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ARTICLE

Medications as Risk Factors of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children: A Pooled Analysis

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What's Known on This Subject

Among the general population, medication is the major cause of SJS or TEN. These fatal diseases have been observed in children, but relative risks of drugs have never been described in this population.

What This Study Adds

This study assesses medication risk factors of SJS/TEN for the first time in a large population of children. Highly suspected and controversial drugs associated with the risk of SJS or TEN in children <15 years of age are described.

ABSTRACT

OBJECTIVE. The aim of this study was to determine the relation of medications to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in children <15 years of age.

METHODS. We conducted a pooled analysis by using data from 2 multicenter international case-control studies: the severe cutaneous adverse reaction (SCAR) study and the multinational severe cutaneous adverse reaction (EuroSCAR) study conducted in France, Germany, Italy, Portugal, the Netherlands, Austria, and Israel. We selected case subjects aged <15 years, hospitalized for Stevens-Johnson syndrome, Stevens-Johnson syndrome/toxic epidermal necrolysis-overlap, or toxic epidermal necrolysis, and age-, gender-, and country-matched hospital controls. Pooled crude odds ratios were estimated and adjusted for confounding by multivariate methods when numbers permitted.

RESULTS. Our study included 80 cases and 216 matched controls. Antiinfective sulfonamides, phenobarbital, carbamazepine, and lamotrigine were strongly associated with the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. Significant associations were highlighted in univariate analysis for valproic acid and nonsteroidal antiinflammatory drugs as a group and for acetaminophen (paracetamol) in multivariate analysis.

CONCLUSIONS. We confirmed 4 previously highly suspected drug risk factors for Stevens-Johnson syndrome/toxic epidermal necrolysis in children: antiinfective sulfonamides, phenobarbital, carbamazepine, and lamotrigine. Among more unexpected risk factors, we suspect that acetaminophen (paracetamol) use increases the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *Pediatrics* 2009;123: e297–e304

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Key Words
Stevens-Johnson syndrome, toxic epidermal necrolysis, Lyell syndrome, severe cutaneous adverse reaction, children, medication risk factors, drugs, pharmacoepidemiology, meta-analysis

Abbreviations
SCAR—severe cutaneous adverse reaction
SJS—Stevens-Johnson syndrome
TEN—toxic epidermal necrolysis
OR—odds ratio
CI—confidence interval
NSAID—nonsteroidal antiinflammatory drug

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STEVENS-JOHNSON SYNDROME (SJS) and toxic epidermal necrolysis (TEN) are 2 rare (1–2 cases per million population per year) but life-threatening mucocutaneous reactions characterized by detachment of epidermis, acute skin blisters, and mucous membrane erosions (Figs 1 and 2).[1] SJS and TEN are variants within a continuous spectrum; detachment of <10% of the total body surface area defines SJS, whereas >30% defines TEN. Intermediate cases are called SJS/TEN–overlap.[2] The mortality risk is high, >40% of TEN cases are fatal, sepsis being the most important cause.[3–5] Other complications such as ocular sequelae are severe and frequent (40%–50% of survivors).[6,7]

Among the general population, including mainly adult patients, it has been estimated that a drug is implicated in ~70% of cases of TEN.[8] Both SJS and TEN are severity variants of the same drug-induced process.[9] Several drugs are highly suspected to cause SJS/TEN and suspected to be the causative agent in 65% of SJS/TEN cases[10]: antiepileptics, antiinfective sulfonamides, oxicam nonsteroidal inflammatory drugs (NSAIDs), nevirapine, and allopurinol. The

TABLE 1 Characteristics of the 2 Pooled Studies

	SCAR	EuroSCAR
Inclusion time	1989–1995	1997–2001
Participative countries	France, Germany, Italy, and Portugal	France, Germany, Italy, the Netherlands, Israel, and Austria
Cases	Hospitalized for SJS, TEN, or SJS/TEN-overlap	
	Diagnosis confirmed by validation committee	
	Age > 1 mo	
	Children included if had mucosal lesions or target lesions and/or skin biopsy	
Controls	Hospitalized for <10 d for acute conditions including infection, trauma, and abdominal emergency, which were not expected to result from medication use	
Matching criteria	Age	
	Gender	
	Country/region	
Population	368 cases and 1704 controls	383 cases and 1502 controls
Children pooled population	80 cases and 216 controls	
	Ratio control/case 3:1	
	Gender ratio: 1:1	
	Median age: cases: 6.2 (3.7–9.9); controls: 6.1 (3.4–10.7)	

potential role of other drugs such as aminopenicillins, valproic acid, acetaminophen (paracetamol), and corticosteroids is more controversial.[8,11–14] Nonmedication factors have also been hypothesized to increase the risk of SJS/TEN: HIV,[15,16] herpesvirus or *Mycoplasma pneumoniae*,[17–20] radiotherapy,[21,22] lupus erythematosus,[23] and collagen vascular disease.[24]

TEN and SJS have been observed worldwide and occur in all age groups including children, infants, and even newborns,[4,5,25–27] but to our knowledge, no specific study has ever assessed drug risk factors in children. Considering that drug prescriptions differ between children and adults and that age can modify drug effects, we hypothesized that medication risk factors of SJS/TEN might be different for children. The 2 largest case-control studies, severe cutaneous adverse reaction (SCAR)[13] and EuroSCAR,[28] were conducted in France, Germany, Italy, Portugal, Netherlands, Austria, and Israel to evaluate the medication risk factors of SJS/TEN in the general population (368 and 383 cases, respectively, of SJS, SJS/TEN-overlap, and TEN). Only 10% of the cases in these 2 studies were children. Therefore, we conducted a pooled analysis combining the data from these 2 studies to determine medication risk factors of SJS/TEN in children <15 years of age. The aims were to (1) describe the characteristics of cases, (2) determine if drugs suspected to be risk factors in the general population were confirmed among children, and (3) investigate if other drugs or factors were associated with these diseases in children.

PATIENTS AND METHODS

We conducted the study by pooling individual data from the 2 case-control studies: SCAR and EuroSCAR[11,13,28,29] (Table 1). Both international multicenter studies had identical methodologies and similar populations, which restricted heterogeneity and therefore allowed pooled analysis.

We selected children who were <15 years of age, hospitalized for SJS, SJS/TEN-overlap, or TEN, and controls matched for age, gender, and country. Controls (ratio was 3:1 in both studies) were patients hospitalized for acute conditions including infection, trauma, and abdominal emergency, which were not expected to result from drug use. The following data were extracted from each database: demographic and clinical data, drug exposures during the month preceding hospitalization, infection, other symptoms or herpes during the last month, history of allergic disease (asthma, atopic dermatitis, eczema, or allergic rhinitis), drug allergy, or other diseases.

Pooling the 2 studies yielded 80 case subjects and 216 matched controls <15 years of age (34 case subjects and 99 controls from SCAR; 46 case subjects and 117 controls from EuroSCAR).

A group of experts blinded for potential exposure reviewed all collected cases by using clinical data, available photographs, and histopathology to confirm the diagnosis of SJS/TEN and determine the date of onset of disease. Because the features of SJS/TEN develop over a few days, an "index day" was determined as the most probable date of onset of the patient's disease. The date of onset of the controls' acute condition was considered as their index day. The window of drug exposure was restricted to 7 days before the probable index day for the analysis, according to the pharmacokinetics hypothesis that a drug could not induce the reaction if totally eliminated from the body. The exposure window was extended to 3 weeks for phenobarbital, which has a longer half-life.

Categorical variables are reported as percentages (numbers) and continuous variables as median (25th–75th percentiles). A 2-tailed χ^2 test was used, and $P \leq .05$ indicated statistical significance.

Homogeneity between studies was tested for each variable by using the Cochran Q test[30] with a significance level of $P < 10\%$. In case of heterogeneity, the outlying group was excluded when identified. Univariate analysis (crude odds ratio [OR]) was performed for all risk factors. Pooled ORs and their 95% confidence intervals

(CIs) were estimated for each exposure by using unconditional logistic regression[31] (Stata 9.1 [Stata Corp, College Station, TX]). When there were <3 exposed controls or cases, exact logistic regression (StatXact and LogXact [Cytel Software, Cambridge, MA]) was used to estimate OR and inferior 95% CI. When there were no exposed controls, the median unbiased estimate was used.[32] When the *P* value of univariate analysis was <.10, and when at least 3 cases and controls were exposed, multivariate analysis was performed. Adjusted for matching variables previously described, highly suspected drugs when present in this study (ie, antiinfective sulfonamides, barbiturates, carbamazepine, phenytoin, and lamotrigine),[11,13,28] fever, and upper respiratory tract infection in the last week (collected from the parents' statements). Acetaminophen, aminopenicillins, valproic acid, NSAIDs, salicylates, and corticosteroids were considered as the other suspected drugs.

Although the index day was determined to provide a standard measure of onset, it was based on symptoms reported by the patient and, therefore, was subject to inaccuracies. Thus, a significant association between SJS/TEN and a medication administered during the first to the third day before the index day could represent treatment of the underlying illness, and not a causal association with SJS/TEN. To limit this confusion between cause and effect of medication use termed as "protopathic bias,"[33] we conducted a sensitivity analysis in which the index day was moved up to 3 days earlier for all drugs that were significant in univariate analysis.

We performed subgroup analyses for all the significant drugs in the univariate analysis, considering only exposures that were not concomitant to a highly suspected drug during the week before the index day.

RESULTS

Among the 80 cases, 26% (n = 21) were classified as having SJS, 34% (n = 27) TEN, and 40% (n = 32) SJS/TEN-overlap. The gender ratio was relatively balanced among cases (male/female = 1.2:1). Mucous membranes were involved in 95% (n = 76) of cases and median percentage of skin detachment was 20% (10%–40%) of the body surface. The median delay between probable index day and admission date was 3 days (25th to 75th percentiles: 2–5). Recent infection with *M pneumoniae* had been reported in 9% (n = 7) of cases. No patients were HIV positive or affected by a chronic rheumatic disease, lupus erythematosus, or cancer. The cases median length of hospitalization was 17 days (25th to 75th percentiles: 11–23). The 4 cases without mucous membrane involvement, included if a skin biopsy evidenced full-thickness necrosis of the epidermis in addition to suggestive photographs, did not differ materially for percentage of skin detachment, length of hospitalization, and delay between index day and admission date (25% [25th to 75th percentiles: 17–40], 18 days [25th to 75th percentiles: 14–33], and 3 days [25th to 75th percentiles: 2.5–4], respectively). Six case patients died (7.5% [95% CI: 2.8%–16%]), among whom 2 had an underlying disease (thalamus astrocytoma and pituitary tumor).

TABLE 2 Heterogeneity Between the 2 Studies for Acetaminophen

	SCAR		EuroSCAR		*Q* Test[a]
	Case (N = 34) n (%)	Controls (N = 99) n (%)	Cases (N = 46) n (%)	Controls (N = 117) n (%)	
Acetaminophen	7 (20)	11 (11)	18 (39)	9 (8)	.07
France	1 (7)	9 (18)	9 (47)	6 (11)	.008
Other countries	6 (32)	2 (4)	9 (33)	3 (5)	.97

[a] *P* value for heterogeneity Cochran *Q* test between the 2 pooled studies.

No heterogeneity between the 2 studies was observed for any nonmedication or medication risk factors except for acetaminophen (Table 2). To take this heterogeneity into account, analyses of exposure to acetaminophen excluded French children from the SCAR study, who in contrast with the other centers and with the French data from EuroSCAR had a low prevalence among cases and a high prevalence among controls.

During the week preceding the index day, 23% (n = 18) of cases and 3% (n = 6) of controls (P < .001) had fever: an upper respiratory tract infection was found in 24% (n = 19) of cases and in 8% (n = 18) of controls (P < .001). No other nonmedication risk factor was significant in univariate analysis, in particular the prevalence of recent herpes infection was similar between cases and controls (13% vs 10%, respectively; P = .50).

According to our exposure definition, cases were exposed to a mean value of 2.4 drugs, whereas controls were exposed to 0.75 drugs. Among cases, 7.5% (n = 6) did not take any drug during the week preceding the index day versus 25% (n = 55) of controls (P < .05). At least 1 highly suspected drug was taken by 39% (n = 31) of cases and by <1% of controls (n = 1) (P < .001). Seventy percent (n = 56) of cases and 15% (n = 33) of controls had been exposed to at least 1 suspected drug (P < .001).

Among the highly suspected drugs, antiinfective sulfonamides, phenobarbital, lamotrigine, and carbamazepine were strongly associated with SJS/TEN in univariate analysis (Table 3). No cases or controls used more than 1 highly suspected drug. Only 1 case was exposed to phenytoin during the last week, and there were no children exposed to allopurinol, nevirapine, or oxicam NSAIDs (ie, piroxicam, tenoxicam, and meloxicam).

Among the other suspected drugs, 3 were found to increase the risk of SJS/TEN in children: valproic acid, acetaminophen, and NSAIDs as a group.

Valproic acid was highly associated to the risk of SJS/TEN by univariate analysis (Table 3). The risk estimate decreased by half but remained significant when the analysis was restricted to the 3 cases not treated with another anticonvulsant (Table 4).

The OR for acetaminophen remained significant in multivariate analysis (Table 3) and when cases exposed to concomitant highly suspected drugs where excluded (Table 4). The time pattern of cases' exposure was different between acetaminophen and highly

TABLE 3 OR Estimates for Medication Exposures in the Week Preceding the Index Day Comparing Cases and Matched Controls

	Cases ($N = 80$) (%)	Controls ($N = 216$) *n* (%)	*Q* Test[a]	Crude OR (95% CI)	Multivariate OR[b] (95% CI)
Antiinfectives					
Sulfonamides	10 (13)	0 (0)	.95	42 (6.6–∞)	NA
Aminopenicillins	8 (10)	9 (4)	.76	2.5 (.9–6.9)	1.8 (0.6–5.6)
Cephalosporins	8 (10)	1 (1)	.50	24 (3.1–∞)	NA
Macrolides	6 (7)	2 (1)	.73	8.6 (1.5–∞)	NA
Antiepileptics	24 (30)	1 (1)	.36	91 (14–∞)	NA
Phenobarbital	12 (15)	1 (1)	.15	37 (5.4–∞)	NA
Valproic acid	7 (9)	0 (0)	.87	28 (4.1–∞)	NA
Lamotrigine	4 (9)[c]	0 (0)	—	14 (1.7–∞)	NA
Carbamazepine	4 (5)	0 (0)	.96	15 (1.8∞)	NA
Benzodiazepines	3 (4)	0 (0)	.48	11 (1.1–∞)	NA
NSAIDs[d]	4 (5)	1 (1)	.54	11 (1.1–∞)	NA
Salicylates	6 (8)	9 (4)	.61	1.8 (.6–5.4)	—
Acetaminophen[e]	24 (37)	11 (7)	.77	8.2 (3.7–18)	5.0 (2.0–13)
Corticosteroids	4 (5)	2 (1)	.25	5.6 (.8–∞)	—
Antihistamines H1	9 (11)	11 (5)	.69	2.4 (.9–5.9)	2.0 (.7–5.8)
Mucolytics	8 (10)	10 (5)	.14	2.3 (.9–6.0)	.7 (.2–2.6)
Vitamines	14 (18)	25 (12)	.86	1.6 (.8–3.3)	—
Vaccine[f]	3 (4)	4 (2)	.38	2.0 (.5–9.4)	—

NA indicates not applicable.

[a] *P* value for heterogeneity Cochran *Q* test between the 2 pooled studies.

[b] Adjustment for matching variables, previously highly suspected drugs when present in this study (ie, antiinfective sulfonamides, phenobarbital, carbamazepine, phenytoin, and lamotrigine), fever, and upper respiratory tract infection in the last week.

[c] Exposure only available for EuroSCAR subjects.

[d] NSAIDs: ibuprofen (1 case), niflumic acid (1 case), ketoprofen (1 case), nimesulid (1 case), and tiaprofenic acid (1 control).

[e] Excluding French children in the SCAR study, therefore 65 cases and 165 controls were analyzed.

[f] In the last month.

suspected drugs (Figs 3 A and B); the reaction often began within the 2 days preceding the index day for acetaminophen, suggesting a possible confusion between cause and effect of the medication. Data excluding exposition when the first administration occurred on either the first, second, or third day before the index day produced estimates of: OR: 8.0 (95% CI: 3.7–17), 5.6 (95% CI: 2.4–13), and 4.4 (95% CI: 1.8–10), respectively. The multivariate OR remained significant when children whose first acetaminophen exposure was within the 2 days preceding the index day were considered as unexposed (17 cases [21%] vs 10 controls [5%]; OR: 5.1 [95% CI: 1.8–14]).

As a group, NSAIDs were significantly associated with the risk of SJS/TEN in univariate analysis (Table 3) and in subgroup analysis (Table 4). No significant association was observed for corticosteroids.

Benzodiazepines were associated with the diseases in univariate analysis, but all 3 cases were also exposed to phenobarbital (Table 4).

Among other drugs commonly used by children, the univariate and multivariate odds ratios for H1 antihista-

TABLE 4 Results of the Subgroup Analysis: OR Estimates for Medication Exposures in the Week Preceding the Index Day After Exclusion of Cases and Controls Exposed to Highly Suspected Drugs (for Medication Significant in Univariate Analysis)

	Cases ($N = 80$) *n* (%)	Controls ($N = 216$) *n* (%)	Crude OR Subgroup Analysis (95% CI)
Cephalosporins	1 (2)	1 (1)	2.7 (0.03–∞)
Macrolides	3 (6)	2 (1)	4.1 (0.5–∞)
Valproic acid	3 (6)	0 (0)	11 (1.1–∞)
NSAIDs	3 (6)	0 (0)	11 (1.1–∞)
Acetaminophen	16 (40)	11 (7)	9.3 (3.9–22)
Benzodiazepines	0 (0)	0 (0)	NA

Sulfonamides, phenobarbital, carbamazepine, and lamotrigine were never concomitant to another highly suspected drug.

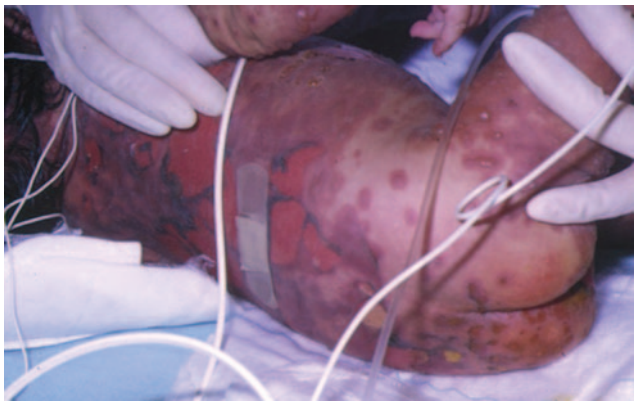

FIGURE 1
Typical pattern of TEN: skin detachment and atypical targets.

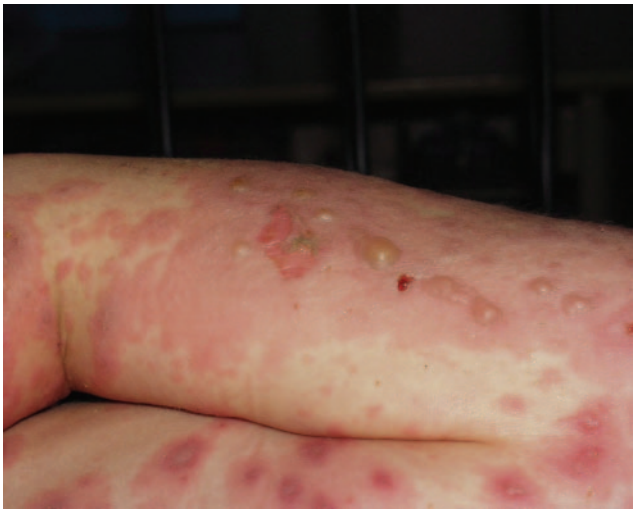

FIGURE 2
Typical pattern of SJS: blisters develop on widespread atypical targets.

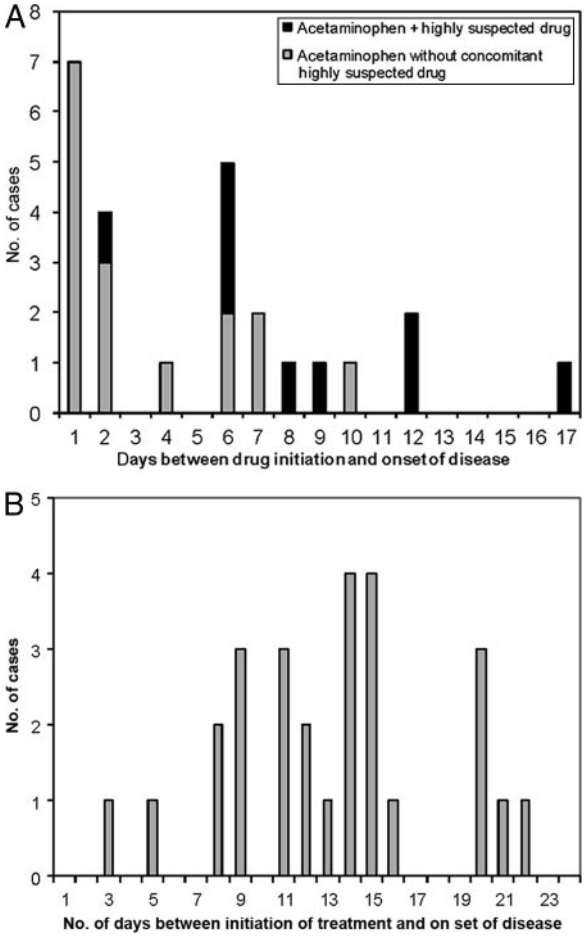

FIGURE 3
Distribution of number of cases according to duration of treatment before the onset of disease for cases exposed to acetaminophen (A) and highly suspected drugs (B). Dark lines indicate cases with comedication of highly suspected drugs prescribed to children (phenobarbital, carbamazepine, lamotrigine, phenytoin, or anti-infective sulfonamides) initiated within <8 weeks before the onset of the disease.

mines were modestly increased, but the lower confidence limits were <1.0.

DISCUSSION

This pharmacoepidemiologic study is the first dedicated to risk factors for SJS/TEN in children <15 years of age. Among highly suspected drugs, antiinfective sulfonamides, phenobarbital, lamotrigine, and carbamazepine were independent risk factors with markedly elevated risk estimates. Valproic acid, NSAIDs as a group, and acetaminophen were significantly associated with these diseases in children. The latter associations were not clearly explained by bias stemming from confusion between the temporal sequence of medication use and the onset of disease or by a concomitant exposure to highly suspected drugs.

To avoid misclassification with staphylococcal scalded skin syndrome, a possible differential diagnosis among young children,[34,35] cases of SJS/TEN presented with at least 1 of the 3 following criteria: mucosal erosion, target lesion, and skin biopsy in both studies.

The rarity of the diseases was such that although a pooled analysis was performed, the sample size remained low. Few exposures to specific medications among controls were also a limitation in previous studies despite inclusion of more than 1000 controls. Our study had enough statistical power to identify a high relative risk of SJS/TEN, for drugs rarely used by controls (eg, antiinfective sulfonamides), and risk factors with weaker associations when the control exposure prevalence was relatively high. The rates of drug use among our controls were consistent with those found in previous studies for aspirin (4%),[36] penicillins (4%),[37] cephalosporins (1%),[37] and macrolides (1%),[37] suggesting that our population was similar.

In contrast with adults,[5,38] the male to female gender ratio was balanced among cases of SJS/ TEN in our study, as in previous studies on children.[8,27] Children represented 10% of the population in both studies, concordant with the incidence of SJS/TEN increasing with age.[39] The mortality rate among our cases was 7.5%, whereas it averaged 20% to 25% among adults,[40] consistent with the hypothesis that increasing age has negative effect on prognosis.[4,5,25,39]

The median delay between index day and hospitalization was 3 days; a special effort should therefore be devoted to earlier diagnosis and referral, which can be important factors leading to improved management and decreased morbidity and mortality.

Several diseases were previously shown to be risk factors in adults: HIV,[15,16] lupus erythematosus,[23] or a chronic rheumatic disease. Although no child in this study was affected by any of these diseases, we cannot exclude their potential risk also in children. Recent herpes infection has been hypothesized to be implicated in the risk of SJS/TEN in the general population, but results are conflicting.[5,10,41] Our study did not show any significant association with recent herpes infection in children.

Cases used more medications than controls in the week preceding the onset of disease, consistent with the hypothesis that medication is the major risk factor for

SJS/TEN in children. Among the highly suspected drugs, we confirmed that antiinfective sulfonamides, phenobarbital, lamotrigine, and carbamazepine were high and independent risk factors for SJS/TEN in children. Antiinfective sulfonamides are the most frequently implicated drugs in SJS/TEN in the general population[5,8,13,42] and have often been suspected in children.[27,43] Several studies including different populations[12–14,44,45] showed that phenobarbital, phenytoin, carbamazepine, and lamotrigine were highly suspected drugs. These antiepileptics have also been implicated in several case reports in children worldwide.[27,43,46,47]

Studies among the general population reported conflicting results suggesting an association with valproic acid could be explained by confounding by comedication with other antiepileptics.[13,14,28] In children, the risk estimate of valproic acid remained significant when other concomitant highly suspected antiepileptics where taken into account, indicating that this drug may independently increase the risk of SJS/TEN.

As a group, NSAIDs were significantly associated, but each case was exposed to a different NSAID, and their low prevalence of use did not allow analysis of individual drugs. Ibuprofen has been a suspected causative agent of several cases of SJS/TEN including US children,[46,48,49] but we observed a single case exposed to ibuprofen.

In the general population, oxicam NSAIDs such as piroxicam have been identified as strong risk factors,[29] but in our study no child was exposed to these drugs, which are usually not prescribed to those <15 years of age.

Our results showed a significant association with acetaminophen in children. The increased risk was consistently present in all regions in the EuroSCAR study (including France) and in all regions in the SCAR study except France. Thus, the latter data were not included in the final analysis of acetaminophen. Although regional heterogeneity in drug risks has been reported in other contexts,[50] the present difference is between 2 time periods in the same region. Given the similarity of the 2 study protocols, we cannot explain this difference, particularly because the association was consistent in the other countries for both time periods. With regard to previous findings, some cases imputable to acetaminophen have been reported in children.[27,51,52] The strongest evidence for a causal role was a positive oral rechallenge in a 7-year-old girl from Israel with TEN. In the original studies on which the present report is based, the responsibility of acetaminophen as a risk factor among the general population was not so clear[13] and strongly suspected to be due to the possibility that prodromic symptoms (pain, fever) of SJS/TEN enhance acetaminophen administration.[28] In the present analysis, the time pattern of exposure to acetaminophen showed that many cases could also be explained by confounding by indication but not only, because results obtained by varying the exposure window showed a remaining significant association. In addition, the increased risk observed for acetaminophen is not explained by the concomitant use of highly suspected drugs; the multivariate and subgroup analyses produced a significant association. The present results are therefore compatible with acetaminophen being a potential risk factor for SJS/TEN in children.

Considering antibiotics other than sulfonamides, we can neither confirm nor exclude a potential association of cephalosporins, macrolides, or ampicillin with SJS/TEN, which have been reported in previous studies including adults and children.[8,13,27,28,43,46] Our results did not confirm a relationship in children with other suspected drugs, such as corticosteroids and salicylates.

Thirty percent of cases were not exposed to a previously suspected drug and 7.5% ($n = 6$) were not exposed to any drug during the last week, suggesting there could be other risk factors; however, we did not identify such factors. Recent infection with *M pneumoniae* had been reported in 9% ($n = 7$) of cases, but data were not available for control patients. Cases caused by vaccines have been reported previously,[53–55] but we did not confirm an increasing risk for SJS/TEN in children with such drugs.

The prevalence of exposure to medication may vary between countries and over time, but the relative risks should remain similar because it generally does not vary geographically. Other factors could lead to differences in relative risks between populations, but to our knowledge, variation of relative risks has been suspected only for carbamazepine in Asian populations.[56,57] Our results may be generalized to US children, because they are widely exposed to the suspected drugs in this study (eg, antiepileptics[58] and acetaminophen).[59]

CONCLUSIONS

SJS and TEN are rare diseases among children with a mortality rate estimated at 7.5%. In our study, children had mucous membrane lesions in 95% of cases and the median percentage of skin detachment was 20% of the body surface (10% to 40%). We did not confirm any suspected nonmedication risk factors. We confirmed 4 highly suspected drugs in children, antiinfective sulfonamides, phenobarbital, carbamazepine, and lamotrigine. Among other suspected drugs, we assume that acetaminophen may substantially increase the risk of SJS/TEN in children.

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SCAR

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REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med.* 1994;331(19):1272–1285
2. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129(1):92–96
3. Mockenhaupt M, Norgauer J. Cutaneous adverse drug reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis. *Allergy Clin Immunol Int.* 2002;14(4):143–150
4. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol.* 1987;123(9):1160–1165
5. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Flechet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981–1985. *Arch Dermatol.* 1990;126(1):37–42
6. Binaghi M, Koso M, Roujeau JC, Coscas G. Ocular complications of Lyell's syndrome: recent concepts apropos of 26 cases [in French]. *J Fr Ophtalmol.* 1985;8(3):239–243
7. Rzany B, Mockenhaupt M, Baur S, et al. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990–1992): structure and results of a population-based registry. *J Clin Epidemiol.* 1996;49(7):769–773
8. Guillaume JC, Roujeau JC, Revuz J, Penso D, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol.* 1987;123(9):1166–1170
9. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol.* 1994;102(6):28S–30S
10. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schroder W, Roujeau JC. 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):1019–1024
11. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, Naldi L, Viboud C, Roujeau JC. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *Aids.* 2001;15(14):1843–1848
12. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology.* 2005;64(7):1134–1138
13. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333(24):1600–1607
14. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study group of the international case control study on severe cutaneous adverse reactions. *Lancet.* 1999;353(9171):2190–2194
15. Saiag P, Caumes E, Chosidow O, Revuz J, Roujeau JC. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol.* 1992;26(4):567–574
16. Coopman SA, Stern RS. Cutaneous drug reactions in human immunodeficiency virus infection. *Arch Dermatol.* 1991;127(5):714–717
17. Fournier S, Bastuji-Garin S, Mentec H, Revuz J, Roujeau JC. Toxic epidermal necrolysis associated with mycoplasma pneumoniae infection. *Eur J Clin Microbiol Infect Dis.* 1995;14(6):558–559
18. Meseguer MA, de Rafael L, Vidal ML. Stevens-Johnson syndrome with isolation of mycoplasma pneumoniae from skin lesions. *Eur J Clin Microbiol.* 1986;5(2):167–168
19. Stutman HR. Stevens-Johnson syndrome and mycoplasma pneumoniae: evidence for cutaneous infection. *J Pediatr.* 1987;111(6 pt 1):845–847
20. Ravin KA, Rappaport LD, Zuckerbraun NS, Wadowsky RM,

Wald ER, Michaels MM. Mycoplasma pneumoniae and atypical Stevens-Johnson syndrome: a case series. *Pediatrics.* 2007; 119(4). Available at: www.pediatrics.org/cgi/content/full/119/4/e1002
21. Ruggiero A, Buonuomo PS, Maurizi P, Cefalo MP, Corsello M, Riccardi R. Stevens-Johnson syndrome in children receiving phenobarbital therapy and cranial radiotherapy. *J Neurooncol.* 2007;85(2):213–215
22. Maiche A, Teerenhovi L. Stevens-Johnson syndrome in patients receiving radiation therapy. *Lancet.* 1985;2(8445):45
23. Burge SM, Dawber RP. Stevens-Johnson syndrome and toxic epidermal necrolysis in a patient with systemic lupus erythematosus. *J Am Acad Dermatol.* 1985;13(4):665–666
24. Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of drug-induced skin diseases. *J Drugs Dermatol.* 2003;2(3):278–299
25. Roujeau JC, Chosidow O, Saiag P, Guillaume JC. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol.* 1990; 23(6 pt 1):1039–1058
26. Hawk RJ, Storer JS, Daum RS. Toxic epidermal necrolysis in a 6-week-old infant. *Pediatr Dermatol.* 1985;2(3):197–200
27. Teillac D, Marsol P, Richard P, et al. Toxic epidermal necrolysis in children (Lyell's syndrome): apropos of 18 cases [in French]. *Arch Fr Pediatr.* 1987;44(8):583–587
28. Mockenhaupt M, Viboud C, Dunant A, et al. 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
29. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. *J Rheumatol.* 2003;30(10):2234–2240
30. Cochran WG. The comparison of percentages in matched samples. *Biometrika.* 1950;37(3–4):256–266
31. Schlesselman JJ. *Case Control Studies: Design, Conduct, Analysis*. New York, NY: Oxford University Press; 1982
32. Hirji K, Tsiatis AA, Mehta CR. Median unbiased estimation for binary data. *Am Stat.* 1989;43(1):7–11
33. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. *Am J Med.* 1980;68(2):255–258
34. Hansen RC. Staphylococcal scalded skin syndrome, toxic shock syndrome, and kawasaki disease. *Pediatr Clin North Am.* 1983; 30(3):533–544
35. Snyder RA, Elias PM. Toxic epidermal necrolysis and staphylococcal scaled syndrome. *Dermatol Clin.* 1983;1:235–248
36. Maison P, Guillemot D, Vauzelle-Kervroedan F, et al. Trends in aspirin, paracetamol and non-steroidal anti-inflammatory drug use in children between 1981 and 1992 in France. *Eur J Clin Pharmacol.* 1998;54(8):659–664
37. Sanz E, Hernandez MA, Ratchina S, et al. Drug utilisation in outpatient children. A comparison among Tenerife, Valencia, and Barcelona (Spain), Toulouse (France), Sofia (Bulgaria), Bratislava (Slovakia) and Smolensk (Russia). *Eur J Clin Pharmacol.* 2004;60(2):127–134
38. Lyell A. A review of toxic epidermal necrolysis in Britain. *Br J Dermatol.* 1967;79(12):662–671
39. Bastuji-Garin S, Zahedi M, Guillaume JC, Roujeau JC. Toxic epidermal necrolysis (Lyell syndrome) in 77 elderly patients. *Age Ageing.* 1993;22(6):450–456
40. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. Scorten: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* 2000;115(2):149–153
41. Golden HE. Stevens-Johnson syndrome associated with herpes simplex virus. *Arch Intern Med.* 1993;153(11):1396
42. Wolkenstein P, Carriere V, Charue D, et al. A slow acetylator genotype is a risk factor for sulphonamide-induced toxic epidermal necrolysis and Stevens-Johnson syndrome. *Pharmacogenetics.* 1995;5(4):255–258
43. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf.* 2002; 25(13):965–972
44. Guberman AH, Besag FM, Brodie MJ, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia.* 1999;40(7):985–991
45. Lin MS, Dai YS, Pwu RF, Chen YH, Chang NC. Risk estimates for drugs suspected of being associated with Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control study. *Intern Med J.* 2005;35(3):188–190
46. Sheridan RL, Schulz JT, Ryan CM, et al. Long-term consequences of toxic epidermal necrolysis in children. *Pediatrics.* 2002;109(1):74–78
47. Lam NS, Yang YH, Wang LC, Lin YT, Chiang BL. Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children. *J Microbiol Immunol Infect.* 2004;37(6):366–370
48. Neuman M, Nicar M. Apoptosis in ibuprofen-induced Stevens-Johnson syndrome. *Transl Res.* 2007;149(5):254–259
49. Dore J, Salisbury RE. Morbidity and mortality of mucocutaneous diseases in the pediatric population at a tertiary care center. *J Burn Care Res.* 2007;28(6):865–870
50. Kaufman D, Kelly JP, Levy M, Shapiro S. *The Drug Etiology of Agranulocytosis and Aplastic Anemia: The International Agranulocytosis and Aplastic Anemia Study*. New York, NY: Oxford University Press; 1991
51. Bygum A, Gregersen JW, Buus SK. Acetaminophen-induced toxic epidermal necrolysis in a child. *Pediatr Dermatol.* 2004; 21(3):236–238
52. Halevi A, Ben-Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother.* 2000;34(1):32–34
53. Ball R, Ball LK, Wise RP, Braun MM, Beeler JA, Salive ME. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J.* 2001;20(2):219–223
54. Dobrosavljevic D, Milinkovic MV, Nikolic MM. Toxic epidermal necrolysis following morbilli-parotitis-rubella vaccination. *J Eur Acad Dermatol Venereol.* 1999;13(1):59–61
55. Shoss RG, Rayhanzadeh S. Toxic epidermal necrolysis following measles vaccination. *Arch Dermatol.* 1974;110(5):766–770
56. Lonjou C, Borot N, Sekula P, et al. 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
57. Lonjou C, Thomas L, Borot N, et al. A marker for Stevens-Johnson syndrome: ethnicity matters. *Pharmacogenomics J.* 2006;6(4):265–268
58. Hunkeler EM, Fireman B, Lee J, et al. Trends in use of antidepressants, lithium, and anticonvulsants in Kaiser Permanente-insured youths, 1994–2003. *J Child Adolesc Psychopharmacol.* 2005;15(1):26–37
59. Slone Epidemiology Center. Patterns of medication use in the United States: 2006. Available at: www.Bu.Edu/slone/slonesurvey/annualrpt/slonesurveywebreport2006.pdf. Accessed December 15, 2008

Medications as Risk Factors of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children: A Pooled Analysis

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