TREATMENT OPTIONS FOR PPR

Rosacea is a chronic condition without a cure. As such, similar to other chronic relapsing and remitting conditions, managing patients' expectations is important. Instead, management of rosacea often requires long-term treatment and lifestyle changes. It is important to treat these patients appropriately because rosacea can feel worse than it looks. The Canadian Clinical Practice Guidelines were published to provide treatment recommendations for patients with varying severities of PPR and other rosacea subtypes, and include considerations for long-term maintenance of the condition.[1]

Canadian Guideline Recommendations for Papules and Pustules

	MILD *(Characterized by a few papules/pustules)*	MODERATE TO SEVERE* *(Characterized by several to numerous/extensive papules/pustules, with or without plaques)*		
FIRST-LINE APPROACH	Topical treatment: Ivermectin ***OR*** Metronidazole ***OR*** Azelaic Acid	Topical treatment: Ivermectin ***OR*** Metronidazole ***OR*** Azelaic Acid	***AND***	Oral treatment: Doxycycline ***OR*** Tetracycline
SECOND-LINE APPROACH *(If response is inadequate after 8–12 weeks of treatment)*		Alternative combination of first-line treatment options ***OR*** Low-dose **isotretinoin**†		
MAINTENANCE *(Consider once rosacea symptoms have improved)*	Ivermectin ***OR*** Metronidazole ***OR*** Azelaic Acid			

Adapted from the Canadian Clinical Practice Guidelines for Rosacea (2016).
Please see guidelines for complete information.
* Consider referral to a dermatologist.
† Please see Product Monograph for additional information.

Once patients' symptoms are under control, first-line recommendations for mild PPR can be considered for long-term maintenance.[1]

"The skin and gut microbiomes also play a role in the pathogenesis of rosacea. The skin microbiome may interact with the innate immune system in triggering rosacea. Small intestinal bacterial overgrowth, H. pylori infection and inflammatory bowel disease are gastrointestinal conditions associated with rosacea. Prolonged use of antibiotics can reduce microbiome diversity and promote antibiotic resistance. APPRILON® (sub-antimicrobial doxycycline) is an effective treatment option that remains below the sub-antimicrobial threshold."

—Dr. Loo

CURRENT TOPICAL TREATMENT OPTIONS FOR PPR

	Dose and Formulation	Mechanism of Action	Efficacy	Common Side Effects
Topical Treatments				
Azelaic Acid	15%; gel	Anti-inflammatory and/or anti-bacterial	Treats the papules, pustules, and erythema Limited to mild to moderate symptoms Results seen from 4 weeks	Temporary skin irritation; burning/stinging or itching sensation; reddening; skin dryness and scaling
Ivermectin	1%; cream	Anti-inflammatory and/or anti-parasitic	Treats the papules and pustules Results seen from 4 weeks	Skin burning sensation
Metronidazole	0.75%, 1%; gel	Anti-inflammatory and/or anti-bacterial	Treats the papules, pustules, and erythema Results should be seen around 3 weeks	Skin irritation; redness; burning/stinging sensation; hypersensitivity; skin dryness and itching
	1%; cream	Anti-inflammatory and/or anti-bacterial	Treats the papules, pustules, and erythema Results should be seen around 4 weeks	Dryness; burning sensation; stinging; inflammation or redness of the skin; rash; itching; contact dermatitis; nausea; stomach upset; cramps; constipation

- Topical ivermectin is the newest treatment option available for PPR
- In clinical trials, ivermectin **significantly extended the duration of remission** of papules and pustules compared to metronidazole 0.75% cream[10]

The duration of remission can be **significantly improved** by treating patients to a 'clear' rating (IGA 0). Based on a *post-hoc* analysis of a 16-week clinical trial examining relapse rates:[9]

- After the treatment period, the median time to relapse was **252 days (8 months)** for 'clear' patients vs. 85 days (3 months) for 'almost clear' patients (difference:167 days [>5 months]; $p<0.0001$)

Relapse was defined as an IGA score of ≥2.
IGA 2 was defined as "few small papules/pustules, very mild erythema".
Median time to relapse was calculated as the time at which ~50% of patients had relapsed.

When considering an appropriate treatment option for your patients with PPR, keep in mind:

- The appropriate treatment option depends on the severity of a patient's PPR.[1] Remember to assess severity and subtype when diagnosing your patients.
- Patients often remain on rosacea treatment long term. Consider treatment options that have proven long-term efficacy.
- If patients' symptoms have not significantly improved or worsen after 8–12 weeks of treatment, consider using an alternate treatment.[1]

"Brimonidine tartrate can be used as a treatment to reduce the redness associated with ETR by vasoconstriction of blood vessels. Persistent erythema also responds well to intense pulsed light or pulsed dye lasers. At DermEffects, we use the Limelight IPL for background redness, the NdYag 1064nm laser for telangiectatic vessels and Laser Genesis for erythema and textural changes. Lastly, corrective camouflage makeup may help conceal rosacea symptoms. Recontouring using electrosurgery or CO_2 lasers improve fibrotic rhinophymas."

—Dr. Loo

ROSACEA MATTERS

Managing papulopustular rosacea in primary care

From the desk of your local dermatologist

Dr. Wei Jing Loo
1560 Hyde Park Rd
London, Ontario, N6H 5L5
Tel: (519) 472-2929
Fax: (519) 472-8484

Pathogenesis and Presentation of Rosacea

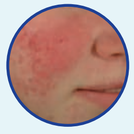
Rosacea is a common and chronic inflammatory skin condition affecting approximately 3.6 million Canadians with several clinical presentations and severities.[1]
In rosacea, the skin exhibits a hyper-responsive innate immune system that responds to environmental triggers. These triggers may initiate or aggravate patients' rosacea symptoms and signs, such as papules, pustules, burning, stinging and redness.[1-4]

Key indicators of rosacea include the presence of one or more of these primary features:[5]

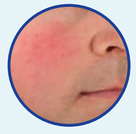
- ✓ Flushing
- ✓ Diffuse erythema
- ✓ Papules/pustules
- ✓ Telangiectases

Subtypes of Rosacea

Based on patients' clinical presentation, rosacea can be classified into 4 subtypes:[1]



Papulopustular Rosacea (PPR)
Inflammatory papules and/or pustules; often presents with centrofacial erythema



Erythematotelangiectatic Rosacea (ETR)
Flushing, telangiectasia and persistent centrofacial erythema

Phymatous Rosacea
Skin thickening and surface nodularities, most commonly affecting the nose

Ocular Rosacea
Blepharitis and conjunctivitis, which often occur in conjunction with other cutaneous features

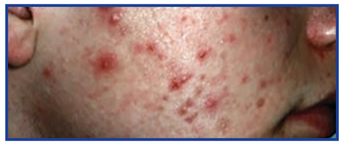
"Patients can have more than one subtype of rosacea at once. PPR and ETR often overlap together. In addition, patients with cutaneous rosacea may also present with ocular symptoms."

—Dr. Loo

DIFFERENTIAL DIAGNOSIS OF ROSACEA AND ACNE

Rosacea's many possible clinical features overlap with a number of other dermatological conditions, which can lead to misdiagnosis.[1,4] A classic example of this is confusing PPR with *acne vulgaris*.[4] However, there are important factors that differentiate PPR from acne:[1,4,5]

- Absence of comedones (i.e., blackheads and whiteheads)
- Appears later in life, often after the age of 30
- Localized to the central third of the face (i.e., cheeks, nose, chin, central forehead)



Patient with *acne vulgaris*

"It is important to differentiate between acne vulgaris and rosacea because topical treatments for acne, such as benzoyl peroxide or tretinoin cream, can potentially worsen rosacea symptoms. It is not uncommon for rosacea patients to have seborrheic dermatitis as well, which can complicate therapy. In addition, perioral and periocular dermatitis are thought to be associated with rosacea, and respond well to standard treatments for rosacea."

—Dr. Loo

POTENTIAL TRIGGERS OF ROSACEA

As you may be aware, the innate immune system responds to a number of triggering factors to cause an inflammatory response that can initiate or aggravate a patient's rosacea symptoms.[2,3] Triggers can include:[3]

- UV light
- Heat
- Stress
- Alcohol
- Spicy food
- Hot drinks
- Intense exercise
- Prolonged use of prescription grade topical corticosteroids

The fear of triggering their rosacea can impact patients' daily lives. For example, a National Rosacea Society survey found that **50%** of patients have refused food or drink that they enjoy for fear of causing a rosacea flare-up.[6]

ROSACEA'S PSYCHOLOGICAL AND SOCIAL IMPACTS

While the effects of rosacea are primarily seen on patients' skin, it can also significantly negatively impact their daily lives.[1] The National Rosacea Society conducted surveys of rosacea patients to understand the condition's impact on their quality of life. In these surveys:[7,8]

- Patients with rosacea are more likely to suffer from anxiety
- They are also subject to emotional and social stigmas, including being viewed as alcohol abusers or as having poor personal hygiene
- 69% are frustrated, and 70% are embarrassed because of their rosacea
- 70% have experienced low self-confidence and low self-esteem
- More than 50% have felt robbed of pleasure or happiness because of their rosacea
- Over 40% of patients have avoided public contact or cancelled social events
- Nearly 1/3 of patients missed work due to their rosacea

Treating patients' rosacea **can improve their quality of life**. In a pooled, *post-hoc* analysis of multiple clinical trials:[9]

- After treatment, **84% of patients who achieved a 'clear' rating** (IGA 0) reported their rosacea having no effect on their quality of life (vs. ~16% of patients at baseline)

These data highlight that the treatment and management of rosacea are important considerations for improving patients' quality of life.

"One of my patients who has suffered with rosacea for over 10 years has expressed to me that his face is brick-red all the time, and his colleagues judge him and think that he is an alcoholic. Another one of my patients has found the flushing to be incapacitating, and has admitted that she cannot stand up and present in public because her face turns a fire-engine red when she is anxious or stressed. She had to quit her job."

—Dr. Loo

IGA = Investigator global assessment. IGA 0 was defined as "no inflammatory lesions, no erythema". IGA 1 was defined as "very few small papules/pustules, very mild erythema".

ADDITIONAL CONSIDERATIONS FOR MANAGING ROSACEA

The management of rosacea extends beyond prescription treatment. There are a variety of other considerations that will aid in the proper care of patients' rosacea.

Proper Application of Topical Treatments for Rosacea

The most common side effect that patients experience when using topical treatments is skin irritation, including skin dryness and sensitivity.[11] Patients with sensitive skin also often complain of burning, stinging and itching.[4] To help minimize these effects, patients should be counselled on the proper application of their topical treatment.

- Encourage patients to cleanse gently with a mild cream cleanser, then dry their skin thoroughly before topical application[12]
- Remind patients to use just a small amount of treatment at each application to avoid unnecessary skin burning, stinging or dryness
- Advise patients to apply their topical treatment across their whole face. Patients should not spot treat their lesions[12]
- Use a moisturiser on the affected area immediately after applying topical treatment

The Importance of Skin Care

In rosacea, the skin becomes dry and sensitive to irritation due to defects in the skin's natural barrier.[4] As such, it is important for patients to follow a skin care regimen that includes gentle, non-irritating products to prepare the skin for topical treatment.[4]

- Patients should choose mild cleansers and moisturizers that help to repair the skin barrier and reduce skin dryness[11]
- As UV light is a known trigger for rosacea, it is important for patients to wear sunscreen to limit their skin's exposure[4]
  - Patients should be encouraged to reapply sunscreen frequently, especially after water exposure or intense exercise
  - I advocate the use of a physical sunscreen (zinc oxide/titanium dioxide), broad spectrum SPF 50+ as part of their daily regimen[13]
  - I also recommend wearing a broad-brimmed hat and sunglasses, and seek shade especially between 11am–3pm
- Patients should avoid using over-the-counter acne treatments, such as salicylic acid and benzoyl peroxide, as these products can worsen their rosacea symptoms
- Avoid skincare products or cosmetics that contain fragrance, alcohol or other irritating ingredients that can aggravate rosacea symptoms[14]

References

1. Asai Y, et al. Canadian Clinical Practice Guidelines for Rosacea. *J Cutan Med Surg.* 2016;20(5):432-445. **2.** Del Rosso JQ, et al. Why is rosacea considered to be an inflammatory disorder? The primary role, clinical relevance, and therapeutic correlations of abnormal innate immune response in rosacea-prone skin. *J Drugs Dermatol.* 2012;11(6):694-700. **3.** Woo YR, et al. Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition. *Int J Mol Sci.* 2016;17(9). **4.** Zouboulis CC, et al. *Pathogenesis and treatment of acne and rosacea.* Berlin; Springer; 2014. **5.** Wilkin J, et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46(4):584-587. **6.** National Rosacea Society. *Social impact of rosacea.* (2016). Available at: https://www.rosacea.org/weblog/social-impact-rosacea. Retrieved December 5, 2016. **7.** Liu RH, et al. Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. *Arch Dermatol.* 2006;142(8):1047-1052. **8.** Huynh TT. Burden of Disease: The Psychosocial Impact of Rosacea on a Patient's Quality of Life. *Am Health Drug Benefits.* 2013;6(6):348-354. **9.** Webster G, et al. Defining treatment success in rosacea as 'clear' may provide multiple patient benefits: results of a pooled analysis. *J Dermatolog Treat.* 2017;28(5):469-474. **10.** Taieb A, et al. Maintenance of remission following successful treatment of papulopustular rosacea with ivermectin 1% cream vs. metronidazole 0.75% cream: 36-week extension of the ATTRACT randomized study. *J Eur Acad Dermatol Venereol.* 2016;30(5):829-836. **11.** Goldberg DJ, et al. Acne and Rosacea: Epidemiology, Diagnosis and Treatment. London: CRC Press; 2011. **12.** Powell F. *Rosacea: Diagnosis and Management.* New York: CRC Press; 2008. **13.** National Rosacea Society. Sunscreen. 2018. Available at: https://www.rosacea.org/patients/skincare/sunscreen. Retrieved May 24, 2018. **14.** National Rosacea Society. Coping with rosacea. 2018. Available at: https://www.rosacea.org/patients/materials/coping/tnpwires.php. Retrieved April 18, 2018.

2216-061BE