Stevens-Johnson’s Syndrome / Toxic Epidermal Necrolysis: An update
Presentation

• Prodrome of fever, flu-like symptoms x 1-3 days
• Photophobia, conjunctival itching, dysphagia, skin tenderness
• Typically two or more mucous membranes
• Dusky atypical target lesions
• Denuded skin / epidermal detachment
  • SJS \(\rightarrow\) < 10% BSA
  • TEN \(\rightarrow\) > 30% BSA
Overall incidence of SJS/TEN 2-13 per million per year

Risk factors include immune dysregulation:
  HIV infection
    • 100-fold increase
  Autoimmune disease
    • 50-fold increase in SLE patients
  Active malignancy (particularly hematologic)
    • 30-to-60-fold increase

Etiology and Pathogenesis

Genetic factors
• HLA-B*15:02 (carbamazepine; OR 79.84, Asian)*
• HLA-A*31:01 (carbamazepine; all ethnic groups)*
• HLA-B*58:01 (allopurinol)

*Pre-screening of HLA type recommended prior to starting carbamazepine

Polymorphisms in Cyt P450 and other factors associated with decreased medication clearance

Etiology and Pathogenesis

Drug-specific CD8 T-cells and natural killer (NK) cells are the major inducers of keratinocyte apoptosis.

Drugs stimulate the immune system by binding to MHC-I and T-cell receptors, resulting in clonal expansion of cytotoxic T-cells.

These cells kill keratinocytes directly and indirectly via release of cytotoxic mediators:

- Soluble Fas ligand
- Perforin / granzyme
- Tumor necrosis factor
- Granulysin

Etiology and Pathogenesis

Granulysin
• Produced and secreted by CD8 and NK cells
• Highly expressed in SJS/TEN
• Levels in blister fluid correlate with disease severity
• Reproducible cytotoxic effect on keratinocytes
• Thought responsible for apoptosis in SJS/TEN

*Being studied as a diagnostic marker and treatment target for SJS/TEN

Medications are the most common cause of SJS/TEN

- Typically within 1-3 weeks (avg = 14 days)
- Unlikely after first 8 weeks of treatment

  - Allopurinol*
  - Anticonvulsants
  - Sulfa antibiotics
  - Nevirapine
  - Oxicam NSAIDs

*Most common in EuroSCAR (17.4%)
Etiology and Pathogenesis

US Derm Hospitalist Study (377 adult patients)

- Most common cause of SJS/TEN, in **89.7%**, was medication reaction, including common culprit drugs:

<table>
<thead>
<tr>
<th>Class of medications</th>
<th>N=338</th>
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<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
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<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>89 (26.3%)</td>
</tr>
<tr>
<td>β-lactam antibiotics</td>
<td>42 (12.4%)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>12 (3.6%)</td>
</tr>
<tr>
<td><strong>Antiepileptic/Mood stabilizers</strong></td>
<td>83 (23.7%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>32 (9.5%)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>30 (8.9%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>7 (2.1%)</td>
</tr>
<tr>
<td><strong>Allopurinol</strong></td>
<td>29 (8.6%)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>18 (5.3%)</td>
</tr>
</tbody>
</table>

Micheletti et al, Society of Dermatology Hospitalists (submitted)
Etiology and Pathogenesis

Derm Hospitalist Study:

• All patients with lamotrigine-induced SJS/TEN (n = 29) survived to discharge

• Exposure to phenytoin increased the risk of death (RR 3.82 (0.99-14.69))

• High mortality among those receiving pip/tazo (Zosyn) (73%) → drug or underlying disease state?

→ For the most part, the specific drug trigger does not contribute significantly to mortality risk in SJS/TEN
Etiology and Pathogenesis

Mycoplasma
• SJS trigger common in children
• Significant mucosal but minimal skin involvement
• Tend to have better outcomes

• Now recognized as a distinct entity, termed **Mycoplasma-induced rash and mucositis (MIRM)**

→ Derm Hospitalist Study: 2% of cases attributed to Mycoplasma; mortality among infectious cases overall 8%

When SJS/TEN is clinically obvious, institute therapy even if histologic confirmation is pending

• However, I do always perform a biopsy for completeness
• In one study, 1/3 of those biopsied received an alternate diagnosis based on histology

Burns. 2016 Feb 1. [Epub ahead of print].
Transferred from an OSH, where he was diagnosed with SJS and treated in a burn unit...

Ultimate diagnosis = severe cutaneous lupus
Transferred from an OSH to our ICU for treatment of SJS/TEN; received IVIG...

Ultimate diagnosis = epidermolysis bullosa acquisita vs anti-epiligrin cicatricial pemphigoid
Patient with SLE on chronic immunosuppression

Acute skin tenderness and widespread denuded skin concerning for SJS/TEN...

Diagnosed with Staph scalded skin syndrome
Patient with acute leukemia 2-3 weeks s/p stem cell transplant

Developed acute dusky erythema, erosions, mucositis, conjunctivitis

SJS/TEN vs grade IV acute GVHD...
SJS Mimickers

Paraneoplastic pemphigus
• When the diagnosis is in doubt, biopsy may be required to guide management

• Histologic appearance of SJS:
  • Keratinocyte necrosis ranging from partial to full thickness (established lesions)
  • Scant perivascular lymphohistiocytic inflammation
• In our hospital, preliminary results of standard biopsy are available by the end of the following business day

• Alternative options:
  • Frozen section biopsy
  • Tzanck smear
  • “Jelly roll”

*Frozen section biopsy:  
Results typically available within 20-30 minutes
→Take the time to discuss with pathology and determine the mechanism for this in your hospital
“Jelly roll”

The blister roof can be submitted for frozen section

Reveals full-thickness epidermal necrosis
Published overall mortality rate for SJS/TEN is 20-25%

RegiSCAR cohort 6-week mortality:
• SJS = 12%
• SJS/TEN = 29%
• TEN = 46%

How do we give our patients the best chance for survival?

What management is supported by the available evidence?
Stop the culprit drug

• Earlier withdrawal = better prognosis
• OR of death = 0.69 for each day sooner
• OR of death = 4.9 for drugs with long half lives

→ Identification of the causative agent is a non-trivial exercise

• Causality assessment tools (e.g., ALDEN) may help but have problems with reliability and agreement
• No substitute for systematic approach by an expert (dermatologist)

Data-Driven Management

Transfer the patient to an ICU or burn unit

• In one study, overall mortality = 32%
• Mortality of those transferred after > 1 week = 51%

*Patients with “mild” SJS or SCORTEN of 0 or 1 should still be cared for in an ICU

• “Mild” SJS is a designation best made in retrospect; patients may progress rapidly from mild presentations
• Published guidelines suggest initial management of SJS/TEN patients in specialized centers due to risk of rapid progression regardless of initial % BSA involved

J Burn Care Rehabil. 2002;23(2):87.
The level of care is a surrogate for supportive care:

- Fluids
- Electrolytes
- Temperature
- Nutrition
- Pain control
- Airway maintenance
- Wound care
- Infection surveillance
- Ophthalmology
- Gynecology
- Urology
- Hematology

- Role of dermatology in diagnosis, identification of culprit drug
- Role of dermatology as team "quarterback"
- Critical role in patient advocacy

- Cleaning, lubrication, steroid drops
- Amniotic membranes, scleral spacers
- 2/3-3/4 Parkland formula
- Enteral, not parenteral

- Bacteremia in 27%: Staph, Pseudomonas, Enterobacteriaceae
- Topical steroids, vaginal dilator, Vaseline gauze
- Vaseline, non-stick gauze
- Clean / sterile technique
- Close observation; may require prolonged intubation
- May develop profound neutropenia
- Urethritis, urinary retention
Despite this, there is wide variability in supportive and systemic care:

- Survey of 102 burn centers showed variability in consultation of other services:
  - Ophthalmology (66%)
  - Dermatology (47%)
  - Gynecology (13%)

ICU versus Burn Center:
• Burn centers are highly skilled in wound care and fluid management, but do they have a dermatologist?
• Burn center may be less familiar with management of complex medical comorbidities
• Patients who are post-transplant, have autoimmune disease, etc. require specialized knowledge and care
• Dermatology hospitalists may be best positioned to provide the differential diagnosis, wound care, and advocacy patients need
• Both are better than non-specialized ward, but supportive care should be more homogeneous and studied prospectively

Besides supportive care, published literature has not consistently shown benefit from the use of any particular systemic therapy for SJS/TEN.

Case series and retrospective cohorts are limited by confounding factors, low numbers, and inherent biases that make drawing conclusions from existing data difficult.
Systemic Corticosteroids:
- Early observational studies indicated a higher complication and mortality rate
- EuroSCAR cohort suggested possible benefit to early steroids, though not statistically significant
- RegiSCAR cohort and systematic review: no mortality advantage over supportive care alone

Systemic Corticosteroids:

- More recently, a meta-analysis of 96 studies in JAMA Dermatology, suggested there is a survival benefit.

- While these results had limitations and were only marginally statistically significant, corticosteroids were felt to be promising.

- On balance, despite concern for increased infection, early use of systemic steroids may be beneficial.

Intravenous Immunoglobulin:

- Data are limited and conflicting

- Thought to inhibit Fas—FasL binding, but this is no longer considered the primary mediator of SJS

Intravenous Immunoglobulin:

• Case series and a systematic review suggested “high-dose,” early IVIG (>2g/kg total) improves survival

• However, a number of reviews, including the recent meta analysis from 2017, have shown no mortality benefit
Intravenous Immunoglobulin:

- For these reasons, IVIG has fallen out of favor in Europe

- However, it continues to be an agent of choice for SJS/TEN among US dermatology hospitalists

A survey of 131 US providers (academic dermatologists and burn centers) reported that:

• Majority do not use systemic steroids
• More likely to use IVIG if more severe disease → majority use IVIG for SJS/TEN overlap and TEN
• Those who see SJS/TEN more frequently are more likely to use IVIG regardless of severity

In our cohort managed by inpatient dermatologists, IVIG was used extensively, alone or in combination (55.6% of patients)

Patients receiving IVIG had more severe disease at presentation:
• Higher median BSA involvement (30% vs 12%, p-value<0.01)
• Higher rate of TEN (28.0% vs 18.7%, p-value=0.01)
• Higher rates of severe ocular, oral, and genitourinary involvement (all p-values <0.05) compared to other treatment groups
Intravenous Immunoglobulin:

• In summary, no high quality evidence supports the use of IVIG in SJS/TEN

• However, those who receive it appear to be sicker to start with, and the effects of this and other confounders may not be completely accounted for by SCORTEN-predicted mortality

→ Early in the disease course, a dose of 1g/kg/day x 3-4 days IVIG can be considered
  • Potential side effects include clot / hyperviscosity
  • Side effect profile more favorable than high-dose steroids

Cyclosporine:

- Anti-apoptotic, inhibits T-cells, including CD8 T-cells
- Dose 3 to 5 mg/kg/day, tapered over one month
- Supported mostly by small, retrospective, and uncontrolled case series

Cyclosporine:
  • Retrospective review of 64 patients
  • Outcome of 15 who received cyclosporine (SMR = 0.43) better than 50 who received IVIG (SMR = 1.43)
    • IVIG dose and timing varied widely
  • Retrospective review of 44 patients
  • Among 24 who received cyclosporine, SMR = 0.42

  • Open, Phase II trial of 29 patients:
    • SCORTEN predicted mortality 2.75; actual = 0

Cyclosporine:

• More recently, two 2017 studies suggested a mortality benefit of cyclosporine via meta-analysis and retrospective case series (49 patients)

• Increasing favor in Europe, but the actual number of treated patients remains small, and the drug has important side effects (renal, immunosuppression)

Cyclosporine:

- **Letter-to-the-editor:**
  - Existing studies either exclude patients with renal insufficiency and other known SJS/TEN mortality risk factors altogether or do not report them
  - In our cohort, renal failure was the greatest mortality RF

- **Recent retrospective cohort study of 174 patients:**
  - No significant benefit from cyclosporine in 95 patients (versus 79 supportive care only)
  - Acute renal failure more common in treatment group
Latest Evidence for Pharmacotherapies

Cyclosporine:

• In summary, cyclosporine is certainly deserving of further study, but there are reasons to temper enthusiasm

• Early use of cyclosporine in young, otherwise healthy patients at a dose of 3-5mg/kg/day is a reasonable treatment option, but we do not have enough data to recommend this in sicker patients

Tumor Necrosis Factor (TNF) inhibitors:

Thalidomide:
• Only double-blind, randomized, placebo-controlled TEN study
• Trial stopped early due to excess mortality (10/12 died, vs 3/10 in placebo)

Suggested reason for caution with respect to TNF inhibitors for SJS/TEN

Tumor Necrosis Factor (TNF) inhibitors:

Etanercept:
• Case series in 8/2014 JAAD
• One 50mg injection
• 10 patients with good outcomes; no controls

Infliximab:
• One 5mg/kg infusion
• Case reports only

Tumor Necrosis Factor (TNF) inhibitors:

96-patient randomized trial of etanercept versus corticosteroids

• SMR = 0.47 among those receiving etanercept (0.80 with corticosteroids)
• Decreased time to skin healing and lower rates of complications compared to corticosteroid group

J Clin Invest. 2018 Feb 5. [Epub ahead of print]
Tumor Necrosis Factor (TNF) inhibitors:

- Recent experience with etanercept is promising
- 25mg or 50mg etanercept twice weekly until skin lesions healed

J Clin Invest. 2018 Feb 5. [Epub ahead of print]
US Derm Hospitalist Study (377 adult patients)

- Overall and subgroup mortality less than predicted by SCORTEN
- Predicted mortality for the overall cohort was **21.1%**, vs **14.7%** actual
- Adjusting for SCORTEN, mortality was lower in the **steroid + IVIG** group compared to IVIG or steroids alone and to supportive care only
  - *Bias toward using IVIG to treat patients with more severe SJS/TEN
  - *Only 5 patients treated with cyclosporine or etanercept

<table>
<thead>
<tr>
<th></th>
<th>Overall N=368</th>
<th>IVIG only N=92</th>
<th>Steroid only N=116</th>
<th>IVIG + Steroid N=54</th>
<th>Supportive care N=117</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td></td>
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<tr>
<td>SCORTEN predicted mortality, N (%)</td>
<td><strong>77.7 (21.1)</strong></td>
<td><strong>21.6 (23.5)</strong></td>
<td><strong>20.8 (17.8)</strong></td>
<td><strong>11.6 (21.2)</strong></td>
<td><strong>22.7 (19.4)</strong></td>
</tr>
<tr>
<td>Observed mortality</td>
<td><strong>54 (14.7)</strong></td>
<td><strong>17 (18.5)</strong></td>
<td><strong>15 (12.9)</strong></td>
<td><strong>6 (10.7)</strong></td>
<td><strong>16 (13.7)</strong></td>
</tr>
<tr>
<td>SMR (95%CI)</td>
<td>0.70 (0.58, 0.79)</td>
<td>0.79 (0.55, 0.92)</td>
<td>0.72 (0.48, 0.89)</td>
<td><strong>0.52 (0.21, 0.79)</strong></td>
<td>0.70 (0.47, 0.87)</td>
</tr>
</tbody>
</table>

Micheletti et al, Society of Dermatology Hospitalists (submitted)
One of the largest existing SJS/TEN cohorts (largest in N America)

Overall survival rate better than reported in the literature and better than predicted by SCORTEN:

• Published mortality rate 20-25% $\rightarrow$ in our cohort, 14.7%
• Large systematic review reported SMR 0.82-0.92 $\rightarrow$ in our cohort, the SMR was 0.70 (0.58, 0.79)

Micheletti et al, Society of Dermatology Hospitalists (submitted).
• Unclear if improved survival reflects excellent supportive care in tertiary centers, the presence of a consulting dermatologist, or inadequacy of SCORTEN as a predictive tool

• The optimal pharmacologic regimen remains uncertain
  • Some small published series support steroids + IVIG
  • Cyclosporine, etanercept, corticosteroids all reasonable
  • Need better ways to account and adjust for prescriber practices, particularly with respect to IVIG severity bias

• Additional analysis of the cohort is ongoing

Micheletti et al, Society of Dermatology Hospitalists (submitted).
At our institution, we favor:

• Admission of all SJS/TEN patients to the MICU
• At least 1:1 nursing care
• Daily dermatology and universal ophthalmology and gynecology consultation
• Early high-dose IVIG (1g/kg/day) x 3-4 days with a goal to try to stop progression (*actively re-evaluating*)
  • Given as soon as the diagnosis is made (regardless of severity); early Rx may be the key with any treatment
All retrospective studies and literature reviews are limited by heterogeneous populations, dosing, and confounding factors.

In general, a lack of consensus regarding the appropriate pharmacologic management of SJS/TEN persists, even among experienced providers.
Next Steps

Research priorities:
• Better understanding of the genetic and immunologic basis of disease with prospective sample collection
• Improved risk assessment so the reaction can be avoided
• Investigation of novel treatments to inhibit granulysin

Next Steps

Research priorities:
• Systematic evaluation of SJS/TEN sequelae and quality of life
  ➢ Survey study
• Establish “expert opinion” standard for supportive care
  ➢ Delphi effort

Next Steps

Research priorities:
• Revision of SCORTEN, which may overestimate mortality
  ➢ Improved prognostic model (SMR 0.99)
• Utilize existing networks to conduct a prospective SJS/TEN study and, ultimately, a randomized controlled trial

Summary

• SJS/TEN is a severe cutaneous adverse drug reactions with published mortality of 20-25%

• Dermatologists play a critical role in diagnosing this disease, differentiating mimickers, identifying and stopping culprit drugs, and coordinating treatment efforts

• Much progress still to make with respect to pathogenesis, prevention, and management → dermatologists can and should be at the forefront of these efforts
The Dermatology Foundation has supported & advanced my career.
Thank you

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