Orolabial Herpes: Fast Facts

- WHO: 60-95% world's population is infected with at least one herpesvirus
- HSV-1 mostly nonsexual transmission; closely associated w/ orolabial and facial disease (may be elsewhere)
- Primary infection followed by latency; Latency in.....
- Dorsal root ganglion and oral mucosa, possibly in keratinocytes
- ASx shedding (1-25% of days) or periodic clinical recurrences
- Seroprevalence studies HSV-1 positivity (USA)
  - >50 years old 75-85%
  - 40-49 years old 65.3%
  - 20-40 years old 57.7%
  - 14-19 years old 39.0%

Orolabial Herpes: Fast Facts

- Most common manifestation of HSV-1: Recurrent lesions
- Common vernacular: “cold sores” or “fever blisters”
- Morphology: grouped vesicles, tender or painful, associated swelling and possibly lymphadenopathy
- How many of those who are seropositive experience recurrent lesions?
  - Guess-estimate: 15-40%
- Frequency of recurrences varies: every other week to every 5-10 years
- Severity of recurrences varies widely
- Generally self-limiting in normal host to 12-17 days
- Resolves without sequelae; but some risk of scarring

Relevant Conflict of Interest Disclosure

- Advisory Board with honorarium: Cipher

Orolabial Herpes: Fast Facts

- Potential stimuli for recurrences
- Emotional stress
- Infection, usually URI
- Ultraviolet light exposure
- Physical fatigue
- Local trauma
- Menses
- Immunosuppression
Smoking associated w/ less frequent and less severe recurrent HSV1

Orolabial Herpes: Clinical Progression
- Prodrome: pain, burning, itching, tingling
  Lasts about 6 hours; ¼ recurrences abort
- Erythema
- Papule formation
- Vesicle formation (few hours from onset)
- Ulcer – soft crust
- Crust formation (72-96 hours from onset)
- Residual: mild erythema, flaking, swelling
- WHY IS THIS SEQUENCE IMPORTANT?
- Early intervention! Short Rx window!

Why Bother Treating?
- Reduce discomfort
- Reduce cosmetic disfigurement
- Speed healing
- Decrease transmission risk
- Reduce scarring risk
- Lower emotional distress
- Reduce recurrence frequency?
- Reduce recurrence severity?
Oh no! A cold sore!
No way…

Why Bother Treating?

- Reduce recurrence frequency?
- Reduce recurrence severity?

Therapeutic Decisions: Recurrent HSV-1

- Episodic therapy
- Continuous suppression

Therapeutic Decisions: Recurrent HSV-1

- Episodic therapy
  - Topical
  - Oral
  - Muco-adhesive
- Continuous suppression

Anti-HSV Drugs

- Acyclovir
- Penciclovir
Acyclovir vrs Penciclovir

“It all evens out in the end...”

- Penciclovir has higher affinity for HSV thymidine kinase compared to acyclovir
- Penciclovir has prolonged intracellular half life (10-20x longer) vrs acyclovir
- Triphosphorylated penciclovir has lower affinity for HSV DNA polymerase
- Triphosphorylated penciclovir binds to DNA polymerase reversibly

Episodic versus Suppressive Therapy

- It is estimated that less than 10% of recurrent orolabial herpes patients have disease of such frequency and/or severity to warrant chronic suppressive anti-viral therapy

Episodic Rx Seems Reasonable

Suppressive Rx Seems Reasonable

Topical Rx Seems Reasonable

Oral Rx Seems Reasonable
Systemic Rx: Intravenous?
Acyclovir 15mg/kg 5x daily x 7 days

Cancer
HIV/AIDS

Systematic analysis: oral valacyclovir 1g BID x 7 days
works just as well as IV acyclovir in immunocompromised
Cochrane Data Systm Rev 2009; 1 Art #CD006706

Episodic v. Suppressive
• Infrequent outbreaks: Episodic
• Mild-Moderate severity: Episodic
• Very frequent: Suppressive
• Very severe: Suppressive!
• Eczema (self/child): Suppressive!
• EM-associated: Suppressive!
• Surgery, Sunburn: Prophylactic suppression
• No prodrome: Suppressive? (If desired)
• Patient preference: Either

“This is the third time I got fever blisters and a rash!”

Recurrent Erythema Multiforme

Why Topical Therapy?
• Few real or potential side effects
• No drug-drug interactions to consider
• No long-term health concerns
• Easily portable, easily started quickly
• Directed therapy: onto the pathology
• Patient empowerment
• Makes sense: wound healing
• Cost effective
• It works…sometimes

Unka Teddy’s Quote:
The fewer pills you take in life, the better off you are....

For many patients, topical therapy for orolabial herpes is sufficient and equivalent to episodic oral therapy. The choice should be on patient by patient basis.
What To Measure?

- Not all studies done in the same way!
- Dx by history + culture, culture, viewing
- Outbreaks monitored by viewing, diary
- Lesions measured, or not
- Cultures done, or not
- Drug compliance considered, or not
- End points: time to loss of hard crust or time to complete healing. Others: loss of pain, negative culture, size

<table>
<thead>
<tr>
<th>Topical Agent</th>
<th>Decrease in resolution time</th>
<th>Decrease in pain duration</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>0.5-2.0 days</td>
<td>None</td>
<td>Vehicle type critical to Rx success</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>0.7-1.2 days</td>
<td>0.6-1.0 day</td>
<td>OK to apply later (papules)</td>
</tr>
<tr>
<td>Docosanol</td>
<td>0.75-1.6 days</td>
<td>0.56 day</td>
<td>Increase in attacks that are aborted</td>
</tr>
<tr>
<td>Acyclovir-HC</td>
<td>1.4 days</td>
<td>1 day</td>
<td>Fewer lesions progress to ulceration</td>
</tr>
</tbody>
</table>

Acyclovir 5% + Hydrocortisone 1%

- Approved: 2009
- Applied 5x daily for 5 days, starting at prodrome if possible
- Reduced percent ulcerated: 58% v 74%
- Reduced time to healing: 1.4 days
- Reduced lesion size: 78 v 155 mm²
- Reduced duration pain: 1 day
- Well tolerated; No major AEs
- No TK mutations or acyclovir resistance

New “Local” Therapy

Muco-adhesive acyclovir 50mg

Muco-adhesive Acyclovir

- Applied at prodrome*
- Single tablet is therapy
- Massive concentration labial mucosa/saliva
- Reduces healing time (v. placebo) by ½ day
- Reduces duration of episode by 1.0 day
- Compared to placebo, 24% more episodes are aborted (no lesions develop): 35% overall
- Disease modifying agent; During 9 month follow-up, increased time to next recurrence by 105 days (mean) or 40 days (median)
Disease Modification?

![Graph showing recurrence of outbreaks over time for Sitavig® placebo and mucoadhesive acyclovir.]  

Recurrence (6-Month Follow-Up)  
(n=537)  

<table>
<thead>
<tr>
<th>Time to next recurrence, Days</th>
<th>Sitavig® placebo</th>
<th>Mucoadhesive Acyclovir</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>199 (days)</td>
<td>304 (days)</td>
<td>+105 Days</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**ABSTRACT**

This abstract has many points, both systemic and local, for the management of vesicular herpes zoster infections. The results show that adding the mucoadhesive formulation to the standard of care, the topical agent valacyclovir, led to a decrease in the frequency of outbreaks. The agent demonstrated the typical patient selection is known to be low in patients with low frequency of outbreaks. The agent is useful in patients with high frequency of outbreaks. The treatment is simple, safe, effective, and cost-effective, even in patients who experience recurrent and/or frequent outbreaks.

**J Drugs Dermatol. 2016 Jun 1;15(6):775-7**

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**• 23 yo Hispanic grad student**  
Part-time medical reception  
10 year hx oro-labial HSV  
HSV – 1 (culture proven)  
**Detailed diary of attacks: 37-68 days apart (5 yrs)**  
Abreva® and Denavir® used  
Anything better?  
Given Muco-adhesive acyclovir

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**• 44 days after presentation, outbreak and applies Sitavig**  
**NEXT episode 142 days later**  
**Subsequent episodes occurred at six, now every nine months**  
**Not a “cure”**  
**Disease modifying drug due to increased interval between prodromes (and/or attacks)**

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**Why Systemic (Oral) Therapy?**

- Availability of multiple agents  
- Various agents all efficacious  
- All agents very safe  
- Almost no drug-drug interactions  
- Several agents with convenient short course regimens  
- Generics now available, lower cost

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**Which Oral Agent?**

- Generic since 1990  
  200 mg, 400 mg, 800mg
- Generic since 2007  
  125 mg, 250 mg, 500 mg
Key Points

- No drug regimen is FDA approved for chronic suppression of HSV1 orolabial herpes
- HSV1 does not suppress as easily as HSV2 does, and therefore benefit is not as great

The long-term use of oral antiviral agents can prevent HSI, but the clinical benefit is small.
Acyclovir-Resistant HSV?
- Mild: Trifluridine ophthalmic soln
- Severe enough to warrant major Rx
- IV Foscarnet
- IV Vidarabine
- IV Cidofovir
- Topical Cidofovir 1-3%
- IL Cidofovir

High Potency Combo Rx (Episodic)
- Valacyclovir 2g BID x 1 day
- PLUS
- Clobetasol 0.05% gel BID x 3 days
- Decreased healing time to 5.8 d total

Herpotherm® (aka “HotKiss”)
Approved device in UK, EU, Australia, Canada, several Latin American countries; Not approved in USA, but available on either E-Bay or Amazon

Heat v. Acyclovir

Heat versus Acyclovir
Remission of Labial HSV?

- Recurrent orolabial herpes, resistant to chronic suppressive Rx (8-10 outbreaks/yr)
- Imiquimod: specific immune upregulation
- 62.5mg of 5% imiquimod applied under occlusion to lesion-free abdominal skin QHS during outbreak (1/4 of a sachet/dose)
- 3 weeks total duration of imiquimod therapy
- During Rx: decreased Sx & healing time (3d)
- After Rx: 21 months NO outbreaks (v. 18 prior)
- Sustained increase: CD4+, CD8+, IFN-gamma

Antivir Therapy 16:863-69, 2011
Ted Rosen, MD

Thanks for your attention!

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