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Canadian Clinical Practice Guidelines for Rosacea

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Abstract

Rosacea is a chronic facial inflammatory dermatosis characterized by background facial erythema and flushing and may be accompanied by inflammatory papules and pustules, cutaneous fibrosis and hyperplasia known as phyma, and ocular involvement. These features can have adverse impact on quality of life, and ocular involvement can lead to visual dysfunction. The past decade has witnessed increased research into pathogenic pathways involved in rosacea and the introduction of novel treatment innovations. The objective of these guidelines is to offer evidence-based recommendations to assist Canadian health care providers in the diagnosis and management of rosacea. These guidelines were developed by an expert panel of Canadian dermatologists taking into consideration the balance of desirable and undesirable outcomes, the quality of supporting evidence, the values and preferences of patients, and the costs of treatment. The 2015 Cochrane review "Interventions in Rosacea" was used as a source of clinical trial evidence on which to base the recommendations.

Keywords

inflammatory dermatoses, laser, dermatology, rosacea

Rosacea is a chronic facial inflammatory dermatosis estimated to affect up to 10% of Western populations.[1,2] Extrapolation to the 2015 Canadian population would estimate that rosacea affects 3.6 million Canadians,[3] and a recent survey found that 46% of respondents with rosacea had been living with symptoms for over 10 years.[4]

Rosacea is characterized by clinical features of facial flushing and redness, which may be accompanied by inflammatory papules and pustules, fibrotic changes and skin thickening known as phyma, and ocular involvement.[5,6] Based on clinical presenting features, rosacea has been classified into 4 subtypes, which may occur concurrently: (1) erythematotelangiectatic rosacea (ETR) is characterized by flushing and persistent centrofacial erythema; (2) papulopustular rosacea (PPR) by the presence of inflammatory papules and pustules with ETR; (3) phymatous by marked skin thickening and surface nodularities, most commonly affecting the nose; and (4) ocular by blepharitis and conjunctivitis, which often occur in conjunction with other cutaneous features and can lead to visual dysfunction in severe cases.[7-9] Representative photographs of rosacea features are presented in Figure 1.

The impact of rosacea on quality of life (QoL) may not be fully appreciated.[10-12] Embarrassment and desire to hide the skin are common among Canadians with rosacea.[4] A recent systematic review found that all studies reported a negative impact on health-related QoL of patients with rosacea,[13] and other studies have identified increased anxiety and depression in this group.[14] Stigmatization can also be an issue with facial redness and with rhinophyma. In particular, the latter has an erroneous cultural association with alcoholism, with synonyms including "rum nose" and "whiskey nose."

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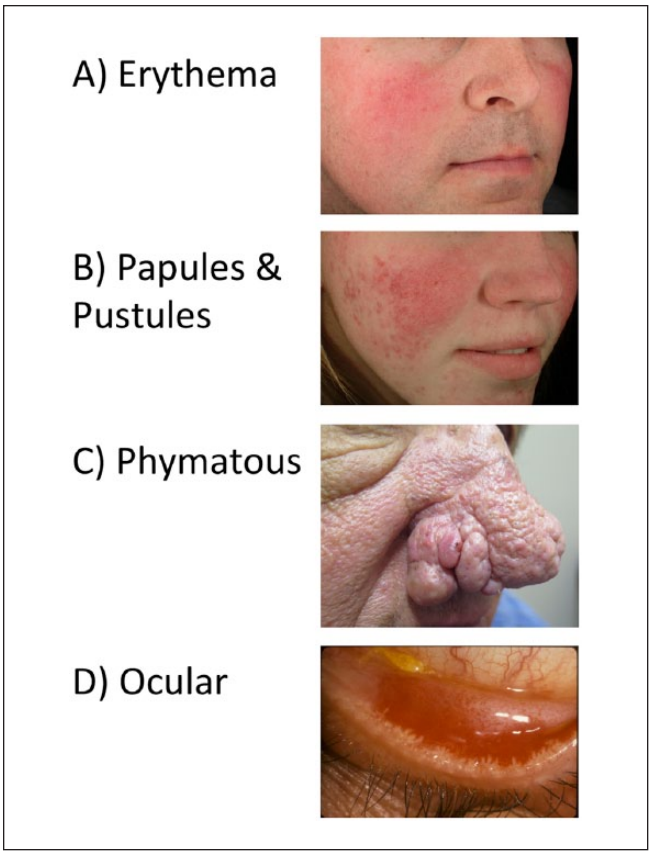

Figure 1. Clinical subtypes of rosacea. Representative photos for (A) mild to moderate fixed-background centrofacial erythema (erythematotelangiectatic rosacea), (B) moderate inflammatory papules with fixed-background centrofacial erythema (papulopustular rosacea), (C) prominent nodules and soft tissue hypertrophy at nasal tip and alar regions with nasal deformation (severe late-stage rhinophyma), and (D) ocular rosacea with lipid inspissation of Meibomian glands lining the lid margin.

Previously, treatment options were limited, but recent advances in the understanding of rosacea pathogenesis have led to development of new treatments.

Objective

The objective of this rosacea clinical practice guideline (CPG) is to assist Canadian health care providers in the diagnosis and management of rosacea.

Scope

The scope of these guidelines is rosacea management in adults based on medications available in Canada. Specifically excluded are the following: pediatric rosacea, pyoderma faciale, granulomatous rosacea, and rosaceiform dermatitides and diagnostic mimics such as democidosis, acne vulgaris, and folliculitis.

Target Audience

This document is intended for Canadian health care providers, including pharmacists, nurse practitioners, family physicians, dermatologists, and other clinicians involved with care of patients with rosacea.

Pathogenesis

While the pathogenesis of rosacea is incompletely understood, recent investigations suggest involvement of the innate immune system and cutaneous neurovascular dysregulation (reviewed in Two et al[15] and Steinhoff et al[16]).

The cutaneous innate immune system is a primordial nonspecific body defense mechanism comprising the intact skin barrier and its structural (keratinocytes, sebocytes) and immune (mast cells, neutrophils, natural killer cells, dendritic cells) cellular elements. Antimicrobial peptides (AMPs), cathelicidins, and defensins are soluble defense factors, which are primarily secreted by keratinocytes in response to external triggers such as injury, UV radiation, barrier disruption, and diverse pathogens such as bacteria, viruses, and fungi. These peptides have proinflammatory and vasoactive properties.

Activation and involvement of the immune system have been demonstrated in all cutaneous subtypes of rosacea, including ETR, previously considered to be due solely to vascular dilation.[17] In rosacea, there is increased expression of both the propeptide and 37–amino acid cathelicidin, LL-37, as well as the enzyme KLK 5 that catalyzes conversion of the propeptide to LL-37.[18] The latter may be due to increased TLR-2 expression from keratinocytes. TLRs, or Toll-like receptors, are pathogen-associated sensor molecules, which act to detect and signal the presence of microbial structures. Potential triggers for TLR-2 in rosacea include the saprophytic mite *Demodex folliculorum*, mite-related bacteria such as *Bacillus oleronius*, and *Staphylococcus epidermidis*.[15] TLRs may also be activated by reactive oxygen species resulting from ultraviolet exposure.

Reactive oxygen species may also activate neurogenic receptors, such as transient receptor potential channels (TRPs), that are expressed on neural tissues, keratinocytes, and endothelial cells.[19] TRPV1 can be activated by heat, ethanol, or spicy food, and TRPA1 can be activated by cold, formalin, or other chemicals. TRP activation induces release of substance P and calcitonin gene–related peptide, leading to pain/edema and vasodilation, respectively.[20] Increased serine protease activity may upregulate TRP and activate protease-activated receptors, which may lead to the decreased barrier function observed in rosacea.[21]

A genome-wide association study of more than 22 000 individuals of European ancestry, of whom just over 10% had a prior diagnosis of rosacea, investigated the influence of genetics in rosacea. In this cohort, significant associations

were found with a single-nucleotide polymorphism and 3 human leukocyte antigen (HLA) alleles, supporting a probable genetic component in the pathogenesis of rosacea.[22]

Severity Grading

Clinical trials for rosacea interventions required the development of severity grading scales for persistent facial erythema and papules/pustules.[23] The Clinician Erythema Assessment (CEA) and Patient Self-Assessment of Erythema (PSA) scales, based on the categories clear/almost clear, mild, moderate and severe, have been shown to be valid[24] and reliable.[24,25] Severity of papules and pustules is assessed as part of global grading scales and is typically rated as clear/almost clear, mild, moderate, and severe.[23] There are presently no specific scales for severity grading of phymatous or ocular rosacea.

A standard grading system encompassing all 4 signs, accompanied with patient photos, has been proposed by Wilkin et al.[26]

Differential Diagnosis

The diagnosis of rosacea is a clinical one, comprising many possible clinical features. For each feature, the following differential diagnoses should be considered:

- Flushing: carcinoid syndrome, systemic mastocytosis, benign cutaneous flushing and perimenopause, medullary carcinoma of the thyroid, and pancreatic and renal cell tumors
- Centrofacial erythema: photodamage, systemic lupus erythematosus, facial dermatitis, seborrheic dermatitis, psoriasis, and keratosis rubra pilaris faceii
- Papules/pustules: acne vulgaris (characterized by presence of comedones) and folliculitis
- Phymatous changes: nonmelanoma skin cancer, granulomatous infiltration (which may be infectious in origin such as rhinoscleroma or noninfectious such as sarcoidosis), and B- and T-cell lymphomas

Methods

Nomination of Expert Panel

Two authors (J.T. and C.L.) recruited an expert panel, via invitations to the medical advisory board of the Acne and Rosacea Society of Canada and the Canadian Dermatology Association, to deliberate and vote on treatments. Criteria for panelist selection included prior guidelines development experience; publication history and/or national prominence in rosacea research; working knowledge of Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)[27]; commitment to completion of online Delphi surveys and authorship of specific sections of the guidelines; and attendance at 1 meeting in Toronto in February 2015. The panel included a chair/methodologist trained in dermatology and epidemiology with no conflict of interest in this therapeutic area (Y.A.). All panelists received no remuneration.

Prior to the meeting, the panelists were surveyed for their most preferred treatments for each of the following clinical presentations of rosacea: erythema, papules/pustules, and phymatous and ocular features. These were then presented in aggregate to the group for feedback and further deliberation.

Literature Search, Review, and Adaptation

The information derived from the panel survey was reviewed in conjunction with a summary of findings tables from a Cochrane review entitled "Interventions for Rosacea,"[28] which provided information on efficacy and quality of evidence of interventions for relevant outcomes.

The Cochrane review did not address flushing or maintenance therapy. To address the former, a literature search was performed up to October 25, 2015, on PubMed to find studies evaluating treatment of flushing associated with rosacea. Keywords used were *clonidine, nadolol, propranolol, carvedilol, rosacea*, and *flushing*. Only relevant studies conducted in English were included in this study. For maintenance, previously identified studies were screened for randomised controlled trials (RCTs) of rosacea that evaluated outcomes beyond 12 weeks, preferably to 1 year.

Formulation and Interpretation of Recommendations

A Delphi voting process, whereby 75% was predetermined to be the threshold for consensus, was undertaken to establish the strength of recommendations. Provided with the evidence from the Cochrane review, the panelists applied predetermined methodology to develop recommendations.[29,30] For each recommendation, a direction, either *against* or *for*, and a strength, either *weak* or *strong*, was given. The panel considered factors within 4 domains (see Table 1) in determining the recommendation strength.[30] Recommendations likely to apply to all or virtually all patients would be given a *strong* recommendation. Recommendations appropriate for some but not all patients (ie, those in whom the net benefit is small or uncertain, the evidence is not of high quality, patient preferences are variable or unknown, or costs or resource use present a barrier) would be determined to be *weak*. Thus, even in the presence of very high-quality evidence (see Table 2) for a given treatment, a *weak* recommendation may be appropriate if other treatments, or no treatment, present viable alternatives.

For scenarios in which confidence in effect estimates was low, trade-offs were closely balanced, patient specific values and preferences were highly variable, and/or costs (resource implications) were unknown, a no recommendation category was available.[30]

Table 1. Determinants of a Recommendation's Strength.

Domains That Contribute to the Strength of Recommendation	Comment
Balance between desirable and undesirable outcomes	The larger the difference between desirable and undesirable outcomes, the more likely a strong recommendation is warranted. The smaller the net benefit, the more likely a weak recommendation is warranted
Confidence in effect estimates (see Table 2)	The higher the quality of evidence, the more likely a strong recommendation is warranted
Confidence in values and preferences and variability	The greater the variability in patient values and preferences for the intervention or the greater the uncertainty in those values and preferences, the more likely a weak recommendation is warranted
Resource use	The higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted

Adapted from Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-725.

Table 2. Significance of the 4 Levels of Evidence.[30]

Quality Level	Current Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimates: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

Estimates of treatment cost were made available to the panelists for consideration during final approval of the recommendations and algorithm.

Specific questions addressed in these guidelines

1. What treatments are available for the redness of rosacea (erythema)?
2. What treatments are available for the inflammatory papules and pustules of rosacea?
3. What treatments are available for the skin thickening (phymatous features) of rosacea?
4. What treatments are available for the ocular signs and symptoms of rosacea?

Disclaimer

The recommendations within these guidelines serve as general advice based on current evidence, not as legal standards. Clinical research evidence is derived from well-defined, tightly controlled group data and may not be adequately specific for the circumstances of individual patients or generalizable to populations outside of the original study groups. Additionally, as evidence-based guidelines focus only on treatments with high-quality evidence, some effective treatment with inadequate evidence may not be represented. Accordingly, the most appropriate treatment for an individual patient derives from informed decision sharing with his or her physician.

Recommendations

This section contains the expert panel's consensus recommendations for specific clinical features of rosacea and the rationale and evidence, if available, underpinning the recommendations. Further guidance in selecting appropriate therapy based on clinical features may be found in the clinical decision-making algorithms in Figures 2 to 5.

Few treatments effectively address multiple clinical features, so treatment should be targeted to the symptoms considered most burdensome by the patient. Combination treatment should be considered if multiple clinical features are present. Gentle skin care, moisturizers, use of sun protection, and avoidance of triggers are recommended, based on expert opinion, for all patients with rosacea.

Erythema

Prior to initiating treatment for background erythema, health care providers should discuss with patients the possibility that papules and pustules, if present, might become more visually prominent upon reduction of background erythema. Initiating treatment for both features concurrently should be considered. A treatment algorithm can be found in Figure 2.

We suggest the following for treatment of erythema of rosacea:

A1. Topical brimonidine. (Weak recommendation: high confidence in effect estimate but perceived variability in patient values and preferences)

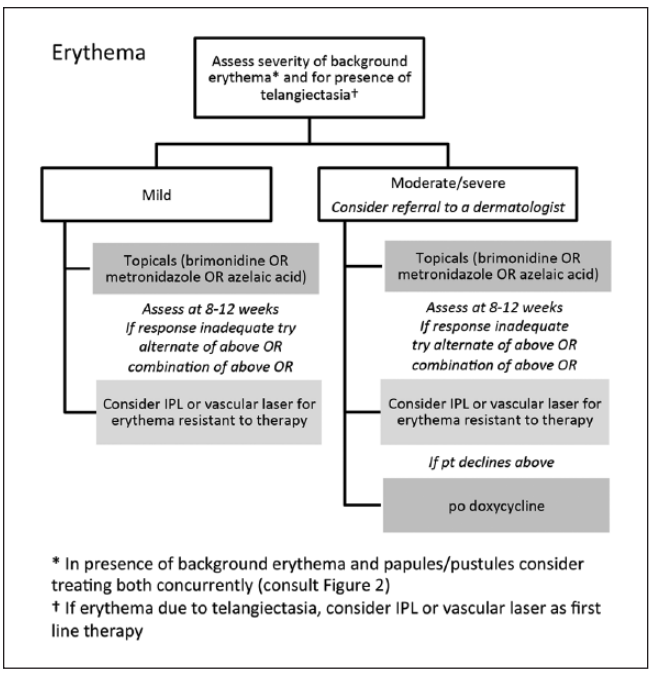

Figure 2. Treatment algorithm for erythema of rosacea. IPL, intense pulsed light.

Topical brimonidine was demonstrated in 2 high-quality studies to be an effective treatment for erythema of rosacea. On day 29 of treatment, a 2-grade improvement on the CEA scale was seen in 31.5% of patients in the brimonidine group but only 9.2% of those on vehicle.[31]

Brimonidine tartrate was well tolerated during 4 weeks of daily treatment, and reported adverse events were mild and transient. The rate of worsening of erythema after the 4-week treatment was approximately 4%.[31] The panel noted that brimonidine is costlier than some other treatments, notably metronidazole, and is not covered by provincial drug formularies at this time. However, it is available on several private plans. Case reports of worsening or rebound erythema are an additional consideration.[32,33]

A2. Topical metronidazole. (Weak recommendation: moderate confidence in effect estimate)

Metronidazole has been shown in 6 studies to confer statistically and clinically significant improvement in erythema by patient and physician assessment and is more effective than placebo.[34-39]

The rate of adverse events for metronidazole is similar to placebo. Reactions, which were generally mild, included itching, skin irritation, and dry skin. Metronidazole is available on many provincial formularies as well as several private plans and has an extensive history of safe use in patients with rosacea.

A3. Topical azelaic acid. (Weak recommendation: high confidence in effect estimate)

Azelaic acid has shown limited efficacy in 5 studies for treatment of erythema of rosacea, with decreases in erythema of 44% to 48% compared with 28% to 38% for placebo.[40-43] No improvement was seen for telangiectasia.

Adverse events, notably irritation, are common, which may prompt health care providers to suggest other treatments first. Azelaic acid is covered by some provincial formularies and private plans.

A4. Vascular laser or intense pulsed light therapy. (Weak recommendation: very low confidence in effect estimate)

Vascular laser treatment (Nd:YAG or pulsed dye laser [PDL]) or intense pulsed light (IPL) may ameliorate erythema. We rated our confidence in the effect estimate as very low because the efficacy of vascular laser or IPL for erythema has not been evaluated by a placebo controlled trial; however, its use was supported by panelists based on clinical experience. Low-quality evidence suggests that PDL is more effective than Nd:YAG and IPL.[44,45]

The efficacy of this intervention depends on training and expertise of the treating physician. Swelling and redness may persist for several weeks with low risk of scarring. Improvement can be rapid and significant; however, multiple sessions may be required. These interventions may be costly and access may be limited. This treatment should be offered to all patients, acknowledging that the patients' preferences and values and treatment cost will influence their decision.

A5. Oral doxycycline. (Weak recommendation; high confidence in effect estimate but variability in patient values and preferences with concerns regarding cost, potential adverse events, and uncertainty concerning efficacy for background erythema without papules/pustules)

There is high-quality evidence showing efficacy of doxycycline for reduction of erythema of rosacea. However, this was based on a study of patients with papulopustular rather than erythematotelangiectatic rosacea. The effect may have been due to reduction in perilesional erythema associated with reduction in papules/pustules, so efficacy for background erythema alone is uncertain. Doxycycline 40 mg (modified release) and 100 mg appear equivalent, with the 100-mg dose being associated with a significantly higher rate of adverse events, primarily gastrointestinal in nature.[46]

Doxycycline, like all tetracycline group antibiotics, is contraindicated during pregnancy and has been associated with side effects such as photosensitivity and esophagitis.[47] The 40-mg dose is significantly more costly than the 100-mg dose and is not covered by provincial drug formularies. For more information, please see "Antibiotic Resistance."

A6. Skin care and camouflage. (Weak recommendation: very low confidence in effect estimate)

Over-the-counter skin care and cosmetic products are used commonly and may ameliorate or conceal mild erythema associated with rosacea. We rated our confidence in

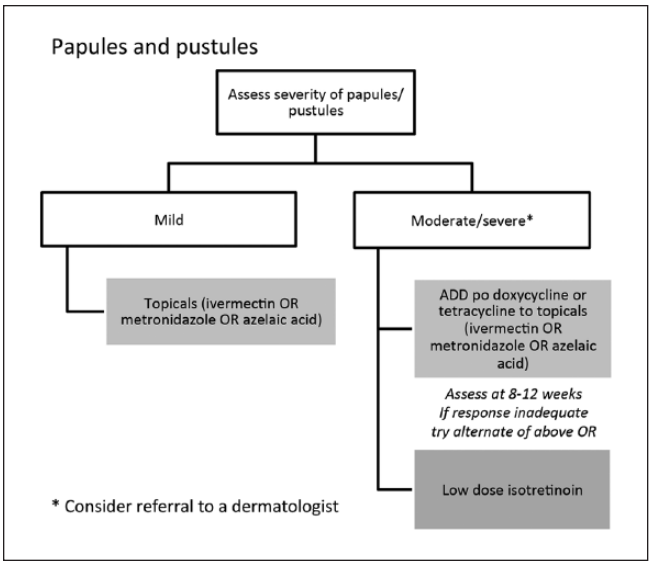

Figure 3. Treatment algorithm for papules and pustules of rosacea.

the effect estimate as very low because efficacy has not been evaluated by an RCT. However, these products are safe and widely available. Properly selected skin care regimens may be beneficial in helping to repair the skin's barrier function, dysfunction of which may contribute to rosacea pathogenesis.[21]

Papules and Pustules

We suggest the following for treatment of papules and pustules of rosacea. A treatment algorithm can be found in Figure 3.

B1. Topical ivermectin. (Weak recommendation: high confidence in effect estimate but variability in patient values and preferences due to cost)

In 2 large RCTs with a combined total of 1371 patients, ivermectin was found to confer statistically significant improvement in patient- and physician-assessed global outcomes and also significant and clinically important reductions in lesions compared with placebo.[48]

Ivermectin was associated with fewer dermatologic adverse events than placebo, with patients reporting less dry skin and itching. The panel noted that ivermectin is costlier than other medications for this indication and is currently not covered by provincial drug formularies; however, it is listed on several private plans.

B2. Topical azelaic acid. (Weak recommendation: moderate confidence in effect estimate)

In 1 study, azelaic acid resulted in a greater reduction in papules and pustules than placebo.[42] For safety and other information, please see Recommendation A3.

B3. Topical metronidazole. (Weak recommendation: moderate confidence in effect estimate)

There is moderate-quality evidence that metronidazole leads to reduction in the number of lesions; however, these data were skewed and inadequately reported.[28] One study comparing the 1% and 0.75% concentrations found no significant difference in efficacy.[49] For safety and other information, please see Recommendation A2.

B4. Oral doxycycline. (Weak recommendation, high confidence in effect estimate but variability in patient values and preferences regarding cost and potential adverse events)

There is high-quality evidence showing efficacy of doxycycline for treatment of papules and pustules of rosacea,[28] and doses of 40 mg (modified release) and 100 mg appear equivalent. For safety and other information, please see Recommendation A5 and "Antibiotic Resistance."

B5. Oral tetracycline. (Weak recommendation: moderate confidence in effect estimate but variability in patient values and preferences regarding potential adverse events)

Oral tetracycline is effective for papules and pustules, with 1 study reporting a mean difference of 14.64 fewer lesions for tetracycline compared with placebo.[50]

Oral tetracycline is generally well tolerated but can cause gastrointestinal disturbances,[47,51] and all tetracycline group antibiotics are contraindicated during pregnancy.[52] Tetracycline is widely available and less costly than doxycycline and most topicals; however, clinicians should discuss with patients whether the benefits outweigh the risks of gastrointestinal distress and potential for selection for antibiotic resistance. For more info, please see "Antibiotic Resistance."

B6. Oral isotretinoin. (Weak recommendation; high confidence in effect estimate but variability in patient values and preferences regarding potential adverse events)

In 1 study, low-dose isotretinoin (0.3 mg/kg) was at least as effective for the reduction of lesions as 100 mg doxycycline.[53] There have been no placebo-controlled trials; however, panelists reported good results in their own practices, and isotretinoin may be a good choice for those in whom tetracycline group antibiotics were not effective or are contraindicated.

Isotretinoin is associated with potential adverse events requiring careful monitoring during treatment and is absolutely contraindicated during pregnancy due to high risk of teratogenicity.[54,55] Low-dose and intermittent-dose regimens may reduce the frequency and severity of adverse events.[56,57] Because isotretinoin treatment for rosacea is likely to be more long term than for acne, its use is cautioned in females of childbearing potential.

Phyma

We suggest the following for treatment of phymatous features of rosacea. A treatment algorithm can be found in Figure 4.

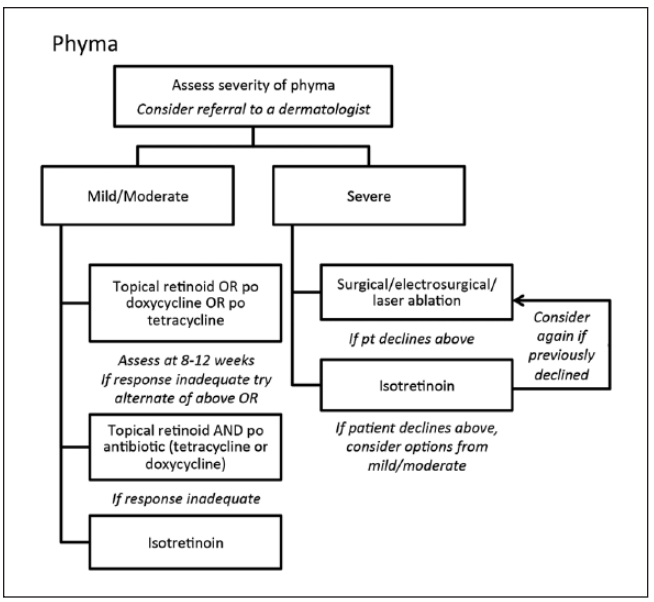

Figure 4. Treatment algorithm for phymatous rosacea.

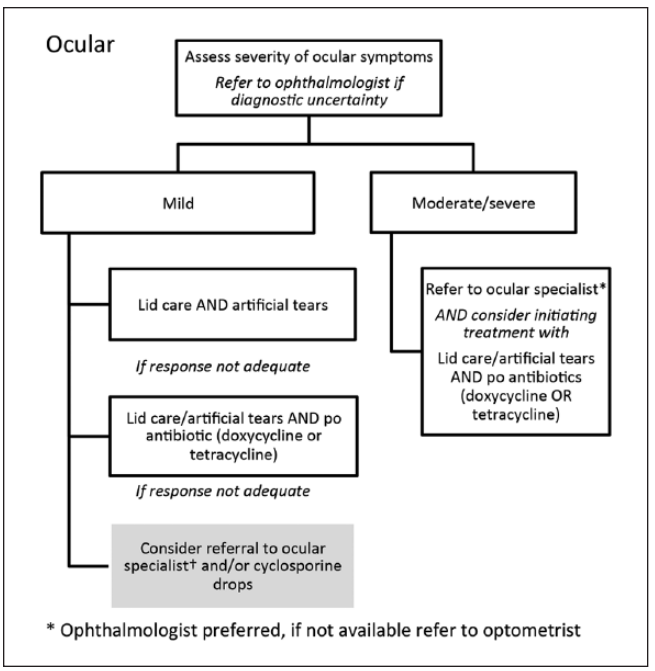

Figure 5. Treatment algorithm for ocular rosacea.

C1. Topical retinoids. (Weak recommendation: very low confidence in effect estimate)

Topical retinoids may help minimize progression of rosacea-associated phyma. We rated our confidence in the effect estimate as very low because efficacy has not been evaluated by RCTs.

The panelists did not report strong anecdotal evidence for efficacy; however, given the lack of noninvasive treatment options for phymatous features of rosacea, topical retinoids represent a safe option for those with mild to moderate involvement that is less costly than procedural treatments.

C2. Oral tetracycline or doxycycline. (Weak recommendation: very low confidence in effect estimate)

Oral tetracycline and doxycycline may also be useful for mild phymatous rosacea, particularly if there is an inflammatory component. Although there have been no RCTs for this indication, clinicians on the panel reported anecdotal benefit for patients. For safety and other information, please see Recommendation B5 and "Antibiotic Resistance."

C3. Ablative laser surgery, using CO_2 or Er:YAG modalities, or surgery, including electrosurgery and cryosurgery. (Weak recommendation: very low confidence in effect estimate and variability in patient values and preferences)

Ablative laser resurfacing, using CO_2 or Er:YAG modalities, and surgery, including electrosurgery, may significantly improve phymatous features of rosacea. We rated our confidence in the effect estimate as very low because the efficacy of these procedural treatments for phymatous features has not been evaluated by RCTs; however, their use was supported by strong panelist sentiment based on clinical experience.

The efficacy of these interventions depends on training and expertise of the treating physician. Treatment may be costly if not covered by provincial health plans, and access may be limited. Swelling and redness may persist for several weeks or longer. These risks are balanced against the potential for excellent outcomes. This option, if available, should be offered to all patients, acknowledging that the patients' preferences and values and treatment cost will influence their decision.

C4. Oral isotretinoin. (Weak recommendation: very low confidence in effect estimate but variability in patient values and preferences regarding potential adverse events)

Oral isotretinoin may be effective at reducing early phymatous features of rosacea. For phymatous features, we rated our confidence in the effect estimate as very low because the outcome has not been validated; however, panelists felt that it may have some benefit in patients with early phymatous changes. For safety and other information, please see Recommendation B6.

Ocular

We suggest the following for treatment of ocular features of rosacea. A treatment algorithm can be found in Figure 5.

D1. Lid care and artificial tears. (Weak recommendation: very low confidence in effect estimate)

Over-the-counter ocular hygiene products and artificial tears are used commonly and may alleviate some of the discomfort and irritation associated with ocular rosacea. We

rated our confidence in the effect estimate as very low because efficacy has not been evaluated by RCTs. These products are safe, widely available, and less costly than cyclosporine drops; however, a hygiene regimen may be time-consuming and inconvenient, which compromises compliance.

D2. Oral doxycycline. (Weak recommendation; low confidence in effect estimate)

Doxycycline's efficacy for ocular rosacea has not been evaluated in a placebo-controlled trial; however, 1 open-label study of 40 mg once daily demonstrated effectiveness,[58] and another comparing doxycycline with tetracycline reported equivalent improvement of ocular rosacea symptoms at 6 months.[59] For safety and other information, please see Recommendation A5 and "Antibiotic Resistance."

D3. Oral tetracycline. (Weak recommendation: low confidence in effect estimate)

Oral tetracycline is commonly prescribed for ocular rosacea, despite an absence of studies specifically studying its efficacy for ocular symptoms. Its mechanism of action for ocular rosacea is likely via an anti-inflammatory effect, and some panelists reported improvement of ocular symptoms with their own patients at doses of 500 to 1000 mg/d. For safety and other information, please see Recommendation B5 and "Antibiotic Resistance."

D4. Cyclosporine drops. (Weak recommendation: low confidence in effect estimate)

Cyclosporine inhibits T-lymphocyte activation and has been shown to reduce the number of activated lymphocytes in the conjunctiva.[60] One double-blind RCT of 37 patients found that topical cyclosporine 0.05% reduced ocular surface disease index (OSDI) (P = .022) and improved tear production (P = .002) compared with artificial tears.[61]

The study found cyclosporine was well tolerated, although 1 patient withdrew from the study, reporting stinging. As cyclosporine suppresses the immune system, it is contraindicated during conjunctival or ocular infection, and assessment by an eye expert may be advisable prior to beginning treatment. Cyclosporine 0.05% drops are more costly compared with oral tetracycline, which is commonly prescribed for ocular rosacea, and their use requires monitoring and discontinuation in the presence of ocular infection; thus, other treatments may be preferable.

D5. Referral to an ocular expert (ophthalmologist preferred). (Weak recommendation: no evidence, based on expert opinion)

Ocular experts may be able to rule out other ocular pathology that may be mistaken for rosacea. This is particularly important if cyclosporine treatment is being considered to rule out infection or if symptoms prove refractory to other rosacea treatment modalities. An ocular expert can also monitor for disease progression and mitigate the risk of complications.

Treatments for Flushing Associated With Rosacea

While studies of flushing in rosacea exist, they suffer from methodological limitations, and results are, in some cases, contradictory. Propranolol, at doses of 20 mg to 40 mg, was found to be effective in 2 open-label studies.[62,63] Studies of clonidine have demonstrated variable effects with some showing reduction in flushing[64,65] and another showing no evidence of benefit.[66] One reported worsening of papulopustular features in some patients.[64] The single study reported for nadolol found no benefit.[67] Carvedilol, a nonselective β-adrenergic antagonist with α1-antagonist selectivity, was shown effective in a case of refractory rosacea-associated flushing.[68] No formal recommendation is made concerning these treatments and they should only be considered for patients with rosacea whose predominant feature is flushing.

Maintenance Therapy of Rosacea

Rosacea requires ongoing care, as it is a chronic condition. While evidence for maintenance therapy is lacking, if improvement is inadequate after 8 to 12 weeks of treatment or if symptoms worsen, escalation of frequency or dose or use of an alternate treatment is advised. Conversely, treatment can be tapered by reduction in frequency or dose once improvement has been achieved. Adequate improvement should be judged based on patient satisfaction and reduction in severity to mild or clear/almost clear. Once rosacea symptoms are under control, those treatments recommended as first line for mild rosacea can be considered for long-term maintenance (Figure 6).

Currently, only 4 studies have investigated long-term efficacy and maintenance therapy, specifically looking at topical metronidazole,[37] topical brimonidine tartrate,[69] topical ivermectin,[70,71] and azelaic acid.[70] Some of these were not included in the Cochrane review as they were either open-label studies or were recently published.[69-71]

Topical brimonidine has been shown to be effective for maintenance therapy of erythema in a 12-month open-label observational study.[69] Long-term use of brimonidine was found to be safe with no evidence of tachyphylaxis. Adverse events included worsening of erythema in 6.5%, worsening of rosacea in 3.6%, and contact dermatitis in 2.2%.

Maintenance therapy with metronidazole was evaluated as an extension of a trial of combination topical metronidazole and oral tetracycline.[37] Those that achieved at least 70% reduction in inflammatory lesions were randomized to receive either topical metronidazole or vehicle as maintenance therapy for a 6-month blinded study. Relapse of

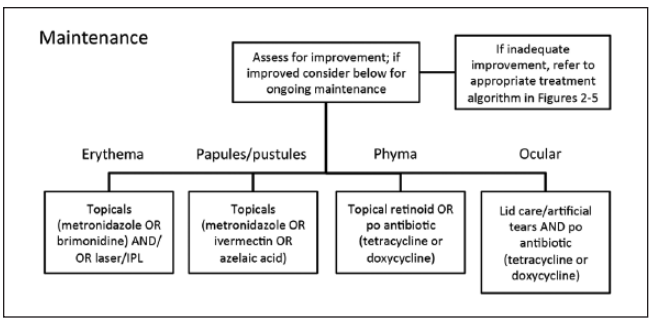

Figure 6. Treatment algorithm for maintenance therapy for rosacea. IPL, intense pulsed light.

rosacea symptoms occurred in 23% and 42% in the metronidazole and control groups, respectively.

Long-term ivermectin was evaluated in a 40-week open-label extension to a 12-week phase 3 vehicle-controlled trial for papules and pustules.[70] In the extension, those originally on vehicle were treated with azelaic acid 15% gel while those on topical ivermectin continued for a total of 52 weeks' duration.[71] There was a lower incidence of related adverse events with topical ivermectin compared with azelaic acid gel. After 52 weeks, the proportion of subjects achieving global scores of clear or almost clear was 73% with topical ivermectin. After 40 weeks of azelaic acid 15% gel, the proportion was 57%.

The potential for remission after a 16-week course of treatment with ivermectin 1% cream once daily or metronidazole cream 0.75% cream twice daily was conducted in patients with moderate to severe papulopustular rosacea. For those achieving clearance/almost clearance, initial treatment with ivermectin 1% cream was shown to significantly extend the duration of remission of papules/pustules compared with those initially treated with metronidazole 0.75% cream.[71]

Antibiotic Resistance

All antibiotics present a potential risk of selection for antibiotic resistance in the microflora of the skin and other sites[72-75]; however, in 2 recent studies, tetracycline resistance was not detected in *Propionibacterium acnes* isolated from acne patients.[76,77] No increase in the number or severity of resistant organisms in skin flora was observed following twice-daily use of 20 mg doxycycline.[78] Thus, sub-antimicrobial doses of doxycycline and tetracycline may mitigate the risk of bacterial resistance.

For oral antibiotics other than doxycycline and tetracycline (minocycline, trimethoprim, azithromycin, erythromycin, and metronidazole), there is no high-quality evidence supporting their use in patients with papules and pustules of rosacea. Panelists suggested that they be considered only for patients in whom tetracycline group antibiotics are contraindicated such as during pregnancy, are ineffective, or are poorly tolerated. Minocycline has been associated with a number of rare but severe side effects, leading panelists to prefer doxycycline or tetracycline.[47] Furthermore, they noted the risk of side effects, especially from long-term use, and price as reasons for avoiding nontetracycline antibiotics.

Implementation

Implementation of these guidelines will be facilitated by widespread dissemination to professional societies involved in the care of patients with rosacea, including presentation at meetings, publications, and online medical education resources.

Consultation, Endorsement, and Testing

Prior to publication, input was sought from the following stakeholders: patients with rosacea from the Acne and Rosacea Society of Canada, the Canadian Dermatology Association, the Canadian Skin Patient Alliance, the Canadian Pharmacists Association, and Canadian Family Physician Association. A listing of comments and feedback from these groups was compiled, and shortcomings considered important and consistently identified were addressed in the manuscript. Pilot testing of the CPG was conducted in clinical practice of some of the authors from November 2015 to January 2016.

Applicability

Treatment recommendations can be applied at time of initial visit and modifications thereafter based on clinical and patient-reported outcomes on follow-up visits. Specific advice for applying recommendations, clinical follow-up, and treatment modification is provided in Figures 2 to 6.

Resource Implications of Applying the Recommendations

These guidelines provide evidence-based treatment recommendations along with cost information. We anticipate that this aggregate information will provide prescribers a means of rationalizing treatment for individual patients with varying values and preferences.

Monitoring or Auditing Criteria

Monitoring and audit criteria include use of appropriate clinical and patient-reported outcomes for rosacea severity, effectiveness, satisfaction with therapy, and adverse effects during initial and follow-up visits.

A potential set of auditing criteria may include some or all of the following elements:

I. Initial assessment
   A. Evaluation of rosacea signs/symptoms
   B. Evaluation of rosacea signs/symptoms severity
   C. Evaluation of impact of rosacea

D. Appropriate selection of treatment(s) based on rosacea signs/symptoms and severity (see recommendations)
E. Treatment counseling
   a. Medication administration, application, and potential adverse events
   b. Appropriate follow-up for monitoring: within 8 to 12 weeks

II. Ongoing management
A. Evaluation of rosacea signs/symptoms
B. Evaluation of rosacea signs/symptoms severity
C. Evaluation of impact of rosacea
D. Evaluation of treatment satisfaction
E. Evaluation of patient perceived improvement (or not)
F. Inquiry into possible adverse events
G. Treatment modification if inadequate effectiveness or adverse event development

Updating

This document will be updated for validity every 5 years. Updates may be provided sooner than scheduled to include significant new developments such as evidence on existing benefits and harms of interventions, development of new treatments, or changes in available treatments.

Discussion

Rosacea is a common condition that has a wide range of presentations and an increasing array of treatment options.[79] CPGs can help navigate these options, particularly when developed by a panel providing expert experiential input within a foundation of best clinical evidence.

Other Guidelines

Prior guidelines on treatment of rosacea are largely consensus based.[5,6,79,80] Here we present a CPG for rosacea based on the recently published update of the Cochrane review "Interventions for Rosacea."[28] The Cochrane Collaboration is a nonprofit, nongovernmental organization that conducts systematic reviews of RCTs. Basing the CPG on this robust and recent systematic review decreases redundancy in literature search, quality assessment, and meta-analyses, which in turn reduces the cost of personnel and funding. The Cochrane study reports effect estimates as relative risks with confidence intervals, which may be most accurate and helpful for experts in epidemiology but can be less familiar to clinicians. This Cochrane review also provides a summary of findings for interventions, in which the body of evidence is graded based on assessments for design limitations, inconsistency in results, indirectness, imprecision, and potential for publication bias, whereby quality is rated as very low, low, moderate, or high.[81,82]

Gaps in Knowledge

Systematic, evidence-based CPGs intrinsically suffer from a development and publication lag time, despite using the most recent systematic review on rosacea that may omit newer literature. Furthermore, the Cochrane review only includes RCTs, so any useful information that could be used to make a recommendation, particularly data gathered from open-label studies, case reports, or case series, may not be available to inform the strength of recommendation. For example, compensatory vasodilation and rebound erythema with use of topical brimonidine have been reported in the literature but are not captured given its recent addition to the treatment arsenal.[32,33] Long-term data on severe but rare adverse events tend to be reported in this manner in the literature, especially for newer treatments.

This process of CPG development and the Cochrane review exposed knowledge gaps for rosacea related to (1) treatment efficacy and risks, particularly with procedural therapies and regimens using a combination of treatments; (2) patient values concerning their rosacea symptoms and the various treatment options; and (3) a lack of standardized assessment of rosacea clinical features.

Treatment Efficacy and Risks

For fixed erythema of rosacea, only brimonidine tartrate has high-quality evidence for its efficacy, and nearly half of patients show no improvement or worsen with its use.[31] Other treatment options, such as metronidazole, azelaic acid, and doxycycline, are less well supported by evidence and had little support for their use among the expert panel. No high-quality evidence exists for treatment of transient erythema (flushing).

Similarly, evidence is lacking on the best method for treatment of phyma. Case reports support the role of surgery for improvement of phyma; however, an important knowledge gap remains concerning the efficacy of medical therapy, such as isotretinoin or oral antibiotics, in reducing progression.

Furthermore, individuals with rosacea rarely present with only one clinical feature; most have multiple components to their presentation, such as erythema and papulopustular lesions or papulopustular lesions and ocular involvement. Clinicians often use combination therapy as needed depending on clinical presentation. However, few studies have addressed combination therapy. Adjunctive skin care therapy in combination with medical therapy is also often recommended but has little supportive evidence.

Patient Values

GRADE methodology requires the consideration of patient values in making recommendations; however, several aspects of the patient perspective are uncertain. It is clear that the

burden of seeking treatment will vary among Canadians, as some will have to travel long distances to see a dermatologist. This would be particularly burdensome for treatments requiring repeated visits, such as vascular laser for erythema. It is unclear how Canadian patients will weigh the financial costs and inconvenience of such barriers to access.

Also, further studies of QoL and other adverse effects are necessary to quantitate the impact of this disease, particularly the less-studied subtypes, phymatous and ocular rosacea.

Lack of Standardized Assessment

The lack of evidence for treatment of specific clinical features of rosacea may be related to the instruments used to measure outcomes. Many are global assessments incorporating multiple clinical features, often based on the rosacea subtypes ETR and PPR. Thus, less common subtypes such as phymatous may be neglected despite their morbidity. Ocular rosacea is another subtype that is poorly studied; no clear definition of ocular rosacea exists, and criteria for appropriate referral to ocular experts need to be determined to avoid unnecessary consultations.

A recent review of methods used to evaluate the severity of rosacea in clinical trials found only 3 of 32 identified studies used standardized assessment methods.[23] Measurements of improvement in rosacea differ greatly depending on therapy used due to the variety of clinical features of rosacea (eg, brimonidine for erythema but not papules/pustules and oral isotretinoin for papules/pustules but not erythema). Future studies need to address improvement of specific features using validated tools.

Conclusion

In developing these recommendations, we weighed (1) the balance of desirable and undesirable outcomes, (2) the quality of the supporting evidence, (3) the values and preferences of patients, and (4) the costs of treatment. For some clinical features—namely, brimonidine for erythema and ivermectin for papules and pustules, respectively—the benefits of treatments outweigh their harms, are supported by strong evidence, are expected to be acceptable to patients, but are more costly than treatments supported by lower quality evidence. For other features, such as phyma, no treatments have been demonstrated to be effective in RCTs, and treatments with the strongest clinician support, such as surgery, are invasive, are more costly than medical treatment, and may not be readily available to all Canadians.

Indeed, accessibility to therapy is a major issue. Many individuals cannot afford the most strongly recommended medications or procedural interventions (laser, IPL therapy). New, effective topical products with lower cost will help with the gap in treatment of this disease and, by superseding systemic antibiotics, could reduce the selection for antibiotic-resistant bacteria.

Whilst the past decade has witnessed considerable progress in clarifying some of the underlying basic mechanisms of disease and the advent of new treatment options, we identify further needs in clinical research, including specific outcome measures relevant to patients regarding QoL, and knowledge gaps in long-term efficacy, combination therapy, and maintenance. Nevertheless, this evidence-based rosacea CPG translates the summary of findings from the most recent Cochrane review on this topic and imbues it with experience and expertise of dermatological experts to guide Canadian health care providers in caring for those with this condition.

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Conflicts and Editorial Independence

The development of these guidelines was funded by Galderma, Pierre Fabre, and Valeant. These guidelines were developed independently by the authors, and the contents and treatment recommendations represent their collective opinion based on best evidence. The following steps were implemented to ensure the recommendations were free from external influence by industry, third-party payers, or governmental agencies.

1. Exclusion of the panel members involved in solicitation of funding (JT, CL) from writing and voting on treatment sections
2. Nondisclosure of funding pharmaceutical company identities until the final draft of the manuscript was submission-ready
3. Exclusion of funding pharmaceutical company input into the conception, design, and development of the CPG project or in the writing of the final manuscript
4. Invitation of all pharmaceutical and cosmetic companies offering rosacea products to participate as funding sponsors for unrestricted educational grants
5. Funds obtained were used for travel, accommodation, meals, and the administrative support group. Honoraria for authors and expert panel participation were not provided.

Contributor Statements

Yuka Asai served as chair and methodologic expert, contributed to the conception and design, contributed to the drafting of the article, provided critical review, and gave final approval of the version to be published. Jerry Tan and Charles W. Lynde contributed to the conception and design, contributed to the drafting of the article, provided critical review, and gave final approval of the version to be published. Chris L. Cochrane contributed to the design, contributed to the drafting of the article, and provided final approval of the version to be published. Akerke Baibergenova, Benjamin Barankin, Shannon Humphrey, Danielle Marcoux, Yves Poulin, Jason K. Rivers, Mariusz Sapijaszko, R. Gary Sibbald, John Toole, Marcie Ulmer, and Catherine Zip provided clinical expertise in developing recommendations, voted on and provided critical review of consensus recommendations, provided critical review of the manuscript, and gave final approval of the version to be published.

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