

Anti-asthmatic drug prescriptions to an Italian paediatric population

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To estimate the prevalence and evaluate the appropriateness of anti-asthmatic drug prescriptions in an Italian paediatric population, drug prescriptions involving 24,407 children < 18 years old, dispensed during 2003 by the retail pharmacies of the local health unit in Lecco, Italy, were analysed. Children ≥ 6 years old receiving anti-asthmatics were categorized into three subgroups based on the number of boxes prescribed: occasional (one box), low (two and three boxes) and high ($\geq$ four boxes) users. A logistic regression analysis was performed to estimate the relationship between the drug use patterns and formulations, antibiotic co-prescriptions, systemic steroid prescriptions and rate of hospitalization. Anti-asthmatic drugs were prescribed to 6594 (12%) children and adolescents; 58% of whom received only one box of the drug. Prevalence varied according to age, with the highest values at 1 and 4 years (24% and 21% respectively), and decreased to 6% in 17-year-old adolescents. Inhaled steroids were the most prescribed drugs (83%). The most common of these was beclomethasone. Occasional, low and high users represented 58%, 29%, and 13%, respectively, of the treated population ≥ 6 years old. High users were found to be at increased risk of systemic steroid prescriptions (OR 8.6) and hospital admission for asthma (OR 6.8). This study confirms that in Italy the prevalence of anti-asthmatic prescription is much higher than prevalence of disease, indicating that anti-asthmatics are over-prescribed. Moreover, steroids, especially nebulized, are mainly prescribed only once in a year, supporting the idea that are prescribed not for asthma, which as chronic disease requires a chronic therapy. The approach to create subgroups on the basis of number of boxes prescribed seems to be effective in estimating asthma severity and appropriateness of the therapies.

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Asthma is the most common chronic disease in children. According to SIDRIA (*Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente*), asthma prevalence did not change significantly in Italy between 1995 and 2002 (from 9.1 to 9.5%) (1, 2). Worldwide, prevalence in 2002 ranges between 1.5% (Borivali) and 32.6% (Wellington) (3). Asthma in childhood represents a huge burden for children and their families in terms of quality of life (4). According

to the 2002 European Health Report – WHO (major causes of the burden of disease), in the ≤ 14 years old population, asthma was the seventh pathological condition in terms of DALYs (disability-adjusted life-year lost per 1000); in Italy was the fourth and represented 2.7% of total DALYs (5). Epidemiological studies suggest that a heterogeneous group of pathological conditions exists that is associated with recurrent respiratory airway obstructions

and distinguishing between these has important implications for management (6). This group contains different asthma phenotypes in which the two most common phenotypes are atopic asthma, more common in school aged children, and episodic viral wheeze, more common in preschool children (7, 8). International guidelines recommend inhaled corticosteroids for long-term control of persistent asthma for all degrees of severity (9, 10). Short-acting β_2 adrenergics (SABA), such as salbutamol, are on the other hand of first choice in an acute attack. Although adherence to guidelines decreases the number of outpatients visits and emergency department visits (11), guidelines are far from being routinely applied in clinical practice (12–15). In paediatric practice, steroids are over-prescribed and used in an inappropriate manner (16), as in viral infection-associated wheezing. The aim of this study was to analyse the prescription profile of anti-asthmatic drugs in a paediatric population in order to assess the feasibility of using prescriptions as potential markers of disease severity, and to evaluate adherence to international guidelines.

Methods

The analysis involved all paediatric prescriptions reimbursed by the Health Service and dispensed by the retail pharmacies of the Local Health Unit of Lecco, Lombardy Region, between 1 January and 31 December 2003. Data were analysed using an anonymous patient code. The studied population is composed by 55,242 children under 18 years, with a prevalence of males (M/F = 1.05), and represented 3.7% of the population ≤ 17 years of Region Lombardy. Anti-asthmatics were classified as drugs belonging to the R03 main therapeutic group of the Anatomical Therapeutic Chemical classification system (ATC). Prevalence data by age and sex were calculated as number of children treated with anti-asthmatic drugs per 100 inhabitants. Comparison of anti-asthmatic prescription prevalence rates between males and females was performed by a Mantel–Haenszel chi-square test (χ^2_{M-H}). The relationship between prescription prevalence and age was analysed by a linear regression model considering sex and comparing angular coefficients by a *t*-test.

To identify potential asthmatic patients, subjects ≥ 6 years of age were distributed in three groups based on number of boxes received during 2003: A) ‘occasional users’, subjects receiving only one box (i.e. a single course of therapy); B) ‘low users’, subjects receiving two

or three boxes; C) ‘high users’, subjects receiving four or more boxes. The threshold of four boxes was chosen because it represents the 90th percentile in distribution of frequency of treated children by number of boxes. Prescription profiles (classes of anti-asthmatics, active principles, formulations and associations) were analysed in these three groups of subjects, taking prescriptions of short-acting β_2 adrenergic agonists into special consideration. To evaluate whether these three groups permit the identification of disease severity, a few indicators were chosen: use of anti-asthmatics only in co-prescription with antibiotics (prescription of antibiotics ± 7 days from anti-asthmatic prescription); appropriate formulation (prescription of metered dose inhaler, MDI or dry powder inhaler, DPI); prescription of systemic steroids; and rate of hospitalization for asthma (ICD IX = 493), considering hospital discharge forms (SDO).

Such indicators (the first two related to asthma, the others to disease severity) were used in a multinomial logistic regression analysis. The odds ratio (OR) and relative 95% confidence interval between the groups were calculated, adjusted also for age and gender. STATA9 software was used for statistical analysis (Stata Corp, College Station, TX, USA). A *p*-value < 0.05 was considered significant.

Results

Prescription profile in the ≤ 17 years old population

Prevalence by gender and age. During 2003, 24,407 children and adolescents (44% of the studied population) received at least one drug prescription, and 6594 of them (27% of those treated) received at least one anti-asthmatic drug. In 74% of cases the prescription was written by the paediatrician. A total of 23 anti-asthmatic drugs were prescribed, corresponding to 13,276 drug boxes. Every treated child received a median of two boxes (min 1, max 39). The average anti-asthmatic prescription prevalence rate was 12%, with two age-dependent peaks (not found for all other drugs), at 1 and 4 years. The prevalence then progressively decreased with increasing age and at 17 years was 6.5%. The slope indicating the reduction in prevalence was more dramatic between 4 and 8 years than between 9 and 17 years of age (Fig. 1).

Overall prevalence of anti-asthmatics was 1.24-fold higher in boys, vs. 1.06 of other drugs prescribed.

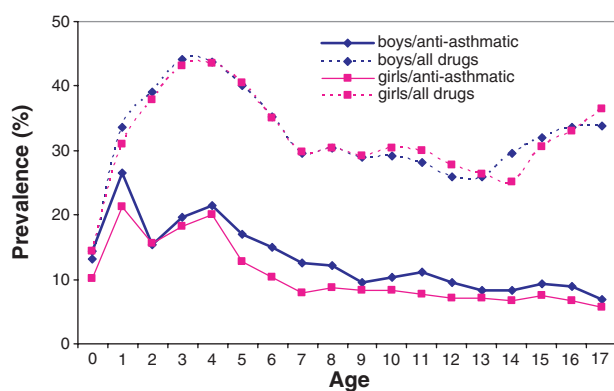


Fig. 1. Sex and age distribution of all drugs (---) and anti-asthmatic (—) prescription prevalence rates.

Distribution by drug class. Inhaled steroids were the more frequently prescribed anti-asthmatics (84% of those treated), while 33% of those treated received an adrenergic agonist. Altogether, these two classes represent 89% of dispensed boxes and their prevalence trend by gender and age is similar to the overall trend of anti-asthmatics. Beclomethasone was the most prescribed anti-asthmatic (58%), followed by salbutamol (31%), and salbutamol in fixed combination with other anti-asthmatic (13%). The first 10 anti-asthmatics in terms of prescription represent 97% of the total of dispensed boxes. A total of 96% of prescriptions concerned inhaled formulations, and three-fourth of these were nebulized solutions/suspensions. Flunisolide and beclomethasone were dispensed almost exclusively in a nebulized formulation (99% and 98% of the boxes, respectively). Salbutamol was prescribed in 74% of the cases as nebulized formulation.

Distribution by number of boxes and drugs. Fifty-eight per cent of children treated with anti-asthmatics received only one box, 26% two boxes, 7% three boxes and 11% four or more boxes. In all, 61% received only one drug, mainly beclomethasone (37%); 27% received two drugs (12% salbutamol + beclomethasone), and 13% received three or more drugs. Forty-two per cent of the anti-asthmatic prescriptions were associated with an antibiotic. A total of 1789 children (27%) received an anti-asthmatic co-prescribed exclusively with an antibiotic.

Prescription profile of preschoolers

A total of 3265 children <6 (18%) received at least one prescription of anti-asthmatic drug. A total of 1741 (53%) received only one box, and

305 (9.3%) four or more boxes. In all, 853 children (26%) received exclusively antibiotic-anti-asthmatic co-prescription and 3040 (93%) only nebulized formulations. The most prescribed drugs were beclomethasone (13.3%), salbutamol (7.7%) and flunisolide (2.7%).

Estimation of asthma prevalence and disease severity

A total of 3329 children and adolescents (9.0%) between 6 and 17 years of age received at least one anti-asthmatic drug prescription. Fifty-eight per cent of children treated with an anti-asthmatic received only one box (group A), 29% received two or three boxes (group B) and 13% received four or more boxes (group C). Beclomethasone and flunisolide were mainly prescribed in a occasional manner (group A), on the contrary, 70% of children treated with montelukast belonged to group C. Beclomethasone was the most prescribed drug in group A (55%) and B (49%), almost exclusively as a nebulized suspension (97% of prescribed boxes), and salbutamol was the most prescribed in group C (51%). In all, 1435 subjects ≥ 6 years of age received at least one prescription of β_2 adrenergics; 1213 received SABA (719 of which received MDI and DPI formulations) and 363 long-acting β_2 adrenergic agonists. The prevalence of prescriptions of SABA ranged from 19% in group A to 69% in group C, with significantly different rates between A and B ($\chi^2 = 13$; $p < 0.001$) and between B and C ($\chi^2 = 29$; $p < 0.001$).

Fig. 2 compares the distribution of drug classes in group B (low users) and C (high users), stratified by prescription of short-acting β_2 adrenergics. In all, 8% of group B and 2% of group C received only short-acting β_2 adrenergic agonists. Among the low users, SABA were prescribed mainly with steroids (47%), whereas nearly two-third of high users treated with SABA also received steroids and long-acting beta adrenergic (LABA). Inhaled steroids alone represent the more frequent therapeutic profile in group B (31% of low users). In all, 5% of subjects in groups B and C received neither a prescription for acute attacks (SABA) nor for maintenance therapy (steroids). In particular, 34 subjects had antileukotrienes, 27 cromons and 8 salmeterol.

Thirty-four per cent of group B were in monotherapy (one drug only), in particular 16% with beclomethasone and 4% with flunisolide or salbutamol, vs. 11% of group C (montelukast or beclomethasone to 3% of subjects, each). In all, 62% of group C received prescriptions of three or more drugs compared with 23% of group B.

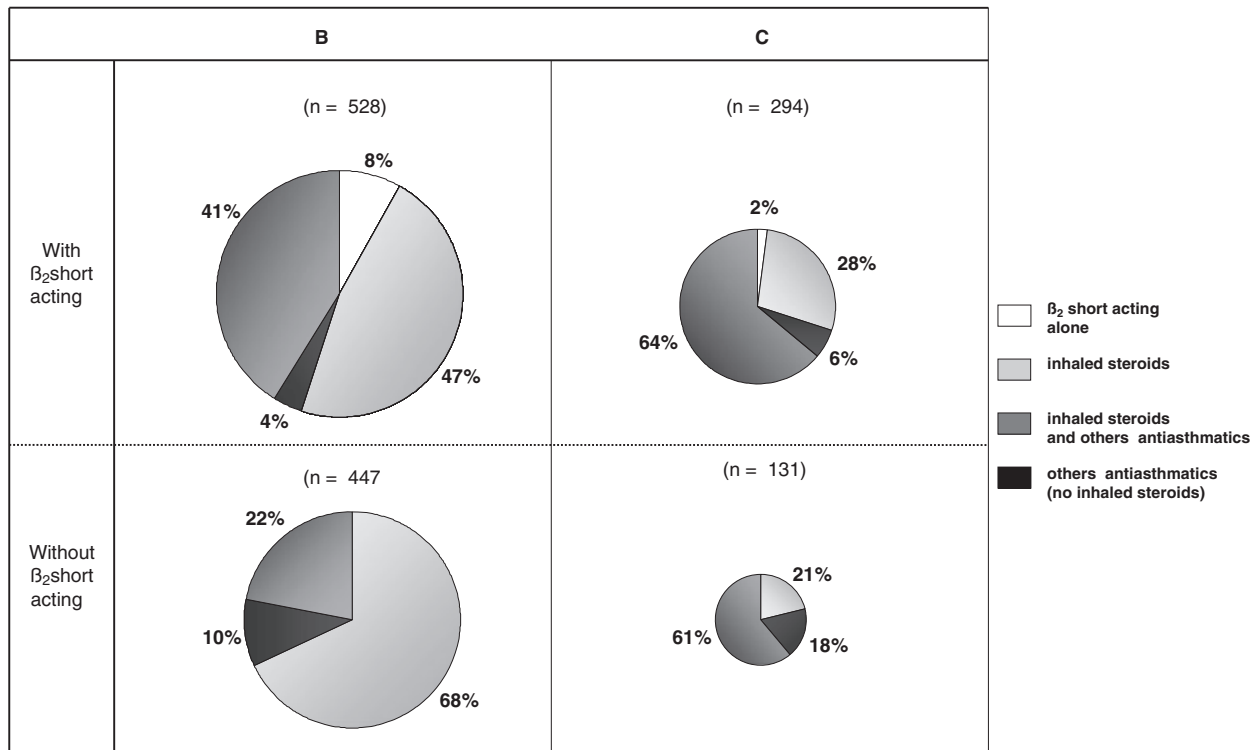


Fig. 2. Prescription profile of anti-asthmatics by class of drugs ≥ 6 years, stratified by prescription of short-acting β_2 adrenergics. B Low users; C High users.

Hospitalization

In all, 3906 subjects underwent hospitalization (7% of the studied population). Asthma was the cause of hospitalization in 86 children. Among children treated with anti-asthmatic drugs, 689 (10%) underwent hospitalization and 76 (1%) of these because of asthma. Among children older than 6 years of age, 170 (5%) were hospitalized and, of these, 21 (0.6%) were hospitalized for asthma.

Multivariate analysis

Table 1 reports the differences between the three groups of subjects resulting from a multivariate logistic regression analysis adjusted for sex and age. Sex represented a risk factor when groups C and A were compared. More specifically, boys had a higher risk than girls [OR 1.33 (1.04–1.71); $p = 0.025$]. On the contrary, no statistically significant differences were found comparing B and A. Considering MDI and DPI (and not nebulized formulations) as appropriate for asthma therapy, exclusive antibiotic–anti-asthmatic co-prescription, and systemic steroid prescriptions, significant differences were found in terms of OR between groups. Furthermore, a significant difference was observed in hospitalization

Table 1. Odds ratio from multinomial logistic regression analysis of anti-asthmatic users

	n (%)	OR (95% CI) [‡]
<i>Appropriate formulation (MDI and DPI)</i>		
A	398 (21%)	—
B	441 (45%)	3.2 (2.69–3.86)*
C	352 (83%)	18.4 (13.67–24.76)*
<i>Exclusive antibiotic co-prescription</i>		
A	758 (39%)	—
B	171 (18%)	0.5 (0.38–0.55)*
C	20 (5%)	0.1 (0.09–0.22)*
<i>Systemic steroids</i>		
A	27 (1.4%)	—
B	25 (2.6%)	2.4 (1.33–4.27)†
C	32 (7.5%)	8.6 (4.47–16.66)*
<i>Hospitalization for asthma</i>		
A	3 (0.2%)	—
B	4 (0.4%)	1.6 (0.32–8.26)
C	14 (3.3%)	6.8 (1.48–31.42)†

MDI, metered dose inhaler; A, occasional users ($n = 1929$); B, low users ($n = 975$); C, high users ($n = 425$).

* $p < 0.0001$, † $p < 0.05$, ‡adjusted odds ratio controlled for gender and age.

rate for asthma between C and B vs. A. On the contrary, no differences were found in the three groups for rate of hospitalization for reasons other than asthma. The concomitant presence of two or more of these indicators was more frequent in group C than in B or A. In group

C, all children were positive for at least two indicators, 10% for three and 0.9% for all four indicators.

Discussion

Estimation of asthma prevalence

The anti-asthmatic prescription pattern observed in this study appears to be consistent with previous Italian reports (12). Although the prevalence rate is lower than in other Italian contexts, the trend is similar, with the highest values observed in preschool age. A total of 58% of children was treated with only one box of anti-asthmatics, in particular with nebulized beclomethasone (which can cover 10 days treatment), suggesting that more than half of treated children received anti-asthmatics for acute diseases different from asthma, i.e. respiratory airway infections. This hypothesis is consistent with two findings. The first was that the highest prevalence rates were estimated in preschoolers. More specifically, two peaks were observed, for both boys and girls, at 12 months (when defences from maternal antibodies decrease) and 4 years (at the time of entry into the community). In particular the peak in the second year of life, consistent with previous finding (12), strongly suggests the hypothesis that anti-asthmatics are mainly used in viral wheezing. The second was that 42% of anti-asthmatics were co-prescribed with antibiotics.

It should be underlined, however, that also 47% of the youths over 6 years old, in which occurrence of viral wheezing is less frequent, received occasional prescriptions of nebulized formulations. These data suggest that anti-asthmatics (especially beclomethasone) are prescribed for respiratory airway infections also in the absence of bronchospasm, as described in other studies (17, 18). The overuse of beclomethasone could be in part due to the fact that in Italy this drug is also licensed for rhinopharyngitis. The lack of information on diagnosis, a major limit of studies based on prescription databases, does not permit the identification of real asthmatic patients. In order to overcome this fault, a few criteria were chosen with the aim to identify potentially asthmatic subjects. The first was age ≥ 6 years; only in school-aged children it is, in fact, possible to discriminate between asthma and recurrent viral wheezing in a reliable manner (68). The other criteria were based on drug consumption, using the number of boxes dispensed as an indicator. In this regard, occasional treatment (prescription of one box only) was an

exclusion criteria, because it is related to conditions other than asthma, or to exercise-induced or intermittent asthma.

Using these criteria, 3.8% asthma prevalence was estimated. This prevalence is inferior to that estimated by the SIDRIA survey (9.0% and 4.5% with persistent asthma) (2).

It is possible that the prevalence of asthma was overestimated in the SIDRIA survey. The reliability of self-reported asthma or asthma-like symptoms as a measure of asthma prevalence is in fact questionable (19–21).

On the contrary, the model used in this study could be biased because of the arbitrariness of the chosen criteria. The 6-year age cut-off could exclude preschoolers with asthma. Moreover, among occasionally treated subjects, 290 (15%) received adequate formulations (MDI and DPI) of β_2 agonists and they could represent false negatives. On the other hand, 278 subjects classified as potentially asthmatic (groups B and C) received nebulized steroid prescriptions only, therefore they could represent false positives (26% and 5%, respectively, for groups B and C).

However, a specificity of 0.86 and a sensitivity of 0.63 in identifying asthmatic patients were reported in a study in which similar criteria were used: subjects ≥ 6 years receiving all classes of anti-asthmatics, excluding those who received only one prescription of steroids or β_2 agonists (15). A recent article (22) using age and number of prescriptions as inclusion criteria reports anti-asthmatic prescriptions in 7.5% of Dutch children only 4.1% of whom were later diagnosed as asthmatic.

To increase specificity and sensitivity, an alternative model could be applied using two inclusion criteria in addition to age ≥ 6 years: the prescription of four or more boxes/year or at least one prescription of a β_2 adrenergic agonist in MDI/DPI formulation. On the basis of these criteria, 1057 potentially asthmatic patients would be identified, corresponding to the asthma prevalence of 2.9%. According to the prescription data, a prevalence ranging between 3% and 4% would therefore be estimated. This is quite similar to those estimated in two recent studies based on prescription databases: 2.6% in Denmark and 5.4% in Norway (15, 23). It is likely that this estimate is more accurate than the one reported in the SIDRIA survey, but it is also possible that an underestimation exists.

Estimation of disease severity

The aim of the study was also to try to estimate disease severity. In this regard, a threshold of

four boxes was identified to categorize high and low users.

The hypothesis that groups B and C may represent different degrees of severity is supported by the different profiles of anti-asthmatic drug prescriptions, as well as by the results of the multivariate analysis.

Group C, compared with B, is characterized by: a higher rate of short-acting β_2 adrenergic agonist use (69 vs. 54%); a higher number of subjects receiving multi-drug therapy (62% of group C received three or more drugs vs. 22% of B); and different associations of classes, for instance 46% of group C received SABA, LABA and steroids (an association suggested by guidelines for moderate-severe persistent asthma) compared with only 22% of group B. Furthermore, group C was characterized by a more frequent use of appropriate formulations (MDI and DPI) and by a very small percentage of children receiving anti-asthmatics only in co-prescription with antibiotics. The different prevalence of systemic steroids use between group B and C, as well as the difference in hospitalization rates, also suggest that high users have a more severe underlying disease.

Comparing these prescription patterns with international guidelines, it appears likely that group B (low users) would identify patients with mild persistent asthma, while group C (high users) would identify most of those with moderate-severe persistent asthma.

Appropriateness of the therapies

Even if the validity of indicators of prescription vs. clinical data in the assessment of the quality of asthma treatments is debated (24), a few inadequacies were evident in prescriptions that did not follow the guideline recommendations. First of all, the wide use of nebulized suspension/solutions: 55% of group B and 17% of group C received this formulation exclusively, even if it is considered appropriate only for children under 5 years of age, when MDI with a spacer device is not clinically effective (25).

Another possible inappropriateness, which regards 4 of 10 potentially asthmatic patients, may be the prescriptions of inhaled steroids, or steroids + LABA without SABA. However, this is a cross-sectional study and no data are available on the drug use during the previous years, thus it is not possible to discriminate between inadequacy or rather an optimal disease control that do not require acute attack therapy.

Ten per cent of high users did not receive steroids (first choice anti-inflammatory maintenance

therapy) and 6% did not receive SABA. A total of seven high user patients received SABA alone, either because not adequately treated or because experiencing intermittent asthma.

A very small percentage of subjects received a therapy with neither SABA nor steroids (5% and 6% groups B and C, respectively). Considering groups B and C together, 58% of antileukotrienes and 9% of LABA were prescribed without steroids. LABA alone would lead to a loss of disease control (26); in particular, salmeterol has been associated with deaths for respiratory failure (27). Nearly all subjects treated with antileukotrienes + steroids belonged to group C.

The lack of information on the prescribed dose does not permit a more accurate evaluation of treatment appropriateness. This could be important, especially for steroids, for which the guidelines recommend an association with another anti-asthmatic instead of an increase in inhaled steroid dose (9, 10).

Conclusion

As reported in other articles (12, 14, 15, 22, 23, 28), anti-asthmatic prescription profile studies are predictive of asthma prevalence and adherence to guidelines. However, qualitative and quantitative differences exist in the profile of anti-asthmatic prescription in Italy compared with other European countries. In Italy the prevalence of anti-asthmatic prescription is two- to three-fold higher than in other countries and in particular inhaled steroids are over-prescribed. Despite some limitations, the model applied in this pilot study, by excluding occasionally treated group, appears to be valuable in identifying potentially asthmatic patients and, in particular, in estimating disease severity. However, this model needs to be validated by obtaining the therapeutic indication from the prescribers.

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