Potential Conflicts

- Consultant to pharmaceutical industry related to drug hypersensitivity reactions.
- All therapeutic comments are off-label.
SCAR Clinical Syndromes
Severe Cutaneous Adverse Reactions

- DRESS
  - Drug Reaction with Eosinophilia and Systemic Symptoms

- AG EP
  - Acute Generalized Exanthematous Pustulosis

- SJS/TEN = TENS
  - Stevens Johnson Syndrome/Toxic Epidermal Necrolysis
A NEW INFECTION ASSOCIATED WITH STERILITIS AND MALARIA
REPORT OF TWO CASES IN CHILDREN *

A. M. STEVENS and C. JOHNSON, M.D.

Stevens and Johnson. Am J Dis Child, 1922

TOXIC DERMATODERROLYSIS:
AN ERUPTION SIMBLING DERMOLYSIS OF THE SKIN.

ALAN LYELL.
Assistant Physician to the Skin Department, Royal Infirmary, Aberdeen.

Alan Lyell. British Journal of Dermatology, 1956
EM - EMM - SJS / TEN - "TEN": 4+ Diseases

Erythema Multiforme

EM Major (& variant)

SJS to TEN

Other TEN-like
A Story

"Patient with SJS in the Emergency"
- Caused by Amoxil – taken for a sore throat

History reveals
- 39 year old woman
- Carbamazepine (Tegretol) for 3 weeks

Does she have SJS? Yes she does!

What caused it? Carbamazepine?
A 39 y/o Indian female with SJS induced by carbamazepine. Feb 2014
“PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE.”
A 39 y/o Indian female with SJS induced by carbamazepine. Feb 2014
A 39 y/o Indian female with SJS Induced by carbamazepine. Feb 2014

The importance of positive HLA test:
• Support diagnosis
• Confirm the suspected offending drug
• Valuable for familial genetic consultation
Pathophysiology of Immune-Mediated Drug Reactions

DRUG

Non-Reactive

Parent drug or Reactive Metabolites

P450s Oxidases
PG synthase

Acetylation
Glutathione
Epoxide hydrolases

Immune Response

Cellular
CD4→ rash
CD8→ blisters
Cytokines
IL-8→ pustules
Drug fits in HLA groove - SJS/TEN
J.T. Reason: Swiss Cheese Model
Model of a Drug Reaction
Putative Risk Factors

- Structure
- Metabolism (CYP)
- Immunogenic (HLA)
- Immune Toxic Response

DRUG

SJS/TEN
Her Brother

- He has been taking carbamazepine for 3 years
- He has had no problems with it.
- We tested him for HLA-B*15:02
- Guess what?
Her Brother

- He has been taking carbamazepine for 3 years
- He has had no problems with it.
- We tested him for HLA-B*15:02
- Guess what?
- He too was HLA-B*15:02 Positive
Epidemiology

- Dodiuk-Gad, Laws, Shear
- Seminars in Cutaneous Medicine and Surgery
- 2014
- “SJS/TEN is rare (1 per million population)”
### TABLE I. Pharmacogenomics of HLA-associated drug hypersensitivity and related drug-induced syndromes

<table>
<thead>
<tr>
<th>Syndrome and drug</th>
<th>HLA Alleles</th>
<th>Populations</th>
<th>Year first described</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS-TEN (SCAR)</td>
<td>B*58:01</td>
<td>Han Chinese, Thai, European, Italian, Korean, Portuguese</td>
<td>2005</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>B*15:02</td>
<td>Han Chinese, Thai, Malaysian, Indian</td>
<td>2004</td>
</tr>
<tr>
<td>CBZ</td>
<td>B*15:11</td>
<td>Korean, Japanese</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>B<em>15:18, B</em>59:01, and Cw*07:04</td>
<td>Japanese</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>A*31:01</td>
<td>Japanese, northern European, Korean</td>
<td>2011</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>B*15:02</td>
<td>Han Chinese</td>
<td>2010</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>B*15:02, positive</td>
<td>Han Chinese</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>B*15:02, no association found</td>
<td>Han Chinese</td>
<td>2010</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>C*04:01</td>
<td>Malawian</td>
<td>2013</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>B<em>15:02; B</em>13:01, Cw<em>08:01, and DRB1</em>16:02</td>
<td>Han Chinese</td>
<td>2007</td>
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<tr>
<td>Phenobarbital</td>
<td>B*51:01</td>
<td>Japanese</td>
<td>2013</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>B*38</td>
<td>European</td>
<td>2008</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>B<em>59, B</em>59:01, Cw<em>01:02 alleles, and B</em>59:01-Cw<em>01:02-A</em>24:02 haplotype</td>
<td>Japanese, Korean, and Japanese</td>
<td>1997, 2011</td>
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<tr>
<td>Sulfonamides</td>
<td>A<em>29, B</em>12, and DR*7</td>
<td>European</td>
<td>1987</td>
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<tr>
<td>Oxicam</td>
<td>B*73</td>
<td>European</td>
<td>2008</td>
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<tr>
<td></td>
<td>A<em>2, B</em>12</td>
<td>European</td>
<td>1987</td>
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<tr>
<td>Strontium ranelate</td>
<td>Under investigation in postmarketing period</td>
<td>Japanese</td>
<td>2009</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>A*02:07</td>
<td>Japanese</td>
<td>2013</td>
</tr>
</tbody>
</table>

Diagnosis of TENS
Shear’s Diagnostic Triangle

Remember: Appearance, Systemic, Histology
### Clinical Classification of Cases of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Erythema Multiforme

Sylvie Bastuji-Garin, MD; Berthold Rzany, MD; Robert S. Stern, MD; Neil H. Shear, MD, FRCPC; Luigi Naldi, MD; Jean-Claude Roujeau, MD

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<table>
<thead>
<tr>
<th>Classification</th>
<th>Bullous EM</th>
<th>SJS</th>
<th>Overlap SJS-TEN</th>
<th>With Spots</th>
<th>Without Spots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detachment</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>10%-30%</td>
<td>&gt;30%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Typical targets</td>
<td>Yes</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Atypical targets</td>
<td>Raised</td>
<td>Flat</td>
<td>Flat</td>
<td>Flat</td>
<td>Flat</td>
</tr>
<tr>
<td>Spots</td>
<td>.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>.</td>
</tr>
</tbody>
</table>

*EM indicates erythema multiforme; SJS, Stevens-Johnson syndrome; and TEN, toxic epidermal necrolysis.
Causality Assessment (via XKCD)

I used to think correlation implied causation.

Then I took a statistics class. Now I don't.

Sounds like the class helped.

Well, maybe.
Treatment

- Hugely variable
- Burn Unit w/ support
- Survey of Canadian & USA units
  - Corticosteroids
  - Cyclosporine
  - Anti-TNF therapy
Treatment part 2

- Eyes
  - Amniotic membrane
- Genitals
  - Examination and daily care
- Post-traumatic syndromes in survivors
We can do better

- Patients that should be screened are not being screened
- Better communication must follow the advance in science
- Care guidelines during and post TEN are needed
Partnering for Success

Pure Public

NIH $ Research Applications

FDA $ UNI.

Pure Private

IND. $ Science Safety Efficacy