CUTANEOUS ADVERSE DRUG REACTIONS IN CHILDREN: AN ANALYSIS OF REPORTS FROM THE CANADIAN PHARMACOGENOMICS NETWORK FOR DRUG SAFETY (CPNDS)

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ABSTRACT

Cutaneous adverse drug reactions (CADRs) are the most prevalent adverse drug reactions (ADRs) in hospitalized children, with an estimated rate of 2-3%. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) is a pan-Canadian active surveillance network identifying genomic biomarkers of risk for serious ADRs. The purpose of this paper is to describe the characteristics of paediatric CADR cases reported to the CPNDS from February 2005 to December 2008. The CPNDS database was mined and details of CADRs and key clinical data from cases were extracted. Reports were individually analyzed and classified in two main groups: severe and non-severe CADRs, with subcategories. In total, 326 CADR cases were included in the study; 214 (65.6%) severe and 112 (34.4%) non-severe CADRs. Overall L-asparaginase (n=56, 16%), amoxicillin (n=29, 8.3%), cotrimoxazole (n=25, 7.2%), carbamazepine (n=17, 4.9%) and lamotrigine (n=13, 3.7%) accounted for 40% of all suspected medications. We have demonstrated the ability to comprehensively collect clinical data on a wide range of severe and non-severe CADRs to drugs commonly used in the care of children. Our study provides additional real world evidence to promote the proactive detection, collection, reporting and assessment of CADRs in children.

Key Words: *Adverse drug reactions; cutaneous; skin reaction; surveillance; children; pharmacovigilance*

An adverse drug reaction (ADR) is an unintended and noxious response to a drug that occurs at doses normally used in humans. ADRs are a major cause of morbidity and mortality, accounting for up to 7% of all hospital admissions and rank as the fifth leading cause of death in the western world.[1,2] Children are particularly at risk, with estimates suggesting that as much as 16.6% of hospitalized children experience ADRs, with nearly 30% of these being severe.[3,4]

Cutaneous adverse drug reactions (CADRs) are the most common ADRs and are frequently the reason for therapy discontinuation.[5,6] Several studies have found CADRs to be the most prevalent ADRs in hospitalized children, with an estimated rate of 2-3%.[7-11] The majority of CADRs in children are not considered serious, although they do account for a substantial proportion of clinical visits with an estimated 2% being severe and life threatening.[12,13]

While surveillance systems have been established for worldwide reporting of ADRs- they rely primarily on spontaneous, voluntary reporting from health care professionals and are thus considered passive. These systems are

designed to detect signals for new, rare and serious ADRs.[14] Few systems exist that encompass an active methodology, whereby a trained surveillance team works in conjunction with health care professionals to target and report specific ADRs to develop drug safety initiatives for patients.

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) was established in 2005.[15,16] It is a pan-Canadian active surveillance network consisting of trained surveillance clinicians in ten pediatric teaching hospitals across Canada, serving >75% of Canada's children. The goal of the network is to improve the safe use of prescription medication by identifying genomic biomarkers of drug risk for serious ADRs. CADRs were one of several targeted ADRs of interest to the research team.

CPNDS surveillance clinicians are exclusively dedicated to identify and report ADRs through active collaboration with physicians, pharmacists and nurses at each surveillance site across Canada. Following patient enrollment into the study, patient ADR reports are completed by surveillance clinicians and sent electronically to the CPNDS master database in Vancouver.

The purpose of this paper is to describe the characteristics of paediatric CADR cases reported to the CPNDS from February 2005-December 2008.

METHODS

The CADR report data was obtained from the CPNDS master database, which holds all reports of ADRs reported to the network. The master database was mined using more than 40 different terms from the literature to identify reports of CADRs reported to CPNDS from February 2005-December 2008. Search terms included rash, urticaria, hives, blister, oedema, allergy, hypersensitivity, erythema multiforme, anaphylaxis, Stevens-Johnson syndrome, among many others. Information taken into consideration from reports included the following: patient's sex and age at the time of the reaction, diagnosis or description of the CADR, details of drug exposure, tests to confirm the CADR, patient's outcome attributable to the CADR and causality of the CADR. Additional information like ancestry (geographic origin of the four grandparents of the child, reported by the parents), as well as presence of interacting diseases, other drugs or clinical conditions (i.e. infections, cancer, asthma, concomitant drugs, food or drug allergies) at time of the reaction, was also available from the database.

The reports were analyzed by a panel of experts. Their role was to assess CADR reports and check for completeness. In instances where a description of the CADR was reported, the panel formulated a unique dermatological diagnosis when possible, based on literature review of the hallmark features for well-characterized cutaneous reactions[17-23] (e.g., hives with swollen lips and dyspnea became anaphylaxis). If further clinical data was necessary, the reporting surveillance clinician was contacted to provide more information on the report. Reports that did not have a rating of at least possible on the Naranjo ADR Probability Scale[24] and did not have a temporal relationship between the drug and the CADR were excluded from analysis. All reports on the CPNDS database are assessed for causality of the suspected ADR using both the Naranjo scale as well as the causality algorithm of the WHO Collaborating Centre for International Drug Monitoring of Uppsala, Sweden.[25] This information as well as the quality of all CADR reports were extracted and analyzed. A grading scheme with 6 levels (grade 0 to 5) was used to assess the quality of documentation based on completeness of information (i.e. available information on reaction, suspected drug, demographics, treatment dates, patient outcome, drug dosage and route of administration) and quality of the clinical information.

CADRs were classified into severe and non-severe categories. For the purpose of this analysis, severe CADRs included anaphylaxis, erythema multiforme (EM), drug rash with eosinophilia and systemic symptoms syndrome (DRESS), serum sickness like reaction (SSLR), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Cases where the CADR was only 'rash' covering greater than or equal to 50% of the body surface area (BSA)[26], as well as other CADRs with possible life-threatening indicators (i.e. hand-foot syndrome)[17], were also included as severe. All CADRs that did not meet the criteria for severe were classified as non-severe: CADR cases where 10 to 40% of the BSA was affected by only

'rash', cases where the cutaneous manifestations were accompanied by non-life-threatening systemic symptoms, and 'rash' only cases where the percentage of BSA affected was not specified. For the classification of cases where 'rash' was the only symptom, we found the skin scoring method validated by Greinix and cols. to be appropriate.[26] This scoring system divides patients´ BSA into 10 regions equaling 10% for each region, was validated for cutaneous manifestations of chronic graft-versus-host disease. Usually, 'rash' is documented by listing the affected regions of the body i.e. 'trunk', 'hands' or 'neck and arms'. Therefore, we found the approach of Greinix and cols. to be more reproducible and suitable to classify our 'rash' cases than other systems (e.g. the rule of nines.) To classify suspected drugs, we used the Anatomical Therapeutic Chemical Classification System (ATC).[27]

RESULTS

Of the 2060 ADR cases enrolled by the CPNDS from February 2005 to December 2008, 336 cases were CADRs according to the search criteria used to mine the database. After applying the exclusion criteria only 10 cases were excluded from the analysis due to lack of information on therapy dates with the suspected drug and impossibility to find the information after reviewing the patient charts again. In total, 326 CADR cases were included in the study corresponding to 309 patients, since some patients developed more than one CADR event during the reported period of time. CADR cases were classified in two main groups: severe (n=214, 65.6%) and non-severe (n=112, 34.4%) cases. Table 1 shows the demographic and clinical data of all CADR groups and cases. 'Rash' cases affecting 50 to 100% of the BSA and anaphylaxis cases were the most common severe CADR reports contained in the CPNDS database, accounting for 27.6% and 19% of the total number of cases of the study, respectively. 28 SJS cases were found but no TEN cases were reported to the CPNDS study. 'Rash' cases involving 10 to 40% of the BSA accounted for a 21.5% of the total of CADR cases and were the most common non-severe CADRs found. 152 (46.6%) of the CADR cases occurred in males and 174 (53.4%) in females; slight gender differences were found between the severe (95 male and 119 female; 44.4% and 55.6% of severe cases, respectively) and non-severe (57 male and 55 female; 50.9% and 49.1% of non-severe cases, respectively) CADR groups.

Analysis of the age distribution showed, for both the severe and for the non-severe cases, a higher incidence of CADRs in children age 2-12 years (n=112, 34.3% severe; n=73, 22.4% non-severe) followed by adolescents (n=62, 19% severe; n=24, 7.4% non-severe) and infants (n=40, 12.3% severe; n=15, 4.6% non-severe). No reports of CADRs in neonates were found in the database.

Reported ancestry of the patients showed a majority of European origin (n=131, 42.4%). Canadian origin was reported for 85 (27.5%) patients and Canada's First Nations origin (pure and mixed) for 16 (5.2%) patients. 64 (20.7%) patients were from various origins including Chinese (n=6, 1.9%), Latin American/Caribbean (n=6, 1.9%), mixed ancestry (n=15, 4.9%) and others. For 13 (4.2%) patients, data on ancestry was not collected or was unknown (i.e. patient and/or parents were adopted). 150 (46%) CADR cases corresponded to patients with cancer, 51 (15.6%) to neurology patients and 125 (38.3%) cases were being treated for a variety of other clinical conditions i.e. surgery, otitis media or respiratory tract infections.

Most of the CADRs both severe and non-severe occurred while patients were experiencing politherapy, 136 (41.7%) and 71 (21.8%) cases, respectively. Cases undergoing monotherapy experienced more severe CADRs (n=78, 23.9%) than non-severe (n=41, 12.6%).

Details about possible interacting diseases (i.e. infections, skin diseases) at time of the reaction were documented for 51 (15.6%) severe and for 26 (8%) non-severe CADR reports. A total of 38 cases, 28 (8.6%) severe and 10 (3.1%) non-severe, reported drugs possibly interacting with the culprit drug. 66 (20.2%) severe and 36 (11%) non-severe cases occurred in patients with an allergy or history of allergies in their families i.e. to drugs, vaccines, food or environmental components. Asthmatic patients or patients with family history of asthma represented 15 (4.6%) of the severe and 11 (3.4%) of the non-severe CADR cases.

TABLE 1 Demographic and clinical characteristics of CADR cases in each group

	Severe CADRs (n=214, 65.6%)							**Non-severe CADRs (n=112, 34.4%)**		
	ANAPH	EM	DRESS	SSLR	SJS	Rash 50-100% BSA	Other severe CADRs[a]	Rash 10-40% BSA	Rash % BSA unknown	Other non-severe CADRs[b]
No. Cases (% of total)	62 (19%)	7 (2.1%)	8 (2.5%)	9 (2.8%)	28 (8.6%)	90 (27.6%)	10 (3.1%)	70 (21.5%)	36 (11%)	6 (1.8%)
Age group distribution[c, d]										
1 mo to <2 y	5	4	0	3	3	25	0	11	3	1
2 to <12 y	33	1	3	6	18	46	5	45	24	4
12 to 19 y	24	2	5	0	7	19	5	14	9	1
Gender[d]										
Male	25	2	4	4	13	44	3	37	18	2
Female	37	5	4	5	15	46	7	33	18	4
Ancestry[e]										
European	27	0	3	0	11	30	4	39	12	5
Canadian	7	6	1	5	8	32	3	14	9	0
First Nations[f]	3	1	1	0	2	5	0	4	0	0
Other[g]	13	0	3	3	6	18	3	8	9	0
Unknown	2	0	0	0	1	2	0	5	2	1
Type of patient at time of the reaction[d]										
Oncology	51	0	0	0	1	35	2	39	19	3
Neurology	0	0	4	1	13	16	1	12	3	1
Other	11	7	4	8	14	39	7	19	14	2
Details of therapy at time of the reaction[d]										
Monotherapy	6	7	6	7	11	38	3	22	16	3
Politherapy	56	0	2	2	17	52	7	48	20	3
Diseases[h]	5	1	3	7	14	20	1	17	9	0
Drugs[i]	8	1	1	0	9	9	0	7	3	0
Other patient characteristics at time of the reaction[d]										
Allergies[j]	22	4	3	2	5	28	2	21	15	0
Asthma[k]	4	1	1	1	2	5	1	9	2	0

Abbreviations: ANAPH, anaphylaxis; EM, erythema multiforme; DRESS, drug rash with eosinophilia and systemic symptoms syndrome; SSLR, serum sickness like reaction; SJS, Stevens-Johnson syndrome; BSA, body surface area; mo, months; y, years.

[a] CADRs that could not be classified in any well-characterized cutaneous disease but for which possible life-threatening systemic symptoms were identified i.e. rash and high fever. [b] CADR descriptions including cutaneous manifestations as well as non-life-threatening systemic symptoms i.e. two hives on back and chills. [c] Age groups were defined as following: neonates 0 to >1 mo; infants 1 mo to <2 y; children 2 to <12y; adolescents 12 to 19y. [d] Based on total number of CADR cases. [e] Based on total number of patients, n=309 patients. [f] Group includes pure First Nations natives as well as mixed. [g] Group includes various pure and mixed ancestries. [h] Interacting diseases at time of the reaction i.e. bacterial or viral infections, skin diseases. [i] Drugs reported as possibly interacting with the suspected drug at time of the reaction. [j] Reported known allergies to drugs, food, environment, of family history of allergies. [k] Asthmatic patient or family history of asthma.

TABLE 2 Medications associated with CADRs in the study

	Severe CADRs (n=227 meds, 65%)							**Non-severe CADRs (n=122 meds, 35%)**		
ATC class[a]	ANAPH	EM	DRESS	SSLR	SJS	Rash 50-100% BSA	Other severe CADRs[b]	Rash 10-40% BSA	Rash % BSA unknown	Other non-severe CADRs[c]
No. meds (% of total)[d]	65 (18.6%)	7 (2%)	8 (2.3%)	9 (2.6%)	31 (8.9%)	97 (27.8%)	10 (2.9%)	77 (22.1%)	39 (11.2%)	6 (1.7%)
A Alimentary tract and metabolism										
A03 Drugs for functional gastrointestinal disorders	1	-	-	-	-	2	-	-	-	-
B Blood and blood forming organs										
B01 Antithrombotic agents	-	-	-	-	-	-	-	1	-	-
D Dermatologicals										
D10 Anti-acne preparations	-	-	-	-	-	1	-	-	1	-
H Systemic hormonal preparations										
H02 Corticosteroids for systemic use	-	-	-	-	-	-	-	-	3	-
J Antiinfectives for systemic use										
J01 Antibacterials for systemic use	8	7	3	9	13	51	4	29	23	1
J02 Antimycotics for systemic use	1	-	-	-	-	1	-	-	-	-
J05 Antivirals for systemic use	-	-	-	-	-	-	-	2	-	-
L Antineoplastic and Immunomodulating agents										
L01 Antineoplastic agents	48	-	-	-	-	16	3	28	9	2
L04 Immunosupressants	1	-	-	-	-	-	1	-	-	-
M Musculo-skeletal system										
M01 Antiinflammatory and antirheumatic products	1	-	-	-	2	2	1	-	1	-
M04 Antigout preparations	1	-	-	-	-	-	-	-	-	-
N Nervous System										
N01 Anesthetics	-	-	-	-	-	1	-	2	-	-
N02 Analgesics	1	-	-	-	-	5	-	2	-	2
N03 Antiepileptics	2	-	5	-	15	16	1	12	2	1
N06 Psychoanaleptics	-	-	-	-	1	1	-	-	-	-
Other	1	-	-	-	-	1	-	1	-	-

Abbreviations: ANAPH, anaphylaxis; EM, erythema multiforme; DRESS, drug rash with eosinophilia and systemic symptoms syndrome; SSLR, serum sickness like reaction; SJS, Stevens-Johnson syndrome; BSA, body surface area; ATC class, Anatomical Therapeutic Chemical classification class; meds= medications.

[a] ATC class: anatomical main groups and therapeutic subgroups are shown. [b] CADRs that could not be classified in any well-characterized cutaneous disease but for which possible life-threatening systemic symptoms were identified i.e. rash and high fever. [c] CADR descriptions including cutaneous manifestations as well as non-life-threatening systemic symptoms i.e. two hives on back and chills. [d] Based on total number of culprit medications.

TABLE 3 Most common drugs implicated in CADRs of the study

Severe CADRs (n= 227 meds)		**No. cases**
Anaphylaxis (n=65)		
	L-asparaginase PEG	22
	L-asparaginase E. coli, etoposide	9 each
	L-asparaginase Erwinia, cefprozil	3 each
EM (n=7)		
	Amoxicillin	3
	Cotrimoxazole	2
	Clindamycin, minocycline	1 each
DRESS (n=8)		
	Carbamazepine	2
	Cotrimoxazole, sulfazalazine, lamotrigine, phenobarbital, clindamycin, phenytoin	1 each
SSLR (n=9)		
	Amoxicillin	6
	Penicillin G, cefprozil, cotrimoxazole	1 each
SJS (n=31)		
	Carbamazepine	7
	Amoxicillin, cotrimoxazole, clarithromycin	4 each
	Lamotrigine	3
	Ibuprofen, phenytoin, oxcarbazepine	2 each
	Zonisamide, fluoxetine, sulfazalazine	1 each
Rash 50-100% BSA (n=97)		
	Cotrimoxazole	10
	L-asparaginase PEG	7
	Amoxicillin, carbamazepine	6 each
	Phenobarbital, azythromycin	4 each
	Lamotrigine, piperacillin	3 each
Other severe CADRs (n=10)		
	Amoxicillin, methotrexate	2 each
	Ceftriaxone, vancomycin, azathioprine, ibuprofen, phenytoin, L-asparaginase PEG	1 each
Non-severe Cutaneous ADRs (n= 122 meds)		
Rash 10-40% BSA (n=77)		
	Methotrexate	8
	Lamotrigine	6
	L-asparaginase PEG, cotrimoxazole	5 each
	Amoxicillin, L-asparaginase E.coli	4 each
	Bleomycin, piperacillin	3 each
	Thiotepa, vancomycin, 6-mercaptopurine, phenytoin, cytarabine, cephalexin, carbamazepine, cefprozil	2 each
Rash % BSA unknown (n=39)		
	Amoxicillin, erythromycin	3 each
	L-asparaginase PEG, L-asparaginase E.coli, cotrimoxazole, penicillin G, cefaclor, bleomycin, dexamethasone	2 each
Other non-severe CADRs (n=6)		
	Bleomycin, morphine, phenobarbital, amoxicillin, codeine, L-asparaginase PEG	1 each

TABLE 4 Patient outcome and causality assessment of the CADR reports of the study

	Severe CADRs (n=214, 65.6%)							**Non-severe CADRs (n=112, 34.4%)**		
	ANAPH	EM	DRESS	SSLR	SJS	Rash 50-100% BSA	Other severe CADRs[a]	Rash 10-40% BSA	Rash % BSA unknown	Other non-severe CADRs[b]
ADR Causality[c]										
Certain	8	0	0	0	0	3	0	3	2	0
Probable/Likely	45	5	8	7	21	57	9	31	18	3
Possible	9	2	0	2	7	28	1	34	15	3
Unlikely	0	0	0	0	0	2	0	2	1	0
Conditional/Unclassified	No case reports with this status were identified.									
Unassessible/Unclassifiable	No case reports with this status were identified.									
ADR Imputability[d]										
Definite	6	0	0	0	0	3	0	2	1	0
Probable	36	3	3	6	14	42	8	29	16	3
Possible	20	4	5	3	14	45	2	39	19	3
Doubtful	Case reports scored as 'doubtful' were excluded from the study (*see* Methods section).									
ADR Outcome										
Death	0	0	0	0	0	0	0	0	0	0
Life-threatening	5	0	0	0	4	0	0	0	0	0
Disability	0	0	0	0	0	0	0	0	0	0
Admitted	12	1	4	2	10	8	3	7	0	0
Hospitalization prolonged	9	1	3	0	1	9	2	4	1	0
Require intervention to prevent damage/permanent impairment	26	5	1	7	13	16	3	12	9	1
Other	10	0	0	0	0	57	2	47	26	5

Abbreviations: ANAPH, anaphylaxis; EM, erythema multiforme; DRESS, drug rash with eosinophilia and systemic symptoms syndrome; SSLR, serum sickness like reaction; SJS, Stevens-Johnson syndrome; BSA, body surface area.

[a] CADRs that could not be classified in any well-characterized cutaneous disease but for which possible life-threatening systemic symptoms were identified i.e. rash and high fever. [b] CADR descriptions including cutaneous manifestations as well as non-life-threatening systemic symptoms i.e. two hives on back and chills.[c] Based on the WHO Collaborating Centre for International Drug Monitoring causality assessment algorithm [25]. [d] Based on Naranjo ADR Probability Scale [24].

A total of 349 medications were implicated as the suspected drug with 12 CADR cases having 2 suspected drugs. Table 2 shows the total number of culprit medications for both, severe and non-severe CADR cases, classified by ATC class. Antibacterials (n=95, 41.8%), antineoplastic agents (n=67, 29.5%) and antiepileptic drugs (n=39, 17.2%) were the most common cause of severe CADRs. Non-severe CADRs were mostly caused by the same drug classes: antibacterials (n=53, 43.4%), antineoplastics (n=39, 32%), and antiepileptics (n=15, 12.3%).

Overall in the study, L-asparaginase (total n=56: n=38 for PEG, n=15 for *E. coli*, n=3 for *Erwinia*), amoxicillin (n=29), cotrimoxazole (n=25), carbamazepine (n=17) and lamotrigine (n=13), accounted for 40% of all suspected medications. Table 3 shows the 5 more common suspected drugs for each group of CADRs. Severe CADRs were mostly caused by L-asparaginase PEG (n=30, 13.2%), amoxicillin (n=21, 9.3%), cotrimoxazole (n=18, 7.9%), carbamazepine (n=15, 6.6%), and lamotrigine (n=7, 3.1%).
The most common culprit drugs for non-severe CADRs were methotrexate (n=8, 6.6%), amoxicillin (n=8, 6.6%), L-asparaginase PEG (n=8, 6.6%), and cotrimoxazole (n=7, 5.7%).

In the CPNDS database 2 methods to assess causality of all CADR reports were used. Application of the algorithm of the WHO Collaborating Centre for International Drug Monitoring[25] resulted in the majority of the reports rated as 'probable or likely': 152 (46.6%) for severe and 52 (16%) for non-severe CADRs. 49 (15%) reports for severe and 52 (16%) for non-severe CADRs were rated as 'possible' (Table 4). Analysis of causality using the Naranjo scale[24] resulted in 160 (49.1%) reports rated as 'probable' (n=112, 34.4% for severe; n=48, 14.7% for non-severe CADRs) and 154 (47.2%) reports rated as 'possible' (n=93, 28.5% for severe; n=61, 18.7% for non-severe CADRs).

No CADR case resulted in death. 40 (12.3%) severe and only 7 (2.1%) non-severe cases resulted in hospital admission. Intervention was required for 71 (21.8%) severe and 22 (6.7%) non-severe cases in order to prevent damage. 'Other' was a common reported outcome (n=69, 21.2% for severe; n=78, 23.9% for non-severe CADR reports) chosen when drug was discontinued and/or switched to a different drug, or when doses of the culprit drug were held but premedication (i.e. with antihistamines) was needed for safe administration of following doses.

Overall, 294 (90.2%) of all reports on CADR cases achieved completeness of information, 199 (93%) severe and 95 (85%) non-severe CADR case reports had a quality grade of 5.

DISCUSSION

To the best of our knowledge this is the first study based on an active surveillance approach reporting on both severe and non-severe CADRs, to a wide variety of drugs used in children. Most of the literature is composed by studies presenting results on all types of ADRs in children[28,29]; studies focused on paediatric CADRs but based on voluntary reporting systems[30,31]; results from questionnaires sent to childrens´ parents[32,33]; or studies based on active surveillance methods focused primarily on severe CADRs in children.[34] There is a paucity of documentation of the prevalence and types of CADRs associated with commonly used drugs in paediatric patients.

Since most CADRs are relatively rare, it has been stressed the importance of building up multi-centric and multinational collaborations to allow for more accurate and standardized identification of higher numbers of cases.[35] Such a strategy will assist in identifying the mechanisms and risk factors (i.e. genetic predisposition) implicated in the development of CADRs. Networks focused on paediatric ADRs can also work in accordance with national and international authorities in order to provide real world evidence of the safety of new as well as old drugs used in children. To date, successful research network initiatives have been collecting and analyzing data specific to CADRs. Multi-national drug safety networks investigating CADRs, such as the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR; originally started as the EuroSCAR and the SCAR studies) have greatly contributed to the knowledge and understanding of conditions like EM, SJS and TEN.[36-39] The European Network for Drug Allergy (ENDA) is also one of several networks embedded in the Global Allergy and Asthma European Network (GA^{2}LEN).[40] The ENDA project aims to optimize diagnosis and reporting of allergy/hypersensitivity ADRs as well as other pharmacovigilance activities.

The CPNDS is a multi-centre cross-Canada network that uses an active surveillance system in Canadian tertiary child health care centres to identify severe ADRs and to further study the genetic determinants of these events.[15,16] The CPNDS has initially focused on ADRs in the paediatric oncology population. Although not an initial focus, we also found a number of severe as well as non-severe drug-induced CADRs. This report is a summary of a 4-year experience of active surveillance for drug-induced cutaneous reactions in children as of December 2008.

We believe it is critical to record complete clinical descriptions on all CADRs that occur in children in order to better understand the aetiology of ADRs and identify patients for further studies (e.g. pharmacogenomic studies).

We classified the CADR cases retrieved from the CPNDS database in severe and non-severe based on the presence of life-threatening indicators i.e. facial edema, mucous membrane erosions, arthralgias or hypotension.[12,17] Our active surveillance method allowed us to collect almost twice as many severe than non-severe CADR cases without a reporting bias for severe CADRs, since the study was not focused on CADRs and because we collect all information on potential ADRs available from patients´ charts. This method has allowed us to identify drug-matched control patients whose DNA samples were also collected for further pharmacogenomics studies.

There were no cases identified of TEN. At the time, the surveillance system did not cover Burn Units, and as it is usual Canadian practice to admit TEN cases to Burn Units, this is not unexpected.

At the beginning of the CPNDS project, three ADRs were targeted for surveillance: cisplatin-induced hearing impairment; anthracycline-induced cardiotoxicity; and codeine-induced infant mortality in breastfed infants. These ADRs were chosen because of their serious long-term morbidity and/or mortality; their high burden of illness on families; and because they likely had a genetic contribution.[16] For that reason, the bias of this study resided in the collection of a high number of ADR cases from pediatric oncology, which accounted for 41.6% and 54.5% of all the severe and non-severe CADR cases, respectively. This predominance of patients with cancer in our study, predominantly acute lymphoblastic leukemia (ALL), resulted in the high prevalence of antineoplastics as the culprit drugs (i.e. L-asparaginase, methotrexate and bleomycin), which has not been reported by other pharmacovigilance studies on CADRs. Few studies have reported on the most common drugs triggering ADRs in paediatric oncology patients when focusing on ADRs in general.[41,42] Despite the frequency of CADRs with chemotherapeutic agents and the stark visibility of these toxicities, there is a scarcity in the literature of large-scale pharmacovigilance studies focusing on this type of ADRs in paediatric oncology.[43]

CADRs attributable to chemotherapy can result in patient morbidity and alteration of the treatment plan.[44] For example, hypersensitivity reactions to L-asparaginase, one of the cornerstones of ALL treatment in children, may have huge impact in the success of the therapy and leukemia-free survival of patients. It has been shown that formation of anti-asparaginase antibodies might reduce its half-life and thus its antileukemic effect through deposition of antigen-antibody complexes in the reticuloendothelial system and prevention of its absorption after intramuscular injection.[45] From these findings, intensive surveillance of CADRs due to asparaginase becomes more relevant in order to assess the burden of these reactions, to optimize their management and prevention (i.e. premedication or desensitization protocols), and to investigate the causative mechanisms of asparaginase-induced CADRs. Pegylated L-asparaginase (L-asparaginase PEG) was initially prepared to provide a long-duration form of the drug as well as to provide a form which would be less likely to cause hypersensitivity reactions in comparison with *E.coli* and *Erwinia* preparations.[46] Interestingly, L-asparaginase PEG was the most common culprit drug overall in our study, causing mainly severe (i.e. anaphylaxis and rashes affecting 50-100% of patients' BSA) but also non-severe CADRs. L-asparaginase PEG was first approved to treat ALL patients who were hypersensitive to the native form of *E. coli*-asparaginase. Today, however, ALL treatment protocols have extended its indication to the treatment of newly diagnosed patients, at least in parts of the world where its availability is not limited by its cost.[45] Patients who developed a

CADR to L-asparaginase PEG in our study were either premedicated for further doses or substituted with *Erwinia* or *E.coli* preparations. Pharmacoepidemiologic data from large-scale scientific studies on asparaginase-induced CADRs and their overall implications in antileukemic treatment safety and effectiveness remain to be further investigated.

Cutaneous reactions are the most common form of adverse drug-induced reactions.[47] This is also true for paediatric ADRs and it has been demonstrated in studies worldwide.[8,28,29,31,41,48-50]

Practically any drug can cause a CADR. Moreover, one drug can cause different clinical patterns i.e., amoxicillin can cause rash, EM, SSLR or SJS.[51-54] The existence of a "multiple drug allergy syndrome", specifically a "multiple antibiotic sensitivity syndrome" in children, has also been suggested and may also be associated with the presence of infections.[55,56] These findings suggest the need for drug-specific and CADR-specific large-scale studies in order to further investigate the pathophysiological mechanisms and the risk factors for these reactions.

Our results regarding the most common suspected drug classes are in agreement with other studies in terms of the identification of antibacterials and antiepileptics as major triggering factors leading up to severe[31,34,57] as well as to non-severe[8,31,58] CADRs in children.

Non-severe CADRs (i.e. rashes) to antibiotics have generally been reported to occur most often with sulfonamides and penicillins. It was estimated that more than 7% of paediatric patients prescribed oral amoxicillin or penicillin in a private practice setting developed rashes.[53] Amoxicillin and cotrimoxazole have been reported to be the most common suspected drugs for a wide variety of skin reactions.[21,59] These two drugs were the most common culprit antibacterials in our study causing non-severe and severe rashes, EM, DRESS, SSLR and SJS.

Rashes are also a common side effect associated with antiepileptic drug use and in adult patients rash rates are higher with phenytoin, lamotrigine and carbamazepine.[60] In children phenobarbital, carbamazepine, and lamotrigine are strongly associated with the risk of severe CADRs like SJS and TEN.[34] In our study, carbamazepine (2 DRESS cases, 7 SJS cases, 6 severe and 2 non-severe rashes) and lamotrigine (1 DRESS case, 3 SJS cases, 3 severe and 6 non-severe rashes) were the antiepileptic drugs most commonly termed as suspected drugs to CADRs. Other studies in children have also found antiepileptics as the most frequently incriminated drugs in EM, SJS and TEN.[57]

63.5% of our CADR cases were undergoing polytherapy at the time of the reaction. Polypharmacy is a well-known predictor of ADRs in children and adults[61,62] and other studies in paediatrics have also reported that patients taking more than one drug are at a higher risk of experiencing CADRs.[59]

Interacting diseases should also be taken into consideration. It has been reported that EM and SJS are mostly triggered by infectious agents in children.[18] In our group of 28 SJS cases 8 of them were reactive for *M. pneumoniae* IgM, 3 were positive to herpes simplex virus type 1 (HSV-1), 2 were positive to Epstein-Barr virus (EBV) and 1 to methicillin resistant *Staphylococcus aureus* (MRSA). In our severe and non-severe rash groups throat infection due to *Streptococcus* was the most common infective disease interacting with the suspected drug. Since the mechanisms of drug-disease interactions require further investigation, unnecessary prescription of antibiotics for viral illnesses in children should be avoided.[59]

Asthmatic patients are also at higher risk of hypersensitivity reactions as well as patients with allergies (i.e. drug allergies, food or environmental allergies) or whose parents have a true drug allergy.[21,63] Only 8% of the CADR cases in our study occurred in asthmatic patients, but allergies seemed to be an important factor associated with certain CADRs. Our findings show that 35% of anaphylaxis cases; 57% of EM cases; 18% of SJS cases; and 34% of non-severe rashes occurred in patients with documented allergies or family history of allergies. This potential risk factor remains to be explored in further studies.

Among other factors that may increase the risk of CADRs, female gender has been one recent controversy. Females within all age groups are at higher risk for ADRs in general but no single risk factor has been identified.[31,63,64] Bigby and cols. reported a 35% higher rate of CADRs among female than male hospitalized patients.[10] Naldi et al. also reported a remarkable

preponderance of females with CADRs (female/male ratio of 1.58) from spontaneous reports in Italy.[31] In their study, groups of children aged under 10 years did not show this phenomenon (female/male ratio of 0.9). Antibiotic rashes in children were found to be more common in girls than in boys older than 9 years old.[53] Our study shows slight differences in gender for the severe (female/male ratio of 1.3) but not for the non-severe (female/male ratio of 1.0) CADR cases. Particularly, in the anaphylaxis, EM and other severe CADRs groups these differences were more evident.

We have also found that children (2 to 12 years old) had the majority of the CADRs. Age has been suggested as a risk factor associated with CADRs, but a careful correlation needs to be determined. Factors such as medication use and incidence of certain infections (i.e. bacterial and viral) in certain age groups may confound a possible association. Khoo and Giam found a mean age of 5.7 years in their study of drug eruptions in children.[59] Hypersensitivity reactions and drug eruptions (i.e. morbiliform eruptions, fixed drug eruptions or SSLR) may appear at any age but are rare in infants under 6 months of age.[59,65] The fact that our study included a high number of children with cancer, most of them with ALL, may have also influenced the prevalence of CADRs in children older than 2 years since the incidence of ALL is greater in children 1 to 5 and 7 years old.[66] A clear correlation between gender and age and the risk of developing ADRs, specifically CADRs, remains to be established.

Research on ethnicity and genetic predisposing factors for CADRs may provide new insights for the prompt identification of patients at risk and the optimization of management and prevention. It has been suggested that the ultimate determinant of success of genetic studies is the identification and careful phenotyping of patients with CADRs.[35] The CPNDS study has enrolled Canadian paediatric patients with a high degree of ethnic diversity and information on ancestry was collected. The vast majority of our CADR cases were from European ancestry under the assumption that the group described as ´Canadian` is most likely to be composed of individuals of European origin. This assumption has been supported by a study from our network on principal component analysis applied to the detection and correction for genetic ancestry differences in a sample of CPNDS patients.[67] Hypersensitivity reactions to drugs like abacavir and carbamazepine have shown to be influenced by ethnicity.[35] However, data on self-reported ancestry obtained from patients needs to be complemented with a validated test to determine the patients´ real ancestry if pharmacogenomics studies on CADRs are to be performed and provide evidence for association between a particular genotype and a certain ancestry.[68] For the CPNDS project, the detailed characterization of our patients including their reported ethnicity, is particularly important in order to help the network in deciding on future target drug-ADR associations. In addition, such patient characterization may be useful in recruiting patients of a specific ethnic group to correct for population stratification in our future pharmacogenomics studies.

Pharmacovigilance algorithms have not shown to be accurate for the diagnosis of drug hypersensitivity reactions[69], and our study also showed discrepancies after assessing all CADR cases with 2 different algorithms. While using the WHO causality algorithm 63% of the reports were probable and 31% possible. The algorithm of Naranjo resulted in 49% of the reports being probable and 47% were rated as possible. Lack of information in reports is the main problem when scoring causality through these algorithms but our study found the vast majority of the reports had a quality grade of 5. This implies that all the information needed to assess imputability was available. We also obtained details on the outcome of the CADR for all our cases, and our active surveillance approach has allowed us to ask surveillance clinicians at each hospital site to update any missing information from patients´ charts into the CPNDS database. We are proactively enrolling drug-matched control groups for further risk factor association studies i.e. genetic predisposing factors. Limitations of our study rely on the nature of the CADR case descriptions in patients´ charts, which sometimes do not contain all the details of the ADR. There are instances where non-severe CADRs are not assessed by dermatologists or clinics when they occur either within the community or in the hospital setting. The consequence of this is that no

formal diagnosis is provided and their documentation may be anecdotal and inaccurate. The challenge remains for clinics and hospital institutions to better document CADRs and our network can serve as a promoter for such optimization.

CONCLUSIONS

We have demonstrated the ability to comprehensively collect, in a short time frame, clinical data on a wide range of severe and non-severe CADRs to a wide variety of drugs used in the care of children. Our study provides additional real world evidence to promote the proactive detection, collection, reporting and assessment of CADRs in children. After this epidemiologic analysis, we anticipate that our future genetic and follow-up studies will provide us with many new insights into the pharmacogenomics, pathophysiology and determinants of drug-induced CADRs.

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Conflict of Interest

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REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Jama 1998 Apr 15;279(15):1200-5.
2. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ Clinical Research 2004; 3;329(7456):15-9.
3. Gonzalez-Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. International Journal of Clinical Pharmacology and Therapeutics 1998 Oct; 36(10):530-3.
4. Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ. A prospective study of adverse drug reactions in hospitalized children. British Journal of Clinical Pharmacology 1999 Jun;47(6):681-8.
5. Gruchalla RS, Beltrani VS. Drug-induced cutaneous reactions. *In:* Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary Approach. [place of publication unknown]: Informa Healthcare 2000;307-309.
6. Bordet R, Gautier S, Louet HL, et al. Analysis of the direct cost of adverse drug reactions in hospitalized patients. Eur J Clin Pharmacol 2001; 56:935-941.
7. Kushwaha KP, Verma RB, Singh YD, et al. Surveillance of drug induced diseases in children. Indian J Pediatr 1994; 61:357-365.

8. Dos Santos BD, Coelho HLL. Adverse drug reactions in hospitalized children in Fortalez, Brazil. Pharmacoepidemiol Drug Saf 2006; 15:635-640.
9. Kidon MI, See Y. Adverse drug reactions in Singapore children. Sing Med J 2004;45:574-577.
10. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,238 consecutive inpatients, 1975 to 1982. JAMA 1986;256:3358-3363.
11. Stewart RB, May FE, Cullen SI. Dermatologic adverse drug reactions in hospitalized patients. Am J Hosp Pharm 1979;36:609-612.
12. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331 (19):1272-1285.
13. Johnson ML, Johnson KG, Engel A. Prevalence, morbidity, and cost of dermatologic diseases. J Am Acad Dermatol 1984;11:930-936.
14. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Euro J Clin Pharmacol 2008;64(8):743-752.
15. Ross CJ, Carleton B, Warn DG, Stenton SB, Rassekh SR, Hayden MR. Genotypic approaches to therapy in children: A national active surveillance network (GATC) to study the pharmacogenomics of severe adverse drug reactions in children. Annals of the New York Academy of Sciences 2007 Sep11;10:177-92.
16. Carleton BC, Poole RL, Smith MA, Leeder JS, Ghannadan R, Ross CJD, Phillips MS, Hayden MR. Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. Pharmacoepidemiol Drug Saf 2009. Published Online: Jun 8 2009.
17. Wolff K, Johnson RA, Suurmond D: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th Edition. Available at: http://www.accessmedicine.com/content.aspx?aID=754605 Accessed: April 2009.
18. Leaute-Labreze C, Lamireau T, Chawki D, Maleville J, Taieb A. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. Arch Dis Child 2000; 83(4):347-52.
19. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333(24):1600-7.
20. Wolkenstein PE, Roujeau JC, Revuz J. Drug-induced Toxic Epidermal Necrolysis. Clinics in Dermatology 1998;16:399-409.
21. Segal AR, Doherty KM, Leggott J, Zlotoff B. Cutaneous reactions to drugs in children. Pediatrics 2007;120:e1082-1096.
22. Cotliar J. Approach to the patient with a suspected drug eruption. Semin Cutan Med Surg 2007;26:147-154.
23. Rook's Textbook of Dermatology 7th Edition. Edited by D.A. Burns, S.M. Breathnach, Neil Cox, and Christopher E. Griffiths. Oxford, England ; Blackwell Publishing ; 2004.
24. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
25. The use of the WHO-UMC system for standardized case causality assessment [monograph on the Internet]. Uppsala: The Uppsala Monitoring Centre; 2005. Available from: http://www.who-umc.org/graphics/4409.pdf. [cited on 2009 June].
26. Greinix HT, Pohlreich D, Maalouf J, et al. A single-centered pilot validation study of a new chronic GVHD skin scoring system. Biology of Blood and Marrow Transplantation 2007; 13(6):715-723.
27. WHO (2009) WHO Collaboration Centre for Drug Statistics Methodology. ATC/DDD index 2009. Available at: http://www.whocc.no/atcddd/ Accessed June, 2009.
28. Planchamp F, Nguyen KA, Vial T, Nasri S, Javouhey E, Gillet Y, Ranchin B, Villard F, Floret D, Cochat P, Gueyffier F, Kassai B, Groupe de travail pharmacovigilance en pediatrie. Active drug monitoring of adverse drug reactions in pediatric emergency department. Archives de Pediatrie 2009;16(2): 106-11.
29. Haffner S, von Laue N, Wirth S, Thurmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. Drug Safety 2005;28(5):453-64.
30. Salvo F, Polimeni G, Cutroneo PM, Leone R, Confortic A, Moretti U, Motola D, Tuccori M, Caputi AP. Allergic reactions to oral drugs: A case/non-case study from an Italian spontaneous reporting database (GIF). Pharmacological Research 2008;58(3-4):202-207.
31. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, Cocci A, Moretti U, Velo G, Leone R. Cutaneous reactions to drugs. An

analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol 1999;48:839-846.
32. Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. Pediatr Allergy Immunol 2008;19:634-638.
33. Orhan F, Karakas T, Cakir M, Akkol N, Bahat E, Sonmez FM, Gedik Y. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. Pediatric Allergy & Immunology 2008;19(1): 82-5.
34. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, Flahault A, Kelly JP, Martin E, Kaufman DW, Maison P. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: A pooled analysis. Pediatrics 2009;123(2):e297-304.
35. Pirmohamed M. Genetic factors in the predisposition to drug-induced hypersensitivity reactions. AAPS J 2006;8(1):e20-26.
36. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: Assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008; 128(1):35-44.
37. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, Bouwes-Bavinck JN, Sidoroff A, de Toma C, Schumacher M, Roujeau JC, Hovnanian A, Mockenhaupt M; *for the RegiSCAR study group*. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18(2): 99-107.
38. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, Graf E, Schumacher M, Hovnanian A, Mockenhaupt M, Roujeau JC; RegiSCAR Group. A marker for Stevens-Johnson syndrome: Ethnicity matters. Pharmacogenomics J 2006;6(4):265-8.
39. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC; *SCAR Study Group*. Severe Cutaneous Adverse Reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol 2002;138(8): 1019-24.
40. Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, Brockow K, et al. Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GA^{2}LEN platform. The Galenda project. Allergy 2009;64:194-203.
41. Buajordet I, Wesenberg F, Brors O, Langslet A. Adverse drug events in children during hospitalization and after discharge in a Norwegian university hospital. Acta Paediatrica 2002; 91(1): 88-94.
42. Mitchell AA, Lacouture PG, Sheehan JE, Kauffman RE, Shapiro S. Adverse drug reactions in children leading to hospital admission. Pediatrics 1988;82(1):24-9.
43. Sanborn RE, Sauer DA. Cutaneous reactions to chemotherapy: commonly seen, less described, little understood. Dermatol Clin 2008;26:103-119.
44. Wyatt AJ, Leonard GD, Sachs DL. Cutaneous reactions to chemotherapy and their management. Am J Clin Dermatol 2006;7(1): 45-63.
45. Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukaemia. J Allergy Clin Immunol 2009;123:895-9.
46. Graham ML. Pegaspargase: a review of clinical studies. Advanced Drug Delivery Reviews 2003; 55:1293-1302.
47. DeShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. JAMA 1997;278: 1895–1906.
48. Khotaei GT, Fattahi F, Pourpak Z, Moinfar Z, Aghaee FM, Gholami K, Moin M. Adverse reactions to antibiotics in hospitalized Iranian children. Journal of Microbiology, Immunology & Infection 2008;41(2):160-4.
49. Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, Rubio E, Palop V. Adverse drug reactions in children reported by means of the yellow card in Spain. Journal of Clinical Epidemiology 2000; 53(10):1076-80.
50. Cutroneo PM, Arcoraci V, Cucinotta G, Inferrera G, Galante F, Sofia A, Ferrera E, Napolitano T, Mazzaglia G, Caputi AP. Adverse drug reactions in childhood. A drug surveillance study in Sicily. Recenti Progressi in Medicina 1998; 89(6):290-5.
51. Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O, Motola D, Dusi G, Caputi AP. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. Journal of Antimicrobial Chemotherapy 2007; 60(1):121-6.
52. Levine LR. Quantitative comparison of adverse reactions to cefaclor vs. amoxicillin in a

surveillance study. Pediatr Infect Dis 1985;4: 358-361.
53. Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children. A survey in a private practice setting. Arch Dermatol 2000; 136:849-854.
54. Hernandez-Salazar A, Rosales SP, Rangel-Frausto S, Criollo E, Archer-Dubon C, Orozco-Topete R. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. Archives of Medical Research 2006;37(7):899-902.
55. Macy E. Multiple antibiotic allergy syndrome. Immunol Allergy Clin North Am 2004;24:533-43.
56. Park J, Matsui D, Rieder MJ. Multiple antibiotic sensitivity syndrome in children. Can J Clin Pharmacol 2000;7(1):e38-41.
57. Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruption among children and adolescents in north India. Pediatric Dermatology 1995;12(2):178-83.
58. Martin-Munoz F, Moreno-Ancillo A, Dominguez-Noche C, Diaz-Pena JM, Garcia-Ara C, Boyano T, Ojeda JA. Evaluation of drug-related hypersensitivity reactions in children. Journal of Investigational Allergology & Clinical Immunology 1999;9(3):172-7.
59. Khoo BP, Giam YC. Drug eruptions in children: a review of 111 cases seen in a tertiary skin referral centre. Singapore Med J 2000;41(11): 525-529.
60. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, Resor SR, Hirsch LJ. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007;68:1701-1709.
61. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 2001; 52:77-83.
62. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse Drug Reactions in Hospitals: A Narrative Review. Current Drug Safety 2007;2:79-87.
63. Gobel BH. Hypersensitivity Reactions to Biological Drugs. Seminars in Oncology Nursing 2007;23(3):191-200.
64. Zopf Y, Rabe C, Neubert A, Gassmann KG, Rascher W, Hahn EG, Brune K, Dormann H. Women encounter ADRs more often than do men. Eur J Clin Pharmacol 2008;64:999-1004.
65. Carder KR. Hypersensitivity reactions in neonates and infants. Dermatologic Therapy 2005;18(2):160-75.
66. The Leukemia and Lymphoma Society. Facts 2008-2009. New York, June 2008. Available at: http://www.leukemia-lymphoma.org/attachments/National/br_1215783647.pdf (Accessed June 2009).
67. Visscher H, Ross CJD, Dubé MP, Brown AMK, Phillips MS, Carleton BC, Hayden MR. Application of principal component analysis to pharmacogenomic studies in Canada. Pharmacogenomics J 2009 (submitted).
68. Payne PW Jr. For Asians only? The perils of ancestry-based drug prescribing. J Law Med Ethics 2008;36(3):585-8.
69. Benahmed S, Picot MC, Dumas F, Demoly P. Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Arch Intern Med 2005;165:1500–1505.