



## **Unmasking rosacea:**

Advancements in the understanding and management of common manifestations of this condition

A modular educational program in rosacea

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# An overview of rosacea

## MODULE 1



## **Unmasking rosacea:**

Advancements in the understanding and management of common manifestations of this condition

[insert name], [insert credentials]

# Presenter's disclosures

- Faculty: [Speaker's name]
- Relationships with commercial interests:
  - **Grants/Research Support:** PharmaCorp ABC
  - **Speakers Bureau/Honoraria:** XYZ Biopharmaceuticals Ltd.
  - **Consulting Fees:** MedX Group Inc.
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# Disclosure of commercial support

- This program has received financial support from Galderma Canada Inc. in the form of an educational grant.
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  - Galderma Canada Inc. distributes and benefits from the sale of products that will be discussed in this program:
    - Anti-inflammatory dose doxycycline 40 mg (APPRILON)
    - Brimonidine gel 0.33% (ONRELTEA)
    - Metronidazole gel 1% and 0.75% (METROGEL), metronidazole lotion 0.75% and metronidazole cream 0.75% (METROCREAM)
    - Ivermectin 1% cream (ROSIVER)

# Mitigating potential bias

- [Explain how potential sources of bias identified in slides 5 and 6 have been mitigated].
- Refer to “Quick Tips” document

# Steering committee members

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- Robert Roscoe, BSc Pharm, ACPR, CDE, CPT
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# Learning objectives

**At the end of this session, participants will be able to:**

1. Effectively diagnose and assess rosacea in their practices.
2. Recognize the factors that contribute to the pathophysiology of rosacea and its chronicity.
3. Summarize the efficacy and safety of currently available and future therapeutic options for the management of rosacea.
4. Identify the different patient types that could benefit from various treatment regimens.

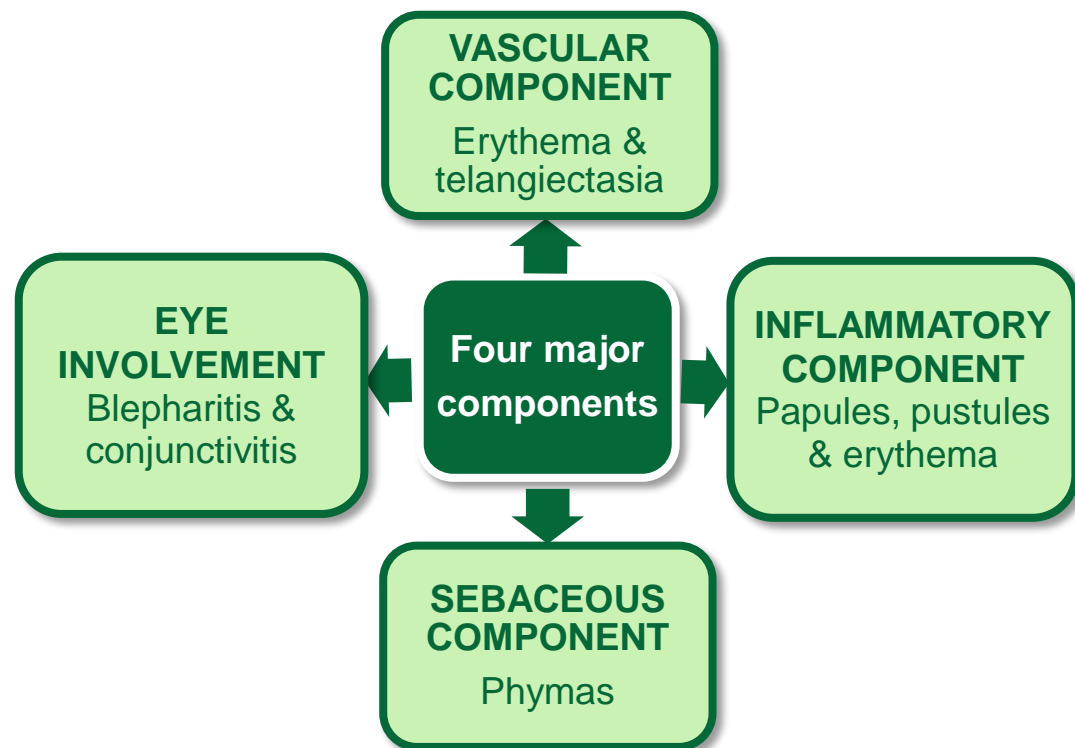


# **Rosacea: A brief overview**

# Rosacea facts

## A common chronic inflammatory skin condition

- Remitting and relapsing course
- Significant psychosocial impact
- Pathophysiology
  - Exact etiology is unknown
  - Chronic inflammation is a key factor



***Many patients are undiagnosed/untreated.***



# Identification and diagnosis of rosacea

# Diagnostic criteria

## Primary features (1 or more usually present)

- Flushing (transient erythema is a common feature)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

## Secondary features (may be present)

- Dry, flaking or scaling
- Edema
- Ocular manifestations
- Peripheral location
- Phymatous changes

# Rosacea subtypes

## SUBTYPE I: Vascular erythematotelangiectatic rosacea (ETR)



## SUBTYPE II: Inflammatory papulopustular rosacea (PPR)





# Rosacea subtypes (cont'd)

## SUBTYPE III: Phymatous rosacea



## SUBTYPE IV: Ocular rosacea



# Many present with erythema and PPR

- Majority of patients initially present with ETR
- Erythema becomes more persistent
- Papules and pustules, and associated erythema appear with continued inflammation
- PPR frequently occurs after or in conjunction with ETR
- May progress without long-term therapy





# Prevalence of ocular problems

- Occurs in **at least 50%** of patients with rosacea, regardless of subtype
- Most common complication is intermittent conjunctivitis, with or without blepharitis
- Ocular changes can become chronic and lead to corneal scarring and perforation



***Ask about and examine patients for ocular involvement for a more accurate and positive diagnosis of rosacea.***

# Differential diagnosis

Disease	Similarities	Differences
Acne vulgaris	<ul style="list-style-type: none"> <li>○ Papules, pustules, erythema</li> </ul>	<ul style="list-style-type: none"> <li>○ Comedones</li> <li>○ Earlier onset</li> <li>○ Not limited to central third of face</li> <li>○ No telangiectasias or flushing</li> </ul>
Perioral/ periorificial dermatitis	<ul style="list-style-type: none"> <li>○ Erythema, papules</li> </ul>	<ul style="list-style-type: none"> <li>○ Periorificial distribution</li> <li>○ Smaller lesions</li> <li>○ No telangiectasia, flushing, or blushing</li> </ul>
Seborrheic dermatitis	<ul style="list-style-type: none"> <li>○ Blepharitis</li> <li>○ Erythema</li> </ul>	<ul style="list-style-type: none"> <li>○ Scaling, eczematous changes</li> <li>○ Paranasal, nasolabial, glabella/eyebrow, extrafacial distribution</li> </ul>
Lupus erythematosus	<ul style="list-style-type: none"> <li>○ Erythema</li> </ul>	<ul style="list-style-type: none"> <li>○ Malar or “butterfly” rash distribution</li> <li>○ Photosensitivity</li> </ul>

# Differential diagnosis (cont'd)

Disease	Similarities	Differences
Contact dermatitis	<ul style="list-style-type: none"> <li>○ Erythema, papules, pustules</li> <li>○ Burning, stinging</li> </ul>	<ul style="list-style-type: none"> <li>○ May follow distribution of causal agent</li> <li>○ Vesicular</li> <li>○ Itchy</li> </ul>
Photodermatitis	<ul style="list-style-type: none"> <li>○ Erythema, papules, plaques</li> </ul>	<ul style="list-style-type: none"> <li>○ Seasonal</li> <li>○ Can also be extrafacial (e.g., forearms and “V” area of neck)</li> <li>○ Photodistribution</li> </ul>
Actinic keratosis	<ul style="list-style-type: none"> <li>○ Erythema, plaques, telangiectasias</li> </ul>	<ul style="list-style-type: none"> <li>○ Adherent scaling (feels like sandpaper)</li> <li>○ Others signs of chronic sun exposure</li> </ul>
Steroid-induced rosacea	<ul style="list-style-type: none"> <li>○ Erythema, papules, pustules, telangiectasias</li> </ul>	<ul style="list-style-type: none"> <li>○ Related to topical application of corticosteroids</li> </ul>



# Pathophysiology of rosacea

# Skin barrier is impaired in rosacea

- Compromised skin barrier in patients with rosacea characterized by:
  - Increased centrofacial TEWL
  - Release of cytokines and associated cutaneous inflammation
- Impairment can progress to:
  - Rosacea dermatitis
  - Heightened skin sensitivity
  - Increased susceptibility towards triggers

TEWL=transepidermal water loss

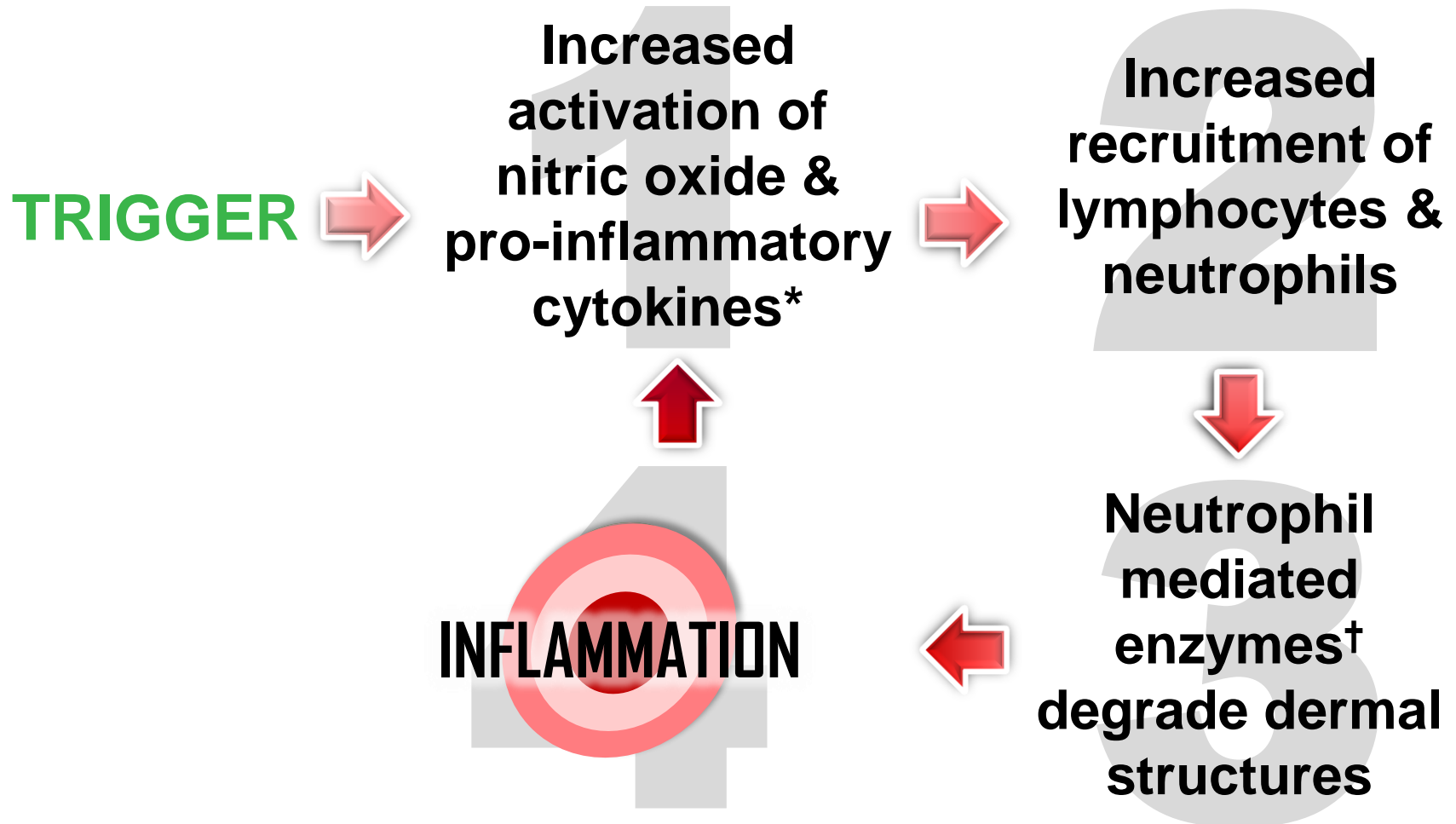
Steinoff M et al. *Journal of Investigative Dermatology Symposium Proceedings*. 2011;15:2–11.

Del Rosso JQ et al. *Cutis*. 2013;92:234-240.

# Rosacea-prone skin is hard-wired to react abnormally to multiple triggers

- Vasodilation
- Neurosensory symptoms
- Acute inflammation
- Chronic inflammation/fixed vascular changes

# The inflammatory process of rosacea

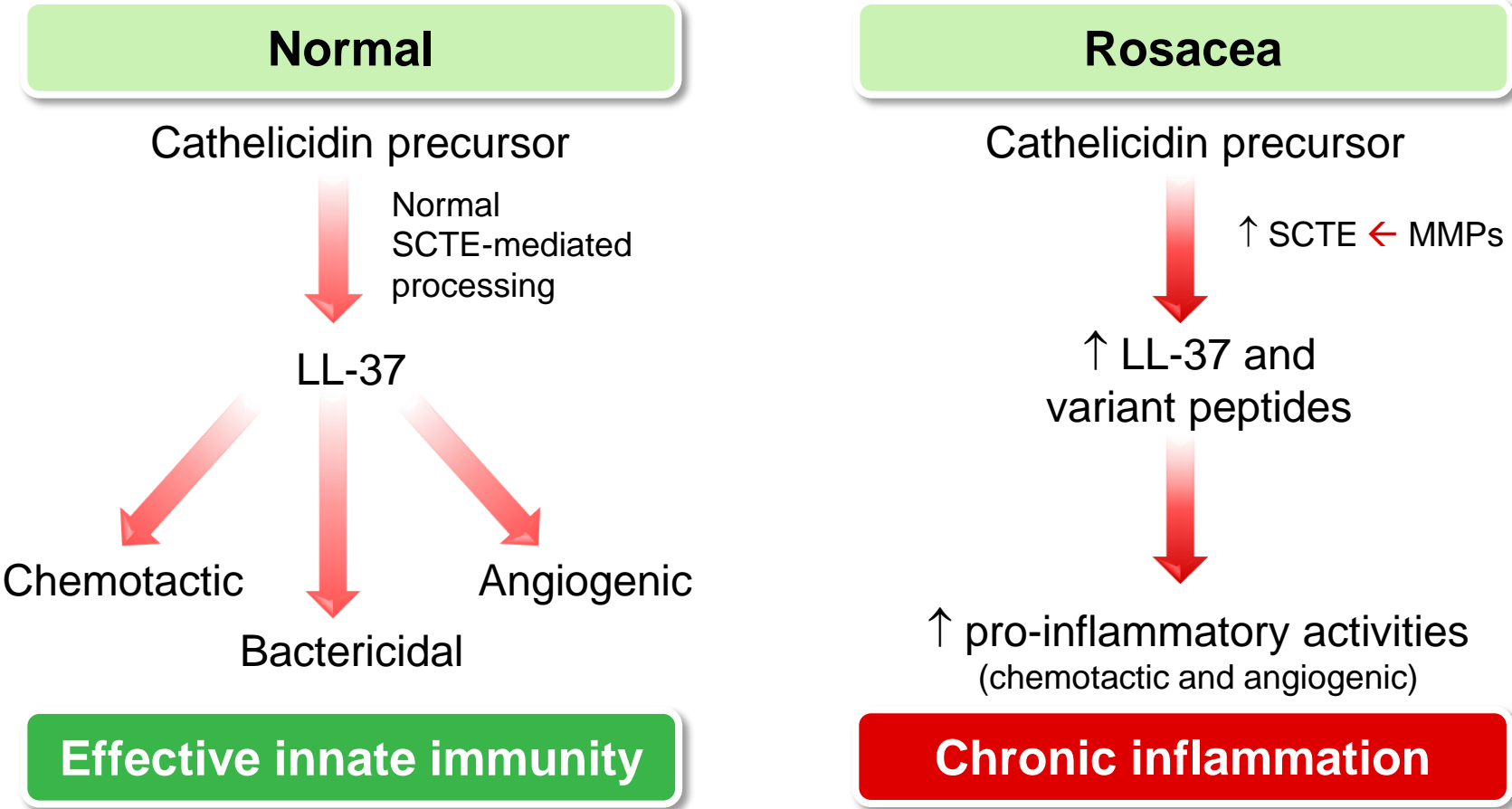


\*Tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukins (IL-1 and IL-6), etc.

†Matrix metalloproteinases (MMPs), reactive oxygen species (ROS), nitric oxide (NO), etc.

Buechner SA. *Dermatology*. 2005;210:100-108. Wise RD. *Compr Ther*. 2007;33:78-81. Jones D. *Cutis*. 2004;74(3 Suppl):17-20, 32-34. Baldwin HE. *J Drugs Dermatol*. 2006;5:16-21.

# Cathelicidin expression is increased in rosacea, contributing to chronic inflammation



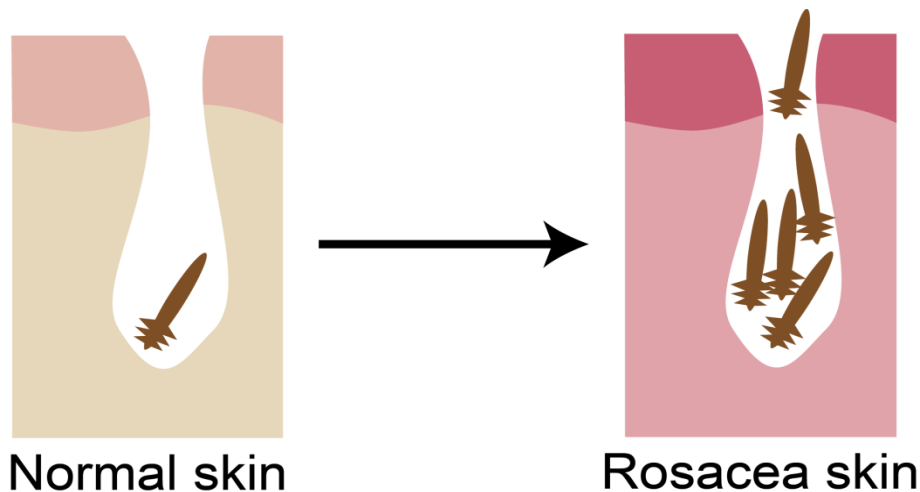
MMPs=matrix metalloproteinases; SCTE=stratum corneum tryptic enzyme

Bevins CL, et al. *Nat Med.* 2007;13:904-906.



# **Demodex burden is also increased, and may trigger inflammation**

- High density of *Demodex* in rosacea skin
  - 35% to 50% of rosacea patients have increased *Demodex* load (>5 mites/cm<sup>2</sup>)
  - 6-fold increase in *Demodex* density in rosacea vs age-matched controls
- *Demodex* is thought to activate and stimulate the immune system, and exacerbate skin barrier disruption





# **Management of rosacea in practice**

# Management strategies

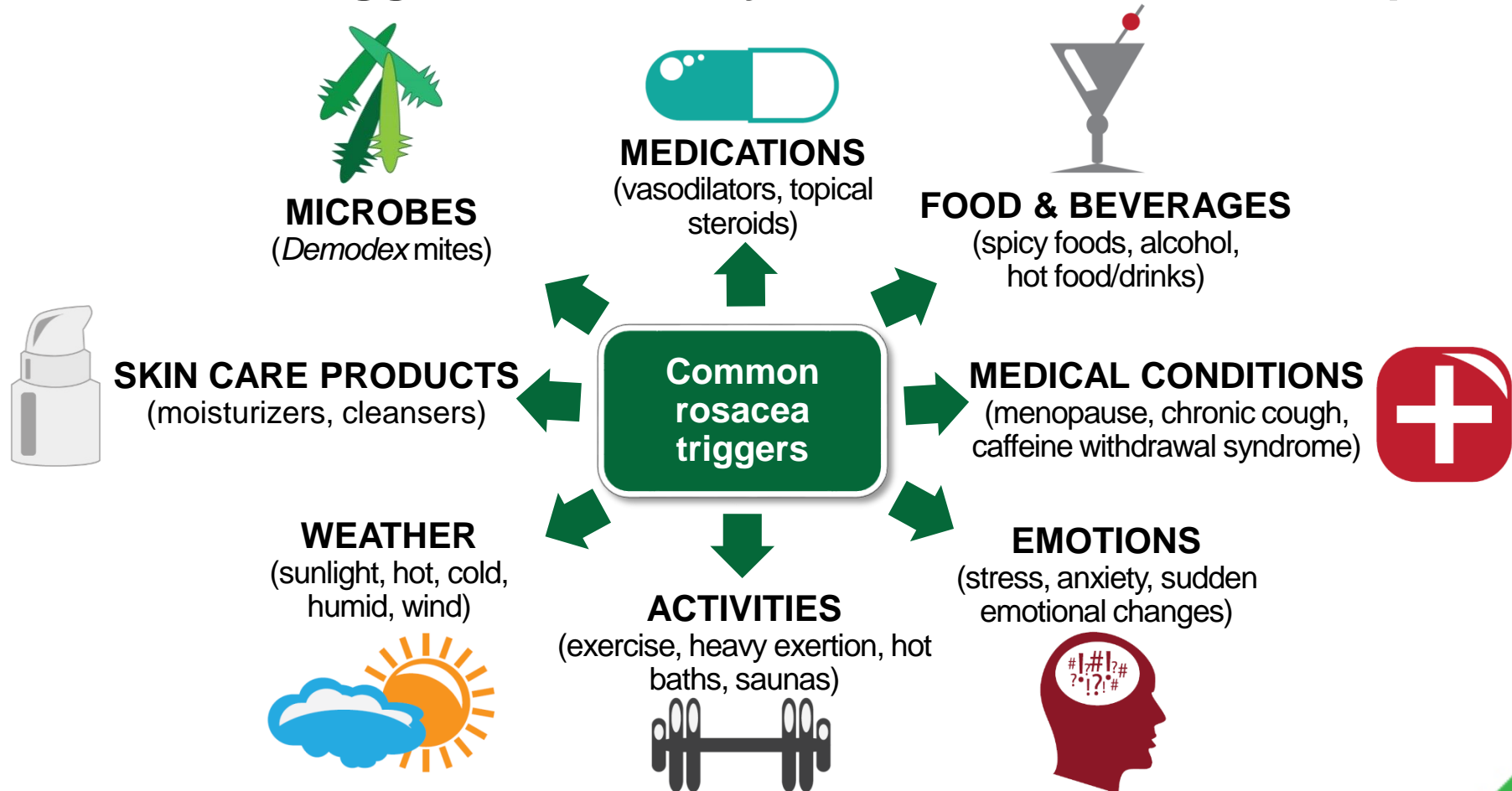
- Patient education and reassurance
  - Avoidance of triggers
  - Gentle skin care
  - Broad spectrum sun protection
- Topical agents
  - Mild to severe disease\*
  - Considered safe for long-term use
- Oral (systemic) agents
  - Anti-inflammatory dose doxycycline approved for initial and ongoing therapy
  - Antibiotics and isotretinoin used with caution due to potential risks
  - Vasoregulating agents (anecdotal)
- Laser and phototherapy
- Surgical intervention

\*Data to support the efficacy of ivermectin in severe rosacea.

Baldwin HE. *J Drugs Dermatol.* 2006;5(1):16-21. Bikowski JB, Goldman MP. *J Drugs Dermatol.* 2004;3(3):251-261.

# Identifying and avoiding individual triggers

Rosacea trigger factors may cause rosacea to flare up



National Rosacea Society. Coping with rosacea brochure.

<http://www.rosacea.org/patients/materials/coping/index.php>. National Rosacea Society. The ecology of your face:

Demodex, rosacea and you. <http://rosacea.org/patients/demodex>.

# Adjunctive skin care recommendations

## CLEANSE

- Mild synthetic cleanser containing emollients
- Avoid fragrances and irritating soaps

## MOISTURIZE

- Fragrance-free, hypoallergenic moisturizer/barrier repair product
- Emollient therapies recommended (helps moisturize, improve skin integrity, reduce trigger penetration and irritation)

## PROTECT

- Use broad spectrum sensitive-skin sunscreen of at least SPF 30 (esp. with zinc oxide and titanium dioxide)  
**or**
- Use moisturizer with sunscreen

# Selected topical therapies for rosacea

- Therapeutic options include:
  - Azelaic acid 15% (gel only)
  - Metronidazole 1% and 0.75% (gel, lotion and cream)
  - Sodium sulfacetamide/sulfur (lotion and cream ± sunscreen)
  - Brimonidine 0.33% (gel only)
  - Ivermectin 1% (cream only)
- Works in rosacea through:
  - Anti-inflammatory effects (e.g., inhibition/downregulation of ROS)
  - Vasoconstrictive effects (brimonidine 0.33% specific)
  - Antiparasitic effects (ivermectin 1% specific)
- Can be used for both induction and maintenance therapy
- Potential side effects/complications include:
  - Cutaneous irritation
  - Antibiotic resistance (traditional topical therapies specific)

ROS=reactive oxygen species

Baldwin HE. *J Drugs Dermatol* 2012;11(6):725-730. Brimonidine Product Monograph. Galderma Canada Inc. February 21, 2014. Ivermectin Product Monograph. Galderma Canada Inc. April 22, 2015.

# Selected systemic therapies for rosacea

- Therapeutic options include:
  - Anti-inflammatory dose doxycycline 40 mg
    - Only Health Canada approved systemic therapy for rosacea
  - Tetracycline class antibiotics
    - Incl. doxycycline 100 mg, minocycline 50/100 mg, tetracycline 250/500 mg
  - Erythromycin 500 mg
- Works in rosacea via anti-inflammatory properties, **not** antibacterial
- Can only be used for induction therapy (exception: anti-inflammatory dose doxycycline\*)
- Potential side effects/complications include:
  - Antibiotic resistance (antibiotic specific)
  - Photosensitivity, candidiasis, GI irritation (mainly antibiotic specific)
  - Skin pigmentation, CNS effects (minocycline specific)

\*Data for use up to 9 months, but no indication for maintenance therapy.



# Treating the rosacea subtypes



# Treating erythematotelangiectatic rosacea (ETR)

## THERAPEUTIC OPTIONS

- New topical: brimonidine
- Traditional topicals: Azelaic acid, metronidazole, or sulfacetamide/sulfur
- Vascular laser therapy
- Oral tetracyclines

## IF NON-RESPONSIVE OR SUB-OPTIMAL RESULTS, CONSIDER...

- Anti-inflammatory dose doxycycline
- Other oral tetracyclines
- Topical clindamycin, pimecrolimus or tacrolimus

**NOTE:** reduction in facial erythema with traditional topical and oral therapies is attributed to resolution of perilesional erythema, and **not** the diffuse erythema that is characteristic of ETR.

Goldgar C et al. Am Fam Physician 2009;80(5):461-468. Baldwin HE. Oral Therapy for the Treatment of Rosacea. [http://www.skintherapyletter.com/CME/art\\_5.php](http://www.skintherapyletter.com/CME/art_5.php). Del Rosso J et al. J Clin Aesthet Dermatol. 2012;5(3):26–36. Brimonidine Product Monograph. Galderma Canada Inc. February 21, 2014.

# The problem of diffuse erythema

- Diffuse erythema is believed to correlate with vascular changes of rosacea
- Traditional therapeutic options for rosacea exhibit low to negligible efficacy against it
  - Traditional topical\* and oral therapies are largely ineffective
  - Laser and light therapies tend to be the most effective
- Diffuse erythema often persists well after inflammatory lesions have resolved

***Recent introduction of topical  $\alpha$ -adrenergic receptor agonists has brought effective control of diffuse erythema.***

\*Traditional topical therapies include azelaic acid, metronidazole and sodium sulfacetamide/sulfur.

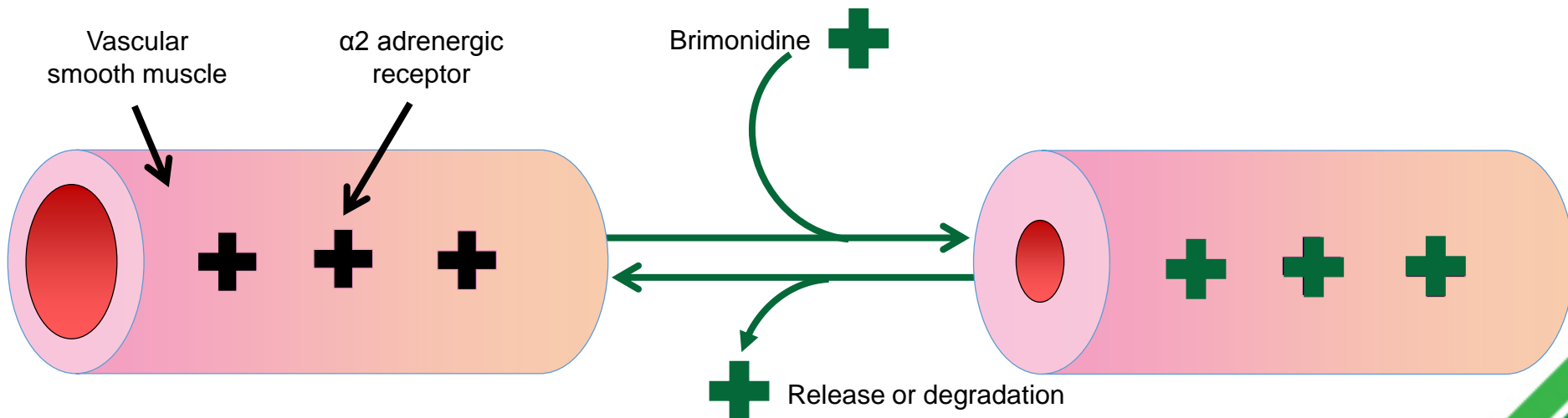
Del Rosso JQ et al. *J Drugs Dermatol.* 2012 ;11(6):694-700. Goldgar C et al. *Am Fam Physician* 2009;80(5):461-468.

# Selective $\alpha$ -adrenergic receptor agonists for erythema

	<b>Brimonidine gel 0.33%</b>	<b>Oxymetazoline 0.05%</b> (Currently not approved for use in Canada)
<b>Receptor</b>	$\alpha_2$	$\alpha_1$
<b>Localization</b>	Vascular smooth muscle	
<b>Vessel type</b>	Small	Large
<b>Predominant receptor</b>	Peripheral vasculature (skin)	Central vasculature

# Potent vasoconstrictive activity of brimonidine gel 0.33%

- Topical treatment applied once-daily to 5 areas of the face
- Active ingredient is brimonidine tartrate, a highly selective  $\alpha_2$ -adrenergic receptor agonist
  - Binding results in vasoconstriction of superficial cutaneous blood flow, with shunting to deeper vasculature
  - Effect is non-permanent and vascular blood flow returns to normal after several hours



# Application of brimonidide gel 0.33% once-daily provided rapid, long-lasting relief of erythema

## Secondary Endpoint



Patient ID# 8076-005  
Photos on Day 29 of treatment

Fowler J et al. *Br J Dermatol.* 166(3):633-641.

# Marked improvement of erythema with brimonidine gel 0.33% sustained for up to 12 months



Patient ID#: 8047-002

***Brimonidine only treats the erythema of rosacea, and may unmask inflammatory lesions (if present).***

# Safety profile of brimonidine gel 0.33% confirmed with long-term use

- No new safety signals with long-term chronic use
- Discontinuations due to adverse events did not increase over time
- Incidence of sensitization was approximately 1%

# General recommendations for using brimonidine in rosacea

- A** **ssess** individual's clinical features and create treatment plan
- E** **ducate** patient about rosacea and brimonidine therapy
- I** **nhibit/minimize** inflammation due to poor skin care/rosacea and use appropriate medical therapy
- O** **ptimize** brimonidine application technique and timing (i.e., "start low, go slow")
- U** **nderstand** how to manage worsening redness



# Marked improvement of erythema with oxymetazoline 0.05% shown in preliminary trials



# Treating papulopustular rosacea (PPR)

## THERAPEUTIC OPTIONS


- New topical ivermectin
- Combo therapy with:
  - Topical azelaic acid, metronidazole or sulfacetamide/sulfur
  - &
  - Anti-inflammatory dose doxycycline or oral tetracyclines
- Vascular laser therapy

## IF NON-RESPONSIVE OR SUB-OPTIMAL RESULTS, CONSIDER...

- Anti-inflammatory dose doxycycline
- Other oral tetracyclines
- Topical clindamycin, pimecrolimus or tacrolimus
- Benzoyl peroxide (refractory cases only)
- Topical tretinoin (refractory cases only)
- Referral for oral isotretinoin

### ***PPR is the easiest subtype to treat***

- May respond to traditional topical therapy
- Topical ivermectin and oral agents more effective

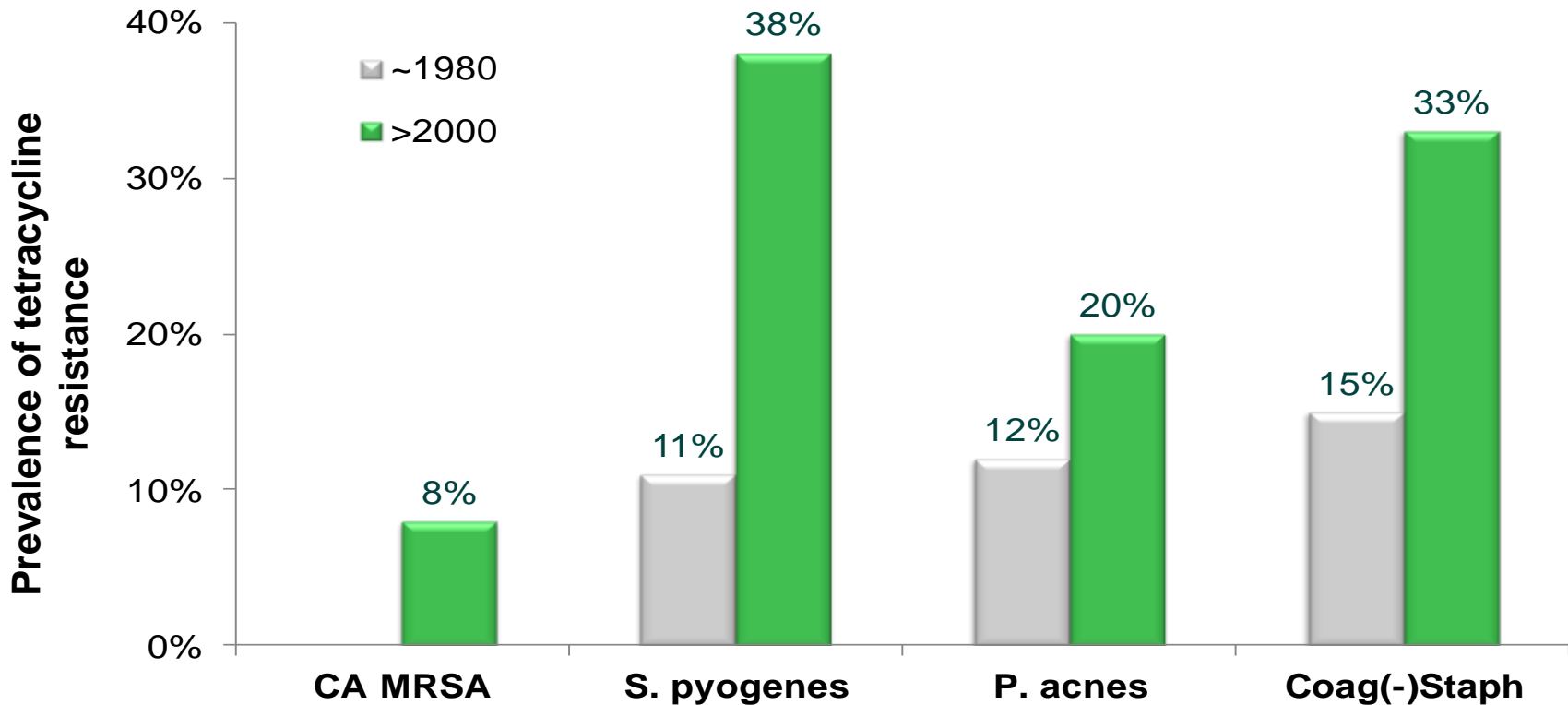


# **A closer look at systemic antibiotics and their role in rosacea**

# Clinical considerations with systemic antibiotics

- Alteration of normal flora presents risk for superimposed infections (e.g. vaginal candidiasis)
- Drug-specific side effects
  - Photosensitivity
  - GI upset
  - Minocycline specific reactions
    - Vertigo (7%)
    - Pigmentation (5%)
    - Hypersensitivity reactions (rare)
    - Lupus-like syndrome reactions (rare)
- Associated with increasing prevalence of antimicrobial drug resistance

# Resistance to tetracycline has increased over the last 3 decades



***Doxycycline 100 mg has been shown to induce microbial resistance in as early as 7 days.***

Moran GJ et al. *N Engl J Med.* 2006;355:666-674. Ayer V et al. *Antimicrob Agents Chemother.* 2007;51:1865-1868. Del Rosso JQ et al. *Dermatol Clin.* 2007;25:127-132. Reynolds R et al. *J Antimicrob Chemother.* 2004;53:1018-1032. Mayon-White RT et al. *J Hyg.* 1982;88:439-452. Markowitz N et al. *Antimicrob Agents Chemother.* 1983;23:450-457. Brown JM et al. *J Med Microbiol.* 1983;16:271-280. Data on file. Galderma Laboratories, L.P.

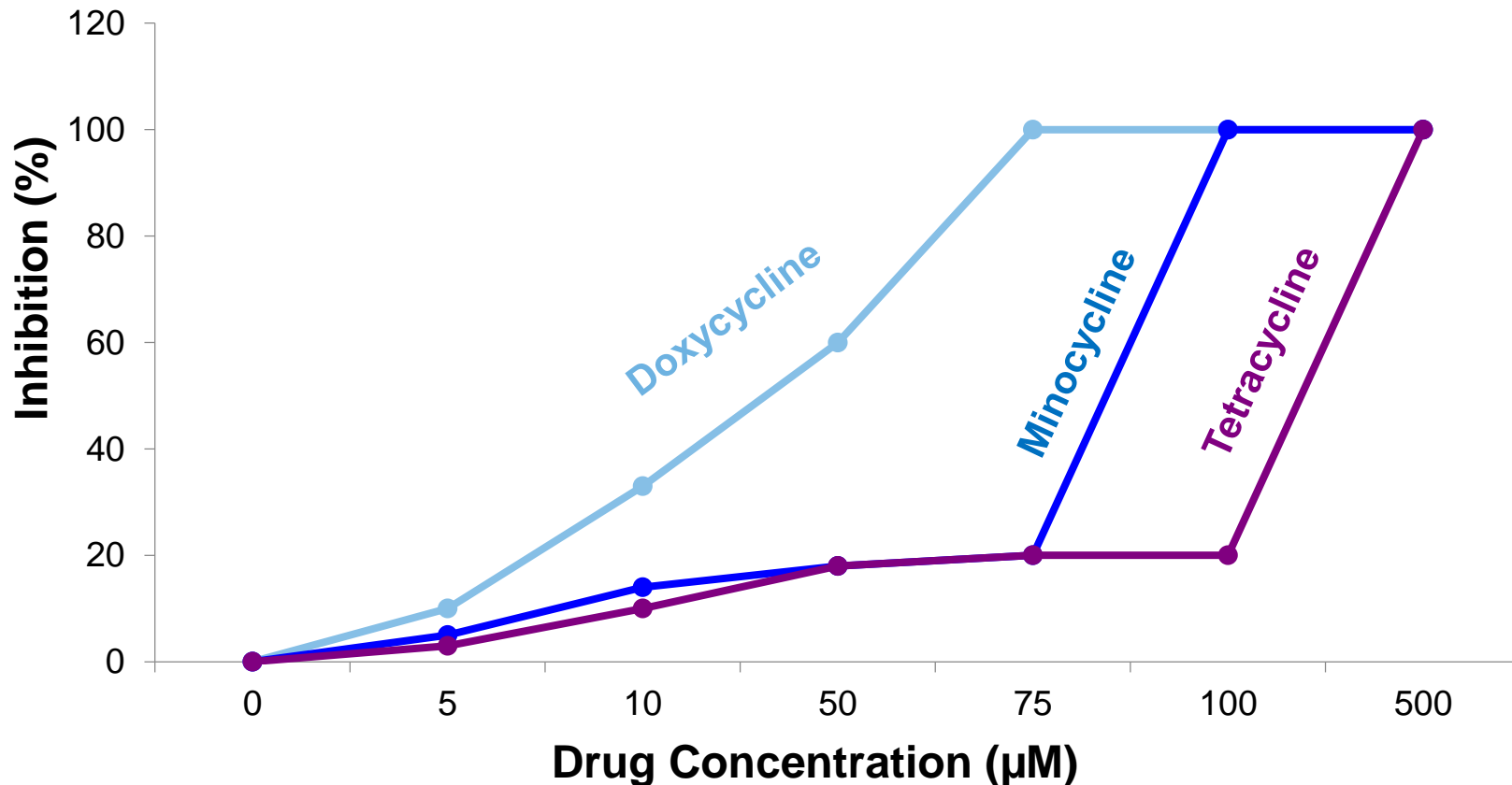
# Are tetracyclines tailor-made for rosacea?

Rosacea	Tetracycline class molecules
Upregulates proinflammatory cytokines	Downregulates proinflammatory cytokines
Promotes angiogenesis	Inhibit angiogenesis
Increased cathelicidins	Inhibits cathelicidins
Increased neutrophil chemotaxis: ↑Nitric oxide ↑Reactive oxygen species ↑MMPs	Inhibit neutrophil chemotaxis: ↓Nitric oxide ↓Reactive oxygen species ↓MMPs

MMPs=matrix metalloproteinases

Cazalis J, et al. *J Periodontol.* 2008;79:1762-1768. Ueyama Y et al. *Br J Oral Maxillofac Surg.* 1994;32:96-99. Pruzanski W et al. *J Rheumatol.* 1998;25:1807-1812. Hoyt JC et al. *J Immunol.* 2006;176:567-572. Akamatsu H, et al. *Acta Derm Venereol.* 1992;72:178-179. Dan L et al. *Curr Eye Res.* 2008;33:653-660. Bevins CL, et al. *Nat Med.* 2007;13:904-906.

# In vitro inhibition of skin collagenase (MMP-8) by tetracyclines



***Doxycycline directly inhibits MMP, reducing cathelicidin-mediated inflammation.***



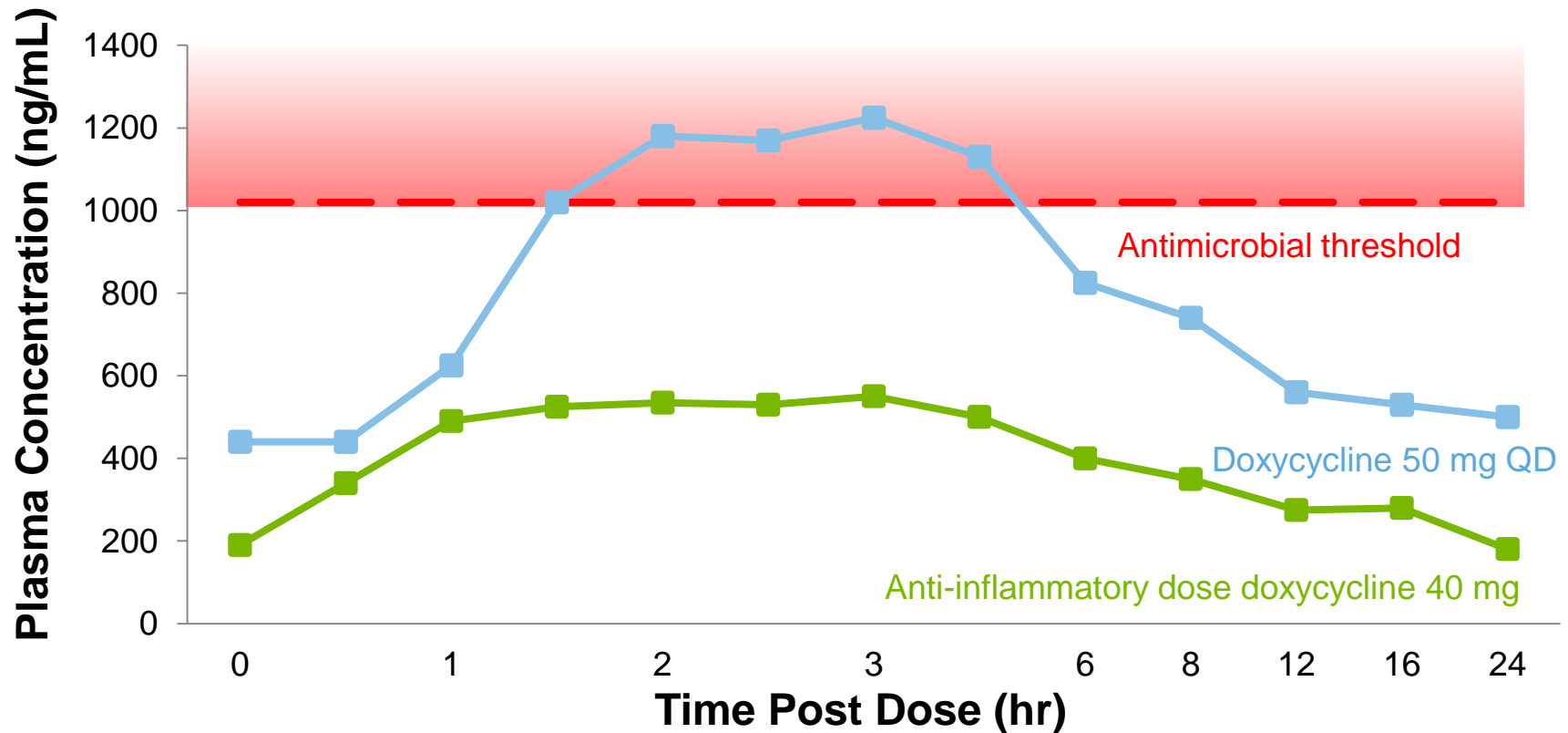
**Anti-inflammatory  
dose doxycycline:  
What improvements  
does it offer?**



# Unique anti-inflammatory dose doxycycline formulation

- Once-daily capsule containing doxycycline in a combination of:
  - 30 mg immediate-release beads
  - 10 mg delayed-release beads
- Formulation allows it to reach levels that achieve **anti-inflammatory activity, but not antimicrobial activity**, and maintain those levels over 24 hours
- **Similar to aspirin** (different dosages = different effects)
  - 81 mg: platelet inhibition
  - 650-1000 mg: anti-inflammatory

# Plasma concentrations remain below the antimicrobial threshold



\*16 healthy adult subjects in the anti-inflammatory dose doxycycline arm measured at 7 days; mean weight, 75 kg.

***Anti-inflammatory dose doxycycline concentration remains below the antimicrobial threshold, unlike doxycycline 50 mg.***

# No reported effect on antimicrobial resistance over 9 months

Mean percent of recovered flora resistant to doxycycline (4 µg/mL) for each treatment

	Anti-inflammatory dose doxycycline (n = 34)		Placebo (n = 36)	
	Mean	Std Dev	Mean	Std Dev
Baseline	12.69	23.16	3.95	7.39
9 Months	17.79	20.85	9.33	20.64
Change from baseline to 9 months	5.09	31.17	5.38	22.02

***Change over 9 months was equivalent between both groups (5.09% and 5.38%).***

# Significantly reduces inflammatory lesions



Baseline

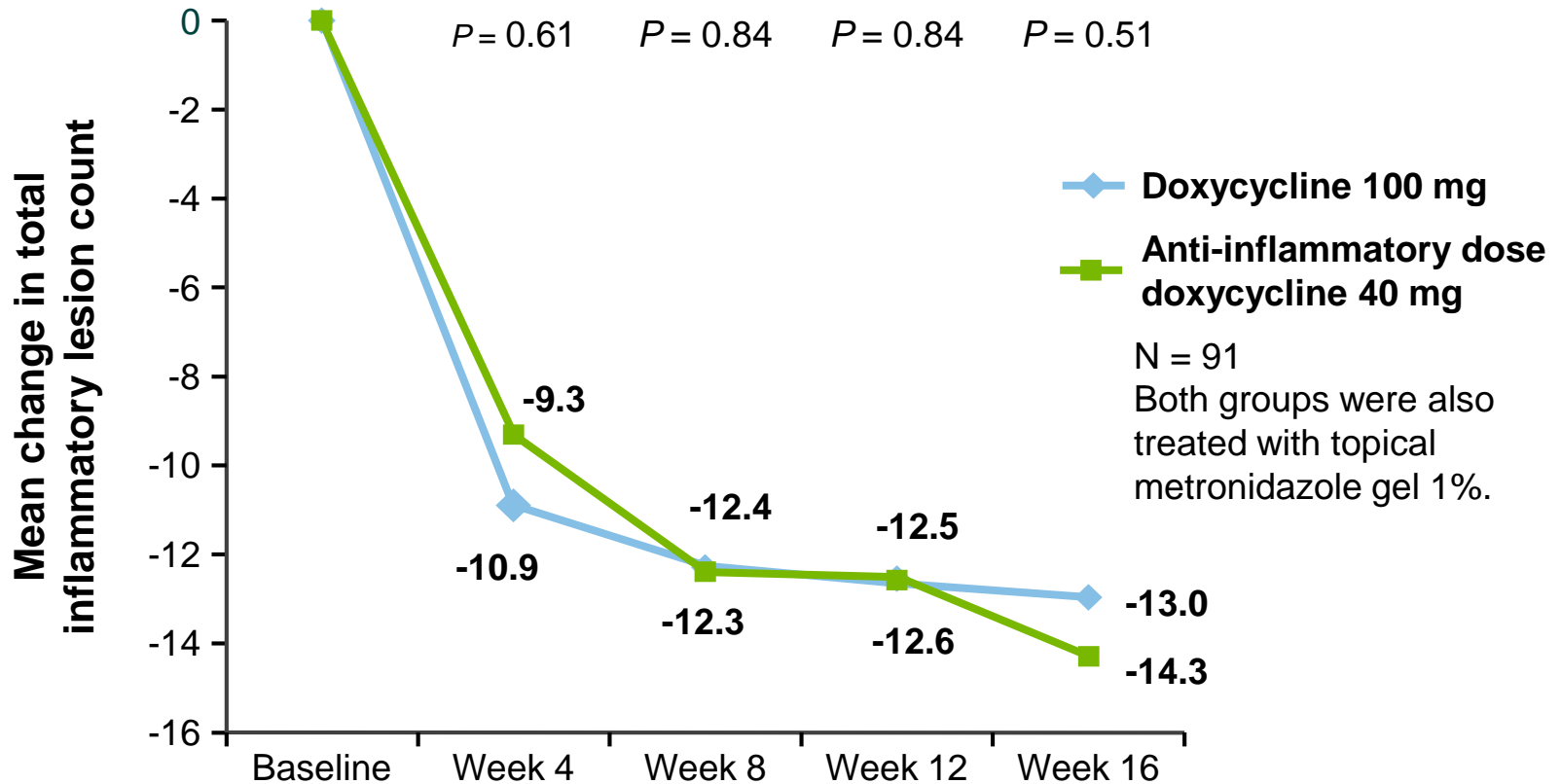


Week 16

Patient 301.203.

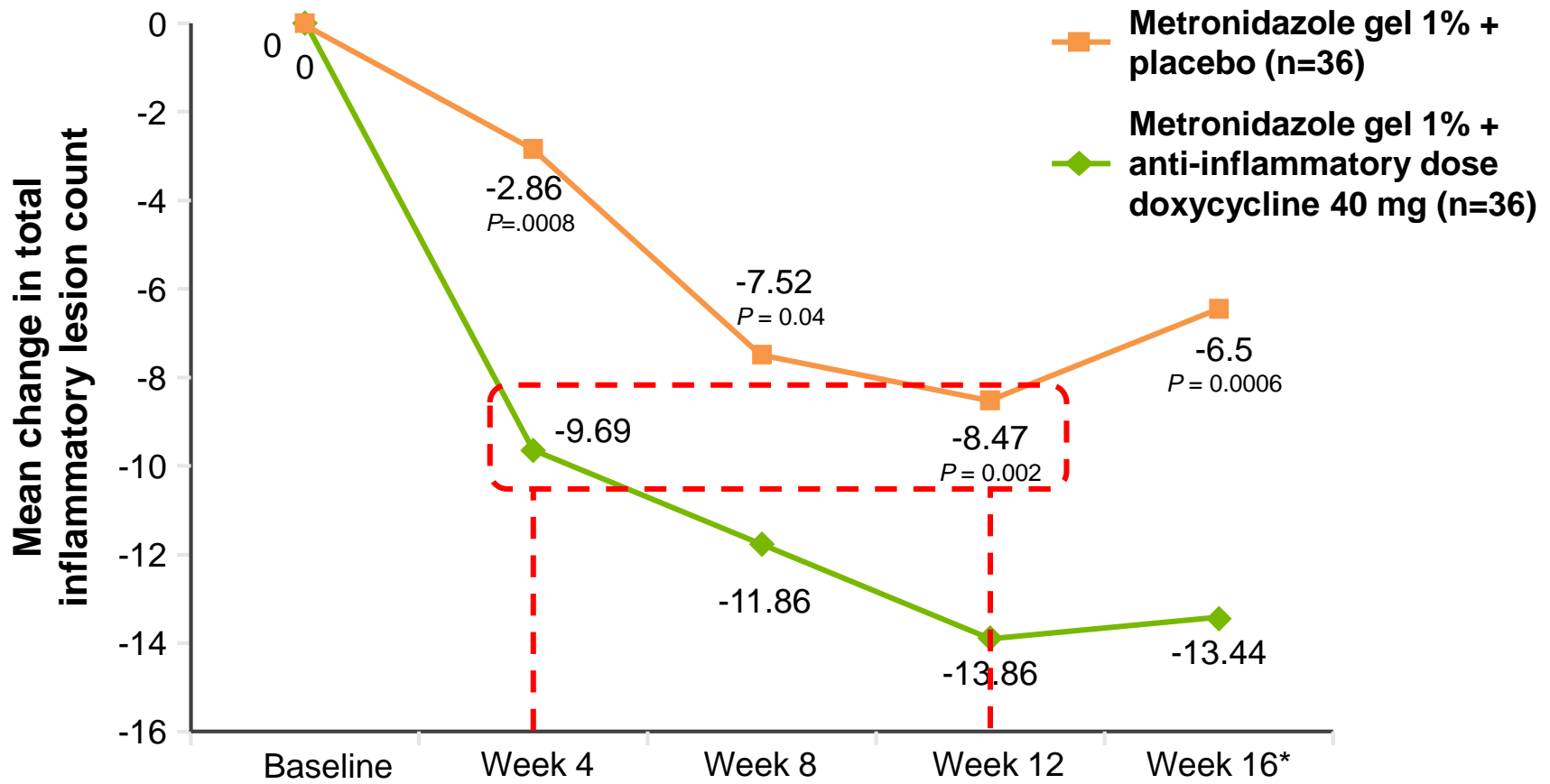
***Reduction in inflammatory lesions was seen in as early as 3 weeks ( $p=0.005$  vs placebo).***

# Similar efficacy as doxycycline 100 mg



***5x less GI disorders reported with anti-inflammatory dose doxycycline vs doxycycline 100 mg.***

# Improves therapeutic outcomes when combined with topical agents



\*Metronidazole was discontinued at week 12. Of the 72 patients enrolled (36 per treatment arm) 64 patients completed the study (30 in the Metronidazole gel 1% plus anti-inflammatory dose doxycycline arm and 34 in the Metronidazole gel 1% plus placebo arm).

Fowler JF Jr. *J Drugs Dermatol.* 2007;6:641-645.

# Discussion question

***A 55 year old male presents with erythematous papules and pustules on his cheeks and nose, a condition he has had for several years. His daughter is getting married in 8 weeks and he would like to be clear for the wedding. Which option would offer him the most rapid response?***

- a) Azelaic acid monotherapy
- b) Metronidazole gel 1% monotherapy
- c) Doxycycline 100 mg monotherapy
- d) Anti-inflammatory dose doxycycline + metronidazole gel 1% combination therapy
- e) Other



# Emerging therapies for papulopustular rosacea (PPR)



# Topical ivermectin cream for PPR

- First new topical treatment for inflammatory lesions of rosacea in nearly 10 years
- Applied once-daily to 5 areas of the face at bedtime
- Hypothetical dual mechanism of action:

## Antiparasitic

- Antivermicide
- *Demodex*:
  - No direct data and few supporting literature
  - Published clinical case series (demodicidosis, blepharitis, skin diseases)
  - Veterinary practice in dogs

## Anti-inflammatory

- Decreases cellular and humoral immune responses
  - Incl. neutrophil phagocytosis and chemotaxis, and oxidant production by phagocytes
- Parent compound avermectin shown to significantly regulate inflammatory cytokines (*in vitro* studies)

PPR=papulopustular rosacea

Zhang X. *Inflamm Res.* 2009;9:354–359. Zhang X. *Inflamm Res.* 2008;57:524–529. Stankiewicz M et al. *Vet Immunol and Immunopathology.*1995;44:347-358. Labro M. *J Antimicrobial Chemotherapy.*1998;41:37-46. Ci X et al. *Fundament Clinical Pharmacol.* 2009;23:449–455.

# Dramatically reduces inflammatory lesions



**Baseline**

IGA=4; lesion count = 63



**Week 12**

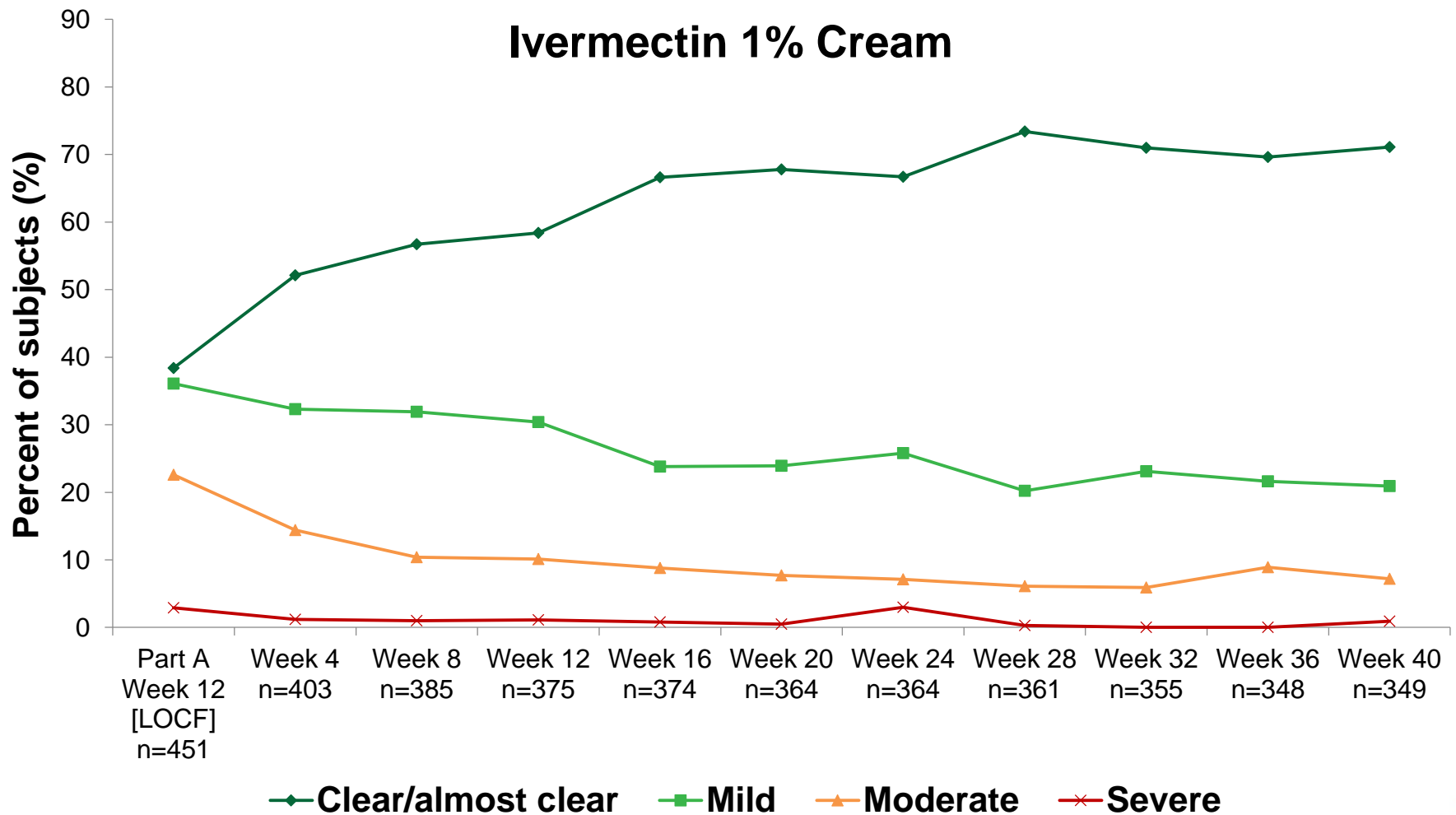
IGA=1; lesion count=2



Subject ID: 8129-008  
Study: 18171

***Significant reductions in inflammatory lesions seen as early as 2 weeks ( $p < 0.001$  vs vehicle cream).***

# Improvement continues with long-term use



# Provides superior improvement vs. metronidazole 0.75% cream



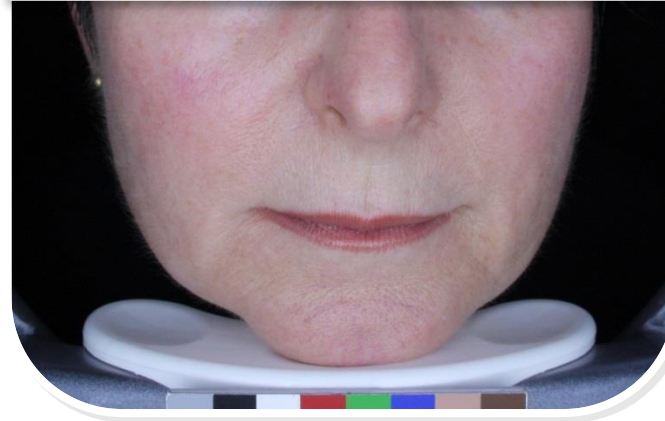
**Baseline**

IGA=3; lesion count = 22



**Week 16**

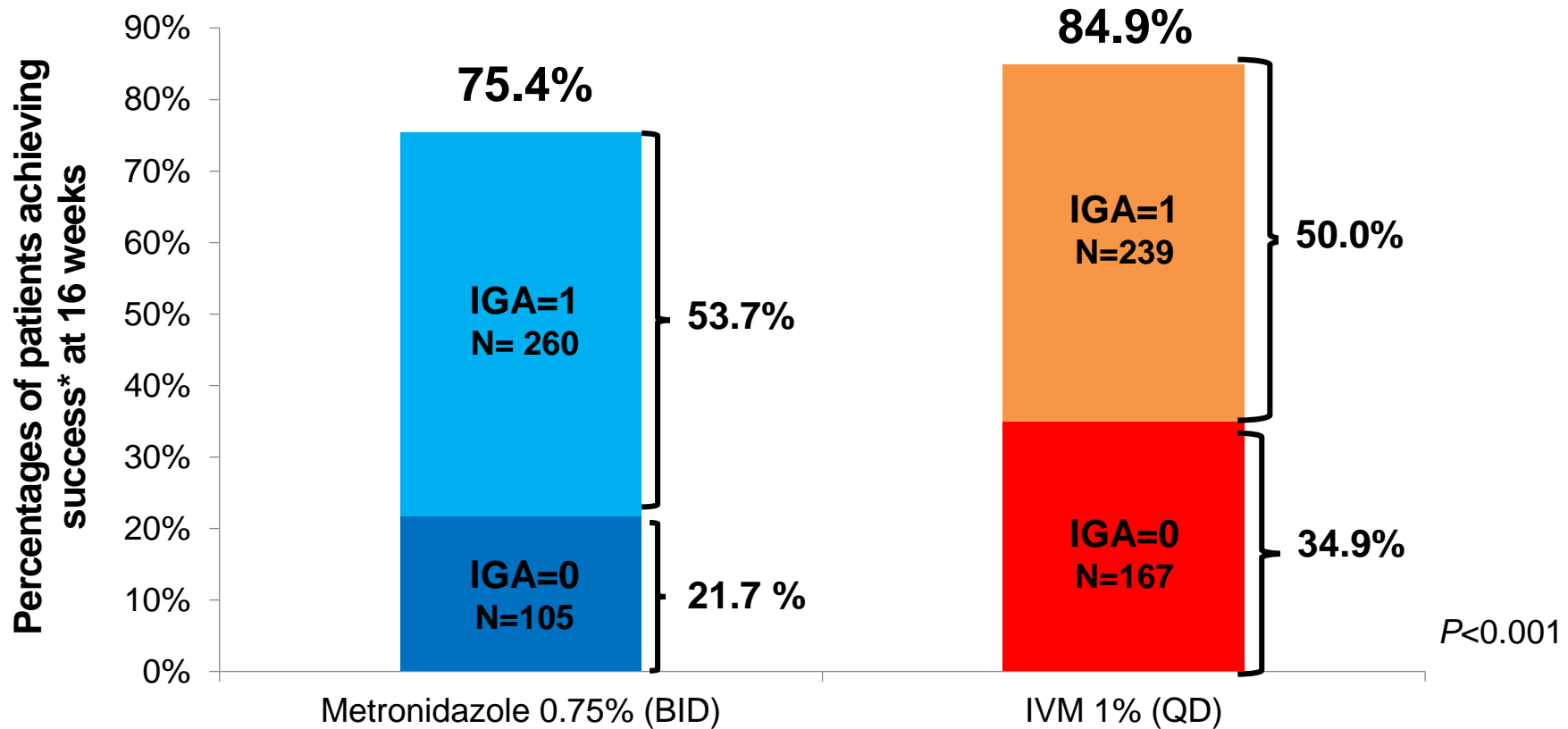
IGA=0; lesion count=0



Subject 40173-5140-009

***Significant reductions in inflammatory lesions seen as early as 3 weeks (vs metronidazole cream 0.75%,  $p=0.040$ ).***

# Helps more patients achieve treatment success vs. metronidazole 0.75% cream



***Nearly 20% more patients with severe rosacea at baseline were successfully treated vs. metronidazole 0.75% cream.***

\*Success was defined as an IGA score of 0 or 1.

Taieb A, et al. *Br J Dermatol.* 2014; DOI: 10.1111/bjd.13408.

# Safety profile similar to vehicle cream

	Ivermectin cream (n=452)	Vehicle cream (n=231)
Total number of related AEs, n	24	25
Total number of subjects with related AEs, n (%) <sup>*</sup>	19 (4.2)	18 (7.8)
Skin burning sensation	8 (1.8)	6 (2.6)
Skin irritation	5 (1.1)	3 (1.3)
Pruritus	2 (0.4)	4 (1.7)
Pain of skin	1 (0.2)	5 (2.2)

***The safety profile remained stable with long-term treatment for up to one year.***

<sup>\*</sup>A subject was counted once even if the subject experienced more than 1 adverse event during the study.

Stein Gold L, et al. *J Drugs Dermatol.* 2014;13:316-323. Stein Gold L, et al. *J Drugs Dermatol.* 2014;13:1380-1386.



# Discussion question

***A 43 year old female presents with moderately severe papulopustular rosacea. She complains of skin stinging and burning, and worsening of symptoms during periods of high stress. She has tried several cosmetic products without much success, and would like a prescription treatment to clear her skin. Of the options listed, which would likely provide her the clearance she wants?***

- a) Azelaic acid monotherapy
- b) Metronidazole gel 1% monotherapy
- c) Ivermectin 1% cream monotherapy
- d) Doxycycline 100 mg monotherapy
- e) Anti-inflammatory dose doxycycline monotherapy

# Treating phymatous and ocular rosacea

## PHYMATOUS ROSACEA

### THERAPEUTIC OPTION

- Oral tetracyclines

**Consider referral** for oral isotretinoin, ablative/pulsed dye laser therapy or electrocauterization

## OCULAR ROSACEA

### THERAPEUTIC OPTIONS

- Topical or oral tetracyclines
- Eyelid hygiene  
(e.g., artificial tears, lid cleansing)

**Consider referral** to an ophthalmologist



# Summary

- Rosacea is a chronic inflammatory skin condition of the central face often characterized by flushing, erythema, papules/pustules and telangiectasias
- Evidence suggests that a compromised skin barrier, neutrophils, lymphocytes and cathelicidins play a key role in the underlying inflammatory nature of rosacea
- Effective treatment of rosacea requires blockage of the inflammatory process

# Summary (cont'd)

- Anti-inflammatory dose doxycycline has been shown to be an effective systemic alternative with the potential to reduce antibiotic resistance and lessen common side effects of its class
- Topical  $\alpha$ -adrenergic receptor agonists may also help to alleviate the diffuse erythema that often persists post-treatment
- Emerging therapies, like ivermectin, may further fulfill unmet needs in rosacea, providing superior efficacy in a treatment that is well-tolerated



**Questions?**




**Thank you!**



# Differential diagnosis of rosacea

Module II



# Red and bumpy? A guide to the differential diagnosis of rosacea

[insert name], [insert credentials]

# Steering committee members

- Melinda Gooderham, MSc, MD, FRCPC
- William Barakett, MD, CCFP, FCFP
- Jerry Katz, MD, CCFP
- Peggy Leighton, MD, CCFP, FCFP
- Robert Roscoe, BSc Pharm, ACPR, CDE, CPT
- Rick Siemens, BSc Pharm, BSc Biol, CDE, CPT

# Learning objectives

**At the end of this session, participants will be able to:**

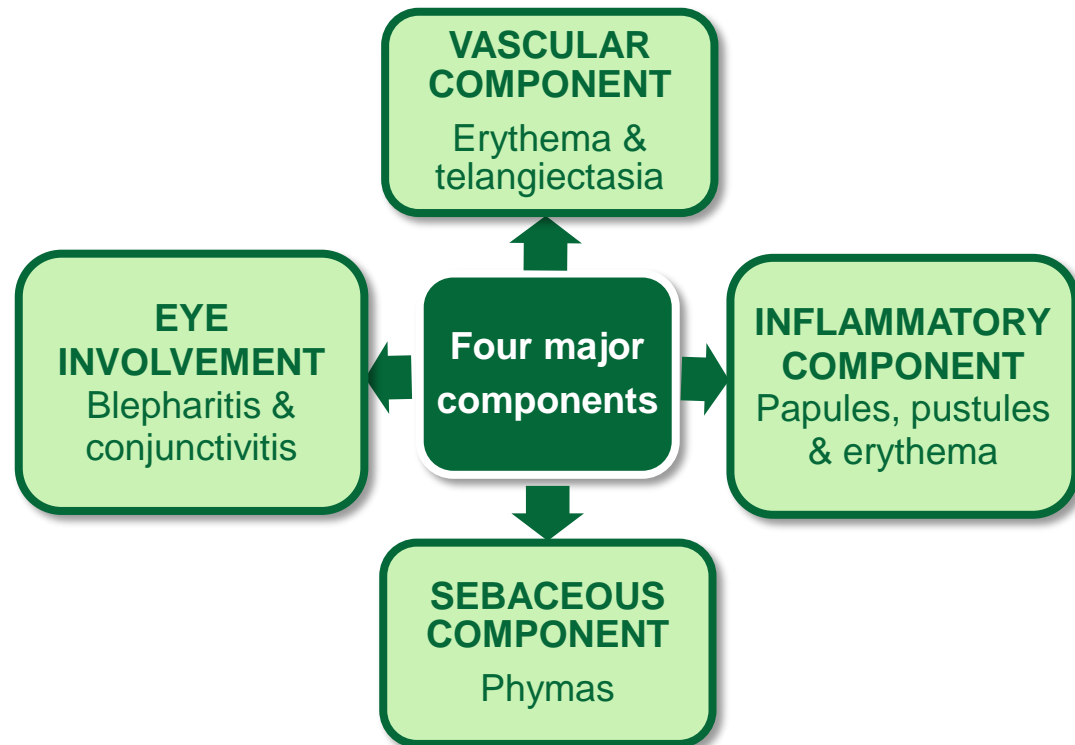
1. Identify key diagnostic features for rosacea and its subtypes.
2. Distinguish the characteristics of skin disorders that commonly mimic rosacea.
3. Develop an appropriate differential that leads to the most probable diagnosis.



# Rosacea facts

## A common chronic inflammatory skin condition

- Remitting and relapsing course
- Significant psychosocial impact
- Pathophysiology
  - Exact etiology is unknown
  - Chronic inflammation is a key factor



***Many patients are undiagnosed/untreated.***

# Diagnostic criteria

## Primary features (1 or more usually present)

- Flushing (transient erythema is a common feature)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

## Secondary features (may be present)

- Dry, flaking or scaling
- Edema
- Ocular manifestations
- Peripheral location
- Phymatous changes

# Rosacea subtypes



## **SUBTYPE I: Vascular erythematotelangiectatic rosacea (ETR)**

### ***Signs/symptoms***

- Flushing
- Redness (erythema)
- Visible red blood vessels (telangiectasias)

### ***Age***

- Young to middle-aged adults

### ***Distribution***

- Central third of the face (i.e., cheek, nose, chin, and central forehead)

# Rosacea subtypes (cont'd)



## **SUBTYPE II: Inflammatory papulopustular rosacea (PPR)**

### ***Signs/symptoms***

- Redness (erythema)
- Papules
- Pustules

### ***Age***

- Young to middle-aged adults

### ***Distribution***

- Central third of the face (i.e., cheek, nose, chin, and central forehead)

# Rosacea subtypes (cont'd)



## **SUBTYPE III: Phymatous rosacea**

### ***Signs/symptoms***

- Thick skin (peau d'orange), nodules
- Irregular skin surface
- Enlargement (nose)

### ***Age***

- Young to middle-aged adults

### ***Distribution***

- Nose (most often), but may occur on chin, forehead, cheeks, or ears



# Rosacea subtypes (cont'd)



## **SUBTYPE IV: Ocular rosacea**

### ***Signs/symptoms***

- Foreign body sensation, burning and stinging
- Dryness and itching, ocular photosensitivity
- Blepharitis, conjunctivitis, blurred vision (rare)

### ***Age***

- Young to middle-aged adults

### ***Distribution***

- Eyes and eyelids

# Rosacea subtypes (cont'd)



## **VARIANT (RARE): Granulomatous rosacea**

### ***Signs/symptoms***

- Non-inflammatory; hard; brown, yellow, or red cutaneous papules; or nodules of uniform size

### ***Age***

- Young to middle-aged adults

### ***Distribution***

- Cheeks and periorificial areas (typically)

# Standard grading system

## SUBTYPE I: Vascular erythematotelangiectatic rosacea (ETR)



## SUBTYPE II: Inflammatory papulopustular rosacea (PPR)





# Standard grading system (cont'd)

## SUBTYPE III: Phymatous rosacea



## SUBTYPE IV: Ocular rosacea



# Many present with erythema and PPR

- Majority of patients initially present with ETR
- Erythema becomes more persistent
- Papules and pustules, and associated erythema appear with continued inflammation
- PPR frequently occurs after or in conjunction with ETR
- May progress without long-term therapy



# Prevalence of ocular problems

- Occurs in **at least 50%** of patients with rosacea, regardless of subtype
- Most common complication is intermittent conjunctivitis, with or without blepharitis
- Ocular changes can become chronic and lead to corneal scarring and perforation



***Ask about and examine patients for ocular involvement for a more accurate and positive diagnosis of rosacea.***

# Discussion question

***Does the patient in this photo have rosacea?***

a) Yes

b) No

***If so, what subtype of rosacea do you suspect this patient has?***





# Acne vulgaris



## *Signs/symptoms*

- **Comedones** (non-inflammatory lesions)
- Papules, pustules, nodules and cysts (inflammatory lesions)
- Redness (erythema) and oily skin (often present)

## *Age*

- **Adolescence** (often after puberty)
- Adults (less typical; women more common)

## *Distribution*

- Face (**not limited to central third**), neck, chest, back and shoulders

# Discussion question

***Does the patient in this photo have rosacea?***

a) Yes

b) No

***If so, what subtype of rosacea do you suspect this patient has?***



# Perioral/periorificial dermatitis



## ***Signs/symptoms***

- Group of **small** papules and pustules (occasionally scaly appearance)
- Underlying redness (erythema)
- **No telangiectasias, flushing or blushing**

## ***Age***

- Women aged 18 to 50
- Children

## ***Distribution***

- **Around the mouth** (spares vermillion border)
- Around the nose and eyes (less common)

# Discussion question

***Does the patient in this photo have rosacea?***

**a) Yes**

**b) No**

***If so, what subtype of rosacea do you suspect this patient has?***





# Seborrheic dermatitis



## ***Signs/symptoms***

- Red skin with **greasy, flaky, white/yellow scales** (may include thick plaques)
- Reddish-orange erythema
- Itching

## ***Age***

- Post –puberty
- Infants 6-12 months of age (“cradle cap”)

## ***Distribution***

- Scalp (very common)
- In and between **eye brows, sides of nose, nasolabial folds and behind ears**

Culp B, Scheinfeld P&T 2009;34(1):38-45. Medline Plus Medical Encyclopedia. Seborrheic dermatitis. US National Library of Medicine. <http://www.nlm.nih.gov/medlineplus/ency/article/000963.htm>. Mayo Clinic. Seborrheic dermatitis. <http://www.mayoclinic.com/health/seborrheic-dermatitis/DS00984>. Johnson BA, Nunley JR. Am Fam Physician 2000;61(9):2703-10. Furst D et al. Skin Manifestations in Rheumatic Disease. Springer New York. 2013.

# Other differential diagnoses

Disease	Similarities	Differences
Lupus erythematosus	<ul style="list-style-type: none"> <li>○ Erythema</li> </ul>	<ul style="list-style-type: none"> <li>○ Malar or “butterfly” rash distribution</li> <li>○ Photosensitivity</li> </ul>
Contact dermatitis	<ul style="list-style-type: none"> <li>○ Erythema, papules, pustules</li> <li>○ Burning, stinging</li> </ul>	<ul style="list-style-type: none"> <li>○ May follow distribution of causal agent</li> <li>○ Vesicular</li> <li>○ Itchy</li> </ul>
Photodermatitis	<ul style="list-style-type: none"> <li>○ Erythema, papules, plaques</li> </ul>	<ul style="list-style-type: none"> <li>○ Seasonal</li> <li>○ Can also be extrafacial (e.g., forearms and “V” area of neck)</li> <li>○ Photodistribution</li> </ul>

# Other differential diagnoses (cont'd)

Disease	Similarities	Differences
Actinic keratosis	<ul style="list-style-type: none"><li>○ Erythema, plaques, telangiectasias</li></ul>	<ul style="list-style-type: none"><li>○ Adherent scaling (feels like sandpaper)</li><li>○ Other signs of chronic sun exposure</li></ul>
Steroid-induced rosacea	<ul style="list-style-type: none"><li>○ Erythema, papules, pustules, telangiectasias</li></ul>	<ul style="list-style-type: none"><li>○ Related to topical application of corticosteroids</li></ul>

# Discussion question

***Which of the following diagnoses BEST describes the patient in the photo?***

- a) Acne vulgaris
- b) Perioral dermatitis
- c) Erythematotelangiectatic rosacea
- d) Papulopustular rosacea
- e) Other



# Summary

- Rosacea is a chronic inflammatory skin condition of the central face often characterized by flushing, erythema, papules/pustules and telangiectasias
- Signs and symptoms of rosacea often co-occur in four unique subtypes: erythematotelangiectatic, papulopustular, ocular and phymatous rosacea
- These signs and symptoms may overlap with other dermatological conditions, so conducting a differential diagnosis is essential
- It is important to take into consideration the age of the patient, sign and symptoms, and distribution of lesions when performing a differential diagnosis



**Questions?**



**Thank you!**