International Experience:
United States (and Canada)

J. Steven Leeder, PharmD, PhD
Division of Clinical Pharmacology, Toxicology
and Therapeutic Innovation
National Collaborative SCAR Initiatives

- No targeted, sustained (funded) US national initiatives analogous to those in other countries
- Institute for Safe Medication Practices (ISMP) periodically reviews severe ADRs reported to the FDA Adverse Event Reporting System
- Canadian Pharmacogenomics Network for Drug Safety includes SJS/TEN focus (pediatric; adults added later)
- NIH-funded organ-specific ADR networks (DILIN) subject to ongoing support for infrastructure
- Recognized need for infrastructure with perceived value to the hospital/institution for sustainability
ADVERSE DRUG EVENTS IN CHILDREN UNDER AGE 18

Table 4. Drugs with reports of severe skin reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>SJS/TEN*</th>
<th>All Cases**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>66</td>
<td>335</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>32</td>
<td>242</td>
</tr>
<tr>
<td>Sulfamethoxazole; trimethoprim</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>5</td>
<td>41</td>
</tr>
</tbody>
</table>

* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).
** Primary analysis group.

This is the second instance in which QuarterWatch has observed a disproportionate signal for lamotrigine and severe skin reactions. In the 2011 annual survey of patients of all ages, lamotrigine also led all other drugs in reports of severe cutaneous events. The FDA’s required Boxed Warning notes that the rates of SJS/TEN appear to be higher in children than in adults, and less severe rashes may appear in 10% of treated patients. [17] Its first line use as adjunctive therapy for seizures should be reevaluated, and its approved use for maintenance in bipolar disorder reconsidered.

Reports of SJS/TEN associated with ibuprofen (MOTRIN, ADVIL) were instrumental in pushing the reported serious adverse event totals for ibuprofen (n=242) higher than other mostly over-the-counter (OTC) pain medications used in children, acetaminophen (TYLENOL, n = 137) and naproxen (ALEVE, n = 61). Also notable for ibuprofen were 34 cases of renal failure and impairment. Acetaminophen, on the other hand, had 32 reports of liver disorders, including 10 cases of liver failure, consistent with its known risks of liver damage.
Canadian Pharmacogenomics Network for Drug Safety: Bruce Carleton, PI

To Date:
8,000 ADR case reports
>70,000 Controls
### Canadian Pharmacogenomics Network for Drug Safety SJS/TEN

<table>
<thead>
<tr>
<th></th>
<th>SJS/TEN</th>
<th>HSS</th>
<th>Total Body Rash (to be defined)</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>10</td>
<td>13</td>
<td>7</td>
<td>143</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>2</td>
<td>9</td>
<td>5</td>
<td>120</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>121</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>16</strong></td>
<td><strong>28</strong></td>
<td><strong>22</strong></td>
<td><strong>384</strong></td>
</tr>
</tbody>
</table>

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**HLA-A*31:01 and HLA-B*15:02 as Genetic Markers for Carbamazepine Hypersensitivity in Children**

U Amstutz¹ ³, CJD Ross¹ ³ ⁴, LI Castro-Pastrana⁵, MJ Rieder⁶ ⁸, NH Shear⁹, MR Hayden⁴, BC Carleton¹ ³ and the CPNDS Consortium

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**Epilepsia 2014; 55:496–506**

**Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions**

Ursula Amstutz, Neil H. Shear, Michael J. Rieder, Soomi Hwang, Vincent Fung, Mary B. Connolly, Shinya Ito, Bruce C. Carleton, and the CPNDS clinical recommendation group.
Children’s Mercy Kansas City Drug Safety Service

- ADR reporting required for JCAHO accreditation
- Reduce/eliminate harm within the hospital system
- Lead to development of pre-emptive interventions
- Feed research program: Pharmacogenomics of Pediatric Drug Safety (PPeDS)
- Led by a clinical pharmacology-trained pediatric Infectious Disease specialist
- Full-time dedicated clinical pharmacist
  - 803 unique ADR in 617 patients by >24 health care practitioners in 2014
### Documentation of High Quality Phenotype Data in EHR

**General Information**

**Suspected drug (original drug in profile, or new):**

- [ ] Acetaminophen
- [ ] Albuterol
- [ ] Amoxicillin
- [ ] Amoxicillin/Cloxacillinate
- [ ] Araprazo
- [ ] Aspirin
- [ ] Azithromycin
- [ ] Cefalexin
- [ ] Cefazolin
- [ ] Cefdinir
- [ ] Cefprozil
- [ ] Ceftiraxone
- [ ] Cefobid
- [ ] Cefpodoxime
- [ ] Chloramphenicol
- [ ] Clindamycin
- [ ] Clindamycine
- [ ] Comsine
- [ ] Dipeptide Hydramine
- [ ] Eslinhydrine
- [ ] Flexomet
- [ ] Ibuprofen
- [ ] Lomotilazine
- [ ] Lorazepam
- [ ] Metformin
- [ ] Metoclopramide
- [ ] Metronidazole
- [ ] Micronaire
- [ ] Montelukast
- [ ] Morphine
- [ ] Nystatine
- [ ] Ondansetron
- [ ] Osteoaxine
- [ ] Oxcarbazepine
- [ ] Oxycodone
- [ ] Oxycodone/Acetaminophen
- [ ] Pegaspargase
- [ ] Penicillin
- [ ] Pantobarbital
- [ ] Phenobarbital
- [ ] Phenytoin
- [ ] Prochlorperazine
- [ ] Promethazine
- [ ] Propofol
- [ ] Propitamub
- [ ] Sulfa drug
- [ ] Sulfamethoxazole/Trimethoprim
- [ ] Vepac Acid
- [ ] Vancomycin
- [ ] Other

**Initial type:**

- [ ] Allergy/Hypersensitivity
- [ ] Side effect
- [ ] Unknown
- [ ] Religious/Preference
- [ ] Precaution
- [ ] Newly reported
- [ ] Not documented

**Initial severity:**

- [ ] Unknown
- [ ] Life threatening: Severe
- [ ] Delay discharge: Severe
- [ ] Permanent disability: Severe
- [ ] Hospital admission: Severe
- [ ] Stop substance: Moderate
- [ ] Requires treatment: Moderate
- [ ] Change substance: Moderate
- [ ] Continue substance: Mild
- [ ] Newly reported
- [ ] Not documented

**Final type:**

- [ ] Allergy/Hypersensitivity
- [ ] Side effect
- [ ] Unknown
- [ ] Religious/Preference
- [ ] Precaution
- [ ] Drug removed from profile

**Final severity:**

- [ ] Unknown
- [ ] Life threatening: Severe
- [ ] Delay discharge: Severe
- [ ] Permanent disability: Severe
- [ ] Hospital admission: Severe
- [ ] Stop substance: Moderate
- [ ] Requires treatment: Moderate
- [ ] Change substance: Moderate
- [ ] Continue substance: Mild
- [ ] Drug removed from profile

- [ ] Changed substance: Moderate
- [ ] Continue substance: Mild
- [ ] Newly reported
- [ ] Not documented

If final type is religious/preference, precaution, or if a drug is removed from the profile, or the severity is MILD, there is no need to complete the remainder of this form.

**Did this reaction occur in the past 30 days?**

- [ ] Yes
- [ ] No
Documentation of High Quality Phenotype Data in EHR

Cutaneous Symptoms

Check all that apply

**Cutaneous description:**
- Angioedema
- Blisters
- Bruising
- Fixed
- Hives/wheals
- Irregular shape
- Itching
- Lip swelling
- Maculopapular
- Migratory
- Pain
- Peeling
- Pustules
- Rash
- Red
- Red Man Syndrome
- Round
- Scaling
- Serum sickness
- Spreading
- Swelling
- Target lesion
- Ulcerations
- Other:

**Location:**
- Head
- Face
- Eyes
- Extremity, left lower
- Extremity, right lower
- Mouth
- Neck
- Torso
- Genitals
- Buttocks
- Extremity, left upper
- Extremity, right upper
Documentation of High Quality Phenotype Data in EHR

Medications

Within 2 weeks prior to the adverse reaction, was the patient receiving any of the following:

1. Any new over the counter substances?  
   - Yes  
   - No  
   - Unknown

2. Any natural remedies?  
   - Yes  
   - No  
   - Unknown

3. Any new foods?  
   - Yes  
   - No  
   - Unknown

4. Any additional new medications?  
   - Yes  
   - No  
   - Unknown

If able to name the medications, list all new medications that the patient may have received:
Documentation of High Quality Phenotype Data in EHR
Documented Data in EHR

If completing more than one questionnaire for this patient, please answer this question only once.

By performing this interview, did you discover any undocumented additional adverse reactions?  

☐ Yes  ☐ No
#### Documentation of High Quality Phenotype Data in EHR

<table>
<thead>
<tr>
<th>D.</th>
<th>Substance</th>
<th>Category</th>
<th>Reactions</th>
<th>Severity</th>
<th>Type</th>
<th>C.</th>
<th>Est. Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>amoxicillin</strong></td>
<td>Drug</td>
<td>Diarrhea</td>
<td>Continue Su...</td>
<td>Side Effect</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type**: Side Effect

Undesirable but expected response based on known properties (nausea, fatigue)

**Substance**

`amoxicillin`

**Reaction(s):** Diarrhea

**Severity**

`Continue Substance` | `Family`

**Info source**

**Comments**

11/05/2014 13:37 CST - IPT DSS: patient had diarrhea but completed course of therapy.
EHR Information Readily Accessible for Research Purposes: Cerner Discover e
EHR Information Readily Accessible for Research Purposes: Cerner Discover e

<table>
<thead>
<tr>
<th>Skin Reaction</th>
<th>Clinical Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generalized maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Facial Swelling/Angioedema</td>
</tr>
<tr>
<td></td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td>Stevens Johnson Syndrome</td>
</tr>
<tr>
<td></td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date of skin reaction start:</th>
<th>dd-MM-YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 SEP 2010</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dermatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated by a dermatologist</td>
</tr>
<tr>
<td>If yes, was drug reaction suspected</td>
</tr>
<tr>
<td>Was a photograph taken?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy conducted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patch Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch test conducted</td>
</tr>
</tbody>
</table>
Developing ADR Infrastructure …

- Currently no national initiative focused on SCAR in US
- Convince healthcare systems that ADR surveillance programs have value to the institution
- Standardize nomenclature and data collection processes
- Provides opportunity for research funds to be applied to the science, not infrastructure

Acknowledgements:

Bruce Carleton, PharmD (CPNDS)
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