Redness and Rosacea

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University of Michigan Medical School
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Yolanda Rosi Helfrich, MD
F017: Redness and Rosacea

DISCLOSURES

I have been an institutional primary investigator for research studies sponsored by Abbvie, Amgen, Novartis, Eli Lilly, Boehringer Ingelhein, Anacor, and Otsuka. I have received no personal payment in exchange for my services. Several years ago, I received honoraria from Galderma.

I will be discussing off-label therapies for rosacea and will note when I do so.
Learning objectives

Following this session, the attendee should be able to:

1. Describe clinical features and pathophysiology of rosacea
2. Recognize skin diseases that can produce facial redness
3. Develop an appropriate plan to manage facial redness
Initial evaluation

- Determine rosacea subtype
- Skin sensitivity?
  - Tolerability of moisturizers & other topical medications?
- Impact on patient?
- Educate about course of disease
Since 2002, 4 Rosacea subtypes

- Papulopustular
- Erythematotelangiectatic
- Phymatous
- Ocular
- One variant: Granulomatous
Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee

Richard L. Gallo, MD, PhD, Richard D. Granstein, MD, Sewon Kang, MD, Mark Mannis, MD, Martin Steinhoff, MD, PhD, Jerry Tan, MD, and Diane Thiboutot, MD
San Diego and Sacramento, California; New York, New York; Baltimore, Maryland; Doha, Qatar; Dublin, Ireland; Windsor, Ontario, Canada; and Hershey, Pennsylvania

(J Am Acad Dermatol 2018;78:148-55.)
Diagnostic phenotypes (at least one required to make diagnosis)

- **Fixed centrofacial erythema in a characteristic pattern that may periodically intensify**
  - Persistent erythema (esp. Fitzpatrick phototypes I-IV)
  - Flushing/blushing (esp. Fitzpatrick phototypes I-IV)

- **Phymatous changes**
  - Rhinophyma most common
  - Other phymas

(J Am Acad Dermatol 2018;78:148-55.)
4 Major Phenotypes:

- May appear with 1 or more diagnostic phenotypes
- Without a diagnostic phenotype, presence of 2 or more major features considered diagnostic

- Papules and Pustules
- Flushing
- Telangiectasia
- Ocular Manifestations
Papules and pustules

Flushing

- Frequent
- Typically prolonged
- Can develop within seconds to minutes in response to stimulating trigger

Telangiectasia

- Centrofacial
- Mostly phototypes I-IV
- Rare in phototypes V and VI
Ocular manifestations

Ocular manifestations

Strongly suggestive signs:
1) Lid margin telangiectases **
2) Interpalpebral conjunctival injection **
3) Spade-shaped infiltrates in the cornea
4) Scleritis and sclerokeratitis

**recognizable by dermatologist

J Amer Acad Dermatol. 69 (6), Supplement 1, December 2013, Pages S36–S41
Secondary phenotypes

- May appear with 1 or more diagnostic or major phenotypes:
- Burning or stinging—typically on erythematous skin without scales, but can have scale. Note: pruritus not typical of rosacea but can occur.
- Edema—may accompany or follow prolonged erythema or flushing.
  - Soft edema may last for days or be aggravated by inflammation.
  - Solid facial edema often a sequela of papules and pustules, but can occur independent of redness, papules, pustules, or phymas.
- Dry appearance; may coexist with seborrheic dermatitis.
## Table 1. Phenotypes of rosacea

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Major†</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed centrofacial erythema in a characteristic pattern that may periodically intensify Phymatous changes</td>
<td>Flushing</td>
<td>Burning sensation</td>
</tr>
<tr>
<td></td>
<td>Papules and pustules</td>
<td>Stinging sensation</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia</td>
<td>Edema</td>
</tr>
<tr>
<td></td>
<td>Ocular manifestations</td>
<td>Dryness</td>
</tr>
<tr>
<td></td>
<td>• Lid margin telangiectasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Interpalpebral conjunctival injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Spade-shaped infiltrates in the cornea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Scleritis and sclerokeratitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocular manifestations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• “Honey crust” and collarette accumulation at the base of the lashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irregularity of the lid margin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Evaporative tear dysfunction (rapid tear breakup time)</td>
</tr>
</tbody>
</table>

*These features by themselves are diagnostic of rosacea.
†Two or more major features may be considered diagnostic.
Papules and pustules of rosacea:

Treatment

**Topical:**
- metronidazole (0.75%, 1%)
- sodium sulfacetamide/sulfur
- azelaic acid (15% gel)
- ivermectin (1% cream)

**Oral:**
- doxycycline 40 mg (Oracea)

**Multiple off-label therapies**
Topical therapy for PPR: guidelines

- At least 6-8 weeks before assessing efficacy
- Include a gentle skin care regimen
- Repair skin barrier
Metronidazole

- Metronidazole 0.75% gel, cream, and lotion twice daily
  (best price GoodRx $106 cash price for 45 gm gel [$53 with coupon])

- Metronidazole 1% gel and cream once daily
  (best price GoodRx $235 cash price for 60 gm gel [$76 with coupon])

-Pregnancy Category B

Retrieved February 19, 2019, for zipcode 48105 from http://www.goodrx.com/
Azelaic acid

- **15% gel twice daily** (best price GoodRx $332 cash price [$98 with coupon] for 50 gm)
- Similar efficacy as compared to metronidazole
- Tolerability: early burning, stinging, irritation
- Pregnancy Category B

Retrieved February 19, 2019, for zipcode 48105 from http://www.goodrx.com/
Practical use

- Combined with oral agents
  - Tetracyclines, especially doxycycline
  - Faster results, better improvement
- Maintain remission/prevent flares
Sodium sulfacetamide 10%/sulfur 5% (SS) preparations

- Leave on formulations—cream, gel, foam, lotion
  (Best price GoodRx $131 cash price for 118 mL sulfacetamide lotion [with coupon $54])
- Cleansers (Best price GoodRx $141 for 16 oz [with coupon $46])
- Limited data
- Can combine with oral agent
- Some malodor

Retrieved February 19, 2019, for zipcode 48105 from http://www.goodrx.com/
Topical ivermectin (1% cream)
(Price $651 cash price [$502 with coupon] for 45 gm on GoodRx)

- Once daily
- Indication: inflammatory lesions
- Demodex folliculorum?
- Mechanism of action:
  - Activation of immunity?
  - Anti-inflammatory

Retrieved February 19, 2019, for zipcode 48105 from
http://www.goodrx.com/
Topical ivermectin (1% cream)

Topical ivermectin (1% cream)

Part A
- Week 12 [LOCF] n=451
- Week 4 n=403
- Week 8 n=385
- Week 12 n=375
- Week 16 n=374
- Week 20 n=364
- Week 24 n=364
- Week 28 n=361
- Week 32 n=355
- Week 36 n=348
- Week 40 n=349

Percent of Subjects
- Ivermectin 1% Cream
  - Clear/almost clear
  - Mild
  - Moderate
  - Severe

At week 16, ivermectin superior
Lesion count reduction: 83% vs 73.7%, p<0.001
IGA clear or almost clear: 84.9% vs 75.4%, p<0.001
AEs comparable, tolerability better for IVM 1%
Oral therapies for PPR

- Doxycycline 40 mg (30/10 extended release)
  - lowest price $534 cash price [$199 with coupon] on GoodRx

- Twice daily doxycycline hyclate 20 mg tabs (off label)
  - lowest price $62 cash price [$23 with coupon] on GoodRx

- Off-label tetracyclines at antimicrobial doses
  - Avoid prolonged duration

- In practical use, often combined with topicals

- Isotretinoin—more recalcitrant disease

Retrieved February 19, 2019, for zipcode 48105 from http://www.goodrx.com/
Fixed centrofacial erythema
(AKA Erythematotelangiectatic Rosacea)

Identification

- Centrofacial fixed erythema
- ± Flushing
- ± Telangiectasia
Centrofacial erythema treatment: Barrier repair
Lesional vs background erythema

KEY POINT: disappears when papules have been absent for some time

May see telangiectasia, either with naked eye or using dermoscopy
Erythema-focussed treatment: Laser and light therapies
Erythema-focused treatment: Laser and light therapies

- Pulsed-dye laser (purpuragenic settings)
  - Improvement in erythema, telangiectasia
  - Improvement in symptoms, DLQI (J Am Acad Dermatol, 2004: 51(4), 592-599)

- Longer-pulse-duration PDL: nonpurpuragenic
  - Facial erythema, can stack PDL pulses for telangiectasia

- 532-nm KTP: most effective for telangiectasia, can treat erythema

- Intense pulsed light: similar efficacy for erythema and telangiectasia as PDL in comparison studies
Efficacy and Safety of Once-Daily Topical Brimonidine Tartrate Gel 0.5% for the Treatment of Moderate to Severe Facial Erythema of Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Studies

Joseph Fowler Jr. MD, a J. Mark Jackson MD, a Angela Moore MD, b Michael Jarratt MD, c Terry Jones MD, d Kappa Meadows MD, e Martin Steinhoff MD, f Diane Rudisill BSc, g and Matthew Leoni MD a on behalf of the Brimonidine Phase III Study Group
Topical brimonidine success

<table>
<thead>
<tr>
<th>Scores</th>
<th>CEA</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, Clear</td>
<td>Clear skin with no signs of erythema</td>
<td>Clear of unwanted redness</td>
</tr>
<tr>
<td>1, Almost clear</td>
<td>Almost clear; slight redness</td>
<td>Nearly clear of unwanted redness</td>
</tr>
<tr>
<td>2, Mild</td>
<td>Mild erythema; definite redness</td>
<td>Somewhat more redness than I prefer</td>
</tr>
<tr>
<td>3, Moderate</td>
<td>Moderate erythema; marked redness</td>
<td>More redness than I prefer</td>
</tr>
<tr>
<td>4, Severe</td>
<td>Severe erythema; fiery redness</td>
<td>Completely unacceptable redness</td>
</tr>
</tbody>
</table>

Images from Galderma

<table>
<thead>
<tr>
<th>Success*</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mirvaso® topical gel (N=129)</td>
<td>Vehicle gel (N=131)</td>
</tr>
<tr>
<td>Hour 3</td>
<td>31%</td>
<td>11%</td>
</tr>
<tr>
<td>Hour 6</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Hour 9</td>
<td>26%</td>
<td>10%</td>
</tr>
<tr>
<td>Hour 12</td>
<td>23%</td>
<td>9%</td>
</tr>
</tbody>
</table>
Optimizing the Use of Topical Brimonidine in Rosacea Management: Panel Recommendations

Emil A. Tanghetti MD,1 J. Mark Jackson MD,2 Kevin Tate Belasco DO MS,3 Amanda Friedrichs MD,4 Firas Hougier MD,5 Sandra Marchese Johnson MD,6 Francisco A. Kerdel MD,7 Dimitry Palceski DO FAOCD,8 H. Chih-ho Hong MD FRCP,9 Anna Hinek MD MSc FRCP,10 Maria Jose Rueda Cadena MD11

Potential increases in erythema associated with topical brimonidine

- Paradoxical erythema
- Return to baseline erythema (expected)
- Exaggerated recurrence of erythema
- Allergic contact dermatitis
Topical Oxymetazoline
(Price $523 with coupon on GoodRx)

- FDA approved January 19, 2017
- Treatment of persistent facial erythema of rosacea
- Study design very similar to that required for approval of topical brimonidine
  - Two clinical trials, 885 patients
  - Success 2-grades of improvement on both clinician’s CEA and patient self assessment

<table>
<thead>
<tr>
<th>Success</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxymetazoline N=222</td>
<td>Vehicle N=218</td>
</tr>
<tr>
<td>Hour 3</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Hour 6</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>Hour 9</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>Hour 12</td>
<td>15%</td>
<td>6%</td>
</tr>
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Retrieved February 19, 2019, for zipcode 48105 from http://www.goodrx.com/

Topical oxymetazoline: adverse reactions

In an open-label extension study, over one year, adverse reactions included:

- worsening inflammatory lesions of rosacea (3%)
- application site dermatitis (3%)
- application site pruritus (2%)
- application site pain (2%)
- application site erythema (2%).

Source: RHOFADE Prescribing Information
Flushing

Wet or dry flush?
Wet = autonomic neural-mediated (+eccrine sweating)
Dry = agents act directly on vascular smooth muscle

What type of dry flush?
Any pain/burning?
  Yes — sensorineural flushing
  No — endogenous or exogenous?
  Ask about food, drugs, tests, etc

J K Wilkin. *The red face: Flushing disorders* 
Clinics in Dermatology 1993;11:211-223
Treatment of flushing:

- **Wet flushing:**
  - Cooling (ice chips in mouth)
  - Clonidine (0.05 mg twice daily)
  - Beta-blocker—nadolol (40 mg) or propranolol
  - Carvedilol—titrated up to 12.5 mg twice daily (J Dermatol Treat, 29:3, 310-313)

- **Dry flushing:**
  - With dysesthesia—low-dose clonidine or nadolol; Second-line amitryptiline 10 mg daily
  - No dysesthesia—avoid exogenous vasodilators
  - Aspirin pretreatment for nicotinic acid
  - Antihistamine
Phymatous changes

J Am Acad Dermatol, **2004: 50**(6), **907-912**
Phymatous changes

- Primarily adult male patients
- Prominent sebaceous hyperplasia & oily skin
- Treatment:
  - Isotretinoin (0.3-1 mg/kg) reported beneficial. Duration of benefit uncertain
  - Laser ablation and surgical debulking to recontour hypertrophy
Ocular

Ocular rosacea

- 50-72% of rosacea patients
  - potential sight-threatening corneal damage
- Clinical diagnosis
  - Severity doesn’t correlate with skin severity
- Symptoms—tearing, redness, foreign body sensation, burning, itching, photophobia, blurring
Ocular rosacea

J Amer Acad Dermatol. 69 (6), Supplement 1, December 2013, Pages S36-S41
Ocular rosacea

J Amer Acad Dermatol. 69 (6), Supplement 1, December 2013, Pages S36-S41
Ocular rosacea management

- Mild disease
  - Lid hygiene
  - Metronidazole gel
  - Topical ivermectin (case report)

- Moderate to severe
  - Topical corticosteroids or cyclosporine
  - Oral tetracyclines, azithromycin in second-line
Granulomatous rosacea

- Variant, not a subtype
- Red-brown papules
- Surrounding erythema not a marked feature but may be present
- Often symmetric, but not necessarily
- Convexities of face, periocular/periorificial
- Histology: granulomas

JEADV, 28 (11): 1336-1343.
Granulomatous rosacea: treatment

- No large-scale studies
- Standard rosacea therapies
  - Systemic tetracyclines
  - Consider topicals (less effective)
- Isotretinoin
Rosacea pathogenesis

- Innate immunity
  - ↑ cathelicidin and kallikrein 5 (SCTE)
- Microorganisms
  - Demodex, Bacillus oleronium, H. pylori
- UV irradiation
- Vascular hyperreactivity
- Genetics
- Not enough coffee?  (JAMA Dermatol. 2018;154(12):1385-1386)
And now...

Some other cases of facial redness
At this point, we will begin utilizing the audience response system.
Case #1

- 38-year-old female
- CC: facial redness, flushing with burning/stinging pain after exposure to heat, sunlight, hot showers, and stress.
- No response to topical metronidazole, topical steroids, or oral antibiotics
- Improves when she sucks on ice chips
- PMH: frequent migraines, fibromyalgia, and depression

What is your diagnosis?

a) Erythematotelangiectatic rosacea
b) Papulopustular rosacea
c) Neurogenic rosacea
d) Idiopathic flushing
e) Carcinoid syndrome
ANSWER: C

a) Erythematotelangiectatic rosacea
b) Papulopustular rosacea
c) **Neurogenic rosacea**
d) Idiopathic flushing
e) Carcinoid syndrome
Neurogenic rosacea

- Dysesthesia out of proportion to flushing or inflammation
- Resembles complex regional pain syndrome and neuropathic itch
- Common triggers: heat, sunlight, hot showers, exercise, stress.
- 10/14 patients experienced relief from cooling with fans or cold compresses

Neurogenic rosacea

- Associated neurologic or neuropsychiatric conditions
  - Complex regional pain syndrome, essential tremor, depression, OCD

- Best treatment:
  - Neuroleptic agents (gabapentin, pregabalin)
  - Tricyclic antidepressants
  - Pain-modifying antidepressants (duloxetine)
  - Caution with laser/light-based treatment 2° photosensitivity
  - Sympathectomy reported helpful (Arch Dermatol. 2012;148(2):270-1)

Case #2

- 28-year-old female
- CC: Facial rash x 2 yrs, worsening, associated burning
- PMH: h/o Atopic dermatitis as child, dry skin
- Using fluocinonide cream on face almost daily for past 2 years

J Am Acad Dermatol. 2015. 72(3):541-549
What is your diagnosis?

a) Erythematotelangiectatic rosacea
b) Papulopustular rosacea
c) Neurogenic rosacea
d) Idiopathic flushing
e) Topical corticosteroid withdrawal syndrome
ANSWER: E

a) Erythematotelangiectatic rosacea
b) Papulopustular rosacea
c) Neurogenic rosacea
d) Idiopathic flushing
e) Topical corticosteroid withdrawal syndrome
Topical corticosteroid withdrawal

- Women (81%) using TCS on face (97%)
  - Primary indication: atopic dermatitis (33.3%), cosmetic use and pigmentary disorders (14.3%)
- Mid- or high-potency TCS (98.6%)
- 85.2% (of 210 patients) used >12 mos

A systematic review of topical corticosteroid withdrawal (“steroid addiction”) in patients with atopic dermatitis and other dermatoses

Tamar Hajar, MD, a Yaacov Leshem, MD, a Jon M. Hanifin, MD, a Susan T. Nedorost, MD, a Peter A. Lio, MD, a Amy S. Fuller, MD, a Julie Block, BA, a and Eric L. Simpson, MD, MCR, a (the National Eczema Association Task Force) Portland, Oregon; Cleveland, Ohio; Chicago, Illinois; and San Rafael, California

J Am Acad Dermatol. 2015. 72(3):541-549
Signs and symptoms of TCS withdrawal

- Erythema (92.3%)
- Sharp cutoff btw red & normal skin
- Papules ± nodules and pustules in ~1/2 of pts
- Burning/stinging
- Worse with heat or sun
- Pruritus
- Pain
- Sensation of facial heat
TCS withdrawal—erythematous type (47.9%)

- 90% had 1° eczematous condition
- Erythema, scaling, papules, nodules, swelling/edema,
- Burning/stinging, pruritus, pain
- ↓ tolerance of emollients
- Develops within 14-21 days of TCS cessation
TCS withdrawal—papulopustular type (52.1%)

- Majority using TCS to treat pigmentary/acneiform disorders
- Prominent papules and pustules, ± nodules
- Less frequent edema and burning/stinging
- Develops within 4-14 days of TCS cessation

J Am Acad Dermatol. 2015. 72(3):541-549
TCS withdrawal: Treatment

- Discontinue TCS
- Supportive care (cool compresses, psychological support)
- Oral antibiotics (tetracyclines), esp for papulopustular variant
- Some authors recommend oral steroid PLUS less potent TCS or topical calcineurin inhibitor
- Most patients responded within 3 months
Topical Steroids in Chinese Cosmetics

Recent media reports in China focused on Zhou Menghan, a 22-year-old Chinese woman who sold masks among her circle of friends on WeChat. She had more than 100,000 fans and customers, and her annual income was more than a million yuan. After a few months, her customers began to post photographs of their facial eruptions on the internet and complained that their skin was destroyed after using the “three noes” masks sold by Zhou. Three noes refer to unbranded, dateless products manufactured by a nameless factory. Most of the complications of using the masks were diagnosed by remains somewhat limited, people for the lowest possible cost. Illegal manufacturers sell these low-quality, some of which contain steroids, to attract new customers. People, eager, wish to become more beautiful to believe the dubious advertising promises of illegal manufacturers.

The inadequate supervision of manufacturers include poor implementing inspection system and an aliDubious inspection. Moreover, the appearance of appearance cosmetics caused by high costs makes them unaffordable. While beauty salons and spas predominantly sell imported cosmetics a lack of standard of these cosmetics is the new business model of small salons and internet sales. The typical challenges; thus, traditional supervision are inadequate, and government supervision is imperative.
Combinations of potent topical steroids, mercury and hydroquinone are common in internationally manufactured skin-lightening products: a spectroscopic study

M. H. Maneli,1 L. Wiesner,2 C. Tinguey,2 L. M. Davids,4 Z. Spengane,1 P. Smith,2 J. C. van Wyk,1 A. Jardine6 and N. P. Khumalo1

1Divisions of Dermatology and 2Clinical Pharmacology, Groot Schuur Hospital, Cape Town, South Africa; and Departments of 4Geological Sciences, 5Human Biology and 6Chemistry, University of Cape Town, Cape Town, South Africa

doi:10.1111/red.12720

Methods. In total, 29 products were examined; of these, 22 products were purchased from informal vendors, and 2 products (out of a total of 29) were purchased over the counter. HQ, Hg2+ and steroids were quantified by high-performance liquid chromatography–ultraviolet spectrophotometry, inductively coupled plasma-mass spectrometry and liquid chromatography–mass spectrometry, respectively.

Results. Of the 29 products, 22 (75.9%), all imported and bought from informal vendors, contained illegal or banned ingredients; 13 (44.8%) contained steroids; 9 CP, 4 BM), 12 (41.4%) contained Hg (30–2300 ppm), and 11 (37.9%) contained HQ. Sequentially, the products originated from Italy (27.3%, n = 6), India (22.7%, n = 5), the Democratic Republic of Congo (DRC) (22.7%, n = 5), Cote d’Ivoire (9.1%, n = 2), USA (9.1%, n = 2), UK (4.5%, n = 1) and France (4.5%, n = 1). Two products, one from India and one from the DRC, contained all four ingredients (HQ, Hg, BM, CP). Of the 12 products containing Hg, 10 also contained HQ and/or a steroid, yet none listed Hg as an ingredient. A significant proportion of the steroid-containing products (76.9%) also contained at least one other skin-lightening agent. Not all internationally available products were tested, which is a limitation of the study.

Conclusion. In spite of a European Union ban on skin lighteners, a third of the products tested were from Europe. Combinations of Hg and ultrapotent steroids were prominent. International law enforcement and random testing is needed to encourage industry compliance and help protect consumers.
Case #3

- 49-yr-old male with h/o rosacea x 12 yrs. Presented with papules and pustules.
- Treated with topical clindamycin and 0.03% tacrolimus ointment QD.
- 3 weeks later, developed acute flare with pustulation.
- KOH revealed multiple Demodex mites, biopsy confirmed rosacea diagnosis with multiple Demodex mites visualized.

What is your diagnosis?

a) New-onset acne
b) Spontaneous papulopustular rosacea flare
c) Demodicosis
d) Rosaceiform dermatitis due to topical tacrolimus
e) I don’t know
ANSWER: D

a) New-onset acne
b) Spontaneous papulopustular rosacea flare
c) Demodicosis
d) Rosaceiform dermatitis due to topical tacrolimus
e) I don’t know
Rosaceiform dermatitis associated with topical tacrolimus

- Immunosuppressive properties might facilitate overgrowth of follicular Demodex

- Vasoactive properties of topical tacrolimus
  - Facial flushing adverse reaction
  - Local vasmotor instability a feature of rosacea; topical tacrolimus may constitute long-term risk factor in sensitive patients
Rosaceiform dermatitis associated with topical tacrolimus

- 49-yr-old woman, h/o atopic dermatitis of head and neck.
- 5 months treatment with topical tacrolimus 0.03%
- Developed telangiectasia and erythematous papules on cheeks and persistent burning sensation with application.
- Responded to doxycycline and d/c of tacrolimus
- Recurred when tacrolimus restarted
- No recurrences after definitive d/c of topical tacrolimus

Case #4

- Patient with h/o chronic Aspergillus sinusitis & osteomyelitis of the base of the skull.
- PMH of rosacea, not active when new study medication started.
- After 4 weeks of therapy, developed cheilitis.
- Developed erythema of face, upper chest, and ears following a vacation. Arms and legs tanned normally.
- Facial erythema and cheilitis persisted for several months, then worsened following a Mediterranean holiday.
- After one year of being on medication, developed slightly pruritic plaques on the neck. Bx consistent with discoid lupus erythematosus.
- Improved somewhat with daily sunscreen (SPF 30). When study medication was stopped, all cutaneous abnormalities began to resolve and cleared over subsequent 4 months.
Case #5

-Patient with Aspergillus infection of the sinuses. Treated with antifungal med.

-After nearly 5 months of therapy, developed severe nasal erythema and mild erythema of the rest of the face, along with cheilitis.

-Still apparent 2 months after discontinuing therapy, but subsided over the following 2 months.

Which medication is most likely to be causing this?

a) Isavuconazole
b) Voriconazole
c) Amphotericin B
d) Itraconazole
e) Ketoconazole
ANSWER: B

a) Isovucconazole
b) Voriconazole
c) Amphotericin B
d) Itraconazole
e) Ketoconazole
Voriconazole

- MOA unclear
- Reminiscent of systemic retinoid effects
  - Cheilitis, xerosis, facial erythema, photosensitivity
  - Inhibits breakdown of Vitamin A $\rightarrow \uparrow$ plasma retinoids?
- Phototoxic reaction
- Occurs in 8-10% of patients
Other cutaneous effects of voriconazole

- ↑ risk of SCC (2.6-fold)
  - Duration of exposure correlates with SCC #
- Possible ↑ risk of melanoma
- Accelerated photoaging
- Porphyria cutanea tarda
- Discoid lupus erythematosus
Case #6

18-year-old female presents with 4-year history of flushing of face, neck, trunk, & abdomen.
What is the most important follow-up question to ask?

- a) Associated diarrhea?
- b) Associated stinging/burning?
- c) Associated hypertension?
- d) Associated sweating?
- e) Associated photosensitivity?
ANSWER: A

a) Associated diarrhea?
b) Associated stinging/burning?
c) Associated hypertension?
d) Associated sweating?
e) Associated photosensitivity?
Carcinoid

- Urinary 5-HIAA (24-hr) = 93 mg (nl 2-6 mg)
- Treatment with octreotide and resection of tumor
- Pt scheduled for liver transplantation
Carcinoid syndrome

- Neuroendocrine tumors of digestive tract and lungs
  - Secrete as many as 40 products
  - Primarily serotonin, histamine, tachykinins, kallikrein and prostaglandins

- Carcinoid syndrome most typically associated with metastatic carcinoid tumors of gut
  - Only 1 in 10 carcinoid tumors will result in carcinoid syndrome
Carcinoid syndrome

- Episodic flushing (85%)
  - Dry flush
  - 30 seconds-30 minutes
  - Assoc w/ ↓ BP and ↑ pulse
- Venous telangiectasia
- Diarrhea (80%)
- Bronchospasm
- Cardiac valve lesions

CMAJ. 2009; 180(13): 1329.
Carcinoid syndrome

- Episodic flushing (85%)
- Venous telangiectasia
- Diarrhea (80%)
- Bronchospasm
- Cardiac valve lesions
- Facial edema

Most sensitive test: 24-hour urine 5-HIAA

Treatment of choice: Surgical resection

Case # 7

- 67-year-old pt with new-onset episodic flushing
- Episodes last 15-30 minutes and are not associated with increased sweating
- Flushing is accompanied by a feeling of warmth, palpitations, and lightheadedness
- During episodes, his head hurts and he notes some abdominal pain
- On questioning, he notes frequent abdominal pain and loose stools
- After episodes, he feels wiped out for several hours

European Journal of Dermatology
April 2015, Volume 25, Issue 2, pp 182–184
What is your diagnosis?

a) Carcinoid syndrome
b) Pheochromocytoma
c) Mastocytosis
d) Neurogenic rosacea
e) Atypical migraine
ANSWER: C

a) Carcinoid syndrome
b) Pheochromocytoma
c) Mastocytosis
d) Neurogenic rosacea
e) Atypical migraine
Mastocytosis

- Mastocytoma
- Urticaria pigmentosa
- Diffuse cutaneous mastocytosis
- TMEP (telangiectasia macularis eruptiva perstans)
Mastocytosis presenting as flushing

Panel 2: Major symptoms and signs of mastocytosis

Cutaneous manifestations
Skin lesions: urticaria pigmentosa, diffuse infiltrative papules and plaques
Pruritus
Dermographism
Urticaria

Mast-cell mediator-related
Prolonged episodes of flushing
Intermittent gastrointestinal complaints, such as diarrhoea, abdominal pain, nausea and vomiting
Palpitations/tachycardia

Less common
Hypotension
Headache
Lightheadedness, dizziness, syncope
Anaphylaxis
Respiratory symptoms
Altered cognitive functions, such as poor attention, irritability, impaired memory, personality change
Peptic ulcer disease, gastritis, duodenitis, malabsorption

Organ infiltration (in systemic mastocytosis)
Hepatomegaly
Splenomegaly
Skeletal lesions
Arthralgias
Bone-marrow infiltration
Lymphadenopathy

Constitutional symptoms (may indicate systemic involvement)
Weakness
Fatigue
Malaise
Fever
Weight loss

Lancet 1997; 349: 1379–85
Flushing of systemic mastocytosis

- Spontaneous or associated with specific triggers
  - Heat, exertion, emotion
  - Meds: aspirin or opioid analgesics
- Duration 15-30 minutes
- Dry flush
- Associated warmth, palpitations, lightheadedness
- May be associated with headache, dyspnea, chest pain, nausea, diarrhea, and paresthesia
- Persistent, severe lethargy lasting for several hours typically occurs and is a **valuable diagnostic clue**
- Severe attacks:
  - assoc hypotension, with potential for life-threatening vasodilatory shock and CV collapse
  - May have associated syncope, dizziness, or confusion due to cerebral hypoperfusion
Diagnosis of systemic mastocytosis

- Requires histologic evidence of mast-cell hyperplasia in at least one tissue other than skin
- Bone marrow biopsy
- No single laboratory test establishes diagnosis:
  - 24 hour urine histamine
  - Increased histamine metabolites N-methylhistamine and N-methylimidazoleacetic acid in urine
  - Mast cell tryptase in serum
- Exclude carcinoid, pheochromocytoma, menopause, medullary thyroid carcinoma
Case # 8

- 61 y.o. female presents with cc of episodic facial redness for one year. Occurs almost daily. Episodes last hours.
- Also notes redness of neck, upper chest, and shoulders.
- Flushing associated with severe nausea, headache, lightheadness.
- No diarrhea, no palpitations.
- Recent onset hypertension, began around same time as flushing.
- Uses ice packs to decrease facial warmth.
- PMH: depression, vulvodynia, and multiple life stressors.
- Very disabling. Cannot do activities she used to enjoy.
What is your diagnosis?

a) Pheochromocytoma
b) Atypical migraine
c) Mastocytosis
d) Mast cell activation syndrome
e) Carcinoid syndrome
ANSWER: D

a) Pheochromocytoma
b) Atypical migraine
c) Mastocytosis
d) Mast cell activation syndrome
e) Carcinoid syndrome
Differential:

- Neurogenic rosacea
- Carcinoid
- Pheochromocytoma
- Severe paroxysmal hypertension (pseudopheochromocytoma)
- Atypical migraine

24 hour urine: normal norepinephrine, epinephrine, dopamine, 5-HIAA. Normal metanephrine, normetanephrine
Mast cell activation syndrome

- Newly described in 2010-2011
- Nothing in dermatologic literature
- Describes patients with systemic mast cell activation symptoms with no evidence of IgE mediated disease or other explanations for secondary mast cell activation
Mast cell activation syndrome: Diagnostic criteria

- Symptoms of mast cell activation involving 2 organ systems
- Positive response to therapy that targets mast cell mediators
- Elevated level of a mast cell mediator DURING an episode
  - Most reliable: serum tryptase within 4 hours of an episode
  - Meaningful elevation: baseline serum tryptase (bT) + 20% bT + 2 ng/mL
- Largest case series 18 patients over 3 years
  - Patients with ≥ 4 signs/symptoms: abdominal pain, diarrhea, flushing, dermographism, memory and concentration difficulties, or headaches
  - Majority had the constellation of dermographism, abdominal pain, and flushing, all had elevation of at least 1 mast cell mediator
  - 67% complete or major regression with medications targeting mast cell mediators.
Mast cell activation syndrome: Treatment

- All patients should be prescribed multiple self-injectable epinephrine devices
- Avoid mast cell activation triggers
- Stepwise approach:
  - H1 antihistamine at 2-4x daily recommended dose (start with nonsedating, supplement with first generation sedating at night as needed)
  - H2 antihistamine if GI symptoms prominent OR as second step
  - Leukotriene blocking agent
  - Trial of oral cromolyn if prominent GI symptoms
  - Third step: consider systemic glucocorticoids with slow taper over months
  - Fourth step: hydroxychloroquine, dapsone, cyclosporine, omalizumab
Case #9:

- 41-year-old female
- Underwent elective total thyroidectomy for multinodular goiter/Graves disease
- PMHx: multiple abortions, tendinitis of right arm, right thoracotomy for intercostal pain, cervical neck pain, tobacco use
- NKDA
- Premedication for surgery: midazolam, glycopyrronium bromide
- Anesthetics: Sufentanil, propofol, cisatracurium, desflurane
- Postop analgesia: diclofenac, propacetemol.
- 90 minutes after surgery, sudden left-sided facial redness; subsequently resolved within 5.5 hours
What is your diagnosis?

a) Frey’s syndrome
b) Trigeminal neuralgia
c) Atypical migraine
d) Atypical zoster
e) Harlequin sign
ANSWER: A

a) Frey’s syndrome
b) Trigeminal neuralgia
c) Atypical migraine
d) Atypical zoster
e) Harlequin sign
Frey’s Syndrome

- AKA Auriculotemporal syndrome
- Parotidectomy—incidence ~53%
  - Acute or delayed presentation
- This case: edematous imitation of the cervical part of the sympathetic trunk?

Frey syndrome associated with eating citrus and vegetables
Frey’s syndrome: Treatment

- Cochrane Review: No high quality evidence
- Botulinum toxin
  - Definitive reduction in sweating
  - Questionable reduction in erythema
  - *(Otolaryngol Head Neck Surg 2000;122:821-7.)*
- Local injection of alcohol, scopolamine, and glycopyrrolate
- Topical antiperspirants—a aluminum chloride
- Would topical brimonidine or topical oxymetazoline work for facial erythema? Possibly
Case #10

- 60-year-old man with 5-year history of periorbital swelling, progressive worsening and unresponsive to topical steroids. Does not wax and wane.
- Lab workup, including C1 esterase inhibitor, C1 and C2, SPEP, UPEP negative.
- MRI: reticular interstitial thickening & enhancement of facial and preseptal subcutaneous tissues.
- Skin bx—Near nl epidermis. In dermis, scant perivascular and focally perifollicular infiltrate composed of lymphocytes and rare plasma cells. Prominent vascular ectasia and stromal edema with scattered reactive fibrocytes.

Photo by Harrold Carter, UMich
What is your diagnosis?

a) Pott’s Puffy Tumor
b) Solid Facial Edema (Morbihan’s Disease)
c) Erysipelas
d) Carcinoid syndrome
e) Pheochromocytoma
ANSWER: B

a) Pott’s Puffy Tumor
b) Solid Facial Edema (Morbihan’s Disease)
c) Erysipelas
d) Carcinoid syndrome
e) Pheochromocytoma
Solid facial edema of rosacea (AKA Morbihan disease)

- Erythema and edema of upper 2/3 of face
- Late stage rosacea?
- Firm, nonpitting edema
- Recurrent inflammation thought to cause fibrotic induration/solid edema
Solid facial edema: Treatment

- Treatment: Notoriously difficult
- Systemic corticosteroids
- Oral abx
- Thalidomide
- Antihistamines
- Isotretinoin
Case #11

- 39 year old female
- 4 week history
- Lesions only on face
- PMH: mild acne as teen
- Meds: none

Arch Dermatol. 1992;128(12):1611-1617
What is your diagnosis?

a) Papulopustular rosacea
b) Acne fulminans
c) Acne conglobate
d) Pyoderma faciale
e) Pyoderma gangrenosum
ANSWER: D

a) Papulopustular rosacea
b) Acne fulminans
c) Acne conglobate
d) Pyoderma faciale
e) Pyoderma gangrenosum
Pyoderma faciale
(AKA Rosacea fulminans)

<table>
<thead>
<tr>
<th>Pyoderma Faciale Fulminans</th>
<th>Acne Fulminans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Men</td>
</tr>
<tr>
<td>Age, y</td>
<td>15-46</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
</tr>
<tr>
<td>Localization</td>
<td>Face, neck, chest, back</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Deep nodules and fluctuating abscesses</td>
</tr>
<tr>
<td>Systemic signs and symptoms</td>
<td>Often none; feel well, mild fever or none, slight leukocytosis, elevated ESR</td>
</tr>
</tbody>
</table>

Arch Dermatol. 1992;128(12):1611-1617
Rosacea fulminans: Treatment

- Oral corticosteroids
- Oral isotretinoin (0.5-1 mg/kg/day) x 4-6 mos
- Oral antibiotics often not helpful

Arch Dermatol. 1992;128(12):1611-1617
Case #12

- Young woman, immunocompetent
- 15-year history of facial erythema
- No treatment
- No evidence of raised borders
- No hair or nail findings
What is your diagnosis?

a) Systemic lupus erythematosus
b) Demodicosis
c) Erythematot telangiectatic rosacea
d) Carcinoid syndrome
e) Tinea faciei
ANSWER: E

a) Systemic lupus erythematosus
b) Demodicosis
c) Erythematotelangiectatic rosacea
d) Carcinoid syndrome
e) Tinea faciei
Tinea faciei
Tinea faciei

- Immunocompetent adult
- Asymptomatic
- Slightly elevated border
- Culture T. rubrum
Tinea faciei

- 10-year-old boy
- Facial rash x 10 days
- Worsened with topical steroids
- H&E septate hyphae
- Culture T. mentag

Pediatric Dermatology, 22: 243–244
Tinea faciei (et colli et pecti)
Case # 13

- 13 year old boy
- 1 year history
- Mildly pruritic, otherwise asymptomatic
- Face, torso, extremities
- Hydrocortisone helps with pruritus
- Adapalene gel no improvement

Arch Dermatol. 2006;142(12):1611-1616.
What is your diagnosis?

a) Erythematotelangiectatic rosacea
b) Keratosis pilaris rubra faciei

c) Erythromelanosisis faciei et colli
d) Loeys-Dietz Syndrome
e) Carcinoid syndrome
ANSWER: B

a) Erythema telangiectatic rosacea
b) Keratosis pilaris rubra faciei
c) Erythromelanosis faciei et colli
d) Loeys-Dietz Syndrome
e) Carcinoid syndrome
Keratosis pilaris rubra faciei

- Common but underrecognized
- Substantial erythema, widespread involvement, tends to persist past puberty
- Variant of keratosis pilaris
- Mean onset age 5
- Males > females
- Minimal to no improvement with treatment
Differential DDx:

- Keratosis pilaris atrophicans faciei (Ulerythema ophryogenes)—
  - Associated scarring
- Keratosis follicularis spinulosa decalvans—scarring hair loss
- Atrophoderma vermiculatum
  - Associated with Loeys-Dietz Syndrome

Images from VisualDx and *JAMA Dermatol.* 2015;151(6):675-677
Case # 14

- 62-year-old man
- 3-month history of right periorbital redness/swelling
- Treatment with amoxicillin/clavulanic acid x 14 days no improvement
- Ophthalmology performed culture
  - Positive for S. aureus
What is your diagnosis?
What is your diagnosis?

a) Erysipelas
b) Solid facial edema
c) Frey’s syndrome
d) Cutaneous T-cell lymphoma
e) Pyoderma faciale
ANSWER: D

a) Erysipelas
b) Solid facial edema
c) Frey’s syndrome
d) Cutaneous T-cell lymphoma
e) Pyoderma faciale
Cutaneous T-cell lymphoma mimicking erysipelas

- IV treatment with cephazoline led to ↓ C-Reactive protein
- Redness and swelling remained
- Radiotherapy for MF with resolution
MF masquerading as seborrhoeic dermatitis
Adnexotropic MF

British Journal of Dermatology 156 (1), pages 1-10,
NK T Cell Lymphoma
Case # 15

- 70 year old male
- History of multiple melanomas and NMSC
- On exam, profound erythema
- Significant telangiectasia
- No flushing, no symptoms

Photo credit: Harrold Carter, University of Michigan
What is your diagnosis?

a) Erysipelas
b) Rosacea
c) Mastocytosis
d) Photodamage
e) Carcinoid
Clinical, Histologic, and Molecular Analysis of Differences Between Erythematotelangiectatic Rosacea and Telangiectatic Photoaging

Yelinda I. Hefflick, MD; Lisa E. Maisel, MD; Yii Cai, PhD; Gary J. Fisher, PhD; Heather Ondrus, MS; Suzanne Nigrel, MD; Eno Sarno-Mauro, MD; James Vandal, PhD; John Voorhees, MD

Objectives: To demonstrate that ETR and TP are distinct dermatologic disorders.

Methods: A case-control observational study comparing clinical, histologic, and gene expression features of 26 participants with ETR, 20 with TP, and 20 age- and sex-matched controls in the Program for Clinical Research in Dermatology at University of Michigan.

Main Outcomes and Measures: Findings of clinical history and examination, light and electron microscopy, immunohistochemical analyses, and real-time quantitative reverse-transcriptase polymerase chain reaction gene expression.

Results: Transient erythema was greater in the ETR group (38/1% graded moderate to severe) than in the TP (20/0%, P = .003) and control groups (10% P = .002). Nontransient erythema was also greater in the ETR group (50% graded moderate to severe) than in the TP (25%, P = .03) and control groups (5%, P = .001). Participants with ETR tended to have erythema and telangiectasia primarily on the central face (70%), whereas those with TP tended to have more lateral involvement (57%, P = .005). Those with ETR had significantly less clinical evidence of photodamage (70% grade 2-4 on a photodamage scale) than those with TP (42%, grade 4-6, P = .03). Histologically, there was less evidence of photodamage in ETR than in TP, which had waxy collagen and solar elastosis surrounding blood vessels. Immunohistochemical analysis demonstrated greater mast cell tryptase staining in ETR samples (0.19%) than in TP (0.04%, P = .03) or control samples (0.01%, P = .002) but no increase in mast cell numbers, indicative of greater mast cell degranulation. Gene expression of matrix metalloproteinase 3 was 4-fold greater in ETR samples than in TP samples (P = .004) and 5-fold higher in control samples (P = .004). Gene expression of the neuropeptides calcitonin gene-related peptide (CGRP) and substance P was significantly increased in ETR compared with TP (9.9-fold [P < .0001] and 5.4-fold [P > .0001], respectively) and control samples (9.2-fold [P < .0001] and 28.4-fold [P < .0001], respectively).

Conclusions and Relevance: Telangiectatic photaging is characterized by less transient and nontransient erythema, a more lateral distribution of erythema and telangiectasia, less neurogenic mast cell activation, and less MMP-mediated matrix remodeling than ETR. These data demonstrate that TP is a distinct clinical entity from ETR that can be distinguished on the basis of clinical, histologic, and gene expression findings.
Erythematotelangiectatic (ETR)

- Flushing (often >10 min)
- Persistent redness of central face and cheeks
- Telangiectasia common
- Other features:
  - Burning, stinging
  - Facial sensitivity
  - Swelling
  - Roughness, scaling


Photo credit: Harrold Carter, University of Michigan
Erythematotelangiectatic

Photo credit: Harrold Carter, University of Michigan
Telangiectatic Photoaging

- Prominent Telangiectasia
- Photodamage
- Lack of Prominent Flushing/Blushing

Photo credit: Harrold Carter, University of Michigan
What Features Differentiate ETR From Telangiectatic Photoaging (TP)?

- 2 subject groups:
  - ETR (n=26)
  - TP (n=20)
- Facial controls (n=11)
Study procedures

- Two 3-mm facial biopsies
  - ETR and TP groups: telangiectatic vessel
  - Control: lateral cheek
- Physical exam
- Extensive history

Photo credit: Harrold Carter, University of Michigan
## Subject population

<table>
<thead>
<tr>
<th></th>
<th>ETR (n=26)</th>
<th>TP (n=20)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>60.1</td>
<td>63.0</td>
<td>54.2</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>18 (69%)</td>
<td>20 (100%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>8 (31%)</td>
<td>0 (0%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>26 (100%)</td>
<td>20 (100%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (18%)</td>
</tr>
</tbody>
</table>
Flushing is more strongly observed in ETR vs TP.
Moderate to Severe Photoaging is More Strongly Observed in TP vs ETR:
Photoaging Rating Scale (0=None to 8=Severe)

* p=0.002  ETR vs TP
More inflammation in ETR than in TP or control

More connective tissue alteration in TP than in ETR

Vessels more dilated in ETR than control. No difference btw ETR & TP

Larger, more numerous sebaceous glands in ETR vs control
Chemokines

* Indicates p < 0.05
Neuropeptides

[Graph showing mRNA fold change for CALCA, CALCB, and TAC1 under different conditions: ETR:Ctrl, TP:Ctrl, and ETR:TP. Significant changes indicated by asterisks (*).]
Matrix remodeling

* Indicates $p < 0.05$
Matrix remodeling

* Indicates p < 0.05
Identifying TP

- Typically older male
- Lateral erythema
- Prominent telangiectasia
- Obvious photodamage
- Lack of prominent flushing
  - If flushing, asymptomatic
- No other rosacea findings
  - No pustules
  - No ocular rosacea
  - No phymatous change

Photo credit: Harrold Carter, University of Michigan
TP treatment

- No studies; likely to respond to laser
- Topical vasoconstrictors
- Topical retinoids helpful in most photodamage
- **KEY POINT:** If no flushing symptoms, oral and topical rosacea rx unlikely helpful; consider alternatives

Photo credit: Harold Carter, University of Michigan
<table>
<thead>
<tr>
<th>ETR</th>
<th>TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td></td>
</tr>
<tr>
<td>Telangiectasia</td>
<td></td>
</tr>
<tr>
<td>Flushing (often symptomatic)</td>
<td>No flushing/min flushing</td>
</tr>
<tr>
<td>Central face</td>
<td>Lateral face</td>
</tr>
<tr>
<td>↑ CGRP-α/β, sub P, mast cell, degranulation</td>
<td>↑ visible &amp; histologic photodamage</td>
</tr>
</tbody>
</table>
The Dermatology Foundation has supported & advanced my career.

I was also fortunate to receive a grant from the National Rosacea Society.