often stated to play a role in this.

The objective of the present study was to obtain more insight into factors associated with both initiation and refill of asthma therapy in infancy. We expected that the influence of non-symptom-related determinants (such as environmental factors) would decrease when a diagnosis of asthma is more likely, i.e. for children in the general population, there is probably a wider range of factors that influence medication prescribing, while for children with physician-diagnosed respiratory symptom, there will be a smaller set of determinants that are associated with drug prescription.

Methods

Study population and setting

All infants in the study were participants of the ‘Wheezing Illnesses Study Leidsche Rijn (WHISTLER)’, a large prospective ongoing population-based birth cohort study on determinants of lower respiratory illnesses, which started December 2001.20 Briefly, healthy infants born in Leidsche Rijn, a new residential area near the city of Utrecht, are enrolled in the study at age 2–3 weeks. Exclusion criteria were gestational age <36 weeks, major congenital abnormalities and neonatal respiratory disease.

The Leidsche Rijn district is provided with a new health care infrastructure, which provides an excellent basis for epidemiological research. Currently, there are four health care centres with each approximately five GPs with supporting staff and a pharmacist. At this moment, the Leidsche Rijn area has ~41 000 inhabitants. The expectation is that in 2023, there are >80 000 inhabitants.

In The Netherlands, parents must register a new birth within 3 days at the city council. The city council provides information on these new births to WHISTLER and ‘Stichting Thuiszorg’. During a visit of a nurse from Stichting Thuiszorg, an organization that routinely visits newborns in the first week after birth for their heel prick test, the parents receive an information brochure about the WHISTLER study. Within 14 days after birth, the WHISTLER staff contacts the households and eligible children are invited to participate. The WHISTLER study has been approved by the Medical Review Ethics Committee of the University Medical Centre Utrecht.

Data collection

At intake (second or third week after birth), the parents filled in a questionnaire on possible prenatal and postnatal risk factors for respiratory illnesses. The infant’s weight and length were measured. Data on parental demographics, socio-economic status and disease history were obtained from the linked database of the Utrecht Health Project, a large health monitoring study in Leidsche Rijn.21 Follow-up data on respiratory symptoms (wheeze and cough) were assessed daily by the parents who filled in diaries during the first year of life. Parents were instructed by research physicians on how to recognize various respiratory symptoms. Further questions were asked about anthropometrics and environmental factors, such as feeding pattern, passive smoking and day-care attendance. New questionnaires were sent on a monthly basis. If parents failed to return the questionnaires, they were contacted by phone. Furthermore, GP and pharmacy records were extracted to collect additional health information. These records include information on prescription data, additional examinations, referral to other primary care staff or secondary care, contact dates and diagnosis.

Patient selection

We selected participating infants from the WHISTLER study. For this study, we only selected children who had information available from both the monthly questionnaires and the GP medical records. Furthermore, complete follow-up data (minimal 9 monthly questionnaires) were a necessary condition for this study. Figure 1 shows three groups in which we investigated determinants related to drug prescription. Determinants of therapy initiation were studied in: (1) the total WHISTLER population with complete follow-up during the first year of life and (2) infants with a respiratory system symptom diagnosis in their first year of life. Furthermore, determinants of refilling asthma prescriptions were studied in (3) infants who started asthma therapy in their first year of life. The second and the third groups are a selection of the first group.

Definition of outcome

Asthma medication prescriptions were collected from medical records. The Anatomical Therapeutical Chemical code R03 (drugs for obstructive airway diseases) was used to select prescriptions. Outcome, initiation of therapy, was defined as at least one prescription for any anti-asthma drug in the first year of life.
Definition of main determinants

Four groups of determinants were studied: (i) general characteristics (the infant’s gender and ethnicity), (ii) parental factors (educational level, asthma or atopy), (iii) environmental factors (feeding pattern, passive smoking, day-care attendance and exposure to pets during the first 3 months of life) and (iv) respiratory symptoms (both parent reported and physician diagnosed). Respiratory system symptom diagnoses were classified in GP medical records using the International Classification of Primary Care (ICPC) codes. We defined a respiratory system symptom diagnosis as the occurrence of a ‘respiratory ICPC code’. Asthma was defined as the occurrence of a R96 code. Parent-reported respiratory symptoms were defined as at least 1 day with symptoms in the first year of life. Above average days with parent-reported symptoms in the first year of life was used as determinant in the regression model (>57 days with respiratory symptoms and >5 days with wheezing symptoms in the first year of life).

Statistical analysis

Logistic regression analysis was used to investigate determinants of drug prescription. Only variables associated with drug prescription in the univariate model were included in the multivariate model (P < 0.05). The inclusion of potential confounding factors in the multivariate regression model was based on the assessment of the influence of each potential confounding factor on the odds ratio (OR) for the association between the univariate-associated factors and the outcome drug prescription. The child’s gender, ethnicity, parental educational level, having an atopic or asthmatic parent, environmental tobacco smoke exposure, pet exposure, day-care attendance, breastfeeding and respiratory symptoms were considered potential confounders. Potential confounders were included in the multivariate model if they induced a ≥10% change in the crude regression coefficient for the determinant of interest. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Study population

Around two-third (67.2%) of the contacted parents agreed to participate in the WHISTLER study and 11.8% did not fulfil the inclusion criteria (5.0% health problems child, 0.7% health problems mother, 1.1% language difficulties, 2.0% >2 months, 1.8% moving out of area, <2 months, 0.4% died and 0.8% other reason). Of the 1820 infants that were included in the WHISTLER study, 1553 (85.3%) had information available from both the monthly questionnaires and the GP medical records. Complete follow-up data (minimal 9 monthly questionnaires) were available for 1202 infants (66.0%) (Fig. 2). There were no differences in medication use or GP diagnosis between children who had complete follow-up data (n = 1202) and children who did not have complete follow-up data (n = 351) with respect to the monthly questionnaires (data not shown). The general characteristics of the study population are shown in Table 1. A total of 16.8% was diagnosed with respiratory symptoms and only 2.4% had a doctor’s diagnosis asthma.

Asthma medication use

Of the 1202 infants, 182 (15.1%) filled an asthma medication prescription in the first year of life, 84 infants (46.2%) filled one prescription, 54 infants (29.7%) filled two prescriptions, 20 infants (11.0%) filled three prescriptions and 24 infants (13.1%) filled at least four prescriptions. SABA were the most frequently used therapy (95.1%), 24.2% used ICS and <8% used other anti-asthma therapies (Fig. 3). Antibiotics were prescribed in 53.8% of the infants.
Factors associated with therapy initiation and refill of therapy

Determinants of asthma therapy initiation were investigated in two groups (Table 2). For the total population, the following factors were associated with a higher chance of starting therapy: male gender, day-care attendance, respiratory system symptom diagnoses and parent-reported respiratory symptoms. Exclusively breastfeeding in the first 3 months of life was associated with a lower chance of starting therapy.

For children with physician-diagnosed respiratory symptoms, day-care attendance and parent-reported respiratory symptoms were independently associated with a higher chance of starting therapy. Exclusively, breastfeeding during the first 3 months of life was borderline significantly associated with a lower chance of therapy initiation ($P = 0.08$). In the multivariate analysis, only maternal ethnicity and physician-diagnosed symptoms were associated with a higher chance of refilling prescriptions (Table 3).

Discussion

Fifteen per cent of the infants in our cohort started asthma therapy in their first year of life and most of them filled only one prescription. Principal reason for both initiation and refill of therapy was the presence of respiratory symptoms: if a physician diagnosed respiratory symptoms or the parents reported symptoms, then asthma therapy was much more likely to be prescribed. Furthermore, day-care attendance was associated with asthma medication prescription.

One of the strength of this study was the availability of complete medication histories for the first year of life.
Therefore, we were able to study initiation of asthma therapy and determinants of medication use early in life. Data on medication retrieval were collected through community pharmacy records. In the Netherlands, pharmacy records are virtually complete with respect to outpatient medication use.25 Another strength of our study is the availability of GP medical records, including the respiratory system symptom diagnoses. It might be difficult to retrieve reliable data on respiratory symptoms, especially in infants, from parents because parents might not always recognize symptoms such as ‘wheeze’. In the present study, we had both physician-reported and parent-reported data regarding respiratory symptoms available. An advantage of this study is the high response rate. About half of the contacted parents participated in the study. This is a high response rate for this kind of research and comparable with other Dutch birth cohort studies.8

It should be noted that the inhabitants of the Leidsche Rijn area we studied had a higher average income and the majority of our study population (95%) was of Caucasian ethnicity.26 However, there was no active selection on these factors; they are a result of the construction process of the Leidsche

**Table 2 Determinants of asthma therapy initiation**

<table>
<thead>
<tr>
<th></th>
<th>Total population (n = 1202)</th>
<th>Respiratory system symptom diagnosis (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis, OR (95% CI)</td>
<td>Multivariate analysis, OR (95% CI)</td>
</tr>
<tr>
<td>Male, gender</td>
<td>2.0 (1.4–2.7)*</td>
<td><strong>1.6 (1.1–2.6)</strong></td>
</tr>
<tr>
<td>Ethnicity, Dutch</td>
<td>0.6 (0.3–1.3)</td>
<td>1.2 (0.2–6.5)</td>
</tr>
<tr>
<td>Educational level, high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>1.3 (0.9–1.9)</td>
<td>2.1 (1.0–4.3)*</td>
</tr>
<tr>
<td>Father</td>
<td>1.2 (0.8–1.7)</td>
<td>0.8 (0.4–1.8)</td>
</tr>
<tr>
<td>Atopic parent</td>
<td>1.2 (0.8–1.6)</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>Asthmatic parent</td>
<td>1.6 (1.0–2.4)*</td>
<td><strong>1.1 (0.6–2.1)</strong></td>
</tr>
<tr>
<td>Exclusively breastfeeding</td>
<td>0.7 (0.5–1.0)*</td>
<td>0.6 (0.3–1.0)*</td>
</tr>
<tr>
<td>Parental smoking</td>
<td>1.0 (0.6–1.4)</td>
<td>0.8 (0.3–2.0)</td>
</tr>
<tr>
<td>Day-care attendance</td>
<td>1.9 (1.4–2.6)*</td>
<td><strong>1.6 (1.0–2.5)</strong></td>
</tr>
<tr>
<td>Exposure to pets</td>
<td>0.9 (0.7–1.3)</td>
<td>1.3 (0.6–2.6)</td>
</tr>
<tr>
<td>Respiratory system symptom diagnosis</td>
<td>50.5 (32.6–78.4)*</td>
<td>50.5 (32.6–78.4)*</td>
</tr>
<tr>
<td>Parent-reported respiratory symptoms</td>
<td>5.2 (3.7–7.4)*</td>
<td>7.8 (4.2–14.5)*</td>
</tr>
</tbody>
</table>

Factors that caused a >10% change in the crude regression coefficient were included in the multivariate model.

*Above average days with respiratory symptoms (>57 days with parent-reported symptoms in the first year of life).

*P < 0.05. Bold interface indicates adjusted OR at P < 0.05 significance level.

**Table 3 Determinants of refilling asthma therapy in the first year of life**

<table>
<thead>
<tr>
<th></th>
<th>Refilling asthma therapy (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis, OR (95% CI)</td>
</tr>
<tr>
<td>Male, gender</td>
<td>1.3 (0.7–2.5)</td>
</tr>
<tr>
<td>Ethnicity, Dutch</td>
<td>5.3 (1.1–26.8)*</td>
</tr>
<tr>
<td>Educational level, high</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>1.2 (0.6–2.3)</td>
</tr>
<tr>
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<td>Atopic parent</td>
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<tr>
<td>Asthmatic parent</td>
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</tr>
<tr>
<td>Exclusively breastfeeding first 3 months</td>
<td>1.2 (0.6–2.3)</td>
</tr>
<tr>
<td>Parental smoking first 3 months</td>
<td>0.7 (0.3–1.6)</td>
</tr>
<tr>
<td>Day-care attendance first 3 months</td>
<td>1.8 (1.0–3.3)*</td>
</tr>
<tr>
<td>Exposure to pets</td>
<td>1.2 (0.6–2.1)</td>
</tr>
<tr>
<td>Respiratory system symptom diagnosis</td>
<td>1.8 (1.0–3.6)</td>
</tr>
<tr>
<td>Parent-reported respiratory symptoms</td>
<td>2.2 (1.2–4.3)*</td>
</tr>
</tbody>
</table>

Factors that caused a 10% change or more in the crude regression coefficient were included in the multivariate model.

*Above average days with respiratory symptoms (>57 days with parent-reported symptoms in the first year of life).

*P < 0.05. Bold interface indicates adjusted OR at P < 0.05 significance level.
Rijn district. Therefore, we do not think that such selection hampers the interpretation of our findings. Furthermore, we do not think that loss to follow-up has biased our results as the baseline characteristics of those with complete follow-up did not differ from those lost to follow-up. Unfortunately, the monthly questionnaires (with daily questions on respiratory symptoms such as wheeze and cough) were not complete for the entire cohort. However, the characteristics of children with complete follow-up data with regard to the monthly questionnaires did not differ from those with incomplete follow-up data. Therefore, we do not think that non-response to return or fill in the monthly questionnaires has led to selection bias.

The daily recording of symptoms by the parents may have caused more awareness and a different perception towards their child’s respiratory symptoms. This could have influenced the parental visits to a physician compared to not in the study included parents and children. However, this limitation is shared with previous surveys.

Respiratory symptoms, both physician diagnosed and parent reported, were associated with a higher chance of drug prescriptions. This was as expected; children who experienced more respiratory symptoms were much more likely to get medication prescribed. Furthermore, day-care attendance in the first 3 months of life was associated with a higher risk of therapy initiation in both groups as well as with a higher risk of refilling prescriptions. Although, day-care attendance is supposed to be protective for childhood asthma,27,28 it has also been suggested that day-care attendance in the first year of life is associated with childhood wheezing.12 This is probably due to more respiratory viruses and does not have to coincide with asthma. Another reason for the finding that the GP prescribes asthma medication more often in children who attend day-care facilities might be the fact that mothers whose children attend day-care are mostly working mothers and therefore, these mothers might be more compelling in getting a prescription. Otherwise, they have to stay at home with their sick child.

In the general population, besides respiratory symptoms and day-care attendance, we found gender and being breastfed to play a role in therapy initiation. Male gender was associated with prescribing of asthma medication. It is common knowledge that the prevalence and incidence of childhood wheezing and asthma are higher in boys.29 Boys are therefore more likely to use asthma medication. This was confirmed by Yuan et al.30 who showed a higher prevalence of asthma medication use among male infants. Infants who were exclusively breastfed during the first 3 months of life showed a lower chance of therapy initiation. The protective effect of breastfeeding for asthma and allergic disorders has been described in many studies. Mother’s milk is a source of immunomodulating factors and breastfeeding reduces external antigen exposure.11 Wright et al.31 showed that exclusive breastfeeding in the first years of life was associated with lower rates of wheeze.

For children with a respiratory system symptom diagnosis, symptoms reported by the parents and day-care attendance were associated with a higher chance of therapy initiation. Being breastfed was borderline significantly associated with a lower chance of therapy initiation. These findings show that when a more solid diagnosis pointing towards asthmatic symptoms is more likely, other factors (such as male gender) are filtered out and respiratory symptoms are the main determinant of medication use. The same was true for refilling prescriptions: respiratory system symptom diagnoses were an important driver of refilling prescriptions. Furthermore, Dutch ethnicity was independently associated with a higher chance of refilling prescriptions. This was against our expectations as most studies on health care utilization among different ethnic groups in the Netherlands demonstrated that children from non-Dutch ethnicity showed higher health care utilization for respiratory symptoms.14,32,33 This was confirmed by an earlier WHISTLER study.14 In contrast, our study shows higher refill rates among Dutch infants. There may be several reasons for this finding. First of all, ethnic minorities may be less adherent and do not refill prescriptions. However, van Dellen et al.34 found no differences in adherence to inhaled steroids among children in different ethnic groups in the Netherlands. In contrast, another study did indicate suboptimal asthma care for immigrant children in the Netherlands.35 Secondly, the GP may prescribe more often medication to Dutch patients. One possible explanation is that non-immigrant parents might be more compelling in getting another prescription for their child when compared to immigrant families.

It is very difficult if not impossible to diagnose asthma in infancy because most respiratory symptoms are transient and diagnostic tools only become useful after the age of 4 years. Therefore, a difficult task for treating physicians and non-symptom-related factors is often stated to play a role in this. Reijonen et al.36 showed that non-symptom-related factors are poor predictors of childhood asthma: a family history of atopy or asthma and environmental factors such as tobacco smoke exposure were no predictors of asthma 3 years after hospital admission for wheezing in infancy. As a consequence of the diagnosing, difficulties in infancy treatment of respiratory symptoms may be hampered. However, our results show that respiratory symptoms are the most important factor in prescription of asthma medication in infancy, which indicates that GPs are careful with prescribing drugs. Especially, patient-reported symptoms are very important in drug prescribing. First of all, patients, or in this case...
the parents of asthmatic patients, themselves can give the best indication of the presence and severity of their disease. Previous research has shown that there is good concordance between patient self-report and medical records on diagnosis for chronic diseases, such as asthma. Furthermore, in ~10% of the physician visits, a patient makes a request for a drug prescription and most of these request are honoured. This patient requesting might influence physician’s prescription behaviour.

It is reassuring to see that non-symptom-related factors play a much less important role. Physicians appear not to be distracted by these other factors and only prescribe medication when the child experiences respiratory symptoms. The current study also showed that refill rates for asthma medication prescriptions are lower in immigrant children. This finding underlines the need for good education of immigrant parents about respiratory symptoms and its management. Primary care physicians and pharmacists should make efforts to improve this knowledge.

Declaration

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Ethical approval: The paediatric medical ethics committee of the University Medical Center Utrecht has approved the protocol of the WHISTLER study.

Conflict of interest: ESK is paid by an unrestricted grant from GSK. CKVdeE received unrestricted grants from GSK and Grunenthal. JAMR is part time professor at the Utrecht University and vice president external scientific collaborations for GSK in Europe and holds stock in GSK. TJMV received research grants from GSK and Wheth. A-HM-vdZ received an unrestricted grant from GSK.

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