

# Adverse drug reactions in Singaporean children

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## ABSTRACT

**Introduction:** Allergic reactions to drugs are considered rare in the paediatric population. Host genetic and environmental factors influence the reported incidence and characteristics of adverse drug reactions (ADRs), and cause significant variation according to the population described and case definition used. We aimed to define the prevalence and characteristics of reported drug allergies in hospitalised children in Singapore.

**Methods:** A retrospective case control study was performed through the hospital's inpatient electronic medical record (EMR) for the period of August 2002 to December 2002. The EMR was used to identify children with a previously-reported ADR. The control group was randomly selected from patients hospitalised during the same period.

**Results:** Of the 8437 patients hospitalised during the study period, reports of previous ADRs were found in the records of 222 patients. The mean age of the patients was 7.4 years, range 2 months to 17 years (95 percent confidence interval [CI] 6.3 - 8.4). There were 146 males and 160 Chinese. The most commonly-involved medications were betalactam antibiotics (45 percent) and non-steroidal anti-inflammatory drug (18.5 percent). Compared to the control group, children with a reported ADR were more likely to be older, with a mean age of 7.4 years versus 4.6 years (*p*-value less than 0.001), male (odds ratio [OR] 1.7, 95 percent CI 1.2-2.4), of Chinese descent (OR 1.8, 95 percent CI 1.5-5), have an associated chronic illness (OR 3.5, 95 percent CI 2.5-5), and a diagnosis of asthma (OR 2.7, 95 percent CI 1.7-4.5).

**Conclusion:** In our paediatric inpatient population, the risk of reported ADRs increases with age, male gender, Chinese descent and the presence of chronic disease. The major drugs involved are betalactam antibiotics and non-steroidal anti-inflammatory drugs.

**Keywords:** adverse drug reaction, betalactam antibiotics, children, drug hypersensitivity, non-steroidal anti-inflammatory drugs

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## INTRODUCTION

Adverse drug reactions (ADRs) are, according to the World Health Organisation's definitions, any undesired toxic effect that appears in the course of the clinical use of a drug<sup>(1)</sup>. These toxic effects are classified according to the predictability of the observed reactions<sup>(2)</sup>. A type A reaction is a predictable, dose-dependent result of the intrinsic toxicity of the drug. Examples of type A reactions are overdose, drug-drug interactions, side effects (nephrotoxicity of aminoglycosides) or secondary effects (changes in gut flora with the use of most antibiotics). Type B reactions are unpredictable, dose-independent, rare effects. These are classified into allergic (immune mediated effects in a sensitised patient) and non-allergic (idiosyncratic or psychogenic) reactions. In most instances, reported ADRs include both types, with usually a majority of type A reactions<sup>(3)</sup>. Though not rare events, the actual reported incidence of ADRs varies according to the population described and the case definition used<sup>(4,5)</sup>. In a meta-analysis of 39 prospective studies on adult ADRs causing or contributing to hospitalisation in the United States<sup>(5)</sup>, the overall incidence was 15.1%. The medications most frequently involved were cytotoxic, cardiovascular, anti-hypertensive, anti-coagulation and non-steroidal anti-inflammatory drugs (NSAIDs). The incidence of ADRs in the paediatric population is significantly lower<sup>(6,7)</sup>, being closer to 1% in the inpatient population. This is probably due to decreased exposure and a lower prevalence of chronic medication and multiple medications (polypharmacy)<sup>(8)</sup>. The drugs usually involved in reported ADRs in children are betalactam and macrolide antibiotics<sup>(9)</sup>. Various genetic and environmental/exposure factors influence the occurrence of ADRs. This study aims to define

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**Table I. Comparison of demographical and clinical characteristics between hospitalised children with a previously reported adverse drug reaction and the control group.**

	Children with ADRs	Controls	OR (95% CI)	p-value
No. of patients	222	450	–	–
Males	146 (66%)	243 (54%)	1.7 (1.2-2.4)	0.003
Chinese	160 (72%)	267 (59%)	1.8 (1.5-5)	0.001
Mean age ( in years)	7.4	3.9	–	<0.001
Chronic disease (excluding asthma)	26%	11%	3.5 (2.5-5)	0.003
Asthma diagnosis	20%	8%	2.7 (1.7-4.5)	0.04

**Table II. Medications associated with reported adverse drug reactions in Singaporean children.**

	No. of patients	Percent
Antibiotics	151	68%
Betalactam antibiotics	100	45%
Other antibiotics	51	23%
Non-steroidal anti-inflammatory drugs	42	19%
Others	29	13%
All medications	222	100%

the prevalence and characteristics of reported drug allergies in a hospitalised paediatric population in Singapore.

## METHODS

A retrospective case control study was performed through the hospital's inpatient electronic medical record (EMR). The EMR for the period of August 2002 to December 2002, was used to identify children with a previously- reported ADR. Demographical data, admission diagnoses, hospital stay and presence of chronic disease was extracted from the same database. Repeat admissions were excluded from analysis. For every child with a reported ADR, two other children were designated as controls. The controls were randomly selected from among all children admitted during the study period who did not report previous ADR. Reports of ADR in the EMR database were taken at face value. We did not attempt to evaluate the presence or absence of immunologically mediated drug reactions in these children.

Continuous data were compared by one-way analysis of variance, and categorical data by chi-square test. The Kruskal-Wallis test was used when variances were unequal among the groups. We compared the ADR group with the controls using logistic regression analysis. Odds ratio (OR) and confidence interval (CI) around these ratios were

calculated since this value approximates the relative risk of diseases with a low incidence. All statistical computations were performed using SPSS for Windows version 9.0 (SPSS Inc, Chicago, Illinois, USA). Only two-tailed tests were used. A p-value of less than 0.05 was considered significant.

## RESULTS

The EMR of 8,437 was screened. Reports of previous ADRs were found in the records of 222 patients (2.6%). Their mean age was 7.4 years, with range of two months to 17 years. There were 146 (66%) males and 160 (72%) Chinese. Fifty eight (26%) patients had an associated chronic illness (excluding asthma), while 44 (20%) had diagnosis of asthma. The average length of hospitalisation was 2.7 days (range 8 hours to 20 days, 3rd quartile 3 days).

The control group comprised of 450 patients admitted during the same period. Compared to the controls, children with a reported ADR were more likely to be older, with a mean age of 7.4 years versus 4.6 years ( $p < 0.001$ ), male (OR 1.7, 95% CI 1.2-2.4), of Chinese descent (OR 1.8, 95% CI 1.5-5), have an associated chronic illness (OR 3.5, 95% CI 2.5-5) and a diagnosis of Asthma (OR 2.7, 95% CI 1.7-4.5) (Table I).

Almost 70% of reported ADRs involved the use of antibiotics, two-thirds of which involve the betalactam family. The second most common pharmacological family involved were the NSAIDs (18.5%) (Table II). The incidence of asthma comorbidity in patients with a reported ADR to NSAIDs was 37% compared to 15% in patients with other ADRs (OR 3.3, 95% CI 1.6-7.0). Even after adjusting for the bias introduced by the high relative incidence of ADRs to NSAID, the likelihood of asthma remained significantly higher compared to controls (OR 2.5, 95% CI 1.4-4.3).

Multiple regression analysis confirmed the presence of asthma, other associated chronic disease, male gender and Chinese descent as independent risk factors for ADR in this population of children. Clinically, 98% of

reactions had skin manifestations. Only two patients reported a serious ADR (anaphylaxis). There were no details in the EMR on the characteristics of the skin reaction reported. Multiple drug allergies (ADRs reported with more than one pharmacological group) were very rare in our patients, comprising 3.6% of reported ADRs. One-half of these children had a severe chronic underlying disease (Lupus encephalitis, chronic granulomatous disease, lymphoma or leukemia). The mean hospital stay was 2.9 days, and was apparently not influenced by the history of reported ADRs.

## DISCUSSION

In adults, ADRs are more commonly reported in middle-aged and elderly women with a history of multiple concomitant medication exposure<sup>(10,11)</sup>. The presence of chronic disease, malignancy<sup>(12,13)</sup>, immunodeficiency<sup>(14-16)</sup>, severe viral infections<sup>(17)</sup> and a prior ADR are all independent risk factors. The male preponderance in patients with reported ADRs, observed in our paediatric population, is partly explained by the low relative age of the entire cohort. 71% of ADR cases were younger than 10 years old and in this subgroup, the male-to-female ratio was 2.3:1. Male preponderance in the younger age group has been previously reported<sup>(18,19)</sup>. For children older than 10 years old, the male-to-female ratio in the ADR group was 1.3:1. This ratio was similar to our inpatient control group.

Atopic disease is not generally considered a risk factor for the development of ADRs. However, asthma appears to be a risk factor for severe reactions<sup>(10)</sup> to any medication and a significant risk factor in adverse reactions to NSAIDs<sup>(20)</sup>. In our study, an increased risk of asthma in cases with a reported ADR to NSAIDs (OR 6.6, 95% CI 3.2-13.6) was also documented. There was also a similar, though less pronounced, increased risk of asthma in cases with non-NSAID ADRs (OR 2.5, 95% CI 1.4-4.3). This may reflect a local population-specific increased susceptibility for drug hypersensitivity in asthmatic patients, or increased exposure to medications likely to have occurred in children with a chronic illness. It may also reflect a secondary effect of our relatively young study group.

The concept of "atopic march" entails a progression of symptoms in the atopic individual, with aeroallergen sensitisation occurring at an early age that temporarily precedes the development of asthma. Longitudinal studies have confirmed that the prevalence of asthma increases during the school years<sup>(22-24)</sup>. In Singapore, the rate of hospitalisation for asthma may not be higher in the school years compared to early childhood, however, the number of patients with

asthma hospitalised after the age of 5 is higher<sup>(25)</sup>. The increased risk of asthma in patients with reported non-NSAID ADRs may be due to their older age compared to patients without a history of reported ADR. As the number of reported severe systemic reactions is very low, it is not possible to ascertain an association between asthma and the severity of drug-related hypersensitivity reactions in this group.

Multiple drug allergies are rare in children. In our study, only 3.6% of children had a history of ADRs to more than one pharmacological family. This may reflect a lower incidence of multiple drug exposure in children, and is supported by the fact that at least one-half of the children had an associated severe illness. Any chronic illness (including asthma) is a major risk factor for ADRs, which is probably, but not solely, due to increased use of medication and polypharmacy<sup>(6)</sup>.

Little is known of ADRs in the Chinese population. Besides genetic differences, environmental factors such as the concomitant use of traditional Chinese medicine and allopathic medication may influence the perceived incidence of ADRs<sup>(26-28)</sup>. The overall incidence of 2.6% probably reflects both under-reporting of mild ADRs and over-reporting of non-immunological ADRs as drug allergies. A prospective investigation, including a thorough drug allergy investigation of suspected ADRs, is needed to better estimate the type and incidence of ADRs in Singaporean children.

In conclusion, in our paediatric inpatient population, the risk of reported ADRs increases with age, male gender, Chinese descent, and the presence of asthma or other chronic disease. The major drugs involved are betalactam antibiotics and NSAIDs. We recommend a prospective investigation of ADRs in outpatient and inpatient settings in Singapore.

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