Australasian Society of Cosmetic Dermatologists

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ROSACEA

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VOLUME 01 / ISSUE 02 / MAY 2021

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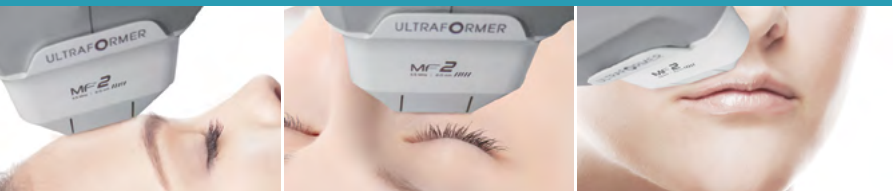


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OPINIONS AND PROGRESS IN
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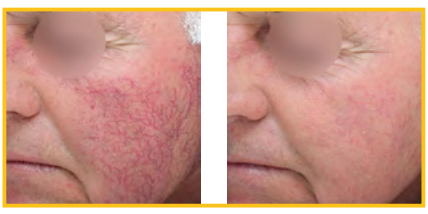

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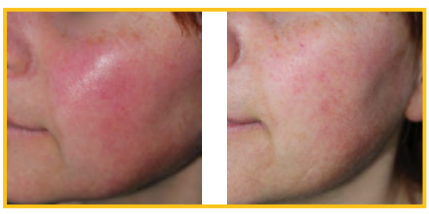

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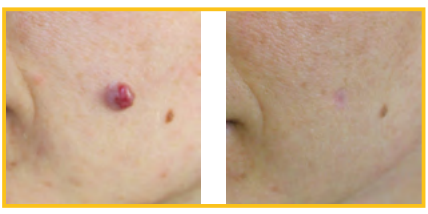

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OPINIONS AND PROGRESS IN
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## Welcome to the second issue of **Opinions and Progress in Cosmetic Dermatology (OPCD) – the official Journal of the Australasian Society of Cosmetic Dermatologists**

Dr Belinda Welsh is our guest editor and she has put together an outstanding collection of articles on key aspects of rosacea, through the OPCD prism.

The inaugural edition, launched in December 2020, was extremely well received and we hope to continue delivering up-to-date evidence-based information that is at the same time practical and clinically useful for cosmetic dermatologists and all other aesthetic practitioners.

Our literature bites have served as a useful prompt for readers to take a deeper dive into any topics of personal interest. With this edition, we are adding 30-second sound bites by contributing authors discussing their work and bringing to life the flavour and motivation for their articles.

We are also introducing "tips and tricks" on various aspects of cosmetic and laser therapeutics delivered as tightly edited 2 to 3-minute audio-visual clips. We hope readers will find this a very useful educational tool to complement our more traditional evidence-based offerings.

We welcome and appreciate any feedback to help us improve on future editions and meet your education needs.

**Co-Editors in Chief**
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## Contents

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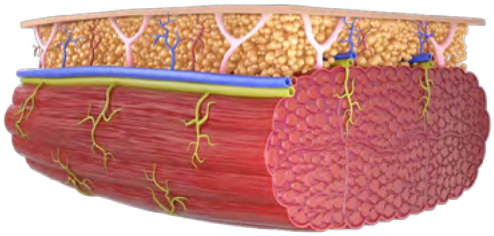

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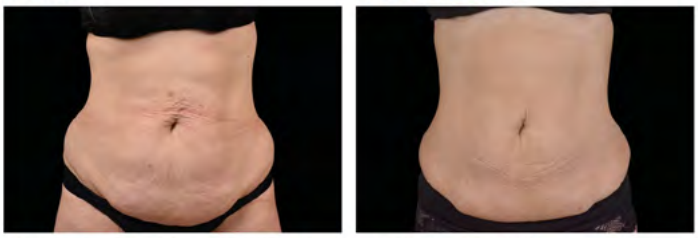

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# Rosacea Guest Editorial

**Guest Editor:** Belinda Welsh[1,2,3]

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CLICK IMAGE TO LINK TO VIDEO DURATION_01:40

Welsh B. Rosacea Guest Editorial. Opin Prog Cosmet Dermatol 2021;1(2):1.

I am delighted to present the second issue of the journal devoted to rosacea. We have brought together a group of international and local experts to explore a diverse range of topics to help foster learning and improve our understanding of this common condition.

In 2021, despite significant advances in our understanding of the pathophysiology of rosacea, it largely remains an enigma. This is remarkable for a disease that it is estimated to affect up to 5.5% of the global population.

This issue begins with a history lesson from Associate Professor Saxon Smith who shows us how rosacea has been represented in art and literature over the centuries.

We explore the current concepts in rosacea pathophysiology. There appears to be a complex interplay between genetics, immune and neurovascular dysregulation with environmental triggers which is yet to be fully elucidated.

We look at how our rapidly evolving understanding of the gut and skin microbiome is broadening our concept of rosacea as a systemic rather than skin limited disease. Increasing evidence is linking rosacea to a wider systemic state of chronic inflammation with cardiometabolic, autoimmune and neurological co-morbidities.

How we classify rosacea, in an effort to better understand it, remains in evolution. We document the recent transition from the subtype classification to the current National Rosacea Society diagnostic criteria.

In the absence of a diagnostic test, clinical acumen remains paramount in diagnosis. A pictorial essay is provided for our readers to help distinguish common rosacea phenotypes as well as differential diagnoses and common overlap conditions.

Ocular involvement in rosacea is common and needs to be kept front of mind when seeing our patients. Advice regarding diagnosis and management for this important association is provided.

The exact mechanism of action of some of our most common treatments remain poorly understood. In addition, the strength of supporting clinical trial evidence for many treatments are surprisingly weak. Treating rosacea requires a broad skill set, encompassing knowledge of skincare, topical and oral medical therapies and lasers and energy-based devices. We cover these topics in depth.

We have introduced a novel approach to covering the laser treatment of rosacea with our "How I do it" videos. We hope these concise, practical videos, from a range of expert laser practitioners, will be helpful and informative.

Although rosacea remains a disease of predominately fair skinned individuals it can occur in all skin types. We are grateful to our Singaporean colleagues Dr Hazel Oon and Professor Chee Leok Goh who provide their perspective and experience in diagnosing and treating rosacea with lasers and energy-based devices.

Finally, we acknowledge that rosacea affects the area of our skin most exposed to the world – our face. This influences how we are perceived by others and our own self-perception. It's effects on psychological well-being can be profound with well documented social implications. No issue would therefore be complete without acknowledging these psychosocial implications and disease burden and looking at ways we can understand our patients' experience to support them through their treatment journey.

Please enjoy this issue.

Dr Belinda Welsh

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# A Historical Representation of Rosacea

Saxon D Smith[1,2]

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Disclosures: *none*

**KEYWORDS:** rosacea, acne rosacea, historical perspective, art, literature

Smith SD. A Historical Representation of Rosacea. Opin Prog Cosmet Dermatol 2021;1(2):3.

Rosacea is a dermatological condition steeped in ties throughout history since the Middle Ages. Literature and art are littered with references to rosacea with a red face betraying underlying emotions, or perhaps alter social relationships because of the associated bias against perceived alcoholics.

One of the earliest descriptions of rosacea can be found written by the father of English literature, Geoffrey Chaucer (1343AD–1400AD), in his seminal works *The Canterbury Tales*. In the prologue,[1] he depicts one of the Canterbury pilgrims with florid rosacea attributed to his alcoholic habits:

> *"A SOMNOUR was ther with us in that place,*
> *That hadde a fyr-reed cherubinnes face...*
> *Of his visage children were aferd.*
> *Ther nas quik-silver, litarge, ne brimstoon,*
> *Boras, ceruce, ne oille of tartre noon,*
> *Ne oynement that wolde dense and byte,*
> *That him mighte helpen of his whelkes whyte,*
> *Nor of the knobbes sittinge on his chekes.*
> *Wel loved he garleek, oynons, and eek lekes,*
> *And for to drinken strong wyn, reed as blood."*

Even William Shakespeare in his works Henry IV, uses a depiction of rosacea as a source of jest when Falstaff makes fun of Lord Barodolph's red nose describing him:[2]

> *"thou art our admiral, thou bearest the lantern in the poop, but 'tis in the nose of thee; thou art the Knight of the Burning Lamp."*

On the other hand, perhaps one of the oldest fine art representations of rosacea has been attributed to the Florentine Renaissance painter Dominco Ghirlandaio (1448AD–1494AD).[3] His c1490AD piece entitled "An old man and his Grandson" depicts an elderly man afflicted by pronounced rhinophymatous rosacea leaning tenderly toward his grandson.[4] This painting can still be admired in the Louvre.

In the medical literature the term "acne rosacea" first appeared in the writings of Thomas Bateman (1778AD–1821AD).[5] He described rosacea as a clinical form of acne. This fledgling explanation of pathophysiology lasted throughout the nineteenth century. It has been suggested that it was not until the beautiful atlas of dermatology by Ferdinand von Hebra (1816AD–1880AD)[6] that the differential diagnosis between acne and rosacea was clearly made.[7]

Rosacea remains a conspicuous disease owing to its centrofacial involvement of erythrotelangectasia, papulopustular, and phymatous changes. However, our understanding of the pathophysiology has significantly changed from these earlier depictions.

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# Rosacea Pathophysiology

Sarah Hanna[1,2], Patricia M Lowe[1,2]

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Disclosures: *none*

**OUTLINE:** Rosacea is a chronic relapsing inflammatory condition which can have significant morbidity, with a significant impact on the individual's self-esteem and quality of life. Rosacea is characterised by persistent facial erythema and inflammatory papulopustules, although, facial telangiectasia, facial flushing, non-pitting facial oedema with erythema, ocular inflammation, and phymatous changes can also occur. Our understanding of the pathophysiology of rosacea has progressed significantly from basic ideas of inflammation to complex ideas of the interplay between genetic and environmental factors, the immune system, and neurogenic inflammation. There is substantial evidence to support a genetic predisposition to rosacea with a higher incidence of rosacea in people of Northern European descent; twin studies and genome-wide associate studies which have identified several single nucleotide polymorphisms in rosacea. Environmental factors associated with rosacea can be both physical and/or biological. Physical factors such as heat and noxious cold, spicy food, ultraviolet radiation, exercise, and alcohol are commonly cited by patients and can be explained by the upregulation of transient receptor vanilloid subfamily receptors, inflammasomes, matrix metalloproteinase's, kallikreins, or protease-activated receptors which may also induce neurogenic inflammation. Interestingly, several biological factors (such as cutaneous and gastrointestinal microorganisms) have been proposed as possible contributors to the pathophysiology of rosacea but are poorly understood. Increasingly, aberrancies in the innate and adaptive immune system with increased transepidermal water loss, and upregulation of Toll-like receptors, proteases, cathelicidins, and inflammasomes, are implicated in the pathophysiology of rosacea as evidenced by whole-transcriptome expression analysis and immunohistochemistry studies. Further, associations with conditions such as inflammatory diseases of the gastrointestinal tract, metabolic conditions, and neurologic and neurodegenerative disorders, presents clues regarding the mechanism of disease. Advances in our understanding of the pathophysiology of rosacea, particularly genetic loci and potential molecular targets for drug therapy, presents exciting research opportunities for the future.

**KEYWORDS:** rosacea, pathophysiology, genetics, environmental, immune

**ABBREVIATIONS:**

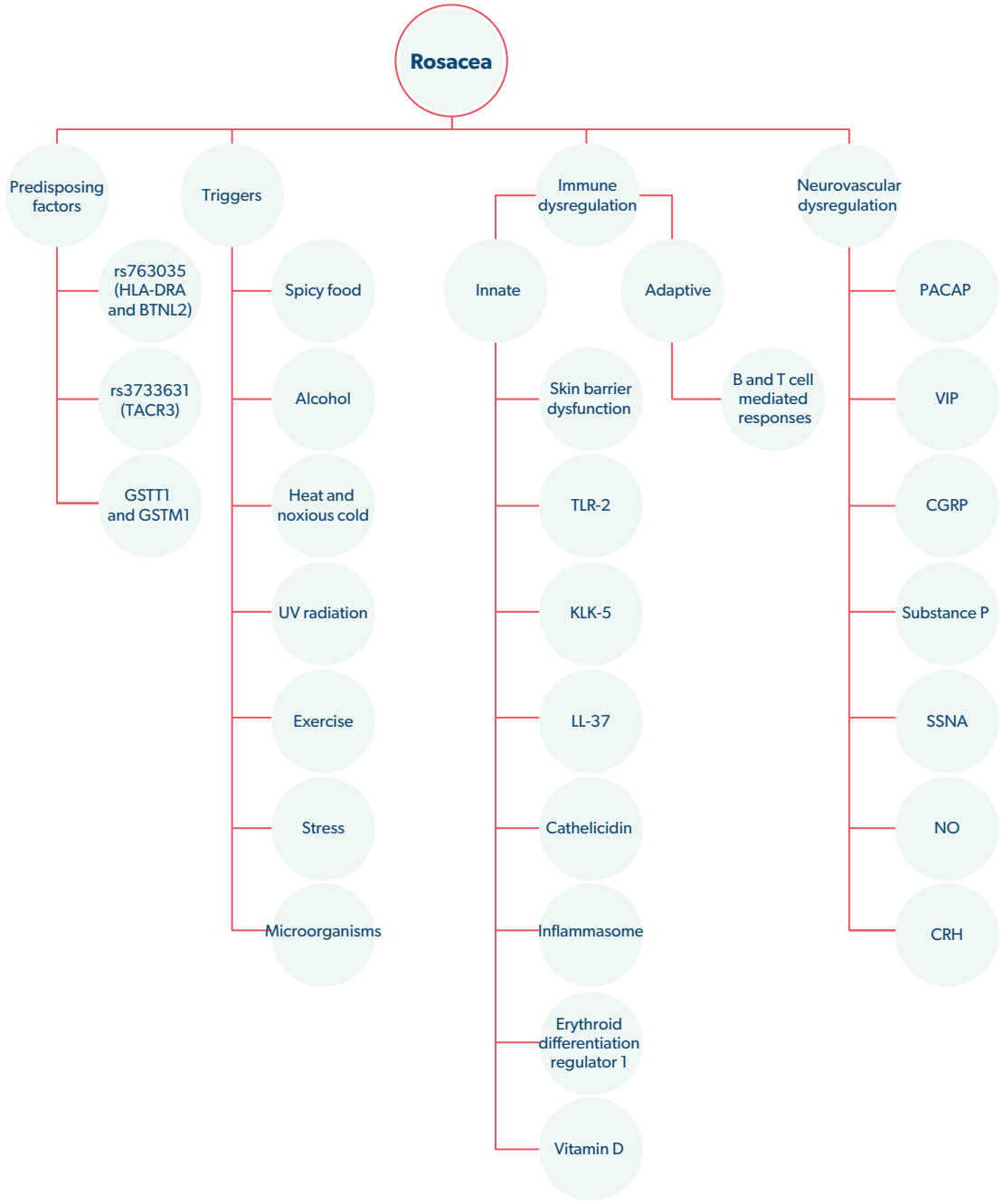
**BTNL2:** Butyrophilin-like 2
**CGRP:** Calcitonin gene-related peptide
**CI:** Confidence interval
**EGF:** Epidermal growth factor
**ETR:** Erythematotelangiectatic rosacea
**GI:** Gastrointestinal
**GST:** Glutathione S-transferase
**GSTM1:** Glutathione S-Transferase Mu 1
**GSTT1:** Glutathione S-transferase theta
**HLA:** human leukocyte antigen
**IL:** Interleukin
**KLK:** Kallikrein
**MMP:** Matrix metalloproteinase
**NLRP3:** NOD-, LRR- and pyrin domain-containing protein 3
**NRS:** National Rosacea Society
**OR:** Odds ratio
**PACAP:** Pituitary adenylate cyclase-activating peptide
**PAR-2:** Protease-activated receptor 2
**PCR:** Polymerase chain reaction
**PPR:** Papulopustular rosacea
**PR:** Phymatous rosacea
**ROS:** Reactive Oxygen Species
**SIBO:** Small intestinal bowel overgrowth
**TEWL:** Transepidermal water loss
**Th:** T helper
**TLR-2:** Toll-like receptor 2
**TNF:** Tumour necrosis factor
**TRP:** Transient receptor potential
**TRPV:** Transient receptor potential vanilloid subfamily receptors
**UV:** Ultraviolet
**VEGF:** Vascular endothelial growth factor
**VIP:** Vasoactive intestinal peptide

Hanna S, Lowe PM. Rosacea Pathophysiology. Opin Prog Cosmet Dermatol 2021;1(2):4-11.

## Introduction

Rosacea is a chronic relapsing inflammatory condition. It refers to a constellation of clinical findings, most significantly, persistent facial erythema and inflammatory papulopustules. Other findings include facial telangiectasia, a tendency for facial flushing, non-pitting facial oedema with erythema, ocular inflammation, and phymatous changes.[1] There are four recognised clinical subtypes of rosacea; erythematotelangiectatic (ETR), papulopustular (PPR), phymatous (PR), and ocular (OR), and clinical variants include granulomatous rosacea and rosacea fulminans.[2] Multiple inter-related pathophysiological mechanisms have been proposed for this condition (Figure 1), with several known environmental and genetic factors; however, the pathophysiological mechanisms remain poorly understood.

**Figure 1.** *Summary figure of rosacea pathophysiology*




*BTNL2: Butyrophilin-like 2; CGRP: calcitonin gene-related; CRH: cortisol releasing hormone; GSTM1: glutathione S-transferase Mu 1; GSTT1: glutathione S-transferase (GST) theta; HLA-DRA: human leukocyte antigen-DRA; KLK-5: kallikrein-5; NO: nitric oxide; PACAP: pituitary adenylate cyclase-activating peptide; SSNA: sympathetic nerve activity; TACR3: tachykinin receptor 3; TLR-2: Toll-like receptor 2; VIP: vasoactive intestinal peptide*

## Genetics

One of the most convincing pieces of evidence supporting a genetic predisposition to rosacea is its higher incidence in people of Northern European descent, particularly the Celtic population. It is hypothesised that rosacea developed as a mutation with an adaptive advantage to protect Celts against life-threatening mycobacterial infections such as lupus vulgaris during UV deficient periods.[3] Furthermore, up to one-third of patients with rosacea have a positive family history of the condition.[4] There have been a small number of studies that have proposed a specific genetic risk locus for rosacea.

In a cohort-based survey of identical and fraternal twins (275 twin pairs) which required a dermatologist to determine a rosacea score according to the National Rosacea Society (NRS) grading system, there was a higher association of NRS scores between identical versus fraternal twins (r=0.69 versus r=0.46, P=0.04), and the calculated genetic contribution was 46%. These associations persisted after adjusting for multicollinearity, suggesting that approximately half of the contribution to the NRS could be accounted for by genetics and the other half by the environment.[5]

An American genome-wide association study by Chang et al. of 22,952 individuals, 2618 with rosacea, identified two significant DNA variations (known as single-nucleotide polymorphisms) associated with rosacea, rs763035 and rs111314066; the former being the most replicable. This variant is intergenic between human leukocyte antigen-DRA (HLA-DRA) and Butyrophilin-like 2 (BTNL2), which are diffusely expressed in endothelial cells and perifollicular inflammatory infiltrates in PPR skin samples. Both HLA-DRA and BTNL2 are associated with the major histocompatibility complex of the adaptive immune system, indicating a central role of immune dysregulation in rosacea pathogenesis.[6]

An endogenous ligand of the tachykinin 3 receptor has also been investigated in the pathophysiology of rosacea by genotyping for rs3733631 by polymerase chain reaction (PCR)-restriction fragment length polymorphism and showed a statistically significant predominance of the C/G or G/G genotype and the G allele in PPR and marginal statistical significance of the C/G or G/G genotype in ETR.[7]

Glutathione S-transferase (GST) theta 1 (GSTT1) and GST Mu 1 (GSTM1) enzymes play a role in cellular defence against reactive oxygen species (ROS). In a study of 45 rosacea patients and 100 controls, Yazici et al. demonstrated a significant association between GSTT1 and GSTM1 null genotypes in the rosacea group. These mutations may give rise to defective enzymes, suggesting that increased oxidative stress may play a role in rosacea pathogenesis.[8]

## Environmental factors

Increased environmental temperature and dietary factors are often cited as potentially exacerbating rosacea. These factors may cause an increase in facial erythema and exacerbate a flushing tendency but there is no evidence that they worsen the inflammatory lesions of PPR, PR, or OR.[9]

Transient receptor potential vanilloid subfamily receptors (TRPV) are a subgroup of the heterogenous transient receptor potential (TRP) cation channels that serve diverse functions. These are widely expressed in vascular endothelial cells, smooth muscles cells and sensory nerve fibres. The first isolated member, TRPV1, also known as the capsaicin receptor, detects and regulates body temperature, and participates in nociception. A 2012 study by Sulk et al. analysed the expression and distribution of TRPV receptors in rosacea skin, compared with healthy skin and lupus erythematosus, and demonstrated increased TRPV1 gene expression in ETR and dermal immunolabelling of TRPV2 and TRPV3.[10] Furthermore, Sulk et al. demonstrated increased immunoreactivity for TRPV2, TRPV4, and TRPV2 gene expression in PPR skin. TRPV3, TRPV4, and gene expression of TRPV1 and TRPV3 was enhanced in PR while TRPV2 was decreased.[10] As TRPV channels are activated by typical rosacea triggers, including temperature changes, spicy food, hot beverages, UV exposure, exercise, and emotional stress, this finding suggests that they are implicated in the pathophysiology of rosacea.

## Physical factors

### Heat and noxious cold

TRPV1, TRPV2, TRPV3, and TRPV4, which were found to be enhanced in rosacea skin, are activated by heat. It is not clear whether noxious cold receptors may trigger rosacea.[10]

### Spicy food

TRPV1 which is enhanced in ETR and PR and expressed on neuronal cells, is known to be activated by capsaicin (spicy food), a commonly known trigger of rosacea.

### Ultraviolet (UV) radiation

Sun exposure is a well-known trigger for rosacea; however, it is unclear to what extent UVA, UVB, or temperature increases account for rosacea symptoms.

The notion that UV light plays a significant role in rosacea pathogenesis is evidenced by the facial distribution and its occurrence on male patients' bald scalp. Biopsies of rosacea skin demonstrate actinic elastosis, but it is unclear whether this is in keeping with the expected degree of photo-damage in susceptible middle-aged patients with Fitzpatrick

1 or 2 skin types or directly related to the pathogenesis of rosacea.[9]

UVA promotes the expression of matrix metalloproteinase 1 (MMP-1) and causes collagen denaturation, whereas UVB increases basic fibroblast growth factor and vascular endothelial growth factor (VEGF)/vascular permeability factor leading to cutaneous angiogenesis.[11,12] UV radiation also contributes to the development of ROS which can promote the activation of the inflammasome, proinflammatory cytokines, and inflammatory mediators produced by keratinocytes and fibroblasts.[13] The inducton of endoplasmic reticulum stress also propragates the inflammatory cascade by UV radiation, which leads to increased expression of transcription factor 4 and eventual activation of Toll-like receptor 2 (TLR-2).[13]

Molecular pathways for UV radiation and rosacea have been suggested, including TRPV channels, given UVB is known to activate TRPV4 on keratinocytes and is increased in the tissue of patients with chronic photodermatitis and rosacea.[10]

An immunohistochemical study by Suhng et al. demonstrated increased expression of interleukin-33 (IL-33), a member of the IL-1 family of cytokines, in the skin of Korean patients with rosacea, particularly ETR, compared to normal controls. The authors then irradiated human cathelicidin antimicrobial peptide (also known as LL-37) treated HaCaT cells (immortalised human keratinocyte cell line) with UVB in vitro. They found that UVB and LL-37 synergistically increased mRNA expression of proinflammatory cytokines, especially IL-33 and IL-1B. Further, LL-37 and IL-33 stimulated VEGF mRNA expression and VEGF release from HaCaT cells. The findings imply that upon exposure to UVB, LL-37 rich rosacea skin may produce IL-33, and thence VEGF, possibly contributing to the angiogenesis and vasodilation seen in rosacea.[14]

### Smoking

In a UK observational study, smoking was associated with a substantially reduced risk of developing rosacea, however, the diagnostic criteria for rosacea in this retrospective review were not clearly defined a priori therefore these results should be interpreted with caution.[15]

### Exercise

Exercising can activate release of neurotransmitters such as acetylcholine, or neuropeptides such as pituitary adenylate cyclase-activating peptide (PACAP), from autonomic nerves thereby providing evidence of the role of neurogenic inflammation in the pathogenesis of rosacea.[16] The inflammasome, TLR-2, and TRPV1, are also thought to be triggered by exercise and thus can contribute to the inflammatory response seen in rosacea.[17]

### Alcohol

Alcohol can act as a trigger for rosacea via several mechanisms. Alcohol can affect the gut microbiome, activate inflammasomes, TLR-2, and TRPV1, all of which have the potential to propagate the inflammatory cascade.[17]

## Biological factors

Imbalance of skin and gastrointestinal (GI) microbiota have been proposed as possible contributors to rosacea's pathophysiology but are poorly understood. Proposed organisms include Demodex mites, cutaneous or GI bacteria, a dysbalanced gut microbiota system (e.g., small intestinal bowel overgrowth [SIBO] syndrome), or stomach infection (e.g., *Helicobacter pylori*).

### Cutaneous microorganisms

Demodex folliculorum is a commensal mite that lives in or near the pilosebaceous units in human skin. Demodex is increased in some patients with rosacea, especially those with phymata, papules and pustules.[18] It remains unclear whether Demodex mites are significantly enhanced in erythematous skin per se, and which molecules or substrates produced by or due to Demodex, account for rosacea. Possible candidates include Bacillus oleronius, proteases or chitins, which can activate protease-activated receptors e.g., protease-activated receptor 2 (PAR-2) or TLRs (e.g., TLR-2), thereby releasing cytokines, chemokines, MMPs, prostanoids, modulating TRPV channel function (including TRPV1, TRPV4, and even TRPA1) and attracting immune cells.[19,20]

Evidence to support the role of Demodex in the pathogenesis of rosacea includes the following observations:

1. 1% ivermectin cream, which reduces Demodex mite numbers, was significantly more effective than cream vehicle in reducing the numbers of inflammatory skin lesions in two extensive studies of PPR.[21]

2. The use of topical calcineurin antagonists and systemic epidermal growth factor (EGF) inhibitor medications, which increase the population of Demodex mites, have been reported to result in rosacea-like dermatoses.[22,23]

Perhaps one of the most convincing studies assessing the role of Demodex in rosacea was a 2017 meta-analysis that included 23 case-control studies and 1513 patients with rosacea. In this meta-analysis, patients with rosacea were more likely to be infested by Demodex mites than the control subjects (odds ratio [OR], 9.039; 95% confidence interval [CI], 4.827-16.925) and had significantly higher Demodex density (standard mean difference, 1.617; 95% CI, 1.090-2.145). However,

the study was limited by interstudy variability, and a causal relationship could not be established by case-control studies.[24]

*Staphylococcus epidermidis* has also been proposed as a microorganism that plays a role in the pathogenesis of PPR and OR. An Australian study isolated a pure growth of *S. epidermidis* in 9 out of 15 patients with pustular rosacea, and no pure growth *of S. epidermidis* was isolated from their ipsilateral (non-affected) cheek skin (P=0.0003). Further, a pure growth of *S. epidermidis* was isolated from the eyelid margins of 4 out of 15 patients with PPR and no pure growth was isolated from the eyelids of age- and sex-matched control subjects (P=0.05).[18]

### Gastrointestinal tract microorganisms

There is increasing evidence that both upper and lower GI health exerts a profound effect on non-GI diseases, including those of the skin. Variations in diet such as alcohol ingestion and high glycaemic index foods may predispose to the growth of a less healthy, less diverse microbiome, subsequently leading to mucosal compromise and enteric inflammation. The intestinal microbial population appears to have an immunomodulatory effect upon non-enteric systems, including the skin, the mechanisms of which remain incompletely understood. Further evidence for this has been demonstrated with foods (e.g., fermented foods, kefir and kimchi) and probiotics that promote microbiome diversity have accelerated clearance of both *H. pylori* and improved rosacea.[25]

The role of *H. pylori* stomach infection in rosacea remains controversial. A 2017 meta-analysis which included 14 studies, 928 rosacea patients and 1527 controls, found that the overall association between *H. pylori* infection and rosacea was not significant (OR 1.68, 95% CI 1.00–2.84, P=0.052), but analysis restricted to C-urea breath test showed a significant association (OR 3.12, 95% CI 1.92–5.07, P<0.0001). Effect of eradication treatment on rosacea symptoms was assessed in seven studies and found no significant effect (RR 1.28, 95% CI 0.98–1.67, P=0.069). The authors concluded that there were weak associations between rosacea and *H. pylori* infection, as well as an effect of *H. pylori* therapy on rosacea.[26] It remains unclear whether there is a pathogenic link between the two conditions or whether *H. pylori* infection represents a proxy for other factors.

More convincing evidence regarding GI involvement in the pathogenesis of rosacea is derived from studies in which patients with SIBO syndrome (e.g., after GI surgeries, metabolic diseases) are treated with rifaximin, and in the majority of cases, the patients with rosacea experienced resolution or at least improvement of their rosacea.[27]

**Table 1.** *Physical and biological factors and their activating pathway*[17]

| Trigger | Activates |
|---|---|
| Emotional stress, heat, exercise, alcohol, spicy food | TRPV1 |
| Heat | TRPV2 |
| UV radiation, humidity, osmotic changes | TRPV4 |
| Cold weather, garlic/mustard oil, skin products and cosmetics (formaldehyde) | TRPA1 |
| Proteinases, microorganisms, skin barrier dysfunction | PAR-2 |
| UV radiation, wind, heavy exercise, alcohol consumption, emotional stress, skin care products and cosmetics, medication, and microorganisms | Inflammasome |
| UV radiation, emotional stress, alcohol, exercise, microorganisms/gut microbiome, topicals, medications | TLR-2 |
| Skin barrier dysfunction | KLK -5. -6, -7, -12 |
| UV radiation, microorganims | MMPs |

## Immune responses

The innate and adaptive immune system may play a principal role in the pathophysiology of rosacea, particularly upregulation. In both the early (perivascular) and later (pilosebaceous) stages of rosacea, infiltrates are strongly composed of T-helper type 1 (Th1) and Th17 cells. There is also marked expression of innate immune cells such as macrophages and mast cells in the erythema and papules of rosacea, neutrophils in the pustules, and plasma cells in phymata.[28]

Buhl et al. used whole-transcriptome expression analysis, quantitative real-time reverse transcriptase PCR, and immunohistochemistry to characterise the inflammatory infiltrate in ETR, PPR and PR. They demonstrated that T-cell activity and IL-17 immunostaining were significantly higher (P<0.05) in rosacea skin than healthy controls or patients with lupus. This increase was accompanied by an increased number of CD4+ cells, especially in PPR. The T-cell response is dominated by Th1/Th17-polarized immune cells, as demonstrated by the significant upregulation of IFN-γ or IL-17. Buhl et al. also demonstrated an increase in gene expression for IL-6, tumour necrosis factor (TNF), IL-20, and CCL20 (P<0.05), which are involved in the induction of IL-17 and IL-22.[28] However, in contrast, rosacea eruptions have been associated with T-cell immunosuppression after

infection or therapeutic intervention (e.g. corticosteroids, calcineurin inhibitors, phototherapy).[23,29,30] Other important molecules involved in rosacea pathophysiology through regulation of adaptive immune responses include erythroid differentiation regulator 1 and IL-18.[31,32]

## Skin barrier dysfunction

The skin barrier in patients with rosacea is impaired due to increased transepidermal water loss (TEWL) and a rise in facial skin pH.[33] Excessive TEWL may facilitate overgrowth of commensal organisms and enhance their access through the impaired skin barrier. The alkaline pH seen in rosacea skin enhances enzyme activity of kallikreins (KLK), such as KLK-5, -6, -7, or -12.[34] KLK-5 activates LL-37 activity which results in erythema, cytokine release, and angiogenesis.[35] In addition, KLK-5 and KLK-7 activate PAR-2, which is involved in several inflammatory responses.

## Toll-like receptors, proteases, and cathelicidin

TLR-2 is upregulated in the facial skin of rosacea patients and induces the upregulation and activation of the innate immune peptide, cathelicidin, via KLK-5, leading to erythema, an immune response, and angiogenesis through the release of serine proteases, MMPs, cytokines, chemokines, and proliferation of endothelial cells.[36] A role of cathelicidins in rosacea inflammation is now widely accepted although direct functional in vivo data in humans is lacking.

TLR-2 can also facilitate the activation of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, which mediates IL-1β release and further inflammatory reactions.[37]

While microbes can activate TLRs on keratinocytes, the upstream stimulator of TLR-2 in rosacea remains unknown. Notably, serum vitamin D is increased in patients with rosacea and has been demonstrated to increase TLR-2 and KLK-5 mRNA expression levels, thereby upregulating TLR-2, KLK-5, and LL-37 levels implicated in the pathophysiology of rosacea.[38]

## Inflammasomes

Inflammasomes are intracellular multiprotein complexes which activate inflammatory responses, particularly the release of pro-inflammatory cytokines. The rosacea inflammasome consists of NLRP3, caspase-1, and the adaptor protein apoptosis-associated speck-like protein (ASC). It coordinates the cleavage and activation of rosacea-upregulated IL-1 and results in enhanced expression of IL-8, neutrophil chemotaxis, IL-1 and TNF-mediated inflammation, and cyclooxygenase-2-mediated prostaglandin E2 synthesis, which results in pustule formation, papule formation, burning pain sensation, and vascular responses.[39]

## Neurovascular processes and neurogenic inflammation

In rosacea, skin hypersensitivity and flushing are partly caused by neural stimulation. The various TRPs appear to cause rosacea's clinical manifestations due to thermal, chemical, and mechanical triggers. As TRP channels can cross-talk with neuropeptide receptors, the interaction between these receptors may be involved in the sustained neurogenic inflammation seen in rosacea, particularly TRPA1 and TRPV1.[10]Activation of TRP on sensory nerves results in the release of vasoactive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), PACAP, and vasoactive intestinal peptide (VIP).[40] Substance P likely contributes to rosacea-associated oedema, while the other neuropeptides act as vasodilatory molecules as they bind the receptors of smooth muscle cells.[41]

Anecdotally, many rosacea patients link emotional stress with its onset or flare. The stress-induced increase in skin sympathetic nerve activity (SSNA) may play a role in the pathophysiology of rosacea. This may be due to increased blood flow (causing erythema), neuroinflammatory responses (resulting in cytokine release), and pain induction,[42] for example, through release of cortisol-releasing hormone,[45] PACAP or nitric oxide.[41]

## Telangiectasia

The pathophysiology of telangiectasia is unknown but differs from sun damage (chronic photodermatitis, heliodermatitis). Biopsies of telangiectasia on patients' facial skin with rosacea showed decreased collagen content and increased microvessel size and density compared to the normal facial skin of matched controls.[44] One theory is that proteases, MMPs, and growth factors from the transforming growth factor or fibroblast growth factor family destroy the extracellular matrix's architecture, thereby reducing tissue resistance for blood vessels, leading to irreversible vasodilation.[45] This theory requires further clarification through research with larger sample sizes.

Other theories of telangiectasia development include that certain neuropeptides (CGRP, PACAP, VIP) bind and activate the receptors of smooth muscle cells, and thus may act as vasodilatory molecules.[41] As discussed previously, the combination of UVB and LL-37 in rosacea skin theoretically increases IL-33 and VEGF production, resulting in vasodilation and angiogenesis.[14]

## Phymata

Phymata, most commonly rhinophyma, is much more prevalent in male than female patients with a ratio ranging from 5:1 to 30:1. It has been postulated that this may be due to androgenic influence.[46]

The pathophysiological link between chronic inflammation and skin fibrosis and/or sebaceous hyperplasia remains unclear. It has been suggested that the phymatous changes of PR may be due to the chronic upregulation of mast cells and B-cells, which are critical contributors to skin fibrosis through the release of MMPs.[28] However, this theory is not consistent with reports from some patients with rhinophyma who have not had previous severe inflammatory PPR, nor why rhinophyma is much more common in males than females.

## Ocular rosacea

Meibomian glands are modified sebaceous glands of the eyelid. The pathogenesis of OR appears closely related to their dysfunction and a consistent finding of OR is reduced tear break-up time due to inadequate lipid components of the tear film. Chronic inflammation of the meibomian glands results in the formation of crops of meibomian cysts. Microorganisms related to the pathophysiology of cutaneous rosacea (Demodex mite, *H. pylori*, *S. epidermidis*) have also been proposed as possible inflammatory triggers for OR.[47]

## Comorbidities and associated clues regarding the mechanism of disease

Studies indicate an increased risk of rosacea with inflammatory diseases of the GI tract, such as Crohn's disease, ulcerative colitis, coeliac disease or SIBO syndrome,[6,25] likely due to shared disease susceptibility via the HLA-DRA locus.

Studies have also demonstrated an association with metabolic conditions such as diabetes,[6] hypertension, dyslipidaemia, and coronary artery disease[48] likely due to low levels of high-density lipoprotein–associated proteins or enzymes (e.g., paraoxonase-1),[49,50] increased cathelicidin levels, or endoplasmic reticulum stress.[35]

There is a positive association between rosacea and neurologic and neurodegenerative disorders such as Alzheimer's disease,[35] Parkinson's disease,[51] migraines,[52] depression,[53] anxiety disorders,[54] complex regional pain syndrome, and glioma.[16]

## Conclusion

Our understanding of the pathophysiology of rosacea has progressed dramatically over the decades from basic ideas of inflammation to complex ideas of the interplay between genetic and environmental factors. Despite being a common condition, rosacea can be debilitating, with a marked effect on self-esteem and a reduction in quality of life. Further advances in our understanding of the pathophysiology of rosacea, particularly genetic loci and potential molecular targets for drug therapy, presents exciting research opportunities for the future.

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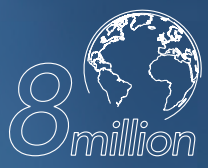


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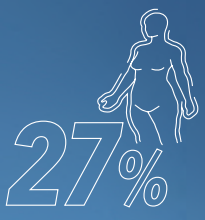


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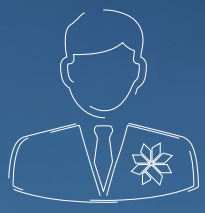

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# Rosacea – Classification, Differential Diagnoses and Overlap Diagnoses: Part 1


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Disclosures: *none*

**OUTLINE:** This is the first of two instalments on the classification, diagnosis and differential diagnosis of rosacea. Part 1 outlines the American National Rosacea Society (NRS) expert committee classification from 2002 and the more recent diagnostic criteria recommendations by the global ROSacea COnsensus (ROSCO) panel in 2017. This paper will focus on history, examination and investigations relevant to rosacea and its differential diagnoses.

**KEYWORDS:** Rosacea, classification, diagnostic criteria, differential diagnosis

Welsh B. Rosacea – Classification, Differential Diagnoses and Overlap Diagnoses: Part 1. Opin Prog Cosmet Dermatol 2021;1(2):13-19.

## Classification

Rosacea is a common, chronic, inflammatory centrofacial dermatosis with a range of morphological signs characterized by exacerbations and remissions. At this time the aetiology and pathophysiology remain incompletely understood and there are no histologic or serologic markers.

The first standard classification system was developed by the American National Rosacea Society (NRS) expert committee in 2002.[1] This classified patients into four subtypes: erythematotelangiectatic (ETR); papulopustular; phymatous; and ocular with one variant, granulomatous rosacea (Table 1). Management recommendations based on these subtypes followed.[2,3]

This classification system helped facilitate better communication between clinicians, researchers and patients and to provide a framework to update as knowledge improved. However, there are challenges and limitations as patients often present with a range of features that span multiple subtypes or may progress between them.[4,5]

Over time, the improved understanding of the pathophysiology as well as a greater appreciation of the various clinical manifestations of rosacea led to a reconsideration of the classification system. In early 2017 revised recommendations were published in the British Journal of Dermatology by the global ROSacea COnsensus (ROSCO) panel comprising 17 international dermatologists and ophthalmologists.[6]

This new system was based on diagnostic criteria. The primary diagnostic features included persistent centrofacial erythema with periods of increased intensity and phymatous changes. Major features, diagnostic when there are at least two, include flushing (transient erythema), inflammatory papules and pustules, centrofacial telangiectasia, and ocular manifestations. Minor features include burning, stinging, oedema or dry sensation of the skin. Furthermore, each feature could be graded on a severity spectrum independent of concurrent phenotypes.

This approach was based on individual phenotypes tailored to the patient. In turn, this led to revised treatment algorithms.[7,8] The NRS expert committee subsequently endorsed these recommendations and updated their classification and management guidelines (Table 2).[9,10]

Rosacea is now recognised as a relapsing and remitting chronic centrofacial syndrome primarily involving the convexities with a variety of signs and symptoms. Currently, one diagnostic or two major phenotypes are required for the clinical diagnosis of rosacea. The most

common patterns or groupings of signs can still be provisionally designated as specific subtypes of rosacea.

However, several questions remain. Granulomatous rosacea was omitted as a variant in the most recent NRS classification and where this currently stands is uncertain. It's features of monomorphic, yellow-brown to red papules and nodules of uniform size that lead to scarring are not shared with rosacea. The key pathologic finding of noncaseating epithelioid granulomas may make it a histologic variant of rosacea rather than a distinct clinical subtype.[9]

The NRS has also deemed there is insufficient basis at present to include rosacea fulminans, steroid induced acneiform eruption, and periorificial dermatitis as types of rosacea, and for clarity, at this time, these conditions should be recognized as separate entities.[9]

Phenotype progression also remains controversial.[5] Evolution from one phenotype to another may or may not occur. Regardless, each individual characteristic e.g. flushing or telangiectasia, may progress from mild to moderate then severe. It is important to address this with patients as there is a popular belief that the natural history of rosacea is slow and progressive, worsening to eventual phymatous change. Currently, there is no convincing evidence in the literature that this actually occurs.

## Differential diagnosis

There is no "gold standard" diagnostic serologic or histopathologic test. Clinical acumen is paramount to exclude differential diagnoses with similar phenotypic features and it is important to remain unbiased to a patient with a label of 'rosacea' either self-diagnosed or diagnosed by another practitioner. The differential diagnosis for rosacea is broad (Table 3) and it is common for rosacea to overlap with other dermatoses (Table 4). Therefore, it is possible to consider the presence of multiple diagnoses in one patient. Management success depends on teasing out each element of the presenting features and addressing each without inadvertently worsening the other.

## Tips for history taking

The first consultation with a patient presenting with facial redness requires time. A complete medical history is of course mandatory but attention to some specific areas is helpful.

### 1) Elicit a sequential history.

Understanding the evolution of symptoms and signs right from the onset is important. Symptoms may have been present for years and the history is often littered with treatments, often self-prescribed, which will modify signs. Most patients are women and will have tried a multitude of skincare products often resulting in a concurrent irritant contact dermatitis. Men tend to be the opposite. Rosacea patients have impaired skin barrier function and sensitivity and have difficulty finding products they can tolerate. Many will not be using sunscreen at all due to irritation.

### 2) Ask about all previous treatments, oral and topical, prescribed or not, and how long they were used.

Prescribed treatments may not have been given adequate time to work so discarded by the patient as no good. Similarly, "laser" treatments may have been performed with any number of devices and providers, with variable success. Patients have often spent large amounts of money with multiple sessions and if these have been unsuccessful then they may believe all laser treatment is ineffective.

### 3) Ask directly about topical steroid use.

Topical steroid use is very common and patients often will not disclose this, sometimes out of feelings of guilt that they should not have been using these. It is not uncommon for topical steroids to have been used at some stage either prescribed, due to early misdiagnosis, or recommended by a well-intentioned relative or friend.

### 4) Ask every patient about ocular symptoms.

Ocular involvement occurs in 60-70% of patients with rosacea and may be easily overlooked by dermatologists.[14] Enquire about signs and symptoms such as burning, itching or watering, grittiness or chronic foreign body sensation, photosensitivity, lid margin or conjunctival erythema and recurrent stye and chalazion formation.

### 5) Understand your patients skin type.

Rosacea can occur in all skin types and having an idea of a patient's skin type, for example, oily and tolerant versus dry and sensitive, is helpful. Patients with tolerant sebaceous skin with enlarged pores may be more prone to phymatous change and this group often tolerate, and benefit from, low dose isotretinoin. Patients with dry sensitive skin may need more help with their skincare regime as they are often intolerant to multiple topicals. This group may also have a co-existent allergic contact dermatitis.

### 6) Ask about trigger factors.

Trigger factors, especially for flushing, is important to elicit for each individual patient (Table 5), as ultimate avoidance of these will be important for successful management. Many people underestimate the importance of environmental management,

for example strict sun protection and avoidance of alcohol, and don't modify these adequately. Stress can be a major trigger for rosacea flares.

7) **Ask about occupational/recreational history.**
This is important to know especially if their work or recreation is outdoors or in extremes of temperature. Unless this is understood, reasons for treatment "failure" can't be fully appreciated.

8) **Flushing.**
If flushing is a significant presenting feature, that is, prolonged and extensive involving the neck and chest with or without sweating, then a detailed history with appropriate investigations is mandatory to exclude an underlying malignancy. There is a long list of causes of flushing including certain foods (especially alcohol) and medications. Whilst beyond the scope of this article the detailed differential diagnosis, investigation and management of patients with non-malignant and malignant causes of flushing has recently been reviewed.[12,13]

9) **The emotional impact**
of rosacea is considerable so many patients need the opportunity to voice their anxieties and have these addressed.

## Examination

Without a diagnostic test clinical acumen and close attention to detail is critical.

Essentials for examination include ensuring all makeup is removed, excellent lighting, magnification and an open mind regarding the diagnosis with an eye to looking for co-existent pathology. Examination findings for common rosacea phenotypes are presented below. Rosacea overlap conditions and rosacea differential diagnoses are presented in Part 2 of this article.

## Investigations

Generally, no investigations are needed when diagnosing rosacea. Serology or histology should be considered to:

1) exclude serious underlying causes of flushing

2) exclude other causes for photosensitivity or an autoimmune disease (antinuclear antibody [ANA] and extractable nuclear antigens [ENA]) and

3) exclude other dermatoses if clinical features are atypical.

Patch testing should be considered if erythema is patchy with dryness and scale and in the setting of intolerance to multiple topical agents.

## Rosacea phenotypes

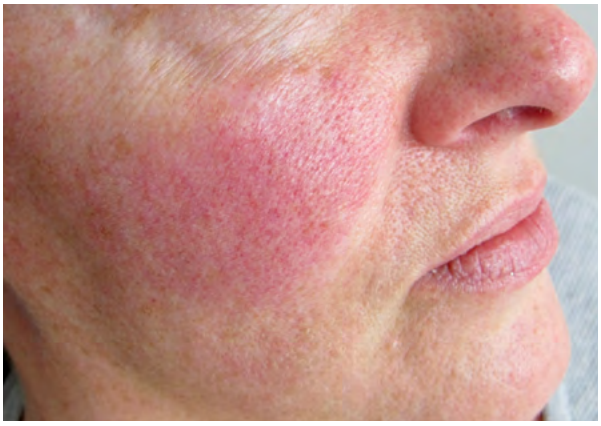


**Image 1**

Fixed central cheek erythema with fine telangiectasia sparing the medial cheek and nose.

Erythematotelangiectatic subtype.

Mild actinic damage with lentigines and solar dyschromia co-exist.

Note – rosacea associated erythema exhibits periocular sparing.

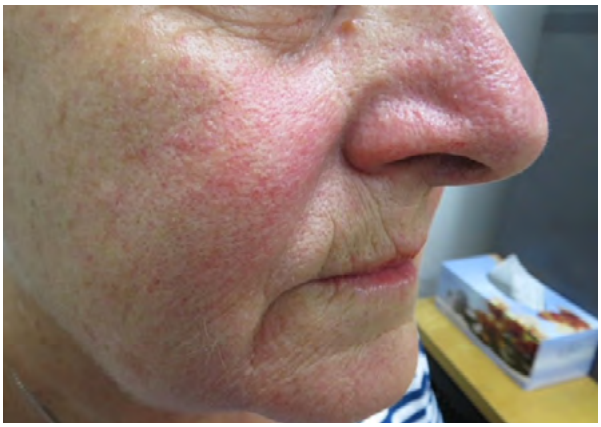


**Image 2**

Fixed medial cheek and nose erythema. Seborrhoeic dermatitis is an important differential diagnosis and can overlap.

Erythematotelangiectatic subtype.

The erythema associated with this medial pattern can be more resistant to vascular laser in the author's experience.

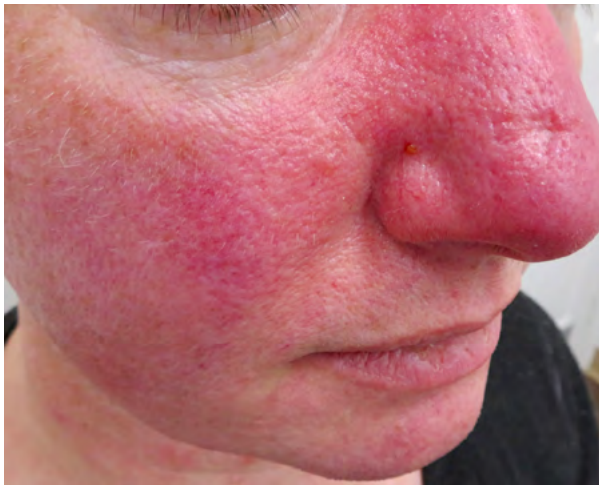
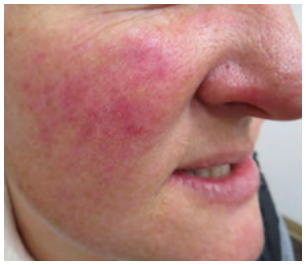


**Image 3**

Severe fixed erythema with telangiectasia over the cheeks and nose with oedema and early phymatous involvement of the nose.

Note the associated actinic damage with lentigines and actinic cheilitis.



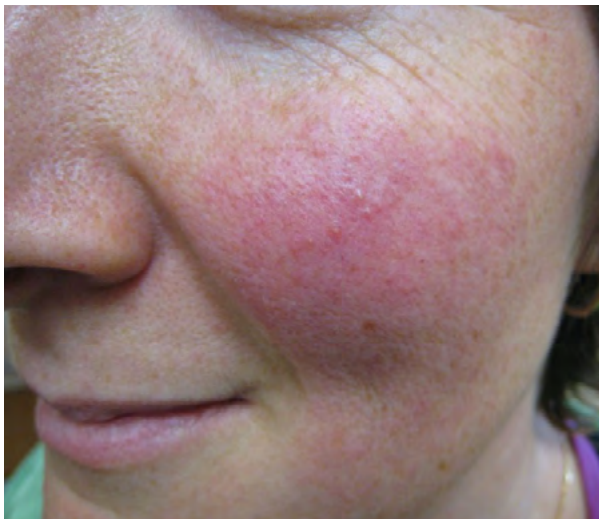


**Image 4 a and b**

Isolated central cheek fixed erythema with a) papules, dryness and scale and b) pustules.

This pattern can spare the nose.

Mild papulopustular subtype.

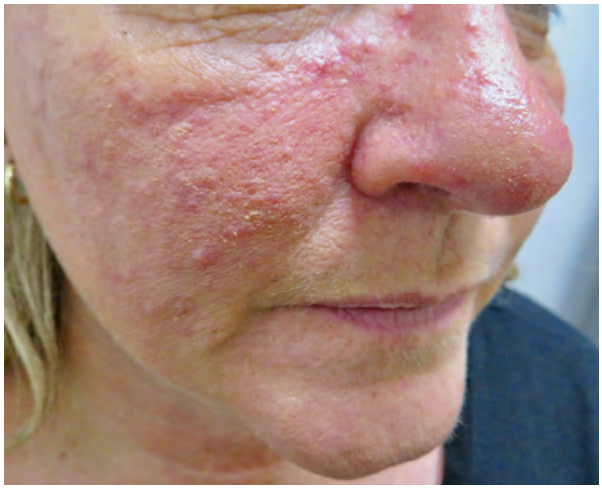
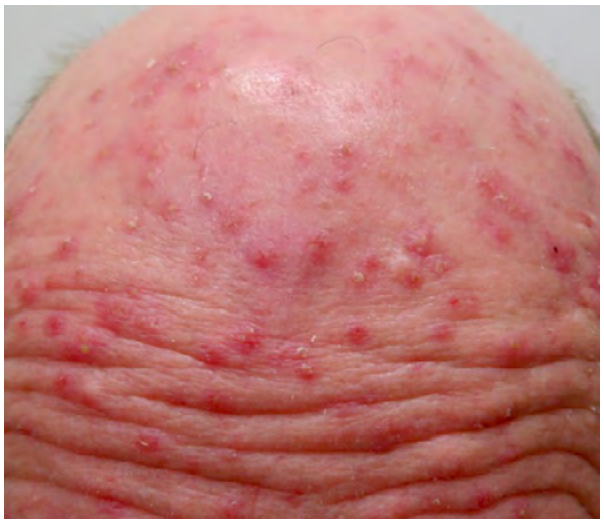


**Image 5**

Severe inflammatory rosacea with large papules and nodules over the cheeks and nose with oedema and dryness and scale. This patient was using thick makeup for camouflage. Removing this with toners and cleansers was causing a secondary irritant dermatitis.

Severe papulopustular subtype.



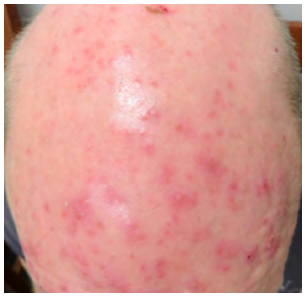
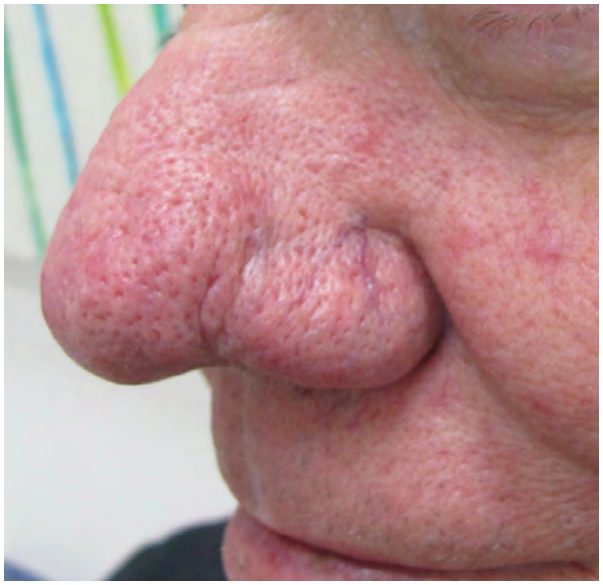
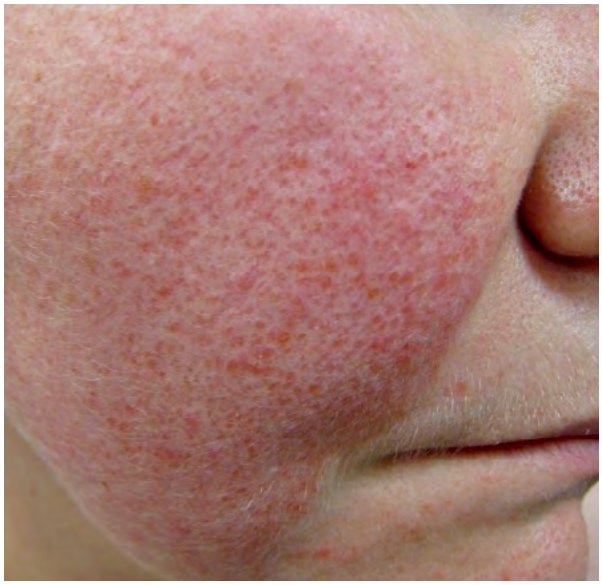


**Image 6 a and b**

Rosacea can involve the forehead and scalp alone. This is more common in men with androgenetic alopecia. Rarely involvement can occur at other extrafacial sites such as the neck chest and back.





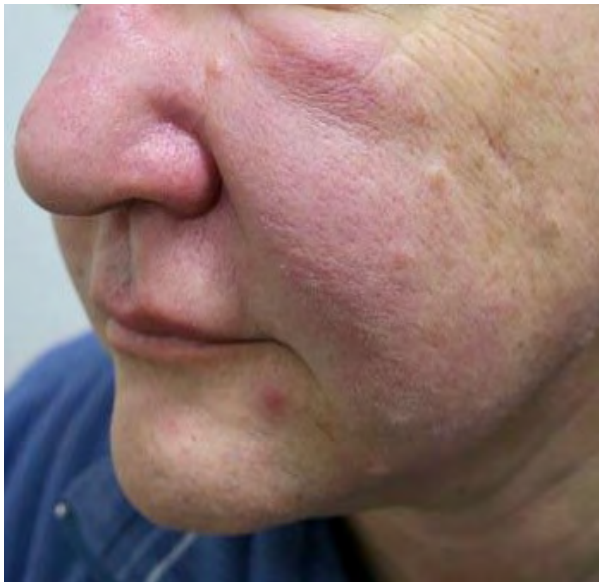


Image 7 a and b

**Phymatous rosacea**
Rhinophyma of the nose. This is the most common type of phymatous change and is more commonly seen in men. Signs include a bulbous nodular nasal contour, sebaceous hyperplasia, patulous pores, and fibrous thickening of the skin.

Extensive phymatous change involving the whole face (persistent facial oedema, Morbihan's disease). This patient demonstrated fixed erythema with flushing, dilated pores and nonpitting oedema involving the forehead, glabella, cheeks, nose and upper lip. Isotretinoin is the treatment of choice for this phenotype.

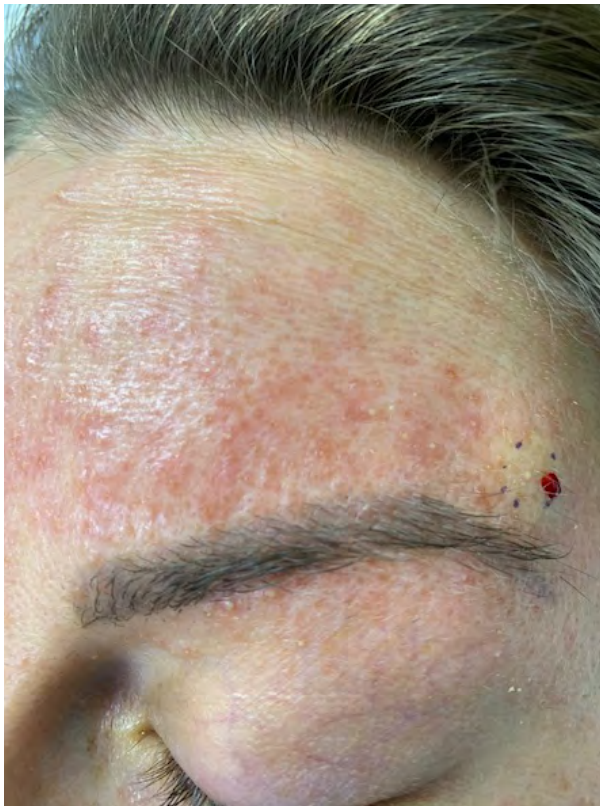


Image 8 a and b

**Granulomatous rosacea (Granulomatous facial dermatitis)**
This can be difficult to diagnose without histopathology (noncaseating epithelioid granulomas with a mixed inflammatory infiltrate). Clinical signs include monomorphic yellow, red, and brown papules which can occur around the eyes nose and mouth. Other signs of rosacea, flushing, erythema and telangiectasia may be seen but are not necessary for the diagnosis. This is more common in middle aged women, and can be chronic and difficult to treat. These patients most likely have overlap with rosacea.

**Table 1.** *NRS rosacea subtype classification*[1]

| Rosacea subtype | Clinical features |
|---|---|
| **Erythematotelangiectatic** | Flushing and persistent central facial erythema with or without telangiectasia |
| **Papulopustular** | Persistent or transient central facial papules and/or pustules often in same stage of development |
| **Phymatous** | Thickened skin, irregular surface nodularities and enlargement, usually beginning as patulous follicles; may occur on the nose, chin, forehead, cheeks, or ears |
| **Ocular** | Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital oedema |
| **Granulomatous rosacea (variant)** | Hard brown, yellow or red cutaneous papules or nodules of uniform size |

**Table 2.** *NRS rosacea diagnostic criteria*[9,10] *

| Diagnostic signs | Clinical features |
|---|---|
| **Fixed centrofacial erythema** | Erythema in a characteristic centrofacial pattern that may periodically intensify |
| **Phymatous changes** | Patulous follicles, skin thickening or fibrosis, glandular hyperplasia, and bulbous appearance of the nose (rhinophyma is the most common form) |
| **Major features** | Without a diagnostic phenotype, the presence of two or more of the following major features may be considered diagnostic:<br>• Papules and pustules<br>• Flushing: Frequent and typically prolonged<br>• Telangiectasia: Predominantly centrofacial in phenotypes I-IV, rarely seen in darker phenotypes<br>• Ocular manifestations |
| **Secondary features** | The following secondary signs and symptoms may appear with one or more diagnostic or major phenotypes:<br>• Burning and stinging<br>• Oedema: Facial oedema<br>• Dry appearance: Central facial skin may be rough and scaly |

** A diagnosis of rosacea may be considered in the presence of one of the following diagnostic cutaneous signs.*

**Table 3.** *Rosacea differential diagnosis*

- Extrinsic photoaging / Actinic damage / Heliodermatitis / Telangiectatic actinic keratoses
- Periorificial dermatitis
- Acne
- Seborrhoeic dermatitis
- Irritant contact dermatitis
- Allergic contact dermatitis
- Keratosis pilaris
- Facial psoriasis
- Steroid induced facial dermatitis
- Steroid induced telangiectasia
- Demodicosis
- Yeast folliculitis
- Systemic lupus erythematosus
- Dermatomyositis
- Cutaneous lymphoma
- Cutaneous sarcoidosis (lupus pernio)
- Perniosis of the nose (chilblains)
- Flushing (due to other causes)

**Table 4.** *Common conditions co-existing with rosacea*

- Rosacea / Extrinsic photoaging / telangiectasia
- Rosacea / Seborrhoeic dermatitis
- Rosacea / Acne
- Rosacea / Irritant contact dermatitis
- Rosacea / Keratosis pilaris

**Table 5.** *Common rosacea trigger factors**

- Sun exposure
- Emotional stress
- Hot weather
- Wind
- Heavy exercise
- Alcohol consumption
- Hot baths
- Cold weather
- Spicy foods
- Humidity
- Indoor heat
- Certain skin care products

**Adapted from the NRS patient survey*

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# Rosacea – Classification, Differential Diagnoses and Overlap Diagnoses: Part 2

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Disclosures: *none*

**OUTLINE:** This is the second of two instalments on the classification, differential diagnosis and overlap diagnoses of rosacea. Part 2 provides a pictorial review of important differential diagnoses to consider when assessing patients with facial erythema. Common conditions which can co-exist and overlap with rosacea are also highlighted.

**KEYWORDS:** Rosacea, differential diagnosis, diagnosis, clinical images, facial erythema

Welsh B. Rosacea – Classification, Differential Diagnoses and Overlap Diagnoses: Part 2. Opin Prog Cosmet Dermatol 2021;1(2):20-25.

## Introduction

The accurate diagnosis of patients who present with facial dermatoses can at times be challenging. An excellent understanding and awareness of possible differential diagnoses is important. The diagnosis of rosacea now requires the clinician to search for clinical signs and symptoms which will fulfil major and minor diagnostic criteria. Many of these features may be seen in other conditions.

There are a number of dermatoses and general medical conditions which primarily affect the face. Therefore, a secondary search must be made for clues to differential diagnoses.

The concept of Occam's razor which is the problem-solving principle that "entities should not be multiplied without necessity" is popular in medicine. Whilst the simplest explanation is usually the right one, it is wise to entertain the possibility of more than one diagnosis when seeing patients with facial dermatoses.

Below is a pictorial essay highlighting the differential diagnoses of rosacea and the clinical features when dermatoses co-exist or overlap with rosacea.

## 1) Rosacea overlap diagnoses

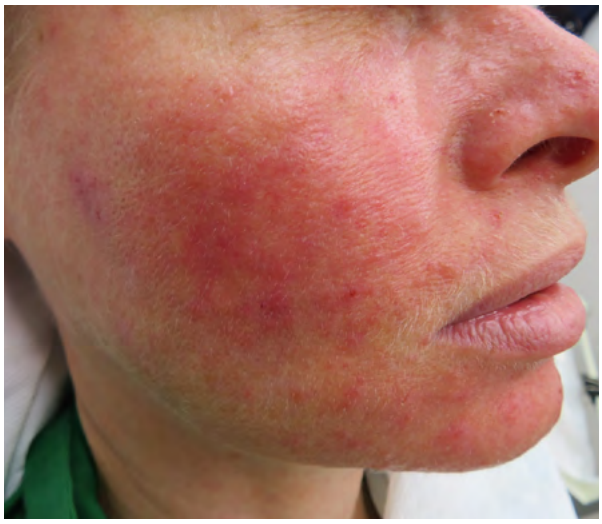


**Image 9**

**Rosacea / irritant contact dermatitis**
This is common and presented in this patient with dry tight shiny skin from overuse of multiple topicals including ivermectin in the form of a horse worming paste. Dry scaly skin should also alert the clinician to this possible coexistent diagnosis.

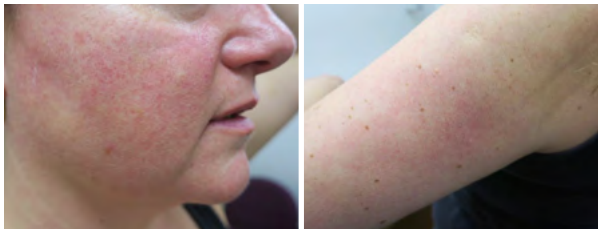


Image 10 a and b

**Rosacea / keratosis pilaris rubra facei**
This can be more difficult to identify in adult patients as it is more subtle. The key finding is erythema and flushing which extends to the jawline. The typical findings of keratosis pilaris may also be present on the postero-lateral upper arms.

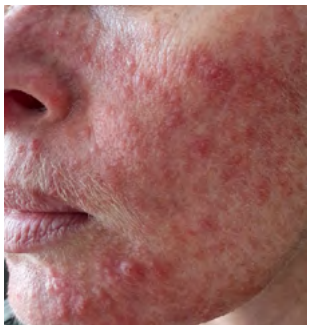


Image 11

**Rosacea / acne**
Acne can be easily be overlooked when it occurs with rosacea. However, papules, pustules and nodules around the chin and lower jawline may suggest this combination. Closed and open comedones are a key feature of acne but not for rosacea. Gently stretching the skin can be helpful to find closed comedones.

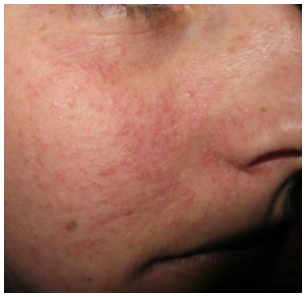


Image 12

**Rosacea / periorificial dermatitis**
This patient demonstrated a more extensive periorificial dermatitis (POD) with papules extending over the cheeks as a result of ongoing potent topical steroid use. This had evolved to overlap with "steroid rosacea" or steroid induced facial dermatitis. The key findings that suggest POD include the perinasal and lower eyelid involvement, and the monomorphic nature of the papules. True rosacea spares the periocular skin.

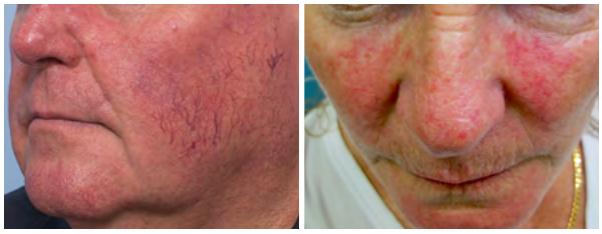
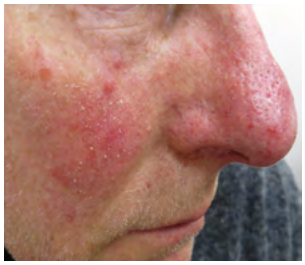


Image 13 a and b

**Rosacea / telangiectatic photoaging**
This is an extremely common combination in clinical practice. Men tend to have larger, coarse telangiectasia extending the lateral cheek. Women tend to have finer telangiectasias on the central and medial cheeks. Dermal atrophy, solar lentigines, dyschromia, actinic keratoses with dryness and scale are all often found on the faces of these patients. Both conditions are associated with epidermal barrier dysfunction. Actinic damage contributes to a component of the background erythema and inflammation and rosacea targeted treatments including vascular laser will not clear this. It must be treated with targeted therapies to achieve overall therapeutic success.



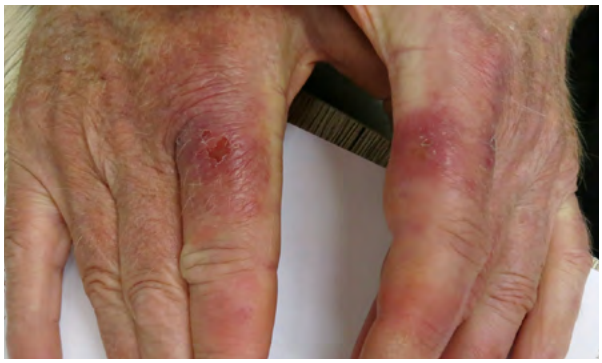


Image 14 a and b

**Rosacea with perniosis (chilblains) of the nose**
This patient presented with clinical signs of rosacea involving the nose and cheeks. He also did not use any skincare products which is indicated by the skin dryness and scale. Despite the introduction of rosacea targeted therapies including vascular laser, his nose remained treatment resistant. On further questioning, it transpired he worked in a very cold environment and had concurrent clinical signs of perniosis (chilblains) on the hands. This can easily be missed if an occupational history is not sought.

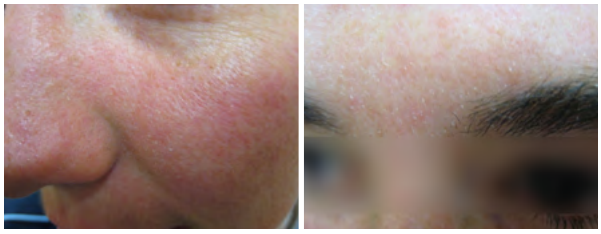
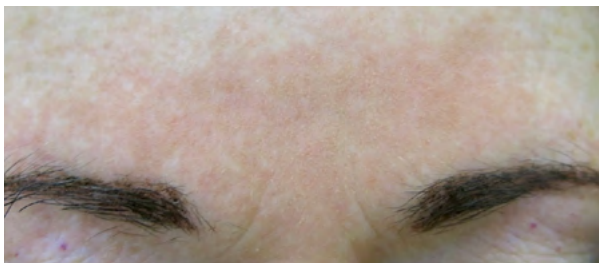


Image 15 a and b

**Rosacea / seborrhoeic dermatitis**
This is another relatively common combination of diagnoses. This patient presented with classic centro-facial fixed erythema and flushing with intermittent papules and pustules of rosacea. However, they also had subtle scaling in the glabella and eyebrows and along the nasolabial fold. Other signs of seborrhoeic dermatitis, erythema and scaling in the scalp (i.e., dandruff), external ear canals and central chest should routinely be sought to support this diagnosis

## 2) Rosacea differential diagnoses



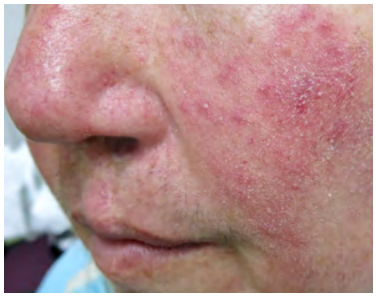
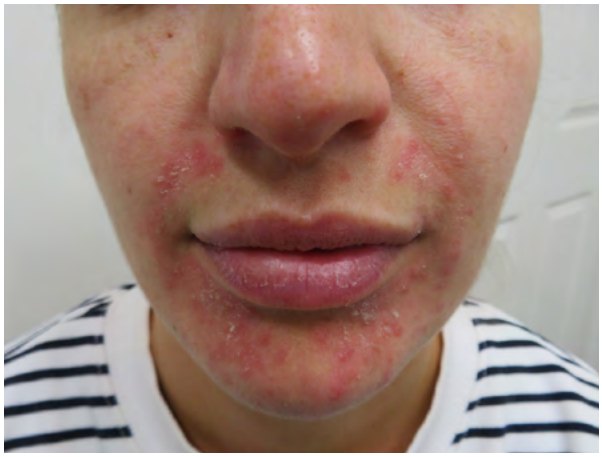


Image 16 a and b

**Demodicosis (a)** as an isolated diagnosis is uncommon. This patient had a 3-year history of a fixed rough well-defined plaque on the glabella and lower forehead with discrete thin white follicular scales at the base of the follicles (pityriasis folliculorum). A biopsy demonstrated a large number of demodex in the hair follicles. This responded to treatment with topical 1% ivermectin cream.

**Demodicosis and papulopustular rosacea (b)** is a more common combination diagnosis. Pityriasis folliculorum can be appreciated on the anteromedial cheek. A high level of clinical suspicion and close examination is required to appreciate this less well described clinical sign. This patient also had an irritant dermatitis with significant dryness and scale as well as signs of photoaging.



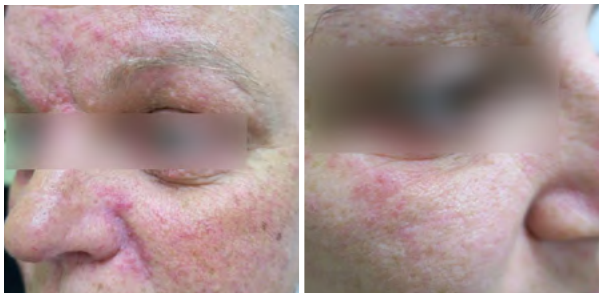


Image 17 a and b and c

**Periorificial dermatitis (previously perioral dermatitis)**
This dry scaly eruption with associated studding of monomorphic red papules classically involves the "muzzle" area for the face - nasolabial folds, labiomental crease and chin. Typically, it spares the vermillion border (a). It is most commonly seen in women but can affect men and children. It can involve other orifices of the face particularly the nose and eyes as well as the glabella (b,c). Isolated periorbital involvement is important to recognise and characteristically affects the lateral lower eyelid.

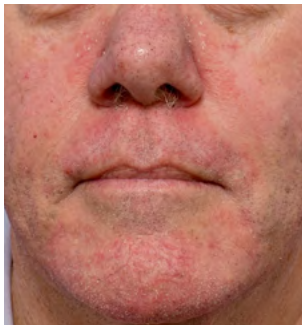


Image 18

**Seborrhoeic dermatitis**
This presented with erythema and "greasy" skin covered with flaky white or yellow scales on the mid face - sides of the nose, eyebrows, eyelids, glabella, upper lip and chin. Other areas that can be affected by seborrhoeic dermatitis include the scalp (dandruff), external ear canals, chest, armpits, groin and submammary area.

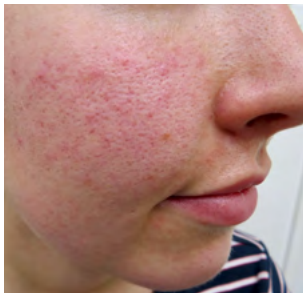


Image 19

### Acne

Inflammatory acne which predominately affects the cheeks can look like rosacea. The key distinguishing clinical feature is the presence of closed and open comedones in acne which do not occur in rosacea.

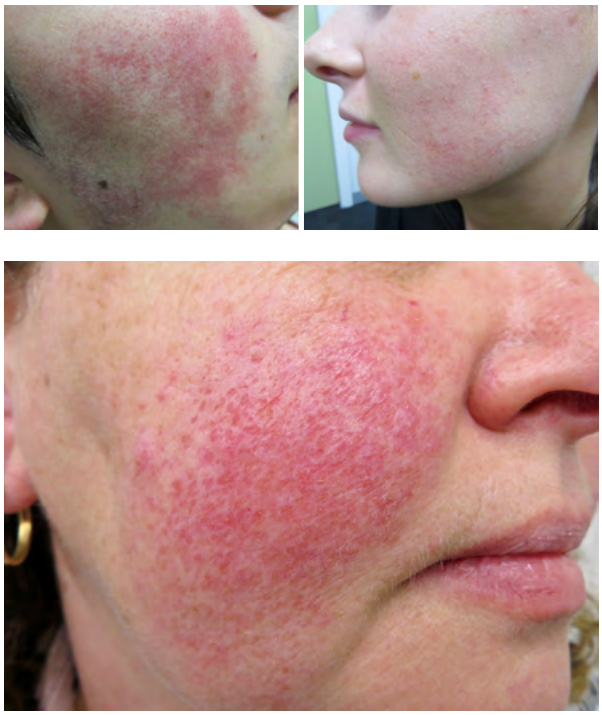


Image 20 a, b and c

### Keratosis pilaris rubra facei

a) Keratosis pilaris rubra facei. This is more common in younger people. This patient had very characteristic deep red confluent erythema with a geographic pattern. This spares the medial cheek and extends to the preauricular area and jawline.

b) Keratosis pilaris with prominent follicular plugging and scatted micropustules.

c) Atrophoderma vermiculatum, also known as folliculitis ulerythematosa reticulata, is a rare variant of keratosis pilaris atrophicans. Onset of this condition was in childhood and it gradually progressed. She displayed the characteristic "honeycomb" atrophic scars with pits and marked erythema.

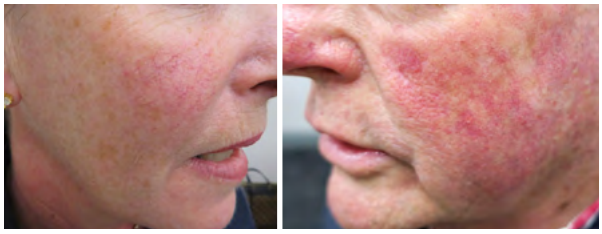


Image 21 a and b

### Telangiectatic photoaging

This is extremely common and can be difficult to distinguish from rosacea. Furthermore, telangiectatic photoaging can often co-exist with rosacea. Actinic telangiectasias are typically accompanied by other characteristic signs of actinic damage (pigmentation, atrophy). Women tend to develop telangiectasias over the central cheeks and men have the changes more frequently on the temples, lateral cheeks and posterolateral neck. Solar keratoses can have underlying telangiectatic mats.

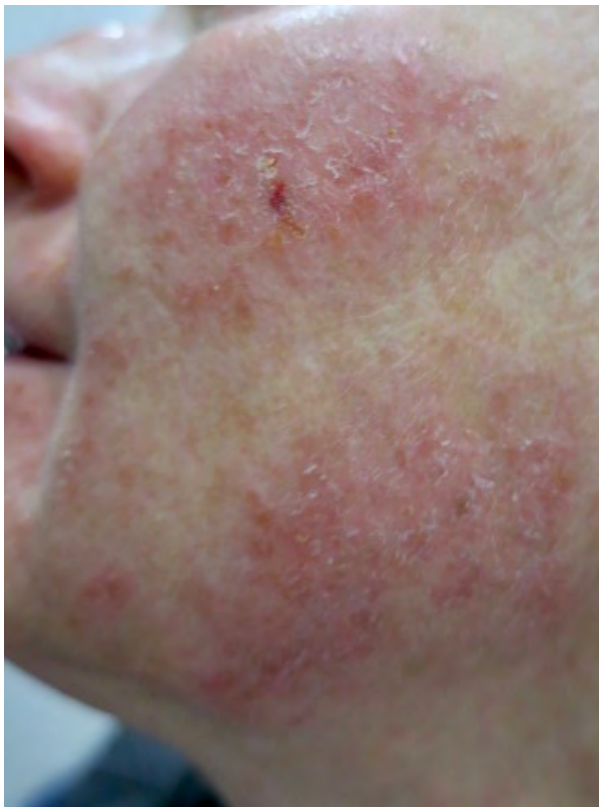


Image 22

### Atopic dermatitis / allergic contact dermatitis

The typical clinical features of atopic dermatitis include patchy erythema, oedema, dryness, scale and crusting with excoriation and lichenification. Often patients will also have a history of atopy and clinical features elsewhere. It is possible for atopic dermatitis to be localised to the face. Furthermore, allergic contact dermatitis is an important differential diagnosis to exclude and may require formal patch testing.

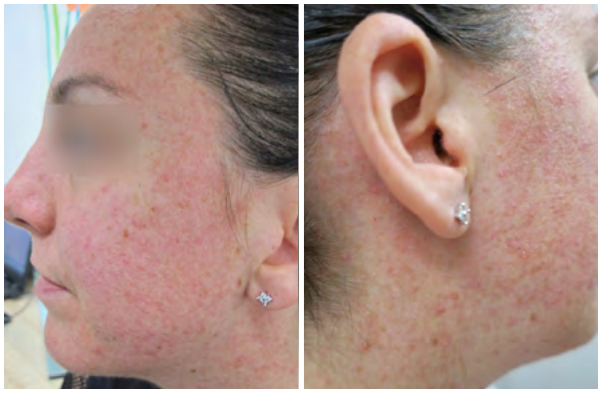


Image 23 a and b

**Pityrosporum (Malassezia) folliculitis**
This is an infection of the pilosebaceous unit caused by lipophilic Malassezia yeasts, particularly *M. globosa*, *M. sympodialis* and *M. restricta*. Malassezia yeast are normal inhabitants of the human skin surface and only cause disease under specific conditions.

Clinically, Malassezia-induced folliculitis presents with diffuse erythema and fine scale with monomorphic micropustules which can extend onto the forehead, neck, hairline, chest and upper back. It is often a pruritic condition. This form of folliculitis can be triggered by heat and humidity, excessive sweating, occlusive skin products and antibiotic use.

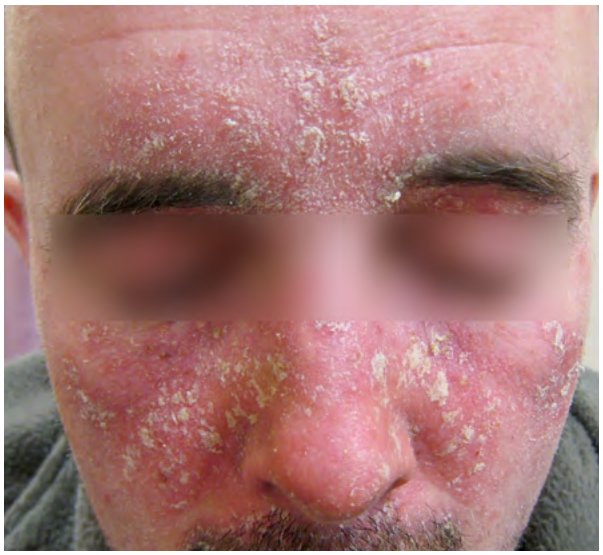


Image 24

**Facial psoriasis**
This patient presented with a florid example of facial psoriasis with erythema and large silver/white scales and crusting also involving the eyelids. The distribution can be similar to seborrhoeic dermatitis and can be difficult to distinguish in milder cases. Signs of psoriasis should be sought elsewhere to help differentiate psoriasis from seborrhoeic dermatitis – for example scalp, elbows, knees and nails.

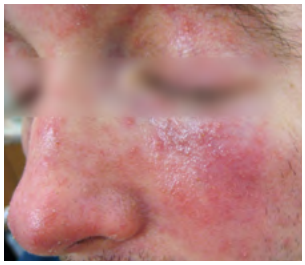


Image 25

**Steroid-induced facial dermatitis**
This is the same patient as in Image 24 after he used potent topical corticosteroids for 2 months. The presence of small pustules can easily be seen. Unsurprisingly, when he tried to wean off the corticosteroid the flushing, erythema and pustules worsened. This responded to oral doxycycline 100 mg for 6 weeks in addition to topical steroid withdrawal.

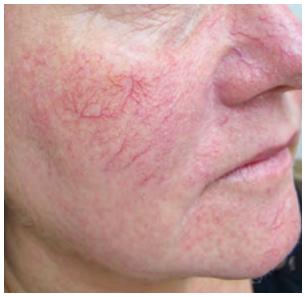


Image 26

**Corticosteroid-induced telangiectasias and atrophy**
This patient had a long history of atopic eczema with long term oral and topical corticosteroid use. She displayed significant dermal atrophy with large telangiectasia.

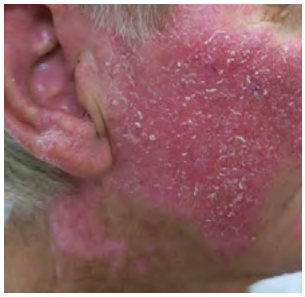


Image 27

**Subacute cutaneous lupus erythematosus**
Subacute cutaneous lupus erythematosus often presents clinically as diffuse confluent deep red erythema with scale in photo-exposed areas extending onto the neck and upper torso. It can resemble psoriasis. However, it is diagnosed on biopsy with typical histopathological features, positive direct immunofluorescence, and serology which showed anti Ro and La antibody positivity.

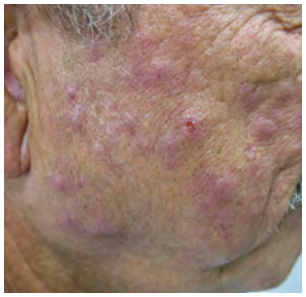
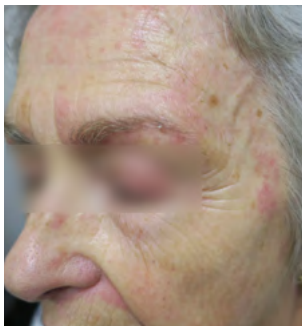


Image 28

**Cutaneous lymphoma**
This patient presented with asymptomatic firm red/blue nodules. Diagnosis of a B cell lymphoma was made on biopsy.



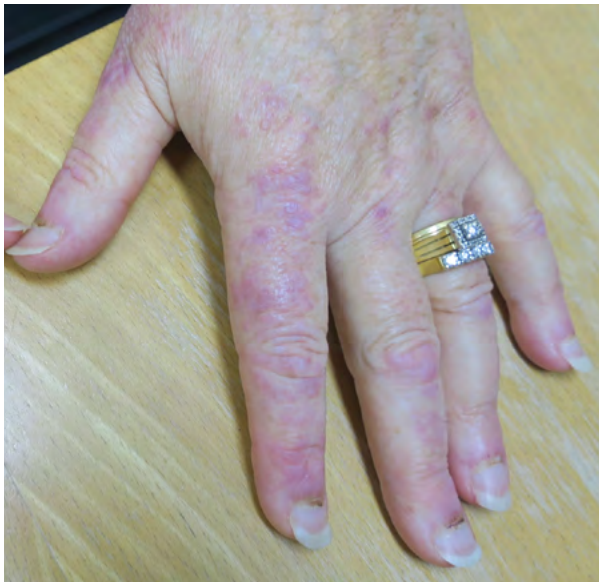


Image 29 a and b

**Dermatomyositis**
This patient demonstrates the characteristic heliotrope rash with bilateral erythema and mild swelling of the eyelids (particularly the upper eyelids). She had a patchy erythematous non-scaly eruption on the face which was photosensitive, pruritic and burning. She also exhibited Gottron's papules over the joints with nail fold swelling and telangiectasia with ragged cuticles. Rosacea spares the periorbital skin. Dermatomyositis will tend to involve the nasolabial fold as seen in this patient.

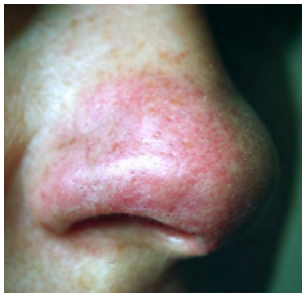


Image 30

**Sarcoidosis (lupus pernio)**
This is an important differential diagnosis of an isolated red nose with tissue swelling. Sarcoidosis can cause raised well defined asymptomatic plaques. Biopsy is required for diagnosis and shows non caseating granulomas. (*Image courtesy of Dermnetnz.org*)

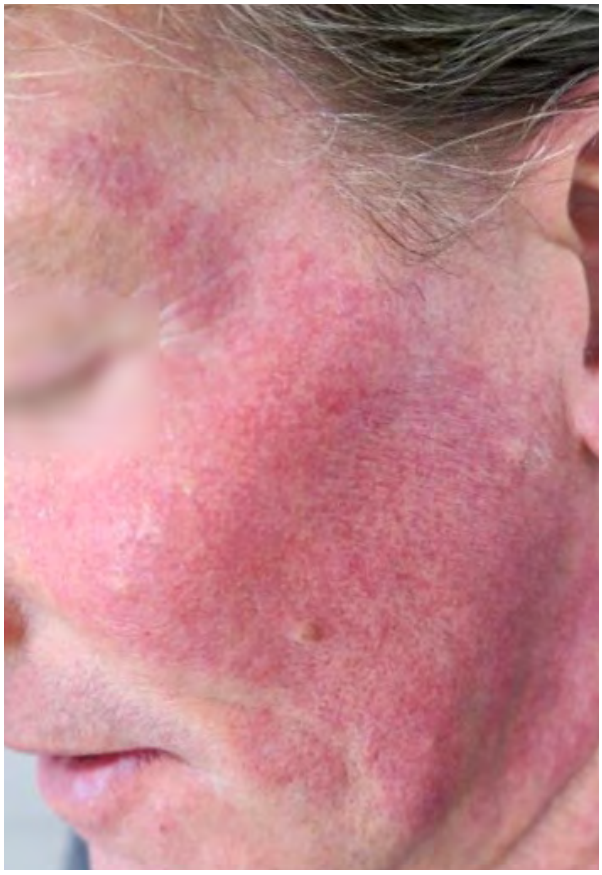


Image 31

**Systemic lupus erythematosus**
The classic butterfly rash of systemic lupus erythematosus (SLE) can mimic erythematotelangiectatic rosacea with erythema over the central face. In this photo there is extension of erythema around the lateral eyebrow and onto the neck which is atypical for rosacea. Papules and pustules, a feature of rosacea, are typically absent in SLE. Furthermore, patients with SLE often report photosensitivity. Patients with acute SLE are unwell and are likely to exhibit other systemic symptoms.

# Is Rosacea a Skin-limited or Systemic Disorder?

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Disclosures: *none*

**OUTLINE:** Rosacea is a common inflammatory skin disease typically prevalent among fair-skinned individuals and manifesting with centrofacial erythema and episodes of inflammatory lesions in the absence of comedones. Over recent years there has been increasing evidence linking rosacea to other systems in the body; some have even posed the question whether rosacea is part of a systemic disorder rather than just skin-limited. Perhaps the most well known association is with certain dietary triggers such as alcohol and spicy food but it is now known that gut health plays a role in certain inflammatory skin diseases, including rosacea. The term "gut dysbiosis" refers to an alteration in the gut microbiome composition which has been associated with worsening of rosacea. Similarly, a relationship was found between inflammatory bowel disease and bacterial overgrowth in the gut and rosacea.

The relationship between rosacea and other organ systems is not limited to the gastrointestinal system alone. Case-control and observational studies have shown a link with cardiovascular diseases, notably cardiometabolic with chronic inflammation being a common feature in both. Other associations were with certain auto-immune diseases as well as the respiratory and neuropsychiatric system. This article explores these associations and poses the question of whether rosacea is skin-limited or part of a systemic entity.

**KEYWORDS:** cardiovascular, diet, gastrointestinal, respiratory, rosacea

Al-Niaimi F. Is Rosacea a Skin-limited or Systemic Disorder? Opin Prog Cosmet Dermatol 2021;1(2):26-28.

## Introduction

Rosacea is a common inflammatory skin condition with a high prevalence among the western population.[1] While the signs and symptoms predominantly appear on the central part of the face, there has been increasing interest and emerging evidence linking it with other organ systems and co-morbidities. One could pose whether rosacea is a cutaneous-limited disease or one with systemic involvement or perhaps a manifestation of wider systemic inflammation.

Currently, the exact pathophysiology of rosacea remains unclear, although it involves aberrant neurovascular signalling and dysregulation of the immune system, particularly the innate system.[2] High levels of cathelicidins (antimicrobial peptides expressed by leukocytes and epithelial cells) have often been found in rosacea patients, in addition to kallikrein-5, matrix metalloproteinases 2 and 9 and increased mast cell infiltration.[1,2] It is well-established that kallikrein-5 cleaves cathelicidin to its more active form of LL-37 which is pro-inflammatory and angiogenic. Interestingly, high expression of cathelicidin has also been found in colonic mucosa of inflammatory bowel disease patients.[3]

The gut-brain-skin axis is a term that has been existent in medical literature for a period of time linking certain inflammatory skin conditions with stress and gut-related pathology.[4] In recent years a better understanding has shed more light on rosacea and its systemic links. Several large case-control observational studies have shown an association between rosacea and several systemic diseases and co-morbidities including gastrointestinal, cardiovascular, respiratory, auto-immune and neurologic disorders. Furthermore, chronic inflammation is a feature of both rosacea and several systemic co-morbidities, notably cardiometabolic disease.[5,6] In addition, genome-wide association studies identified loci for rosacea that were also associated with several auto-immune diseases such as diabetes mellitus, coeliac disease, and rheumatoid arthritis.[7]

## Rosacea and the gastrointestinal system

Association studies linking rosacea to the gastrointestinal system have shown a link with inflammatory bowel disease and overgrowth of gut bacteria (both *Helicobacter pylori* and small intestinal bowel over growth).[8] The microenvironment in the gut is increasingly linked to skin inflammation with gut dysbiosis (an alteration in the harmonious composition of the gut microbiome) playing an important role. This can either be through the mediation of inflammation or through mucosal barrier compromise.[9] Gut dysbiosis is influenced by age, food consumption, stress and antibiotics (in antimicrobial doses). Intestinal inflammation and gut dysbiosis activate the plasma kallikrein-kinin system pathway which is pro-inflammatory in rosacea.[10] In addition, gut dysbiosis leads to mucosal barrier compromise with pro-inflammatory substances circulating in the bloodstream. Control of the gut microbiome as well as inflammation can have a positive effect on the control of rosacea symptoms and is increasingly recognised as part of the overall management of rosacea through dietary modification, consumption of probiotics, as well as control and eradication of potentially pathogenic microbes such as *H. pylori* and small intestinal bowel overgrowth.[11] Gastrin-induced flushing has also been linked to the presence of *H. pylori*.[8]

## Rosacea and the skin microbiome

The skin microbiome is also increasingly recognised to play a role in several inflammatory cutaneous diseases including rosacea.[12] The skin microbiome refers to the diverse microbial population unique to each individual comprising bacteria, viruses, fungi, and mites. Some are skin resident and act as symbiont and others are invaders and often pathogenic. Advances in genomic sequencing research instead of outdated culture-based techniques has enabled a much better understanding of the microbiome's composition. The skin microbiome is in a delicate environment affected by a number of factors such as the skin's acidity, temperature, lipid composition, humidity, stress, pollution, dehydration, and local skin changes such as dry or moist skin.[13] All these factors can alter the harmony and composition of the delicate balance of the microbiome leading in some cases to a pro-inflammatory state. In rosacea the presence of the mite Demodex folliculorum and the bacteria *Bacillus oleronius* it carries elicit a pro-inflammatory state through activation of pattern-recognition Toll-like receptors 2 (expressed on keratinocytes and dendritic cells) as well as interleukin-8 and tumour necrosis factor-alpha with downstream activation of inflammatory pathways.[14] This link is further strengthened by the observation of improvement in rosacea symptoms with antiparasitic drugs (targeting the mites) and tetracycline-based antibiotics (primarily targeting *B. oleronius*). Toll-like receptors 2 are further activated by stress and ultraviolet radiation, the latter of which increases the production of the antimicrobial peptide cathelicidin, mostly secondary to UV-induced vitamin D3 production, a possible explanation for the low prevalence of rosacea among higher skin type individuals who tend to have lower levels of vitamin D3.[15]

## Rosacea and cardiovascular syndromes

Chronic inflammation in rosacea has also been linked to cardiometabolic risks with case-control studies showing a high incidence of hypertension, dyslipidaemia, obesity, and an elevated fasting glucose level in patients with rosacea.[16] Both rosacea and dyslipidaemia patients express low levels of a protective high-density lipoprotein-associated antioxidant termed paraoxonase-1 (PON-1) as well as a relatively high inflammatory baseline level of C-reactive protein (CRP), a finding in most cardiometabolic diseases.[17] Interestingly, current smokers have a somewhat protective effect on their rosacea symptoms, possibly due to the vasoconstrictive effects of smoking and worsening of rosacea symptoms has been observed in past smokers.[18] It currently remains unclear if strict control of all cardiometabolic factors and diseases can positively correlate to rosacea severity and symptoms although increasingly this association is being observed and clinicians may want to consider this in patients with severe or treatment-resistant rosacea.

## Rosacea and neurologic disorders

Neuropsychiatric associations with rosacea include depression, anxiety, migraine and Parkinson's disease.[19,20] As mentioned previously, stress can worsen rosacea through stress-mediated inflammation and alteration of the gut microbiome (leading to gut dysbiosis).

## Conclusions

In summary, increasing evidence links rosacea to a wider systemic state of chronic inflammation and its associations with particularly the gastrointestinal and cardiovascular systems. This may warrant some adjustments in the approach and management of rosacea patients, particularly in the presence of systemic symptoms. Clinicians should be aware of the systemic associations and co-morbidities of rosacea.

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# The Psychological Burden of Rosacea

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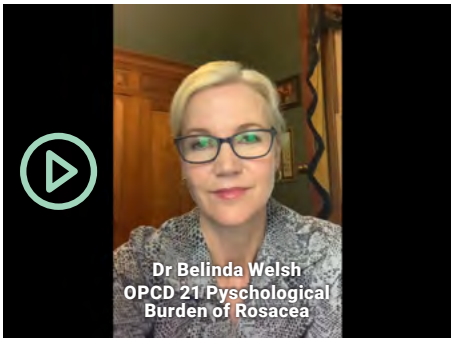


CLICK IMAGE TO LINK TO VIDEO DURATION_00:53

**OUTLINE:** Living with a chronic and highly visible affliction such as rosacea comes with considerable psychosocial consequences. Patients have to deal with their own emotions as well as the reactions of those around them which can include negative first impressions and judgement as to their lifestyle choices. As a clinician, appreciation of this can provide insight into factors that may shape patient behaviours and decision making. Acknowledging and understanding this is an important part of managing patients with this chronic condition. The result is better adherence to treatment and improved patient quality of life and satisfaction.

**KEYWORDS:** rosacea, psychological burden, quality of life

Welsh B, Honigman R. The Psychological Burden of Rosacea. Opin Prog Cosmet Dermatol 2021;1(2):29-32.

Rosacea is a common, chronic, highly visible skin disease. Despite breakthroughs in our understanding of pathophysiology it largely remains an enigma. What is clear, is that having a chronic facial skin condition for which there is no one simple treatment, and certainly no cure, poses a number of challenges for both patients and physicians.

Worldwide estimates suggest rosacea may affect up to 5.5% of the global population[1] and up to 10% of Celtic or fair-skinned populations.[2] Rosacea occurs in skin of colour[3,4] but may be overlooked because of skin pigmentation. Women are affected two to three times more frequently than men[5] whilst the incidence of rhinophyma occurs more often in men.[2]

The most common patient concerns are flushing, persistent redness, sometimes an intolerable burning sensation, papules and pustules.[6] Patients may also report feelings of shame and embarrassment at their appearance as well as depressive symptoms including low confidence, low self-esteem, loss of interest in life and in relationships, impaired concentration at work and anxiety.[7]

Many patients struggle with their skin problems well before they seek help and may have tried various skincare regimes to try to camouflage redness and inflammation. In some instances, these treatments may aggravate already highly sensitive inflamed skin, modifying the clinical picture and contributing to more distress and emotional trauma. Access to the internet and social media offers a multitude of opportunities for self-diagnosis and management, often based on an overwhelming amount of information of variable quality which can drive patients to deviate from traditional medicine and seek non-prescription therapies.[8]

Online support groups and forums offer patients a space to share health information[9] as well as an option for negative commentary including poor experiences with medications, difficulties in accessing dermatologists, financial barriers to treatment and distrust of clinicians. In these instances, a diagnosis of rosacea can be delayed, or go underdiagnosed because patients minimise their symptoms.[10] They may not voluntarily share information with their treating clinicians leading to symptoms not being well recognised, the impact of which can be physically and emotionally underestimated.[7,11] Surprisingly, US studies suggest only about 10% of people seek conventional medical treatment ahead of alternative solutions.[12-14] A Canadian study showed that symptomatic patients[15] can wait on average 7 months to 5 years before receiving a diagnosis and then only half are aware the condition even exists.[16]

Disfiguring skin disorders such as rosacea can cause emotional and psychological turmoil[17,18] with wide-ranging negative effects on health-related quality of life (HRQoL).[19-22] Rosacea patients often experience distress, anxiety, guilt, shame, low self-esteem, poor

self-perception, depression, poor quality of life,[23,24] and poor body image.[10,20,25] Poor sleep has been shown to be associated with symptoms[26] while poor HRQoL appears to be associated with disease severity and age: younger patients having worse Dermatology Life Questionnaire Index (DLQI) scores.[27] A direct relationship between rosacea severity and depression, possibly due to stigmatisation and somatic symptoms, was found to contribute to poor quality of life. Depression was also associated with poor treatment adherence.[28]

Stressful life events, an anxious or immature personality and social anxiety have been found to play an important role in exacerbation and possible onset of rosacea[23] with some patients at greater risk of anxiety disorders independent of their disease severity, especially if they have prior psychiatric morbidity.[29]

Fear of unpredictable facial flushing can be stressful, embarrassing and debilitating, trapping sufferers in a cycle where fear of flushing flares the skin, in turn making flushing worse,[2] and further increasing fear of social rejection.[19,20,25,30,31] Patients also experience guilt, shame, poor self-image and rejection[32] when their features include papules and pustules.[10,20,25,33]

Rosacea and facial erythema can be challenging as sufferers not only have to manage their own negative self-perception, but also negative perceptions and reactions of others. Feelings of shame in sufferers are not simply associated with appearance, but also with an awareness that they might be seen to have caused the condition through excessive alcohol consumption[10,19] which was historically thought to be a cause, along with psychiatric illness or violent temper.[23]

In a study by Haliou[31] young men with rosacea reported feeling 'dirty or ugly because of their skin and perceived 'being stared at and receiving rude comments or jokes regarding their skin'. This was considered more because of implications on social desirability than the disease itself and they were more likely to avoid social interaction because of these social slurs.[20]

Women with rosacea have been perceived as having less favourable personality characteristics, lifestyles and career skills and considered less physically, socially and professionally attractive than those without rosacea.[16] They were generally perceived as being stressed, tired, shy, lonely and insecure compared to those without rosacea who were perceived as intelligent, confident, happy, healthy, fun and successful.[18]

Similarly, in a study of workplace attitudes to rosacea,[25] poor health and negative personality traits were attributed to pictures of faces digitally altered to portray redness of rosacea while clear faces were related to positive health, demonstrating that people with facial erythema were often judged unfairly and negatively in the workplace. Not surprisingly, these individuals suffer emotionally and socially and often fear their condition will impede career advancement.[27]

## Implications for management

Various studies have demonstrated the importance of acknowledging the psychological distress associated with rosacea and establishing the physical and psychosocial impact on each individual patient.[19]

A better understanding of the patient perspective by the clinician[34] can lead to better patient adherence to treatment and thus improved quality of life, general mood and satisfaction. Clinicians are advised to pay close attention to signs of depression in rosacea patients and determine if psychiatric treatment or referral for psychological evaluation is indicated. Clinicians may feel underprepared when managing complex psychosocial issues and this may be perceived by the patient as disinterest and they may not feel confident divulging the full extent of their distress.

An appreciation of the patient's lived experience of the disease and lifestyle can provide insight into factors that may shape patient behaviour and decision making to enable more comprehensive treatment and better outcomes. It is important to try to shine a light on any emotional damage and allow patients to verbalise any fears. They may question whether rosacea is in fact the correct diagnosis, as some patients may have had several different diagnoses and may have become distrustful of clinicians and treatment opinions. They may come with a fixed idea of the disease and 'best' treatment based on what others have told them.

Patients should be informed that there is no cure for rosacea, but there are a variety of treatments available which can effectively manage the disorder and minimise the progression of symptoms. Patients can take an active role in the treatment of rosacea by learning about trigger factors and taking avoidance measures.

Some suggestions include:

- Provide high quality information and education.
- Offer a clear management plan.
- Encourage acceptance that they have a chronic medical condition that can cycle through flares and remissions.
- Explain this can't be changed but they can take control of their condition and restore their appearance by complying with long term therapy and avoiding lifestyle factors that aggravate their situation.

- Advise them that medications take time to be effective and improvement may be slow. Patients often expect overnight changes. Perseverance is the key.
- If patients become distressed at comments or stares, help them see that people can be unaware of rosacea and that many reactions are simply caused by ignorance and curiosity, rather than any negative intent. It may be helpful for them to explain their condition to people who they see regularly – especially at work – to minimise distress.
- Put to rest the misconceptions that rosacea is caused by poor hygiene or excessive drinking.
- Encourage the patient to take care of their mental health and talk to family and partners or support services to avoid becoming isolated or distressed. In some cases, they may benefit from referral for counselling.
- Keep away from social media.
- Being empathic, open minded and non-judgemental, especially if patients confess to trying multiple treatments ("I understand you may have done, x, y, z but perhaps we could try…") may help gain patient trust earlier.
- Suggest to patients that even though they may find their self-confidence suffering as a result of their appearance, the situation can be turned around by taking action to control symptoms of rosacea and become a treatment partner.

## CASE STUDY

A 50-year-old woman presents to her dermatologist with a 2-year history of swelling and redness of the nose which occurs predominantly later in the day and evening. It occurs at random, and can even be triggered by sitting in a hot car. She also experiences a hot and pulsating sensation in her nose on waking. These sensations usually present with heightened anxiety, panic and rapid and intrusive thoughts, out of fear for what's happening and the ensuing embarrassment of people's comments regarding her red nose.

She says she has become pre-occupied with the fear that her nose may randomly swell and go red as she is unable to cover it with makeup. She has been to various health professionals and fears there is no explanation for the 'invisible puzzle she is unable to solve'. She says she desperately 'needs' to understand what's happening and why as she has never been in a situation like this before where she is unable to cope or not feel in control and says the condition is debilitating and rules her life, leading to her suffering extreme anxiety and at one stage, even suicidal ideation.

She is worried how she presents socially and at work and is embarrassed by constantly being asked if she is hot or whether she feels ok. She has begun turning down social arrangements especially in the evening. Even though her partner is very caring and supportive, she is worried he will leave her because of the way she feels she looks and because she is constantly anxious about her nose.

She has been advised that her condition doesn't present as 'typical' rosacea and she is fearful of the ultimate diagnosis and progress of the condition, which she has convinced herself, will develop into rhinophyma. She has joined a Facebook group of women who suffer facial redness and keeps a collection of photos of middle-aged women with rhinophyma and facial erythema which she constantly compares herself to.

She is constantly sending photos of her face to her dermatologist and persistent in seeking regular laser treatment which she says is slowly helping. She says she is very stressed because she lives in constant fear that her face will go red and she will feel shame and embarrassment. She is appreciative of the support of her dermatologist who she feels has acknowledged her symptoms and suggested psychological support which she has begun receiving. She has agreed to stop looking at Facebook and the photos on her phone.

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# Rosacea Diagnosis and Management with a Focus on Laser and Light Devices – the Asian Perspective


CLICK IMAGE TO LINK TO VIDEO DURATION_00:52

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Disclosures: *HH Oon has served as a speaker, advisory board member and researcher for Galderma. She is also a clinical investigator for Janssen, Novartis and Pfizer and an advisory board member for AbbVie. CL Goh has served as consultant to Neoasia, distributor of Candela lasers in Singapore and speaker for ISISPharma, Paris.*

**OUTLINE:** Rosacea is a chronic skin disorder involving the convexities of the face. The prevalence in Asia is under-reported as the clinical presentation of erythema in darker skin types (types IV-VI) is more difficult to discern. In this review, we discuss the epidemiology of rosacea in Asia, the transition from subtype to phenotype classification, inherent issues with grading of erythema, differential diagnoses specific to Asians and treatment modalities with a focus on light and laser therapies. The patient-centric approach to rosacea in darker skin types requires combination therapy to target the multiple specific features of each patient for expedient, effective treatment and to maximise patient satisfaction. There is a higher potential risk of skin irritation from topicals and post-inflammatory hyperpigmentation from laser therapy. Choice of vascular lasers and light, treatment protocol are discussed in depth.

**KEYWORDS:** rosacea, phenotype approach, Asia, skin of colour, treatment, lasers and light

Oon HH, Goh CL. Rosacea Diagnosis and Management with a Focus on Laser and Light Devices – the Asian Perspective. Opin Prog Cosmet Dermatol 2021;1(2):33-39.

## Epidemiology

Rosacea is a chronic skin disorder with a worldwide prevalence of 5.46% in the adult population, occurring most often in the 46-60 age group and affecting more women than men.[1] Of the studies that stratified rosacea by clinical subtypes in a systematic review and meta-analysis[1] (three population-based studies and two studies of dermatology outpatients), the prevalence of erythematotelangiectatic rosacea (ETR) was 72-80%, papulopustular rosacea (PPR) was 18-28%, phymatous rosacea was 4-8% and ocular rosacea was 1-8%.

While rosacea has traditionally been considered a disease of the fair-skinned of Celtic and European descent, the reported prevalence in people with skin of colour has varied, with estimates as high as 40 million cases and rates up to 10%.[2] These figures may represent an underestimate in Asia as rosacea erythema may be masked by melanin, hence resulting in a delay by the patient in seeking medical attention for a perceived cosmetic condition and diagnostic confusion by the clinician.

In a multi-ethnic study in Singapore with main racial groups of Chinese, Malays and Indians,[3] ETR was more common in racial groups such as Chinese and Caucasians. ETR was seen in 56.3% and PPR in 37%. Indians and Caucasians were more likely to have PPR compared to ETR (OR: 3.4 and OR: 2.1, respectively). Older males were more likely to have phymatous rosacea (95%; OR: 3.82). Ocular rosacea occurred in 2.1% unlike other studies which have quoted approximately 50%.[5]

## Pathophysiology of rosacea in Asians

The pathophysiology of rosacea is not well understood. Dysregulation of the innate and adaptive immune systems causes increased levels of pro-inflammatory cytokines, nitric oxide radical species, Toll-like receptor 2 (TLR2) signalling and vascular growth factors. Microbial triggers such as Demodex mites, *Helicobacter pylori* in the gut and ultraviolet light exposure are believed to activate signalling pathways.[4,5]

It has been postulated that Southeast Asians, Koreans and darker skin type individuals have less observed persistent facial erythema, because studies of skin circulation and microvascular endothelial function comparing them to White patients showed lower vascular endothelial function and reactive hyperaemia in response to occlusion and local heating.[2]

## Diagnosis, clinical features and key differential diagnoses of rosacea in Asians

Primary features of rosacea in the 2002 National Rosacea Society classification include flushing, non-transient erythema, telangiectasia, papules and pustules. Secondary features include plaques, oedema, phymatous changes and ocular manifestations. Based on these signs and symptoms, rosacea was classified into four subtypes - erythematotelangiectatic, papulopustular, phymatous and ocular rosacea. Consequently, rosacea features are now phenotype-based and should take into account the individual clinical features and symptoms as one patient may cross multiple subtypes.[5,6] The ROSacea COnsensus panel recommendations are as follows:[6]

- Diagnostic features:
  - Persistent centrofacial erythema associated with periodic intensification by potential trigger factors
  - Phymatous changes
- Major features:
  - Flushing/transient centrofacial erythema
  - Inflammatory papules and pustules
  - Telangiectasia
  - Ocular (lid margin telangiectasia, blepharitis, keratitis/conjunctivitis/ sclerokeratitis)
- Minor features
  - Burning sensation of the skin
  - Stinging sensation of the skin
  - Dry sensation of the skin
  - Oedema

Erythema may be difficult to discern in Asian patients with skin phototypes IV-VI. The masking of visible erythema can lead to diagnostic confusion and a delay in diagnosis. An Indian ETR patient with type V skin may instead report significant burning and stinging while having only mild redness on the Clinician Erythema Assessment (CEA) scale (Figure 1). In this context, upgrade criteria should apply to the grading of rosacea erythema as this denotes a higher grade of redness than visible, greater disease burden and need for treatment escalation.

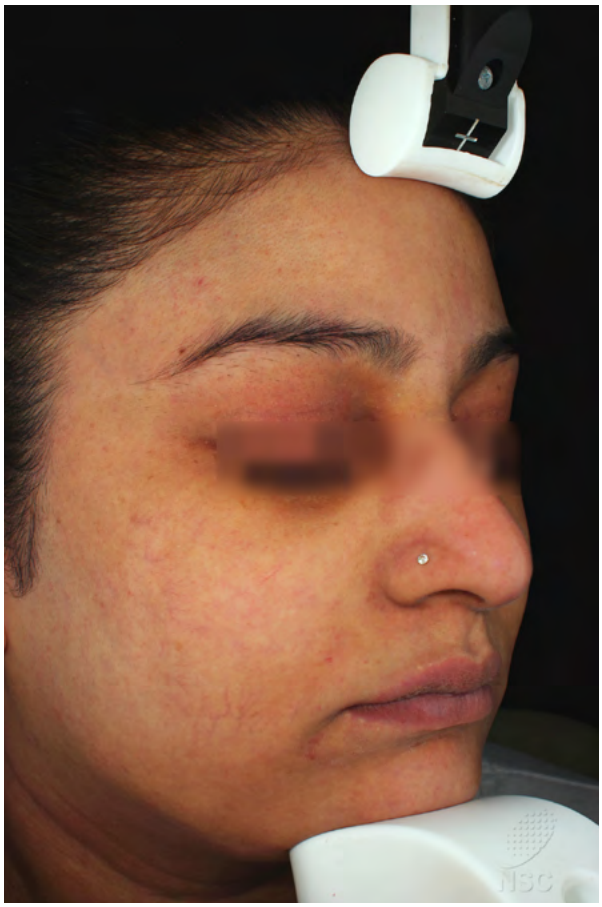

**Figure 1.**
*Mild facial erythema in darker skin phototype (skin phototype V) should prompt the clinician to screen for a history of burning and stinging and examination for extent of facial dryness. If present, an upgrading of the rosacea erythema grading should be considered.*

Granulomatous rosacea (GR) is also seen more frequently in darker skin types[2,7] and the diagnosis is sometimes made in hindsight when the skin biopsy is performed or only after scarring has ensued. Histology of GR, when pathognomonic, shows non-caseating granulomatous in the superficial and mid dermis, manifesting as a large, central empty space or may be small, palisaded, elastolytic or diffuse.[7]

Key considerations for differentials of rosacea based on the presenting phenotype are listed in Table 1.

**Table 1.** *Key differentials of rosacea in Asians based on phenotypic presentation.*[2,7,8]
*Text in **bold** denotes conditions more commonly seen in Asians.*

| Clinical feature | Differential diagnosis |
|---|---|
| Centrofacial erythema | Facial eczema (atopic, irritant and allergic contact dermatitis), seborrheic dermatitis, facial psoriasis, telangiectatic photoaging (more pronounced at lateral face/neck), lupus erythematosus, dermatomyositis, photodermatoses, **erythromelanosis follicularis faciei et colli**, keratosis pilaris atrophicans |
| Flushing | Carcinoid syndrome, systemic mastocytosis, menopausal flushing, medullary carcinoma of the thyroid, pancreatic and renal cell tumours |
| Papulopustular | Acne vulgaris (presence of comedones), steroid acne, perioral dermatitis, demodicosis, **acne agminata** (periorbital predilection, more often in Japanese, caseating granulomas on histology) |
| Phymatous changes/oedema | Non-melanoma skin cancers, granulomatous inflammation (infective e.g. rhinoscleroma, non-infective e.g. sarcoidosis), angiosarcoma, B- and T-cell lymphomas, Melkerson-Rosenthal syndrome |
| Granulomatous changes | Granulomatous inflammation (infective, non-infective e.g. **micropapular sarcoid, acne agminata**), B- and T-cell lymphomas (e.g. granulomatous mycosis fungoides) |
| Ocular involvement | Allergic/viral/bacterial/chlamydia conjunctivitis, chronic/staph/seborrheic blepharitis, isolated meibomian gland dysfunction/chalazion, sebaceous gland carcinoma, episcleritis/scleritis/uveitis, keratoconjunctivitis sicca, mucous membrane pemphigoid |

## Management of rosacea in Asians

Rosacea treatment should be tailored to the individual patient phenotype (persistent/transient erythema, papules/pustules, telangiectasia and phyma), disease burden (duration, frequency, intensity, extent of involvement, triggers and impact on daily life) and goals of treatment. When mutually agreed upon by patient and clinician, achieving clear to almost clear skin should be the primary target when treating rosacea in order to minimize disease impact on quality of life, maximize time to disease relapse and increase treatment satisfaction.[6] Combination therapy to target the multiple specific features of each patient is often necessary for expedient and effective treatment.

To address the barrier dysfunction in rosacea, general skin care measures should include gentle cleansers, broad spectrum sunscreen of at least SPF 30, frequent moisturising and trigger avoidance. Patients with ocular rosacea should be instructed on lid hygiene and use of preservative-free lubricating eye drops.

Phyma should be assessed for activity and treatment based on whether it is active (inflamed) or burnt-out. Active phyma should be treated with oral doxycycline, a tetracycline derivative or isotretinoin. For persistent facial erythema, alpha-2 adrenergic receptor agonists such as brimonidine gel and oxymetazoline cream are helpful. Asian skin has purported increased susceptibility to irritation with topical therapy such as retinoid therapy and post-inflammatory hyperpigmentation.[9] Patients should be counselled on the irritant potential of topicals such as brimonidine gel, metronidazole gel and azelaic acid cream. Ideally, skin barrier defects should be addressed prior to starting treatment. This improves tolerability and reduces discontinuation of treatment. Access to oxymetazoline cream 1% remains difficult as it is not widely distributed in Asia and Australia. Off-label oxymetazoline 0.05% nasal spray or drops can be considered. Oral doxycycline is helpful for papulopustular, inflammatory phyma and moderate to severe cases of ocular rosacea. Due to potential development of antibiotic resistance with prolonged use, clinicians should restrict and revisit usage of oral antibiotics. The subantimicrobial modified release doxycycline 40 mg is preferred over the 100 mg oral formulation and topical minocycline foam can be considered if available. Emerging therapies include microencapsulated benzoyl peroxide, TLR-2 inhibitors, TRPV-1 antagonists and topical timolol, a non-selective β-blocker FDA approved for the treatment of glaucoma and infantile haemangioma.[10]

## Lasers and light devices for treating ETR

Due to the risk of post-inflammatory hyperpigmentation, the use of lasers (e.g., pulsed dye laser and 532 nm potassium titanyl phosphate [KTP]) and intense pulsed light (IPL) for facial erythema or telangiectasia should be undertaken by healthcare providers familiar with darker skin phototypes and at more conservative settings.

The specific treatment of choice for ETR is elimination of the dilated vessels with vascular lasers and IPL. However, as the dilated vessels varies in size, colour, depth, density, characteristics, skin thickness, and skin colour, the choice of vascular lasers and its setting becomes critical to ensure effective vessel ablation.

A variety of laser and light-based devices have been demonstrated to be useful in the treatment of ETR. They include:

- Pulsed dye laser (585/595 nm)
- KTP laser (532 nm)
- Long pulsed Alexandrite laser (755 nm)
- Long pulsed Nd:YAG lasers (532/1064 nm)
- Long pulsed diode laser (900 nm)
- Copper vapour laser (510/578 nm)
- Intense pulsed light (500-1000 nm).

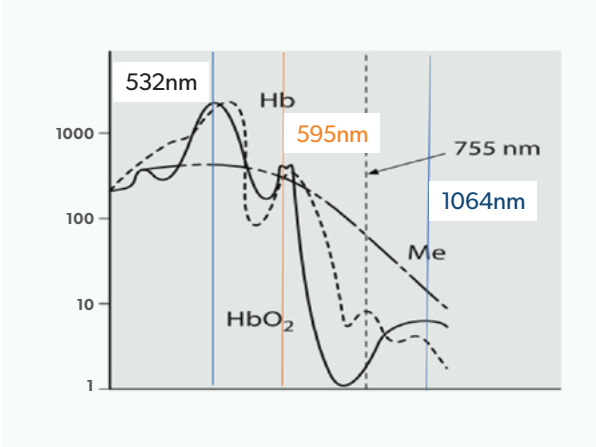


**Figure 2.** *Absorption spectrum of haemoglobin, oxyhaemoglobin and methaemoglobin*

Pulsed dye laser (PDL) is the most commonly used vascular laser, followed by long pulsed Nd:YAG lasers and IPL.

## Pulsed dye laser (585/595 nm)

### Indication: all telangiectactic vessels and diffuse erythema

PDL emits a wavelength of 585 or 595 nm and targets oxyhaemoglobin, leading to destruction of blood vessels. Several studies have confirmed the safety and efficacy of PDL in ETR.[11,12] PDL is the vascular laser of choice for ETR as it allows the operator to adjust the fluence, pulse duration and spot size to the optimal parameters.

PDL emits wavelengths of 585 or 595 nm – close to absorption peaks of oxyhaemoglobin. It has a tunable pulse duration of 450 µs to 40 ms to treat vessels of various calibres. Its spot size varies from 3-15 mm and additionally has an elliptical spot (10x3 mm) to treat linear telangiectatic threads. The large spot size of >10 mm allows for deeper penetration and a gentler vascular coagulation. It also allows large areas to be treated quickly and is useful when treating diffuse erythema of ETR. Cryogen cooling allows a larger spot and higher fluence to be used with minimal tissue injury especially in patients with skin of colour. PDL is reported to achieve 50% reduction in erythema, 55% reduction in flushing and 75% reduction in telangiectasia following 1-3 treatments. For large telangiectatic threads, a long pulse (10-40 ms depending on calibre) and stacking may be needed – to achieve the visible end point of vessel blanching or transient purpura. Complete clearance was seen in ten patients, and eight patients displayed more than 80% improvement after ultra long pulse PDL (ULPDL) treatment. ULPDL treatment delivered using a 3 mm x 10 mm elliptical spot was non-purpuric and highly effective in the treatment of nasal telangiectasia resistant to KTP laser and PDL (pulse width <10 ms).[13]

Complications from PDL include purpura especially when a short pulse width (450 µs) is used. Subpurpuric treatment using a longer pulse width protocol requires more than 2-6 treatments to achieve similar effects (preferred when treating darker skin types). When treating diffuse facial erythema, a larger spot size of 10-12 mm performed with 2-3 passes helps to prevent reticulation.

A double-blind, randomised, controlled split face study comparing the effectiveness of a 595 nm PDL and a 0.3 ms 1064 nm Nd:YAG laser in 16 patients with diffuse facial erythema showed slightly more improvement for the PDL treatment arm. PDL reduced facial redness by 6.4% more from baseline than Nd:YAG (P=0.0199). Nd:YAG laser was associated with less pain (P=0.0028). Subjects rated redness as improved by 52% with PDL versus 34% with Nd:YAG (P=0.031).[14]

## Potassium titanyl phosphate laser (532 nm KTP laser)

### Indication: superficial small calibre telangiectactic vessels

This laser is a frequency-doubled 1064 nm Nd:YAG laser. The KTP laser emits green light at 532 nm, which is well absorbed by haemoglobin but penetrates relatively superficially. A millisecond pulse width of 15-30 ms is utilized. The KTP laser is effective against small superficial telangiectatic vessels of up to 1 mm diameter due to its short wavelength. It has been reported that 40% of patients observed a reduction of >70% of telangiectasia after a single treatment.[15]

KTP laser may cause dyschromia and textural changes when used on skin of colour because there is significant absorption by melanin at 532 nm. Thus, patients with darker skin types or tanned skin may have an increased risk of side effects with a 532 nm laser beam, including epidermal burn and hypo and hyperpigmentation.

## Long pulsed neodynium-yttrium-aluminum garnet laser (1064 nm LPNd:YAG)

### Indication: large and deep telangiectic vessels, diffuse erythema

The LPNd:YAG laser is a solid state laser with primary 1064 nm wavelength. It is the preferred laser for laser assisted hair removal in skin of colour. LPNd:YAG laser is effective for the treatment of vascular lesions and because of its long 106 nm wavelength, has the advantage of being able to penetrate 6-10 mm into skin. The 1064 nm LPNd:YAG laser wavelength is absorbed by haemoglobin and methaemoglobin causing deep vessel destruction. It may be more effective than PDL in destroying the deeper bluish vessels.

Several reports have confirmed that LPNd:YAG laser is effective for the destruction of large nasal telangiectatic veins.[16] A study compared the efficacy of LPNd:YAG and PDL in treating rosacea-associated nasal telangiectasia where each patient was treated with PDL on the left side of the nasal bridge, and LPNd:YAG laser on the right side, three times with 4-week intervals. The study concluded that good improvement was seen in six PDL and seven LPNd:YAG patients, and excellent improvement in five PDL and four LPNd:YAG patients. There was no significant difference (P=0.62) between the groups. Overall improvement was similar; however, LPNd:YAG induced a greater response in thick, dilated vessels, while erythema with mild telangiectasia was more responsive to PDL.[17]

LPNd:YAG laser treatment carries a higher risk of potential collateral damage around vessels (such as burns) and pain during the procedure. This must be considered when using this laser to destroy large vessels especially when used on skin of colour. An efficient cooling system is mandatory. To avoid overheating the epidermis and causing textural changes, ensure that the skin surface of the field to be treated is adequately chilled with contact cooling, cryogen or air-cooling. It is imperative to carefully check the vessel response after each laser shot. Stacking must be done with caution.

## Intense pulsed light (IPL 515-1200 nm)

### Indication: Superficial and small telangiectic vessels, mild diffuse erythema

IPL is a non-laser flashlamp that produces noncoherent broad band light with wavelengths in the range of 515 to 1200 nm. It has tunable pulse widths ranging from 0.5 ms to 150 ms. Filters are used to remove unwanted wavelengths. IPL has been shown in many studies to be efficacious in treating superficial vascular lesions in photoaging, rosacea and vascular anomalies and dyschromia. Complications are rare and there is generally no downtime. IPL delivers a broad spectrum of wavelengths altered by cut-off filters to adjust to the patient's skin type and the lesion depth. The variable pulse width allows for targeting of different sized vessels at different depths. The large spot size of the IPL facilitates treatment of large areas of the face and is useful for treating diffuse erythema and flushing of rosacea. In one report, an average of two treatments resulted in facial clearing of 75-100% in the majority of patients (93%). Subsequent reports have confirmed IPL effectiveness for ETR.[18] A recent study reported that short-pulsed (1.5 ms) IPL and PDL with two treatment sessions 4 weeks apart were similarly effective for decreasing facial redness when non-purpuric low fluence was used. The IPL was faster and did not require consumables. An average of 60% improvement on the side treated with IPL was observed as opposed to 45% on the other side.[19] In a study comparing non-purpuragenic PDL with IPL for facial erythema, telangiectasia, and symptoms of facial erythema rosacea, three monthly treatment sessions were performed with initial PDL settings of 10 mm spot size, 7 J/cm$^2$, 6 ms pulse duration, and initial IPL settings of 560 nm filter, a pulse train of 2.4 ms and 6.0 ms in duration separated by a 15 ms delay, and a starting fluence of 25 J/cm$^2$; results showed that PDL and IPL produced a significant reduction in cutaneous erythema, telangiectasia, and patient reported associated symptoms. No significant difference was noted between PDL and IPL treatments.[20]

Complications including purpura, oedema and burns from IPL treatment are uncommon and there is generally little downtime if correct patient selection is performed. Patients with darker skin type e.g. type V and VI are not suitable for IPL treatment as epidermal

melanin in darker skin type tends to pick up the shorter IPL wavelengths and burn the skin. Similarly, patients with tanned skin should postpone IPL treatment until the skin colour returns to normal.

To avoid burns appropriate cut off filters should be used for different skin types and depths of penetration. For example, for type II-III skin, a cut off filter of 515 nm is safe but for skin type IV, a cut off filter of >550 nm should be used. The variable pulse duration (0.5 to 100 ms) allows for targeting vessels of different sizes at different depths. The large spot size of IPL sapphire tip reduces treatment time and allows bigger areas to be treated which is especially useful for treating diffuse facial erythema. It is important to note that treatment efficacy and settings of different brands of IPL devices varies and are not interchangeable.

## Copper vapor laser (510/578 nm CVL)

### Indication: Superficial telangiectatic vessels and various sizes

The copper vapor laser (CVL) is a dual wavelength laser for treating pigmentary and vascular lesions. The wavelengths of light emitted by a CVL are 510 and 578 nm, targeting melanin and oxyhaemoglobin, respectively. In contrast to other yellow light lasers, the CVL emits a train of pulses with a duration of 20–25 ns and 10,000–15,000 pulses per second. Because of the very short gap between each pulse of light, the biological effect of the CVL is similar to that of a continuous wave laser.

CVL has been reported to improve rhinophyma. A case report on a 52-year-old Caucasian male with typical clinical signs of rhinophyma revealed successful management with three sessions of CVL treatment. Such treatment resulted in restoration of the natural appearance of the nose, including removal of dysplastic superficial skin vessels, resolution of inflammation, decline in sebum production and disappearance of nasal hypertrophy.[21]

## Considerations when using lasers and light devices for ETR

Advances in lasers and light devices has enable effective removal of telangiectatic vessels and diffuse facial erythema in rosacea. But to achieve optimal outcome several factors must be taken into consideration namely:

- Clinical assessment: confirm the correct diagnosis.
- Ascertain the type of vascular lesions to be treated:
  - Characteristics e.g. angioma, spider angioma, telangiectasia threads, diffuse erythema
  - Diameter of the vessels
  - Depth of the vessels
- Colour of the lesions – oxyhaemoglobin vs methaemoglobin.
- Choice of vascular laser/device: e.g. PDL, IPL, LPNd:YAG, KTP etc.
- Treatment protocol used, taking into consideration: fluence, pulse width and spot size, filter selection (for IPL) and skin cooling.
- Post-laser skin care.

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# Ocular Rosacea Update

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Disclosures: *none*

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**OUTLINE:** Ocular rosacea is an underdiagnosed clinical entity that causes significant functional and social impairment. Its clinical features include recurrent styes and chalazia, blepharitis, blepharoconjunctivitis and meibomian gland inspissation. Conservative, medical and non-medical treatment options are available in the management of ocular rosacea.

**KEYWORDS:** rosacea, blepharitis, chalazion, conjunctivitis, dry eyes

Chen Y. Ocular Rosacea Update. Opin Prog Cosmet Dermatol 2021;1(2):40-41.

Rosacea is a chronic skin condition with a variable presentation of telangiectasia, malar rash, papule and pustule formation.[1,2] Ocular involvement occurs in 60-70% of patients with rosacea and may precede skin involvement.[1,3] In severe cases, corneal involvement can be in the form of punctate epithelial erosions, peripheral corneal ulceration and vascularisation.[4] When patients with facial rosacea are seen by dermatologists, ocular manifestations may be overlooked. On the other hand, when patients are seen by ophthalmologists, a detailed skin examination is frequently not performed, leading to underdiagnosis of ocular rosacea.

The aetiology of rosacea is still being investigated. Its inflammatory nature is suggested by the presence of elevated pro-inflammatory cytokines in the tear film, including interleukin-1 alpha, beta and metalloproteinase-9 and 8.[5,6] The innate immune system appears to play a major role in the pathogenesis of rosacea. It is thought that environmental stimuli trigger the innate immune system to increase expression of cytokines and anti-microbial molecules in the skin, such as cathelicidin, which promotes vasodilation, angiogenesis, extracellular matrix production, and leukocyte migration.[7] These environmental stimuli can include the presence of various skin bacteria and Demodex, a microscopic mite.[8]

Risk factors for rosacea includes topical steroid use, European descent and family history. Studies have also found increased prevalence of various bacteria and Demodex in facial and ocular rosacea.[9]

The diagnosis of cutaneous and ocular rosacea remains clinical. Ocular symptoms include chronic foreign body sensation, lid margin erythema, and recurrent stye and chalazion formation.[8,10] Signs include blepharitis, blepharoconjunctivitis, and meibomian gland inspissation (**Figure 1**). Untreated ocular rosacea can lead to corneal complications such as cornea scarring, corneal neovascularisation and corneal ulceration (peripheral ulcerative keratitis). In children, ocular features may dominate the clinical presentation.[2] Hence, ophthalmic review in children with facial rosacea is of paramount importance.

Management of ocular rosacea requires timely diagnosis and a collaborative approach with the patient. Developing patient understanding of the condition, including its triggers and its chronicity, assists in ensuring patient cooperation and compliance with treatment. Conservative treatment of blepharitis and chalazia includes warm compression of the eyelid, eyelid massage and hygiene. Adequate eyelid heat can be provided via heat masks which better retain heat. Eyelid massage is performed with targeted pressure towards the meibomian glands in both lower and upper eyelids. Eyelid hygiene is performed with baby shampoo or a formulated cleanser. A number of studies have reported the use of intense pulsed light (IPL) targeting the skin just below the lower eyelid in patients with ocular rosacea.[11,12] These reports have suggested an improvement in meibomian gland function and dry eyes in these patients with minimal side effects. Topical antibiotics such as chloromycetin can be applied to the eyelid margin before bedtime to reduce the eyelid flora load. For more severe cases of ocular rosacea, systemic

antibiotics including doxycycline (40 mg per day), minocycline (100 mg-200 mg per day), erythromycin (250 mg to 1g per day), azithromycin (1 g per day) can be taken for a period of 6-12 weeks (**Figure 2**).[2,13,14] In cases of ocular surface inflammation, a limited course of topical steroids, such as fluorometholone 0.1%, 2-4 times per day, may be used. If prolonged steroid use is required to prevent relapse, then 0.05% cyclosporin applied twice daily for 3 months can avoid steroid-related side effects such as intraocular pressure rise, microbial keratitis and cataracts.[15]

Dietary modification can also be helpful, including omega-3 supplementation and reduction of alcohol, hot drinks and spicy foods.[16]

Ocular rosacea is an underdiagnosed clinical entity that causes significant functional and social impairment. The challenge in its management lies in its chronicity and need for significant patient input and compliance.

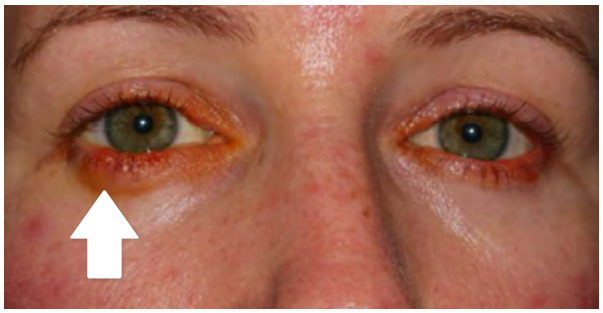

**Figure 1a.** *Ocular rosacea: blepharitis, stye formation (arrow)*

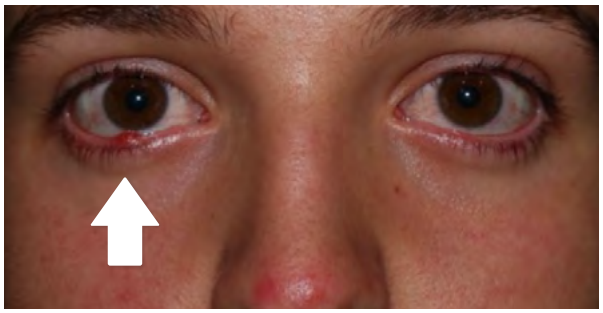

**Figure 1b.** *Ocular rosacea: blepharitis, blepharoconjunctivitis, chalazion and pyogenic granuloma formation (arrow)*

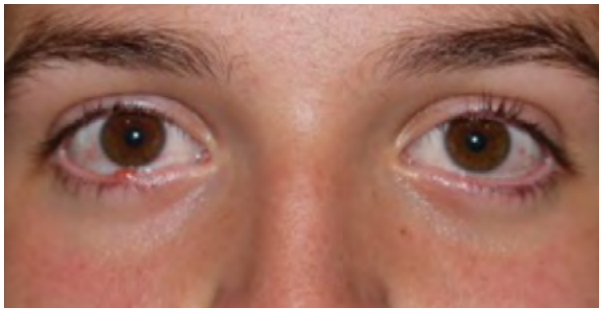

**Figure 2.** *Patient from Figure 1b showing improvement in ocular and facial rosacea after 6 weeks of systemic antibiotic treatment (erythromycin)*

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# Physical Therapies — video presentations

# *"How I do it"*

Welsh B, Dawes-Higgs E, Al-Niaimi F, Wines N, Tanghette E. Physical Therapies — video presentations. "How I do it". Opin Prog Cosmet Dermatol 2021;1(2):42.

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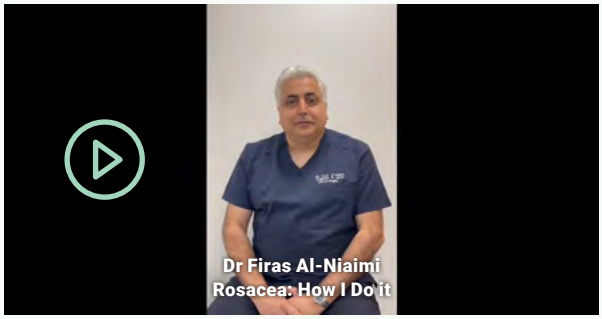


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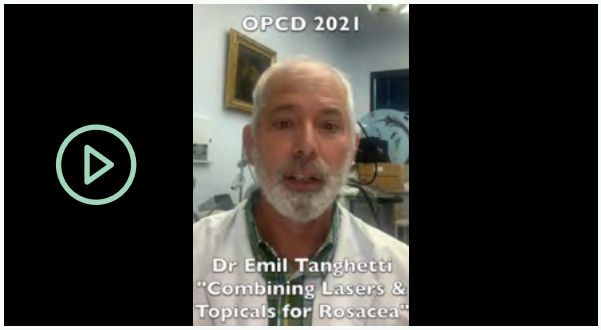


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# Management of Rhinophyma: A Review of Current Literature


CLICK IMAGE TO LINK TO VIDEO DURATION_00:35

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Disclosures: *Dr Davin Lim is a KOL for Lutronic.*

**OUTLINE:** Rhinophyma is a condition of progressive disfigurement and destruction of the nasal unit associated with rosacea that can lead to both psychological and physical disturbance to the patient's wellbeing. The current management for rhinophyma can be categorised as medical versus surgical. The efficacy of medical therapy remains equivocal in terms of slowing the progression of the disease and has not been shown to reverse structural distortion. At present, surgical management remains the mainstay of treatment for rhinophyma with a variety of modalities such as surgical excision, electrosurgery, radiofrequency ablation, cryotherapy, and laser therapy, available to dermatologists. The evidence of a single best treatment option for rhinophyma remains controversial due to the lack of studies demonstrating a high level of evidence regarding comparative treatment outcomes associated with individual modes of surgical treatment. Each treatment has its advantages and disadvantages, and clinicians need to be aware of them to ensure best patient outcomes. The current consensus favours fully ablative laser re-surfacing as the treatment of choice for its excellent cosmetic outcome and low rates of complications. Ultimately, the severity of disease, patient preference, time-consumption, cost, and the expertise and experience of the treating clinician are factors to be considered when selecting the optimum treatment modality for individual patients with the disease.

**KEYWORDS:** rhinophyma, rosacea, CO2 laser

Sun C, Sim D, Bekhor P. Management of Rhinophyma: A Review of Current Literature. Opin Prog Cosmet Dermatol 2021;1(2):43-48.

## Introduction

Rhinophyma is a disfiguring disease characterised by progressive disruption of the nasal architecture and affects the overall aesthetics of the nasal unit.[1] The deformity occurs as a bulbous growth of mainly the lower two-thirds of the nose accompanied by coarsened texture, overlying telangiectasia, and dilated pores.[2] Disfiguring skin disorders, such as rhinophyma, have a pronounced effect on patient's self-confidence and mental wellbeing overall.[3] In addition to cosmetic disfigurement, advanced disease may affect the airway and lead to nasal obstruction and airway collapse.[4] Therefore, patients may be motivated by cosmetic disturbance, psychological wellbeing as well as airway issues to seek treatment.[2] In this article, we perform a systematic review of the current medical and surgical management for this condition.

## Methods

We conducted a review of current existing medical and surgical treatments for rhinophyma using the MESH term "rhinophyma" and text word "treatment" through MEDLINE via Ovid. The two search terms are combined using the Boolean operator "AND". The included studies comprised of case reports, case series, retrospective studies, and non-randomised, non-blinded control trials. Non-English articles and animal studies were excluded in the search. Additional studies were included from the references list of articles selected from the initial search conducted with MEDLINE to fill the gap in aspects of treatment modalities not adequately explored with the initial search.

## Epidemiology and pathophysiology

Rhinophyma predominantly affects Caucasians between their fifth and seventh decade of life with a low level of incidence amongst those of Asian and African heritage.[1] Rhinophyma can occur in the advanced stage of rosacea but also can occur *de novo*.[5] Rosacea has been reported to have either a high prevalence in females or an equal prevalence between genders.[1,6] In contrast, rhinophyma is more common in men with an estimated male-to-female ratio ranging from 5:1 to 30:1.[1] Rhinophyma has

been historically linked to alcoholism; nevertheless, there are no evidence-based studies revealing a relationship between alcohol consumption in the pathogenesis of rhinophyma.[3]

Rosacea has been linked with colonisation of sebaceous glands by Demodex folliculorum.[6] The increased skin vascularity and chronic inflammation of rosacea is generally accepted as the mechanism of progression to rhinophyma. The histopathology of rhinophyma can either resemble fully developed rosacea with sebaceous gland hyperplasia, follicular plugging, dilatation of the pilosebaceous unit and telangiectasia; or a fibromatous variant which has been linked to the fibrogenic cytokines TGFb1 and TGFb2.[5] The histopathological variants are not predictive of clinical expression of rhinophyma.[5]

## Treatment

The early historical attempts at treating rhinophyma mainly comprised of surgical excisions. Dieffenbach removed rhinophymatous skin via excision and primary closure in 1845. Later in 1851, von Langenback excised nasal skin and allowed healing via secondary intention. In 1864, Stromeyer performed partial thickness excision with the aim to allow re-epithelialisation through preserved sebaceous gland. Skin grafting was added to the repertoire by Wood in 1942. Radiation therapy was employed in the 1920s and 1930s which has fallen out of practice in the modern era due to increased rate of malignancies.[4] Nevertheless, it may still be considered for those who are poor surgical candidates.[4]

### Medical treatment

In the early stages of rhinophyma, antibiotics with anti-inflammatory properties such as the tetracycline class as well as oral retinoids such as isotretinoin are employed. However, neither antibiotics nor retinoids have been conclusively demonstrated to stop the progression of the disease or reverse the deformities.[1,4,6] Therefore, the mainstay treatment for rhinophyma will require ablative therapy.[6]

### Surgical treatment

While surgical management remains the preferred treatment for rhinophyma, there is no definitive consensus regarding the best modality of therapy. Many different approaches have been developed including scalpel excision, dermabrasion, electrosurgery, electrocautery, radiofrequency ablation, laser ablation, or a combination of the above therapies (Table 1). The best approach has not been established in the absence of strong evidence suggesting the superiority of any particular method.

#### *1. Surgical excision*

Surgical excision is among the earliest techniques used to treat rhinophyma. Full thickness excision has lost popularity due to the risk of secondary intention healing causing significant scarring in the absence of an epithelial reservoir to facilitate healing.[3,7] Partial thickness excision is now the most common approach with the aim preserving a base of pilosebaceous units resulting in a better cosmetic outcome.[4]

Surgical excision is a less time consuming and resource demanding procedure in comparison to laser treatment, particularly in the case of more pronounced forms of rhinophyma. Bulk excision of tissue also allows histological examination of removed skins. Although rhinophyma is a benign process, a variety of malignancies such as basal cell carcinoma, squamous carcinoma, and sebaceous gland carcinoma have been reported in the literature.[2]

The main disadvantage of surgical excision lies in accurately judging the depth of excision to achieve the balance between avoiding scarring and preventing further recurrence of disease. In a retrospective study by Schweinzer and colleagues with a cohort of 143 patients undergoing scalpel decortication of rhinophymatous nodules, the overall cosmetic outcome was promising with 77% of patients reporting the cosmetic result as “good” or “very good”. The rate of recurrence was 38% which highlights the issue with judging the depth of excision that is commonly encountered in this approach.[3] The inaccuracy in excision depth is a result of the poor haemostatic control associated with a traditional “cold blade” surgical approach. The use of various more modern cutting instruments with modality for anticoagulation and adjunct therapy such as incorporating adrenaline into local anaesthetics to reduce haemorrhage during the procedure have been reported in the literature to mitigate this issue. Shaw scalpel, which incorporates an electrically heated surgical blade, has been reported as a more haemostatic technique by Seiverling and colleagues.[8] A case report by Dufresne used an ultrasonic scalpel to coagulate small vessels in the treatment of rhinophyma but the thermal injury to the surrounding disease-free tissue remains a point of contention.[9] Novel dressings such as amniotic membrane, which has been shown to modulate TGFB levels as an anti-fibrotic therapy, have also been trialled in a case report by Yoo et al. as a method of reducing the risk of scarring if the removal is too deep.[10]

#### *2. Dermabrasion*

The invention of dermabrasion, which involves removing the upper to mid layers of the skin with an abrasive device, has been credited to Kromeyer in early 1900s using rasps and burrs with rotation.[11] A variety of dermabraders are available in the modern era with a range of end pieces that allow precise resurfacing and treatment.[12] As a treatment for rhinophyma, it is rarely used as single modality but rather as an adjunct for finer contouring post bulk excision. Poor haemostatic

control remains a downside to this modality along with complications of hypopigmentation and scarring.[12] One modern technique of hydro-dermabrasion is the Versajet Hydrosurgery system, which is based on the Venturi effect of fluid dynamic whereby a hair-thin stream of sterile saline is accelerated through a constricted opening with concomitant decrease in pressure to create a suction effect that lifts and removes tissue during the cutting and debriding process.[13,14] Taghizadeh[14] and Yildiz[13] reported two separate cases of treating rhinophyma with hydro-dermabrasion with considerably less bleeding which often obscures the surgical field leading to inaccurate depth of debridement. Currently, the use of this method has only been reported in literature in conjunction with surgical debulking.

### 3. Cryotherapy

Cryotherapy provides a simple, quick, and economically efficient method of surgically destroying tissue in the treatment of rhinophyma. A case series comprising of 5 patients by Sonnex and Dawber in 1983 demonstrated that treatment of rhinophyma with liquid nitrogen spray leads to satisfactory cosmetic outcome for patients.[15] A case report by Kempiak et al. reported cryotherapy as a convenient treatment method eliminating the need for operative anaesthesia and reducing treatment duration.[16] The disadvantage of this modality is the associated complications of pigmentary damage, particularly in the case of patients with darker skin types, scarring, and decreased control of depth and contouring of the nasal unit. Additionally, multiple treatment sessions are needed as the prolonged freezing cycle increases the rate of complications.[16]

### 4. Electrosurgery, electrocautery, and radiosurgery

Electrical energy remains a popular surgical modality used by dermatologists for numerous indications including rhinophyma. Electrosurgery involves the use of an alternating current that directly heats up the tissue, while electrocautery is the application of heat from an external source generated from electrical energy. Radiosurgery involves reshaping tissue with radiofrequency via a cutting loop (Figure 1).[4] In a case report by Greenbaum et al., where three patients were treated with both electrosurgery and carbon dioxide (CO2) laser therapy on each side of the nose, the cosmetic out and healing time were comparable between the two modalities.[17] The operating time for electrosurgery was about one-half of laser therapy and good haemostatic control was present in both. In addition, electrosurgery maintains the advantage of cost-efficiency and wider availability. The main disadvantage of electrosurgery is the damage of adjacent tissue through the accumulation of heat.[17,18] In a case series of 8 patients by Rex et al., younger patients seem to amount a more intense inflammatory response to electrosurgery leading to more pronounced risk of scarring.[18] This could be a result of greater depth of tissue destruction associated with electrosurgery as compared with CO2 laser therapy.

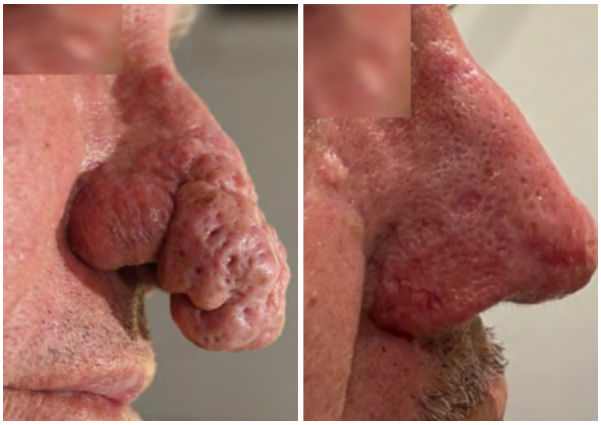

**Figure 1.** *Severe rhinophyma before and after treatment with radiofrequency loop ablation (photo courtesy of Dr Davin Lim)*

### 5. Laser therapy

Laser ablation allows both debulking and sculpting of the rhinophymatous tissue in a bloodless field. The CO2 laser, which has emerged as the laser treatment of choice for rhinophyma, was first reported in the 1980s for the treatment of rhinophyma.[2] CO2 laser emits light energy in the infrared portion of the spectrum, at 10 600 nm, and is absorbed by water resulting in non-selective tissue vaporisation.[19] Early CO2 laser systems utilised continuous wave delivery systems which resulted in a high incidence of scarring.[19,20] The development of high energy, pulsed and scanning CO2 systems allowed short pulse width limiting thermal injury which leads to more precise ablation of epidermal and dermal tissue minimising risk of scarring.[19]

CO2 ablative laser therapy offers excellent control of bleeding with effective coagulation of blood vessels up to 0.5 mm diameter.[4,19] This leads to the advantage of a dry operative field for better tissue visualisation and judgement of the depth of tissue being removed. The depth of ablation can also be ascertained by the capacity to manually express sebum from the base of the treatment field, the absence of which serves as a proxy marker that desired treatment depth has been reached.[21] Other operators prefer to end the procedure when still able to express sebum, which confirms the presence of viable sebaceous glands at the base of the laser wound. The cosmetic outcome of CO2 laser therapy for rhinophyma treatment is excellent and the rate of complications is low. In a retrospective study of 124 patients, Madan and colleagues showed the patient's perception of post-treatment outcome as good or excellent in 118 and poor in 6 patients. Scarring and hypopigmentation were each seen in 4 patients, and only 2 patients developed notching of nasal ala.[21] Although CO2 laser may theoretically have longer treatment duration due to the need for

multiple passes over target skin, a retrospective review by Bekhor and colleagues demonstrated that using CO2 laser with continuous computerised scanning (Sharplan Feathertouch, now rebranded as Lumenis Acupulse Laser) allowed treatment to be conducted in a fast and time-efficient single pass technique with excellent cosmetic outcome and no major complications (Figure 2).[20]

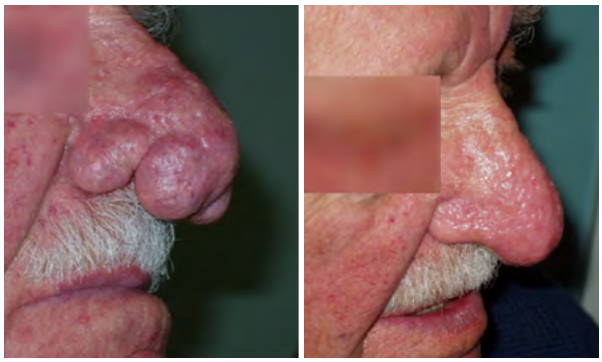

**Figure 2.** *Severe rhinophyma before and after treatment with Sharplan Feathertouch continuous scanning ablative carbon dioxide laser (Lim, 2009)*

Fractionated CO2 laser resurfacing has also been reported as treatment for rhinophyma in the literature. While traditionally the suboptimal energy penetration of non-ablative therapy has largely precluded its use in rhinophyma, the development of fractional thermolysis which heats tissue in columns called microscopic treatment zones (MTZ), while leaving healthy surrounding tissue to aid healing and reduce complications, has been reported as a treatment for rhinophyma.[22] A case series by Serowka and colleagues demonstrated satisfactory cosmetic outcome in five patients with mild to moderate rhinophyma treated with this technique.[22] The time to re-epithelialisation was faster as healthy surrounding tissues were left behind with each microscopic treatment zone and none of the patients experienced any adverse events such as scarring or hypopigmentation. However, fractionated treatment does not allow the same amount of tissue debulking as traditional fully ablative CO2 laser therapy and may be limited to mild to moderate rhinophyma.[22] For sculpting patients with high disease burden, fully ablative laser therapy remains first line.[22]

Er:YAG laser (erbium-doped yttrium aluminium garnet laser) has also been used to treat rhinophyma. Fincher et al. reported a case series of six patients with mild to severe rhinophyma with very good to excellent treatment outcomes and zero rate of complication. Its wavelength of 2940 nm is more specific for water absorption, and therefore, will induce less collateral heat injury. Er:YAG laser produces less thermal energy than CO2 laser which reduces the associated risks of scarring and pigmentation changes.[23] More efficient absorption of energy by intracellular and extracellular water results in a smaller thermal zone, leading to more rapid re-epithelialisation time compared to CO2 laser.[23] Lower thermal energy output, however, creates the disadvantage of limited coagulative power to maintain optimal visualisation of the treatment field without additional adjuncts such as topical epinephrine soaks and electrocautery to achieve adequate haemostasis.[23] This is laser is also very slow and most operators would not regard it as a primary treatment for rhinophyma though it is in common use as part of a CO2 ablation to remove nonviable tissue and possibly increase the rapidity of healing.

## Discussion

The optimal surgical treatment for rhinophyma has not been established in the literature due to limited high evidence studies to guide medical practitioners. The current literature includes studies regarding a variety of different modalities including surgical excision, cryotherapy, electrosurgery, dermabrasion, and laser therapy. With the possible exception of CO2 laser and surgical decortication, the studies centred around other treatment options are mainly in the forms of case reports and series with inadequate study population size to offer strong evidence of efficacy or rate of complications. To our knowledge, there has not been any randomised controlled trials comparing one modality to another in terms of treatment outcomes and associated risks. The only article that was found through literature search performed as part of this review compared CO2 laser and electrosurgery in a small case series.

The severity of disease may help determine whether a debulking or sculpting modality or combination therapy should be used. Mild to moderate disease may be amenable to fractional ablative CO2 or fully ablative erbium lasers; while severe nodular disease may be more conveniently managed with ablative CO2 laser, surgical decortication or electrosurgery. The availability of specialised equipment and operators, may also contribute as factors to the decision process. In the absence of appropriately designed and powered studies to demonstrate differences in treatment outcomes between modalities, dermatologists need to take into consideration the above factors as well as their own expertise and anecdotal experience in managing patients with rhinophyma.

Regardless of which treatment option one decides to use, it is important to maintain adequate control of haemostasis allowing clear visualisation of the treatment field. Vigilance regarding the depth of tissue removal is critical to avoid scarring and associated alar notching.

**Table 1:** *Summary of surgical treatment for rhinophyma*

| Treatment Modality | Advantage | Disadvantage | Supporting Literature |
|---|---|---|---|
| **Cold knife excision** | 1. specimen for histopathology<br>2. low cost and easy handling<br>3. no requirement for specialised equipment<br>4. no thermal damage to surrounding tissue | 1. poor haemostatic control<br>2. poor judgement of depth due to bleeding<br>3. increased risk of scarring | 2,3,4 |
| **Hot knife excision (e.g. Ultrasonic scalpel, Shaw scalpel, etc.)** | 1. specimen for histopathology<br>2. good haemostatic control<br>3. better depth judgement compared to cold knife method | 1. thermal damage to surrounding non-lesional tissue | 8,9 |
| **Dermabrasion** | 1. useful as an adjunct for fine contouring post-surgical excision | 1. poor haemostatic control<br>2. cannot be used for bulky disease | 11,12 |
| **Versajet** | 1. intra-operative haemostasis and removal and lesion debris allowing accurate assessment of depth of excision<br>2. can be used for excision of bulky lesions as well as fine contouring | 1. specialised equipment<br>2. high cost associated with treatment | 13,14 |
| **Cryotherapy** | 1. low cost and readily assessable treatment modality<br>2. no requirement for anaesthesia<br>3. good haemostatic control | 1. high risk of pigmentary changes especially in patients with darker skin type<br>2. may require multiple treatment sessions | 15,16 |
| **Electrosurgery** | 1. low cost and readily available<br>2. good haemostatic control intra-operatively<br>3. shorter operating time compared to laser therapy | 1. thermal damage to healthy surrounding tissue<br>2. increased risk of scarring in younger patients | 4,17,18 |
| **Ablative carbon dioxide laser** | 1. excellent haemostatic control<br>2. good cosmetic outcome with low rated of complications (scarring, hypopigmentation, alar notching)<br>3. can be used for both debulking and fine contouring | 1. high cost<br>2. specialised training and equipment | 2,4,19,20,21 |
| **Non-ablative carbon dioxide laser** | 1. good haemostatic control<br>2. faster re-epithelialisation time due to healthy columns of tissue surrounding treated tissue | 1. inability to perform debulking procedure in severe disease<br>2. significantly longer duration of procedure | 22 |
| **Er:YAG laser** | 1. more controlled tissue ablation compared to CO2 laser<br>2. reduced risk of scarring and hypopigmentation due to lower thermal energy output<br>3. faster re-epithelialisation time | 1. limited coagulative power for adequate haemostasis<br>2. impaired visualisation of the treatment field due to bleeding | 4,24 |

## Conclusion

Rhinophyma is a condition of progressive disfigurement of the nasal unit associated with rosacea that can lead to both psychological and physical disturbance to the patient's wellbeing. The efficacy of medical therapy remains equivocal in terms of slowing the progression of the disease and has not been shown to reverse structural distortion. Surgical management remains the mainstay of treatment for rhinophyma with a variety of modalities available to dermatologists reported in the literature. The evidence of a single best treatment option for rhinophyma remains controversial with a paucity of studies demonstrating a high level of evidence regarding comparative treatment outcomes associated with individual modes of surgical treatment. The decision regarding treatment modality depends on severity of disease, patient preference, time-consumption, cost, and the expertise and experience of the treating clinician.

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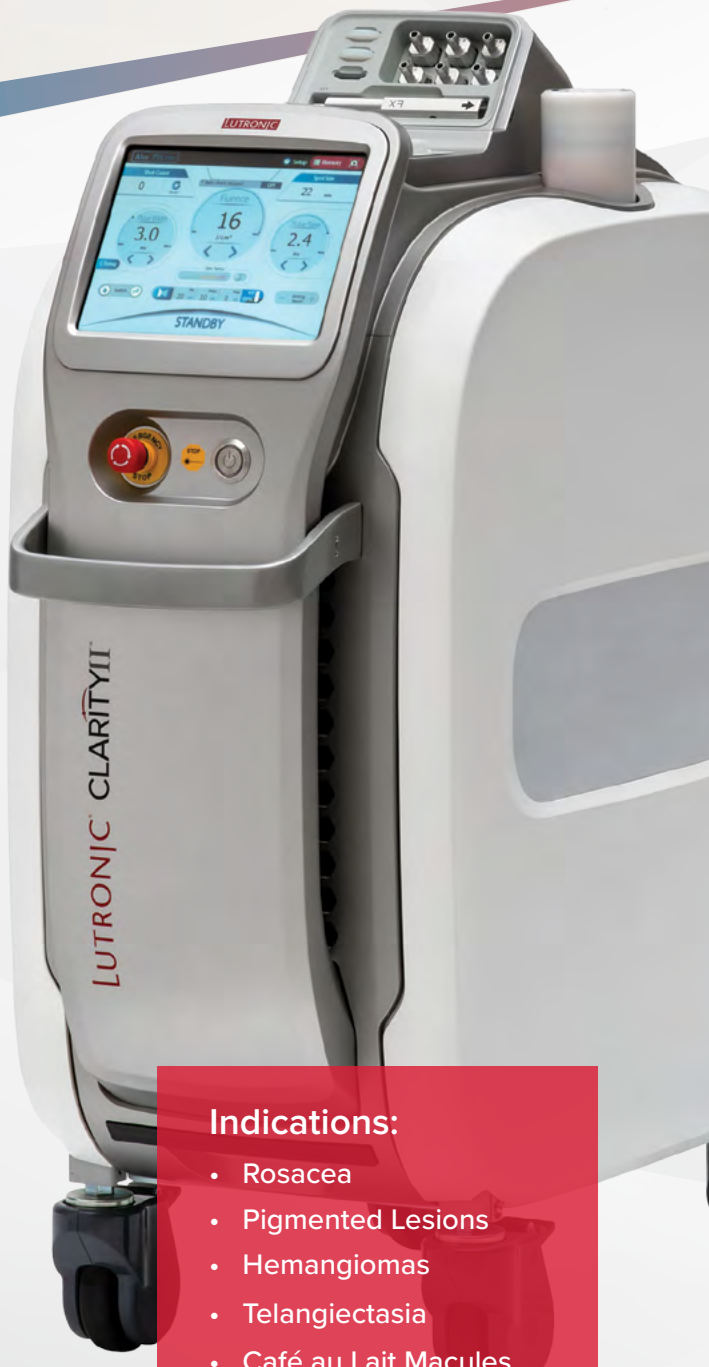


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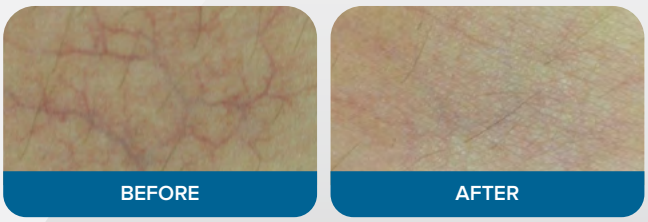


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- Hemangiomas
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- Café au Lait Macules
- Hair Removal
- Wrinkle Reduction

# Cosmeceuticals in the Treatment of Rosacea

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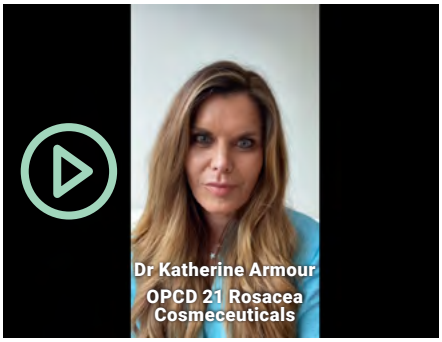
Disclosures: *Katherine Armour is the founder of Bespoke Skin Technology, and has consulted to Galderma (Cetaphil) and L'Oreal Paris Skincare*

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**OUTLINE:** Rosacea is a common inflammatory dermatosis, primarily affecting the face. Cosmeceuticals are increasingly playing a useful role in treating these patients in combination with standard medical and laser therapies.

**KEYWORDS:** rosacea, skincare, cosmeceuticals, antioxidants

Armour K. Cosmeceuticals in the Treatment of Rosacea. Opin Prog Cosmet Dermatol 2021;1(2):50-52.

## Introduction

Rosacea is a common inflammatory dermatosis primarily affecting the central face, cheeks, forehead, chin, and nose.[1] It often follows a relapsing and remitting course and has a markedly negative impact on quality of life in those afflicted.[2,3] The pathophysiology of rosacea is complex and multifactorial. Genetics, triggers such as ultraviolet radiation, microbial stimuli, immune dysfunction, and neurovascular dysregulation all contribute.[1] The role of the innate immune system is particularly significant,[1] with evidence of overexpression of Toll-like receptors (TLR) in the membrane of epidermal keratinocytes.[1] When activated through physical and chemical stimuli, these TLR activate a downstream pathway which augments the inflammatory response.[1] Disturbances in the epidermal barrier are also found in the skin of rosacea patients, leading to increased transepidermal water loss.[4]

A decreased tolerance to topical products is well-documented in this patient group,[5] whose skin has also been noted to be more alkaline in pH than that of healthy controls.[6] Therefore, in terms of basic skincare, the most appropriate cleansers and moisturisers are designed specifically for sensitive skin. Appropriate formulas for cleansers are based on lipid-free or high levels of non-ionic or amphoteric surfactants with an acidic pH closer to the natural pH of skin.[7] Gentle facial moisturisers assist with restoration of epidermal barrier function[1] and should feel soothing upon application. Rosacea is commonly exacerbated by sun exposure. So, daily use of a broad-spectrum sun protection is imperative to mitigate this. Physical sunscreens are particularly well-tolerated in this patient group.

Cosmeceutical skincare products to combat rosacea can be useful adjuncts to medical and laser therapy, to improve outcomes for patients. Mechanistically, these ingredients can be divided into three main groups: those that protect/repair the epidermal barrier; those with anti-inflammatory properties; and anti-oxidants. These ingredients have been chosen based on the known pathophysiology of rosacea. An ideal regimen to approach skincare for the rosacea patient will combine ingredients from each group in addition to sun protection and colour camouflage.[7]

## Ingredients which protect/repair the epidermal barrier

***Niacinamide*** – this ingredient improves stratum corneum barrier function. Thus, the potential impact of topical triggers of flares is reduced, and sensory irritation from external insults is diminished.[7] In a 2005 study in which patients with erythematotelangiectatic and papulopustular rosacea applied a niacinamide-containing moisturiser for 4 weeks, improvements were noted in skin barrier function (measured as transepidermal water loss) and symptoms and signs of rosacea.[8]

***Hydroxypropyl chitosan and colloidal oatmeal*** – both provide protective barriers which have proven helpful in rosacea treatment.[7] The avenanthramides present in colloidal oatmeal also have known anti-inflammatory actions.[9]

***Panthenol*** – is also a barrier-enhancing humectant used to hydrate the skin and prevent barrier damage.[10]

***Allantoin*** – enhances the water-holding capacity of the extracellular matrix, improving barrier function.[11]

## Cosmeceutical ingredients with anti-inflammatory properties

Ingredients to target the inflammation caused by the hyper-responsiveness of the innate immune system in rosacea, comprise the largest group of cosmeceutical actives to treat this condition.[7]

***Feverfew*** – the active compounds of feverfew include parthenolide and tanetin, which inhibit the release of prostaglandins and serotonin.[7]

***Glycyrrhiza inflata*** – contains licochalcone A which inhibits keratinocytes release of prostaglandins in response to UVB-induced erythema.[11]

***Gingko biloba*** – decreases circulation at the capillary level and reduces inflammation through antioxidant effects.[11]

***Aloe vera*** – inhibits the cyclooxygenase pathway.[11]

***Bisabolol*** – is an extract of chamomile which acts as a potent ant-inflammatory.[10]

## Antioxidant ingredients in the treatment of rosacea

Active inflammation in rosacea can lead to the generation and release of reactive oxygen species (ROS). This is exacerbated by ultraviolet exposure in a compromised barrier. Neutralising ROS by applying topical antioxidants can be useful in treating rosacea.

***Vitamin C –*** a small study of rosacea patients showed reduced erythema after use of 5% vitamin C.[7] Stronger preparations of vitamin C may be irritating in this patient group.

***Green tea (Camellia sinensis) –*** contains numerous polyphenols which reduce ultraviolet B (UVB)-induced inflammation by functioning as antioxidants.[11]

Topical pharmaceutical preparations such as oxymetazoline and brimonidine act as a1-adrenergic agonists, and effectively reduce facial redness in rosacea via vasoconstriction. In the cosmeceutical realm, topical caffeine may lead to vasoconstriction. However, it can be irritating in rosacea patients.[7]

Cosmeceutical skincare ingredients are a useful addition to medical and physical therapies in our rosacea patient, and are worth including in our consultations with these patients along with general skincare advice. Readily available "anti-redness" skincare, moisturisers and cleansers are listed in Tables 1 and 2.

**Table 1.** *Readily available "anti-redness" skincare in Australia**

| Product name | Active ingredients |
|---|---|
| Bioderma Sensibio AR – Anti-Redness Care | Rosactiv™ (green tea and soy) – suppresses tryptase release<br>Green tea, enoxolone – anti-inflammatory |
| The Ordinary Niacinamide 10% + Zinc 1% serum | Niacinamide – anti-inflammatory AO and skin barrier repair<br>Zinc – soothing |
| Avene Antirougeurs Fort Redness Relief Concentrate | Ruscus extract – venous vasoconstrictor |
| La Roche Posay Rosaliac Intense Anti-Redness Serum | Ambophenol – rich in polyphenols, anti-inflammatory<br>Neurosensine – soothing |
| Medik8 Calmwise Serum | Teprenone – telomere stabilisation which enhances skin barrier function<br>Sage – anti-inflammatory AO |
| Propaira Rozaway Cream | Niacinamide – anti-inflammatory AO<br>Zinc – soothing<br>Bisabolol – anti-inflammatory<br>Allantoin – soothing |
| Synergie Skin DermaCalm | Acetyl tetrapeptide 40 – combats redness by decreasing interleukin 6 and 8<br>Acetyl hexapeptide 49 – reduces sensation of itch and heat<br>Hydrolysed tomato skin – potent AO<br>Canadian willowherb – soothing |
| SkinCeuticals Redness Neutralizer | Palmitoyl tripeptide 8 – reduces increases in skin temperature, anti-inflammatory<br>Eperua falcata bark extract and bisabolol – anti-inflammatory, soothing |

**This table is not an exhaustive list of available products, but lists readily available, suitable products currently available in Australia.*

*AO – antioxidant*

**Table 2.** *Appropriate simple moisturisers and cleansers for the rosacea patient**

| Moisturisers | Cleansers |
|---|---|
| **Bioderma**<br>Sensibio Rich<br>Sensibio Light<br>Atoderm Creme | **Bioderma**<br>Sensibio Gel Moussant (Soap-free) |
| **Avene**<br>Tolerance Extreme Cream<br>Skin Recovery Cream<br>Skin Recovery Cream Rich<br>Hydrance Rich Hydrating Cream<br>Hydrance Light Hydrating Emulsion | **Avene**<br>Antirougeurs Clean Soothing Cleansing Lotion<br>Tolerance Extreme Cleansing Lotion<br>Extremely Gentle Cleanser Lotion |
| **CeraVe**<br>Facial Moisturising Lotion | **CeraVe**<br>Hydrating Cleanser |
| **Cetaphil**<br>Daily Advance Ultra Hydrating Lotion<br>Moisturising Cream<br>Moisturising Lotion | **Cetaphil**<br>Gentle Skin Cleanser |
| **La Roche Posay**<br>Toleraine Sensitive Facial Moisturiser<br>Toleraine Sensitive Riche Facial Moisturiser<br>Toleraine Ultra Light Sensitive Moisturiser<br>Toleraine Ultra Overnight Sensitive Moisturiser | **La Roche Posay**<br>Toleraine Caring Wash Cleanser<br>Toleraine Dermo Cleanser |
| **QV Face**<br>Ultra Calming Moisturiser | **QV Face**<br>Gentle Cleanser |

**This list is comprises easily accessible moisturiser and cleanser options for patients with rosacea living in Australia. This list is by no means exhaustive.*

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# Basics of Skin Care in Rosacea

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Disclosures: *none*

**OUTLINE:** A brief look at the basics of caring for skin with rosacea.

**KEYWORDS:** rosacea, cleanser, moisturiser, hygiene, gut

Greive KA. Basics of Skin Care in Rosacea. Opin Prog Cosmet Dermatol 2021;1(2):53-54.

## Introduction

Rosacea is an inflammatory skin condition, generally affecting the pilosebaceous units and blood vessels of the face; it is chronic and relapsing.[1,2] Characteristics include sensitive skin, flushing, erythema, papules and pustules.[1] Skin sensitivity is a condition where the skin is hyper-reactive to environmental factors such as heat, cold and skin care products, resulting in adverse sensations such as stinging, burning, tingling, itching or prickling.[3] The inflammation associated with rosacea can increase the sensations of sensitive skin[2] and can make choosing basic skin care products challenging.

Like many things in life, when it comes to skin care for rosacea, simple is best. Basic skin care for rosacea should focus on skin hydration, barrier function and sun protection.[4] The product combination that suits one person may not be ideal for another, so persistence in trialling products and approaches is key to finding the best solution for the individual. Within this framework there are five key tips to keep in mind.

### 1. Choose a simple, quality, cleansing and moisturising routine

A complicated multi-step process is not needed to look after the skin. A good quality, simple, often inexpensive, cleanser and moisturiser are the best tools to use to care for skin[5] with rosacea.

### 2. Choose a soap free cleanser[2]

Soap is highly alkaline and will effectively remove the skins natural protection leaving it feeling tight and dry, while also vulnerable to environmental irritants.[5] Today there are many 'pH balanced' or 'pH neutral' soap-free cleansing options, but if water is all skin will tolerate, avoid waterproof or heavy topical products that will need a solvent to remove.[2]

### 3. Choose products that are free from fragrance, colours, and essential oils

Fragrance, colours, and essential oils can make a skin care product look and smell attractive, but they are unnecessary for the function of a cleanser or moisturiser and increase the likelihood that the product will cause skin irritation.[5]

### 4. Avoid touching your face throughout the day[6]

On average we can touch our face 23 times every hour,[7] and although increased levels of hand hygiene are currently practised in the fight against COVID-19, hands can still play a role in transferring environmental irritants to the face, with touch itself being an aggravating factor for some types of rosacea.[8]

### 5. Wear sunscreen daily if possible

Sun exposure is known to trigger or exacerbate rosacea, so daily sun protection is recommended.[2,9] The easiest way to accomplish this is with a facial moisturiser containing sunscreen, however, if a suitable product cannot be found, then physical sun protection measures should be used. Ultimately the best sun protection and sun protection factor is the one we are willing to wear each, and every day. This may differ among individuals, with any sunscreen being preferable to none.

How the skin is nourished from the outside-in is important, but so too is nourishment from the inside-out. It has long been recommended that those with rosacea avoid alcohol, spicy foods or hot drinks,[10] however with rosacea understood to be a chronic inflammatory skin condition, the gut-skin connection is receiving more attention.[1,3] From this research we are beginning to understand how a fibre-rich diet based around plants, can shift the gut bacteria composition

in favour of beneficial bacteria, which in turn can have an anti-inflammatory effect on the body, including the skin.[3]

Simple, quality, consistent skin care is essential in helping to maintain healthy skin when rosacea is a factor; and can help maintain skin in a receptive state for any topical treatments that may be recommended by a treating specialist. Persistence is the key to any skin care, with rosacea usually being a long-term condition.

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# An Update on Rosacea Medical Management

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**OUTLINE:** Rosacea is a chronic multivariant inflammatory condition with exacerbations and remissions requiring both a goal to initial improvement and a commitment to long term management of flares and maintenance therapy. Whilst various clinical manifestations of rosacea have been defined there is an evolution from isolated clinical subtype management to a phenotypic paradigm that is individually specific as patients may evolve from one subtype to another or have phenotypic features of differing subtypes at one time. Rosacea is not curable but rather controllable using a combination of topical, oral and energy-based treatments tailored to specific needs of the individual which vary in time. Quality patient education is vital to patient outcomes. Traditional consultations elevated to include video-based material and education may improve results so patients can fully understand how to manage their rosacea. The article overviews existing and emerging therapies and aims to provide current up-to-date information to enable effective acute and long-term management of rosacea.

**KEYWORDS:** rosacea, topical treatment, systemic treatment, lifestyle, management, phenotypes, therapy

Wines N, Alexander P, Andric S, Dawes-Higgs L, Donohue S, Harris A, Ng S, McKay C, Polcz M, O'Connor A, Tomizawa A. An Update on Rosacea Medical Management. Opin Prog Cosmet Dermatol 2021;1(2):55-66.

## Introduction

Rosacea has a significant psychosocial impact on quality of life. Effective management starts with quality patient education. Both an acute management plan and a long-term plan are required. Whilst there is no cure for rosacea, clinical features are controlled using a range of topical, oral and energy-based device treatments in isolation or combination tailored to the individual's specific needs and clinical presentation which may vary in time.

There are no diagnostic laboratory tests for rosacea. Diagnosis is based on clinical and historical features. Phenotypic variants of rosacea have been defined by the National Rosacea Society and updated in 2017.[1] The original standard classification of rosacea identified the most common patterns or groupings of signs and symptoms and designated them as follows: subtype 1, erythematotelangiectatic (ET); subtype 2, papulopustular; subtype 3, phymatous; and subtype 4, ocular. The issue with this subtype classification is that the frequent simultaneous occurrence of more than one subtype and the potential progression from one subtype to another was not considered and hence an updated phenotypic classification was established (Table 1).[1] This system enables therapy to be personalized to achieve optimal outcome.

**Table 1.** *Phenotypes of rosacea*

| Diagnostic* | Major† | Secondary |
|---|---|---|
| Fixed centrofacial erythema in a characteristic pattern that may periodically intensify<br><br>Phymatous changes | Flushing<br>Papules and pustules<br>Telangiectasia<br>Ocular manifestations:<br>• Lid margin telangiectasia<br>• Interpalpebral conjunctival injection<br>• Spade-shaped infiltrates in the cornea<br>• Scleritis and sclerokeratitis | Burning sensation<br>Stinging sensation<br>Oedema<br>Dryness<br>Ocular manifestations:<br>• "Honey crust" and collarette accumulation at the base of the lashes<br>• Irregularity of the lid margin Evaporative tear dysfunction (rapid tear breakup time) |

* *These features by themselves are diagnostic of rosacea*

† *Two or more major features may be considered diagnostic*

## Patient education and counselling

Investment in quality patient education is vital to patient compliance, satisfaction and outcome[2] and could be considered the most essential component to the medical management of rosacea. Patients with rosacea have reduced quality of life and also higher rates of psychiatric illnesses[3], both of which are improved with quality management.[3]

This management starts with education and counselling. Methods of successful education have advanced beyond traditional oral and written forms to now include audio (such as podcasts) and video means. Group education may also be effective when applied to long-term disease management such as with rosacea.[2]

It is essential to communicate the chronicity of rosacea, it's exacerbating factors and remitting nature, and the goal of initial improvement followed by long term maintenance of the condition. Education in rosacea involves a multifaceted approach. Individualised triggering factors need to be determined and understood. These triggers include the ingestion of hot foods and drinks along with alcohol, mainly red wine. Other triggers include heat, sunlight and irritating skin care products. We have found that having patients maintain a diary of their disease progress photographically on their phone as well as documenting potential triggers in the notes section of their phones is useful to help both the physician and patient understand the natural history of their rosacea. Other key factors to cover when educating patients are outlined in Table 2.

The emotional, social and professional impact of rosacea upon a patient's life needs to be established and may affect choice of treatment, with a potentially more aggressive approach selected for those in who the psychosocial impact is significant. A positive correlation between psychological intervention and dermatological disorders has been established and cannot be underestimated.[4]

Efficiency of the education process can be enabled by training supporting clinic staff, using patient information sheets, or by developing your own clinic video-based education.

**Table 2.** *Patient education – key points to communicate*

- Cause of rosacea
- Exacerbating and remitting nature
- Need for short term control and commitment to long term maintenance
- Potential triggers and documenting these
- The value of maintaining a photographic diary of their skin
- The different phenotypes of rosacea
- How and when to use medications consistently
- Tips to manage flares and maintain control: value of continuing topical therapy after signs and symptoms of the acute rosacea flare have resolved in order to maintain remission and prevent recurrence[5]
- An understanding of the clinical phenotypes and subtypes of rosacea
- How to use skin care*
- Tips to manage the emotional impact of rosacea

**Gentle cleansing morning and night with fingertips, avoiding scrubbing and soap cleansers. Regular use of a moisturizer is also suggested to assist in reducing epidermal barrier dysfunction that occurs in association with rosacea.*[6,7]

## Lifestyle, diet and rosacea

Management of rosacea flares effectively requires the identification of individual lifestyle and environmental triggers. What affects one rosacea sufferer may not affect another. Patients commonly enquire about the influence of dietary factors on their rosacea.

A National Rosacea Society survey of over 400 patients found that 78% of rosacea sufferers had altered their diet in the attempt to manage their rosacea. Of these patients, 95% reported a reduction in symptoms.[8]

One proposed way to consider food triggers is to group them into categories including heat- related, alcohol-related, capsaicin-related and cinnamaldehyde-related. Heat-related foods include hot beverages such as tea, hot chocolate and coffee (30% report coffee to be a trigger). Alcohol is a frequent trigger and may include wine (50%) beer and spirits (42%). Capsaicin is found in spicy foods (75%) and includes sauces, cayenne and red peppers. Lastly, cinnamaldehyde is found in a range of foods some of which include tomatoes, chocolate and citrus.[9] Niacin-containing foods such as turkey, peanut, tuna, liver and chicken have also been reported to cause flushing.[10]

Dairy products (yoghurt, sour cream, cheese but not cottage cheese), chocolate and vanilla, soy sauce, yeast extracts (but not bread), vinegar, eggplants, avocado, spinach, beans (lima, navy or pea), bananas, red plums, raisins and figs may also exacerbate symptoms in some patients.[11] A recent case-control study of 1347 Chinese patients with rosacea and 1290 matched controls found that high-frequency intake of fatty food and tea resulted in exacerbation of rosacea. High fat intake was associated with ET and phymatous rosacea, whilst tea was only associated with ET rosacea. Dairy products showed negative correlations with ET rosacea and papulopustular rosacea.[12]

Dietary pathogenesis of symptoms is believed to be via the transient receptor potential vanilloid 1 (TRVP1), also known as the capsaicin receptor. This is located on sensory nerves and keratinocytes, and is activated by sun exposure, hot drinks, alcohol, spicy foods, vanilla, cinnamon, and caffeine. Transient receptor potential ankyrin receptor 1 (TRPA1) is located on perivascular sensory neurons in the dermis and is activated by cold temperature and formalin-containing foods (crustaceans, noodles, tofu, shitake mushroom). When activated, these receptors release substance P and calcitonin gene-related peptide which induce a transient inflammatory response. Calcitonin gene-related peptide dilates arterioles, whereas substance P particularly affects post-capillary venules, resulting in flushing and oedema.[10]

### Dietary micronutrient supplementation

Currently there is no convincing evidence that specific nutrients alleviate rosacea symptoms however further research is warranted in the case of zinc and omega-3 fatty acids.[9]

Zinc is fundamental for the innate immune system and acts as an antioxidant and anti-inflammatory molecule. It has shown benefit in other cutaneous inflammatory disorders but, to date, evidence for zinc supplementation in rosacea has shown conflicting results. One trial noted improvement of rosacea after dietary supplementation of zinc sulphate 100 mg three times daily.[13] Omega-3 fatty acids are polyunsaturated fatty acids including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and alpha linoleic acid (ALA). They are substrates for prostaglandins that inhibit pro-inflammatory pathways. One randomised control trial found a statistically significant improvement in subjects with rosacea who ingested 325 mg of EPA and 175 mg EPA twice daily for three months.[14]

### The skin-gut axis

The skin-gut axis proposes an inherent link between gut dysbiosis and inflammatory skin disease.[10] Population-based studies have highlighted an increased risk of rosacea in patients with certain gastrointestinal diseases such as coeliac disease, *Helicobacter pylori* infection, inflammatory bowel disease and irritable bowel syndrome. Small intestinal bacterial overgrowth (SIBO) is 2–20 times greater in rosacea patients than the general public.[10] Eradication of *H. pylori* and SIBO in patients via antibiotic administration has resulted in resolution of rosacea symptoms compared to placebo.[15]

Microbiome diversity established with probiotics or fermented foods (such as kefir or kimchi) have also been shown to hasten clearance of *H. pylori* and resulted in improvement of rosacea.[16] Probiotics are an attractive therapeutic avenue given their relatively low side effect profile. Further research is required however, as probiotic use does not necessarily lead to growth of favourable gut microorganisms.[15] Furthermore, their effect has shown to be short-lived after cessation of supplementation. The effect of different strains of probiotics for different conditions merits further research.[16] Whether or not diet can influence microbial dysbiosis has yet to be defined in rosacea.

When treating patients with rosacea, consider the individual nature of a patient's triggers, as well as the impact of long-term antibiotic use on gut microflora. Prebiotics, fibre-rich foods from plant sources, supporting the growth of healthy gut microorganisms, and the importance of a healthy diet for general health as well as skin health cannot be overstated.

## Topical and systemic treatment of rosacea

Patients are often treated with a combination of therapies including topical and oral agents simultaneously with or without laser or light devices. The selection of treatment is influenced by the clinical phenotype, severity of rosacea, psychosocial impact of the disease and physician experience.

Prior to commencing treatment, we highly recommend pre-treatment and progressive photos (front, oblique left and right views) be taken using standardised photography to monitor progress. We find patients do not recall their improvement with treatment and we find this improves their satisfaction with treatment.

Mild inflammatory papulopustular rosacea is usually initially managed with topical therapy alone. More significant rosacea requires a combination of topical and oral therapy (plus or minus energy-based devices). It has long been known that after discontinuing conventional therapy, one-fourth of patients relapse after one month and two-thirds relapse after six months.[17] A long term plan for management of recurrence needs to be established. Often topical therapy is prescribed to maintain remission. If topical therapy alone does not sustain control, intermittent oral treatment is usually required. Severe variants of inflammatory rosacea requiring multiple courses of antibiotics to achieve improvement may require consideration of oral retinoid therapy.

Certain circumstances can make management difficult. Such as when treatment is contraindicated or during pregnancy. Pregnancy can result in exacerbation of rosacea or the appearance of rosacea for the first time and proposes a therapeutic dilemma as many traditional therapies are contraindicated. This is covered in more detail below.

The use of energy-based devices for rosacea is covered elsewhere within this edition. Device use is determined by availability of equipment and physician experience. In our experience combined medical and energy based light treatment leads to enhanced patient outcomes and prolongation of results and remission. Laser intervention is sometimes seen as aesthetic rather than as an important continuum in patient medical management. The extent to which lasers prevent recurrence and sustain remission is yet to be determined in a formal study.

An overview of existing and emerging therapies follows aiming to provide current up to date information to enable effective selection of treatment for individual patients.

## Standard topical therapy

### Metronidazole

Topical 1% metronidazole cream has a long history of safety and efficacy in the treatment of papulopustular rosacea backed by multiple blinded randomised vehicle-controlled trials.[18-21] Topical metronidazole is thought to exhibit anti-inflammatory properties by reducing generation of reactive oxygen species.[22] Metronidazole 0.75% cream and 0.75% gel is marketed as Rozex in Australia and has Therapeutic Goods Administration (TGA) approval. It is recommended to be applied twice a day for up to 3-4 months and is safe in pregnancy.

### Azelaic acid

Topical 15% azelaic acid gel, foam and 20% azelaic acid cream has also been shown to be efficacious in multiple blinded randomised vehicle-controlled trials for the treatment of papulopustular rosacea.[23] It also has a long safety record but may be more irritating than topical metronidazole.[24] Azelaic acid has antimicrobial and anti-inflammatory properties and inhibits follicular keratinization.[23] In comparison, trials of daily topical metronidazole, 15% azelaic acid gel twice daily was shown to be similar in efficacy to 1% metronidazole gel but superior to 0.75% metronidazole gel.[25,26] In Australia 15% azelaic acid gel and 20% azelaic acid lotion are approved by the TGA and are marketed as Finacea and Azclear lotion, respectively, and are safe to use during pregnancy.

### Ivermectin

Topical 1% ivermectin cream is a novel treatment for papulopustular rosacea. It has both acaricidal and anti-inflammatory actions against Demodex mites.[27] Ivermectin 1% cream is applied to facial skin daily for up to 12 weeks. In two randomised, controlled, double blind, vehicle-controlled pivotal studies ivermectin 1% cream achieved treatment success in 38.4% and 40.1% of subjects.[28] In an industry sponsored blinded randomised controlled trial of 962 participants daily 1% ivermectin cream was shown to be more efficacious than twice daily topical 0.75% metronidazole cream for papulopustular rosacea and had better tolerability.[29] Mild stinging and burning can occur on application. In Australia ivermectin is marketed as Soolantra and is Category C in pregnancy.

### Sodium sulfacetamide

A series of eight patients with papulopustular rosacea showed an improvement with topical 10% sodium sulfacetamide and 5% sulphur foam.[30] Topical 10% sodium sulfacetamide and 5% sulphur foam combined with sunscreen (Rosac cream) was shown to be more beneficial than 0.75% metronidazole cream for papulopustular rosacea and erythema but it was noted 7 out of 75 of those treated with the combination had poor tolerance because of possible sulphur drug

allergy.[31] Sodium sulfacetamide is not approved by the TGA and is not available in Australia.

### Clindamycin

In a randomised vehicle-controlled trial involving 629 participants with papulopustular rosacea, topical 1% cream and 0.3% cream were no more effective than placebo.[32] Topical clindamycin is neither approved by the TGA in Australia nor the FDA.

### Retinoids

There is limited evidence for the use of topical retinoids in the management of papulopustular rosacea. A small randomised controlled study comparing topical tretinoin 0.025% cream and low dose isotretinoin (10 mg/day) in 22 subjects over 16 weeks reported benefit in both treatment groups. However, the rate of improvement was more rapid in the oral isotretinoin group.[33]

### Permethrin

Topical 5% permethrin gel was compared to placebo in 20 patients with papulopustular rosacea in a split face randomised trial. Blinded analysis at 12 weeks showed an improvement in Demodex mite density although both sides showed improvement in symptoms.[34] In another randomised controlled trial of 63 patients with papulopustular rosacea twice daily topical 5% permethrin had a similar benefit to daily 0.75% topical metronidazole gel.[35]

### Pimecrolimus

Two randomised vehicle-controlled trials showed no benefit of topical pimecrolimus in patients with papulopustular rosacea.[36,37] One randomised open-label trial showed topical 1% pimecrolimus was no better than 1% metronidazole cream.[38] Interestingly there have been reports of topical pimecrolimus and topical tacrolimus causing rosacea-like eruptions.[39,40]

### Dapsone

Topical dapsone is a sulfone antibacterial with anti-inflammatory actions. Whilst previously approved, it is no longer available in Australia unless compounded. Dapsone 7.5% gel is applied once daily for up to 12 weeks. It should be avoided in those with known glucose-6-phosphate dehydrogenase deficiency.[41]

### Brimonidine

Brimonidine tartrate is a potent vasoconstrictor and a highly selective alpha-2 adrenergic receptor agonist used to reduce facial redness in rosacea. It is available as a 0.33% gel that is applied once daily exhibiting a response within 30 minutes of application.[42] In a 1-year open label study the safety and consistent efficacy of using 0.5% brimonidine gel was demonstrated in the long-term treatment of moderate to severe erythema.[43] Adverse effects include burning dysaesthesia, flushing, worsening erythema and contact dermatitis. A paradoxical erythema reaction with chronic use of topical brimonidine 0.33% gel has been reported.[44]

### Oxymetazoline

Oxymetazoline hydrochloride is a primary alpha-1a agonist that lessens persistent facial erythema associated with rosacea through vasoconstriction of the cutaneous microvasculature. It is available as a 1% cream that is applied topically to facial skin daily. Reported side effects include application-site dermatitis, paraesthesia, pruritus and pain.[45] In the open label REVEAL trial 36.7% of patients achieved a 2-grade or greater composite improvement from baseline in Clinician Erythema Assessment and 43.4% in Subject Self-Assessment at 52 weeks. Only 0.7% of patients experienced a rebound effect.[45]

## Combination topical therapy

### Clindamycin and tretinoin

A small randomised placebo-controlled trial of 30 rosacea patients found a combined clindamycin 1.2% and tretinoin 0.025% gel to be effective in reducing papulopustular lesions, but not in decreasing in facial erythema.[46] Another randomised, double blind, placebo-controlled pilot study involving 79 subjects with moderate-to-severe papulopustular rosacea using a combined clindamycin 1.2% and tretinoin 0.025% gel did not find a significant difference in papule and pustule count between study groups after 12 weeks.[47] A significant improvement in the telangiectatic component of rosacea was however reported.

### Clindamycin and benzoyl peroxide

A single randomised, double-blind, vehicle-controlled trial of 53 patients with moderate-to-severe rosacea evaluated a daily application of a fixed combination 5% benzoyl peroxide and 1% clindamycin gel over 12 weeks.[48] A 71.3% reduction in papule and pustule count was reported for the intervention group. Decreased severity scores for erythema, flushing/blushing, and papules/pustules were also reported for the treatment group.[48]

### Permethrin and tea tree oil

A single randomised, double-blind, controlled study of 35 patients with papulopustular rosacea evaluated permethrin 2.5% in combination with tea tree oil in a topical gel applied twice daily over a 12-week period. A reduction in Demodex mite density and clinical manifestations including papules, pustules and non-transient erythema were reported in the intervention group.[49]

## Emerging topical therapies

### Topical minocycline

In a recent randomised controlled trial enrolling 1522 patients, a novel topical minocycline 1.5% foam was used to treat patients with moderate-to-severe papulopustular rosacea. Participants applied a thin layer of the foam over all areas of the face daily for 12 weeks. There was a statistically significant reduction in the inflammatory lesion count by an average of 18 lesions versus 15 in the placebo group. There was also an improvement in the rate of Investigator Global Assessment (IGA) endpoint success achieved.[50] An open-label extension study demonstrated a favourable safety and tolerability profile for topical minocycline 1.5% foam up to 52 weeks.[51] In another randomised controlled trial with 270 patients with papulopustular rosacea and less than 40 inflammatory lesions, patients were randomised to daily 1% and 3% minocycline gel or vehicle for 12 weeks. Results showed a statistically significant difference in lesion counts with a drop of 12.6 and 13.1 lesions with minocycline 1% and 3%, respectively, versus 7.9 with the vehicle. Treated patients also had slightly higher IGA score which was statistically significant for the 3% concentration but not the 1% concentration. Both of these studies were industry sponsored.[52]

### Topical tranexamic acid

A study comprising 20 patients with ET rosacea compared four sessions of topical tranexamic acid infused dressings versus topical tranexamic acid infused dressings with micro-needling; an improvement in erythema was seen in all patients.[53]

### Topical benzyl benzoate and crotamiton

Benzyl benzoate and crotamiton at different concentrations were used in a retrospective observational study of 394 patients with papulopustular rosacea and demodicosis. Results showed a decrease in Demodex mite density and improvement in symptoms.[54]

### Timolol

In an open-label prospective study of 58 patients with ET and papulopustular rosacea treated with daily topical 0.5% timolol maleate showed some improvement in the ET but not papulopustular component of the rosacea.[55]

### 8-beta glycyrrhetinic acid

8-beta glycyrrhetinic acid is a non-steroidal anti-inflammatory. A vehicle-controlled study of 24 patients with rosacea showed an improvement in erythema but not papules and pustules.[56] Another non-controlled study using the combination cream consisting of 8-beta glycyrrhetinic acid, glutathione analogue, azelaic acid and sunscreen showed an improvement in inflammatory lesions.[57]

## Standard systemic therapies

### Tetracyclines

Tetracycline family antibiotics, namely doxycycline and minocycline, have been a mainstay of treatment for papulopustular rosacea for five decades. They are effective in ocular, periorificial and pyoderma faciale subtypes.[58-60] Typically, a course is prescribed over 6-12 weeks, alone or combined with topical therapies. The mechanism of action is understood to be anti-inflammatory by inhibition of neutrophil migration, inhibition of multiple matrix metalloproteinases, down regulation of cytokines and scavenging for reactive oxygen species.[58]

### Doxycycline

Doxycycline 50-100 mg daily is frequently a first choice as initial oral therapy. A sub-antimicrobial dose appears to be as effective with fewer associated side effects, such as vaginal candidiasis, with a reduced capacity for development of antibiotic resistance.[61,62] Sub-antimicrobial dosing refers to dosing <50 mg/day as above this level may exceed the Minimal Inhibitory Concentration (MIC) of some bacteria, exerting an antibiotic effect via the 30S subunit of the bacterial ribosome.[58,63,64]

Adverse reactions of doxycycline include dose-related photosensitivity and pill oesophagitis.[65,66] These may be managed with patient counselling in regards to photoprotection and tablet ingestion with water and staying upright. Patients with pre-existing hiatus hernia may be at higher risk but not those with gastro-oesophageal reflux disease.[67] Cautious prescription of doxycycline is recommended in severe liver disease but it is preferred over minocycline in renal failure.[68] Doxycycline should be taken with food to augment absorption.

Assessment of therapeutic effect is recommended at 6-8 weeks.[69]As metallic ions can reduce GI absorption of tetracyclines, especially in the case of ferrous sulphate and minocycline, taking a history is important.[70]

### Minocycline

Minocycline may have a therapeutic advantage on account of its higher lipophilicity and subsequent penetration of the pilosebaceous unit. Minocycline is dosed at 50-100 mg once or twice daily, or sustained-action formula 1 mg/kg daily is prescribed for 4-12 weeks. The uncommon but more significant side effect profile must be weighed up when prescribing. Possible adverse effects include dyspigmentation of nailbeds, skin, teeth, bone, mucous membranes and sclera. This is mainly seen in long term therapy.[71,72] Benign intracranial hypertension is rare, but dizziness and vertigo may occur.[73] Although uncommon, drug hypersensitivity reactions and ANCA-positive vasculitis

have been reported, as well as autoimmune hepatitis and drug induced lupus.[68,71,72,74]

Tetracycline is less frequently used but can also be prescribed in a dose 250-500 mg twice daily for 4-12 weeks. Other reported tetracyclines for use in rosacea include oxytetracycline 250-500 mg daily and lymecycline 408 mg daily, but these are not readily available in Australia.

Tetracyclines as a class are pregnancy category D owing to foetal tooth discolouration after gestation >14 weeks and are excreted in low concentrations in breast milk. They are similarly avoided in children <9 years old to prevent yellow staining of teeth.[68]

## Alternate antibiotic therapies for rosacea

Alternate oral antibiotics are often used in patients who have difficulty tolerating tetracyclines due to side effects of gastrointestinal upset, candidiasis and photosensitivity.

These include macrolides such as erythromycin and less commonly azithromycin, clarithromycin and clindamycin. Sulfonamide drugs such as trimethoprim/sulfamethoxazole (Bactrim) have also been used[75,76] however are less commonly prescribed due to risk of severe adverse drug reactions.

### Macrolides

Like tetracyclines, the mechanism of action of macrolides relates to anti-inflammatory effects in addition to reduction of reaction oxygen species. Erythromycin, the most commonly prescribed macrolide for rosacea, inhibits pro-inflammatory cytokines such as IL-8 and decreases neutrophil oxidative bursts.[77] Erythromycin is commonly prescribed for pregnant women beyond the first trimester and can be used in breastfeeding. It is pregnancy category A. Azithromycin, which is pregnancy category B1, has fewer drug interactions than erythromycin and is less commonly prescribed. Despite this, it has proven efficacy in limited case studies with a dosing schedule of 500 mg/day for 2 weeks.[77,78]

## Isotretinoin

Isotretinoin may be considered as an important adjunct to systemic treatment of the inflammatory-subtypes of rosacea. Careful patient selection is required to optimize compliance with appropriate precautions, monitoring, surveillance, and prevention due to the risk of teratogenicity in premenopausal female patients of childbearing age.

Efficacy of isotretinoin (13-cis-retinoic acid) in the treatment of rosacea has been described since 1981.[78] Larger studies have demonstrated efficacy in treatment of papulopustular rosacea; in addition, there have been case reports of effective treatment of perioral granulomatous rosacea and the prefibrotic stage of sebaceous-type rhinophyma.[79,80] Ocular rosacea has also been treated effectively with isotretinoin with no reduction in visual acuity or serious complications (n=39).[81] Treatment with isotretinoin has also been effective in rosacea fulminans (pyoderma faciale) in combination with oral prednisolone.[82]

The mechanism of action of isotretinoin is possibly due to its ability to decrease the size of sebaceous glands, reduce sebum production, and inhibition of inflammation.[79,83] Isotretinoin has also been shown to reduce facial cutaneous blood flow by means of laser-Doppler at 10 weeks.[79]

Rademaker et al. demonstrated that very low-doses of isotretinoin (e.g. 10-20 mg once to five times a week, equivalent to 5 mg/day) has also shown to be effective for mild to moderate papulopustular rosacea (n=52).[84] In a recent randomised controlled trial (n=156), dosing of 0.25 mg/kg/day for a minimum of 4 months resulted in 57% of isotretinoin recipients reaching the primary endpoint of 90% reduction of the number of papules/pustules compared with baseline.[85] A large-scale randomised multicentre trial in 2010 (n=573) found that 24% of patients treated with isotretinoin 0.3 mg/kg/day achieved remission, compared with 13.6% of doxycycline-treated patients.[86] With a daily dose of 0.3 mg/kg for recalcitrant papulopustular rosacea, a minimum of 3-to-4 months duration of therapy is often required.

Given that symptoms often recur after ceasing isotretinoin therapy, continuous microdosing (CMI) may be considered in patients who prefer to avoid relapse upon discontinuation. In a case control study (n=12), patients were initially treated with isotretinoin 10-20 mg daily over 4 to 6 months. Oral isotretinoin was then reduced to CMI ranging from 0.03 mg to 0.17 mg/kg/day (mean 0.07 mg/kg/day). The efficacy of CMI was well-demonstrated by low mean post-treatment DLQI scores in the treatment group. Three patients were on CMI for longer than 30 months, and mean cumulative annual doses ranged from 11 to 62 mg/kg (mean 24.4 mg/kg).[87]

## Agents for flushing: clonidine, propranolol, carvedilol

Treatment of ET rosacea associated with severe flushing and persistent erythema is challenging. Treatment options historically have included beta-adrenergic blockers, alpha-adrenergic blockers e.g.,

clonidine, opiate antagonists (naloxone), serotonin antagonists (ondansetron) and endoscopic thoracic sympathectomy.[88]

Beta-adrenergic blockers (carvedilol, nadolol, propranolol) can suppress flushing reactions but are limited by side effects of bradycardia, bronchospasm and hypotension in a rosacea population who are normally normotensive. A case series was reported of refractory ET rosacea effectively treated with low dose carvedilol with a reduction in cheek temperature and visual analog score within 3 weeks of therapy.[89]

Alpha-adrenergic receptor agonists such as clonidine are another agent used to reduce flushing and malar hyperthermia as an off-label use for patients whose predominant feature is flushing. However topical alpha2 agonists are generally preferred being more targeted and associated with less risk of systemic side effects. Topical brimonidine can reduce erythema for a maximum of 12 hours via direct cutaneous vasoconstriction but has been linked with rebound erythema post treatment and is not generally effective against established telangiectasias.[90]

## Emerging non topical therapies

### Hydroxychloroquine

In a pilot study of 66 patients with papulopustular rosacea patients were randomised to receive either hydroxychloroquine 200 mg twice daily, doxycycline 100 mg daily or placebo. Blinded review at 8 weeks showed hydroxychloroquine was non-inferior in terms of quality-of-life measures but measures of erythema were inconclusive.[91] A pilot study of oral sarecycline, an oral tetracycline antibiotic approved for acne by the FDA for the treatment of papulopustular rosacea, showed the drug was effective, safe, and well-tolerated for treating papulopustular rosacea with superior efficacy compared to controls at 12 weeks.[92]

### Unpublished studies

A phase I trial of secukinumab was recently completed for papulopustular rosacea after research investigated the role of IL-17 in the pathogenesis of rosacea.[93] Subcutaneous injections of erenumab, a monoclonal antibody against calcitonin gene-related peptide receptor is currently recruiting to demonstrate effectiveness for ET rosacea and a placebo-controlled study of rifaximin, an antibiotic, is currently recruiting, although a similar trial was withdrawn in 2014.

To summarise, there are a variety of topical and oral treatments available for rosacea. Selection of treatment combinations is determined by the underlying phenotype of rosacea. Table 3 outlines current treatment options.

**Table 3.** *Treatment options for rosacea based on clinical features*

| Treatment Option | Papulopustular | Telangiectasia | Flushing | Phyma |
|---|---|---|---|---|
| **Topicals** | | | | |
| Metronidazole | ✓ | | | |
| Azelaic acid* | ✓ | | | |
| Ivermectin | ✓ | | | |
| Sodium sulfacetamide | ✓ | | | |
| Clindamycin* | ✓ | | | |
| Retinoids | ✓ | | | ✓ |
| Permethrin | ✓ | | | |
| Pimecrolimus | ✓ | | | |
| Dapsone | ✓ | | | |
| Brimonidine | | ✓ | ✓ | |
| Oxymetazoline | | ✓ | ✓ | |
| **Combined topicals** | | | | |
| Clindamycin 1% + benzoyl peroxide 5%* | ✓ | | | |
| **Oral therapy** | | | | |
| Doxycycline | ✓ | | | |
| Minocycline | ✓ | | | |
| Isotretinoin | ✓ | | | |
| Azithromycin | ✓ | | | ✓ |
| Trimethoprim | ✓ | | | |
| Sulfamethoxazole | ✓ | | | |
| Beta-adrenergic blockers (carvedilol, nadolol, propranolol) | | | ✓ | |
| **Alpha-adrenergic blockers** | | | ✓ | |
| **Energy based device**** | | ✓ | ✓ | ✓ |

**safe in pregnancy*

*** covered elsewhere in this edition*

## Rosacea management during pregnancy

Pregnancy poses a therapeutic dilemma given most of the recognised and effective treatments for rosacea including tetracycline antibiotics and many of the topical therapies are all contraindicated or relatively contraindicated during pregnancy.[94] Tetracyclines are associated with discolouration of the teeth and impaired bone growth, isotretinoin is associated with congenital anomalies, and metronidazole is not recommended before the second trimester.

Due to the above concerns, there is an incorrect assumption that rosacea cannot be managed effectively during pregnancy, leaving many women untreated until postpartum resulting in considerable physical, emotional and social implications. We believe with careful education regarding skin care, safe topical therapy and in some cases safe oral therapy it is possible to gain control of rosacea during pregnancy.

To our knowledge there are no specific guidelines or trials relating to the course of rosacea or management during pregnancy. In our experience rosacea can occur for the first time in pregnancy and certainly pre-existing rosacea can flare substantially during pregnancy and for some patients may continue whilst breastfeeding. There are case reports for rosacea fulminans during pregnancy.[95-97]

Given the lack of evidence we can only share our approach to treatment. For mild-to-moderate rosacea we commence treatment with topical therapy. Topical azelaic acid is safe in pregnancy, has anti-inflammatory properties and the added benefit of reducing post-inflammatory hyperpigmentation which can occur in patients with Fitzpatrick type 3 and above skin. About 4% of the drug is absorbed systemically when applied topically.[94,98] Topical dapsone, salicylic acid and benzoyl peroxide are category C medications and hence we avoid using these. Topical clindamycin is safe in pregnancy and can also be tried.[94,98]

For those non-responsive to topicals or with more severe disease oral therapies may need to be considered. Erythromycin is a macrolide and as mentioned previously is a category A medication. It crosses the placenta poorly; hence low concentrations are expected in foetal tissue. Erythromycin is generally considered safe during any stage of pregnancy when administered for a few weeks.[99] There is a risk of pyloric stenosis with erythromycin. Azithromycin (category B1) is an alternate option, but there is less available safety data than erythromycin.[94]Amoxicillin use in the first trimester is associated with a risk of cleft palate.[100] Cephalexin has not been associated with foetal defects in animal studies, with inadequate controlled data from human subjects.[101] Trimethoprim exposure in the first trimester results in double the risk of miscarriage.[102]

Due to the lack of extensive guidelines and information there is little to go with by way of understanding the safe duration of therapies or the effect of chronic use of antibiotics on the foetus. First trimester use is best avoided and oral therapy limited to 4-6 weeks is likely to be sensible.

The value of physical therapies such as safe chemical peels and light emitting diode blue and red light laser therapies during pregnancy has not been established but in our experience have been helpful.

Studies examining the use of glycolic acid peels in human pregnancy have not been conducted. Using topical glycolic acid during pregnancy should not be of concern, as only a minimal amount is expected to be absorbed systemically.[103]

A number of large studies have been published in which researchers examined the outcomes of women who had taken low-dose acetylsalicylic acid during pregnancy and there was no increase in the baseline risk of adverse events, such as major malformations, preterm birth, or low birth weight. No studies have been conducted in pregnancy on topical use of salicylic acid however, as such a relatively small proportion is absorbed through the skin, it is unlikely to pose any risk to a developing baby.[104]

Light emitting diode (LED) is considered safe in pregnancy. LED combined with photodynamic therapy has been demonstrated to be effective for rosacea,[105] however aminolevulinic acid is classified as pregnancy category C. There are recent case reports demonstrating that coupled blue and red diode therapy is effective for papulopustular rosacea.[106] The benefit of LED for rosacea in pregnancy requires more study but is an interesting option given the degree to which treatments are contraindicated in pregnancy.

## CONCLUSION

The goal of managing rosacea effectively is to focus on initial improvement as well as a planned commitment to long term management of flares and maintenance therapy. Management focuses on a phenotypic paradigm that is individually specific as patients may evolve from one subtype to another or have phenotypic features of differing subtypes at one time. A combination of topical, oral and energy-based treatments tailored to specific needs of the individual which vary in time leads to control of the condition. Quality patient education is vital to patient outcomes. The article overviews existing and emerging therapies and aims to provide current up-to-date information to enable effective acute and long-term management of rosacea.

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# For Patients Who Deal With Rosacea, Cutera Excel V+ Lasers Offer Excellent Results

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1. Chicago, IL, USA

Sponsor: **Cutera**

Bhatia AC. For Patients Who Deal With Rosacea, Cutera Excel V+ Lasers Offer Excellent Results. Opin Prog Cosmet Dermatol 2021;1(2):68-69.

## Background

Rosacea is a chronic facial skin disorder that usually presents with redness and/or flushing. Although rosacea symptoms typically come and go, they often become more persistent over time and can lead to facial swelling, pimples or pustules, and visible blood vessels. According to the National Rosacea Society, 450 million people worldwide are affected by rosacea, yet only a small number of those affected get treatment.[1] Cosmetic laser treatments can dramatically improve the redness and quality of the skin — restoring patients' sense of self-worth and attractiveness.

## Features and triggers

While rosacea has no cure and the cause is unknown, factors including genetics, an immune system response to a bacterium, Demodex, or cathelicidin may be contributing factors to rosacea.[2]

The features of rosacea are often categorized in four stages: pre-rosacea with symptoms of frequent flushing, stage 1 and stage 2 with increasing and more persistent erythema and skin sensitivity, followed by stage 3, which manifests in large inflammatory nodules, tissue hyperplasia and rhinophyma.[3]

Rosacea is often exacerbated by factors such as extreme temperature, emotional stress, physical exercise, certain foods and alcohol; thus, impacting the quality of life for affected individuals.[4] In surveys conducted by the National Rosacea Society, seventy-six percent of rosacea patients reported that the condition lowered their self-confidence and self-esteem and seventy-five percent of individuals said the disorder had adversely affected their professional interactions.[5,6]

## The treatment of rosacea

Rosacea is managed primarily with the aid of oral and topical therapies. However, laser treatments can offer an effective method for improving the appearance of the visible symptoms of rosacea, including redness and flushing, visible blood vessels, and in severe cases, pustules.

Cutera's Excel V+ laser is among the most advanced vascular lasers on the market. By delivering two clinically proven laser wavelengths, 532 nm and 1064 nm, Excel V+ can address more than 20 treatment indications. The versatility of Excel V+ is pivotal for a dermatology practice. It features a high-powered 532 nm laser, and a large 16 mm spot size which allows for faster treatments on the face. The Excel V+ also features the Dermastat handpiece, a small 2 mm spot size handpiece, that facilitates the tracing of small vessels and lesions, especially around the nose for very targeted treatments.

The Excel V+'s integrated contact cooling is one of the most powerful cooling systems in any cosmetic laser and provides pre-, parallel, and post bulk cooling to increase the comfort as well as the safety and effectiveness of the treatments. The sapphire tip cooling can be adjusted from 5-20 °C, depending on the indication being treated.

The 1064 nm laser is particularly effective in the treatment of deeper blood vessels and vascular concerns that are often present with severe cases of rosacea. Additionally, the 1064 nm wavelength can be used for Cutera's signature Laser Genesis procedure, as well as to treat veins in the legs, venous lakes, venous malformations, and port-wine stains. The 1064 nm laser is also capable of treating hemangiomas and facilitating the resolution of bruising, laser hair removal, active acne, and acne scarring.

Cutera's 1064 nm wavelength can also be found on the Xeo device, a multi-application platform that offers practices the ability to treat a range of indications with both laser and light-based modalities.

## My approach to rosacea

When treating severe rosacea, I rely on both the 532 and 1064 nm laser wavelengths of the Excel V+. My go-to settings for the Excel V+ for background erythema are 10 mm, 8-9 J/cm², 8-10 ms with a cooling of 5 °C. Depending on the severity of their conditions, patients typically require a series of 2-4 treatments. A transient violaceous hue of the blood vessels is a reliable endpoint after a treatment. With the efficient cooling, very little swelling is seen for most patients.

For patients presenting with early stages, or less severe cases, of rosacea, the 1064 nm Laser Genesis procedure can be utilized to target the microvasculature in the skin. It offers a safe, no downtime solution and can be performed on all skin types.

Excel V+ provides the necessary wavelengths and versatility to effectively treat rosacea. Along with topical and oral therapies for rosacea, lasers play a key role to aid in the rapid resolution of the visible signs and symptoms of rosacea. I often start patients on oral or topical therapies, recommend appropriate lifestyle modifications, and then offer lasers to help with visible signs of rosacea. More often than not, they are happy to learn about these treatments and to start them (figures 1-3).

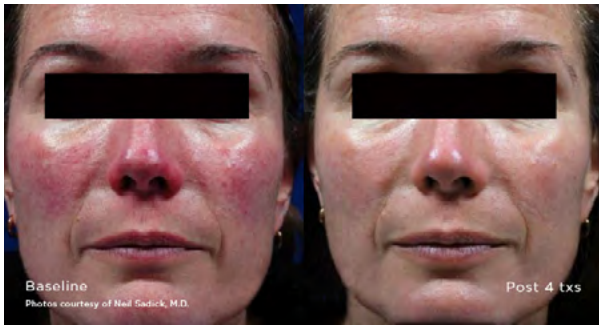


**Figure 1.**

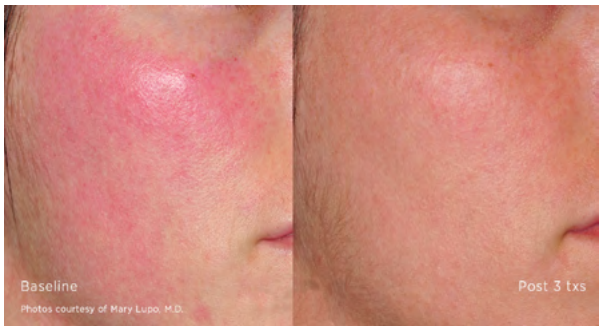


**Figure 2.**

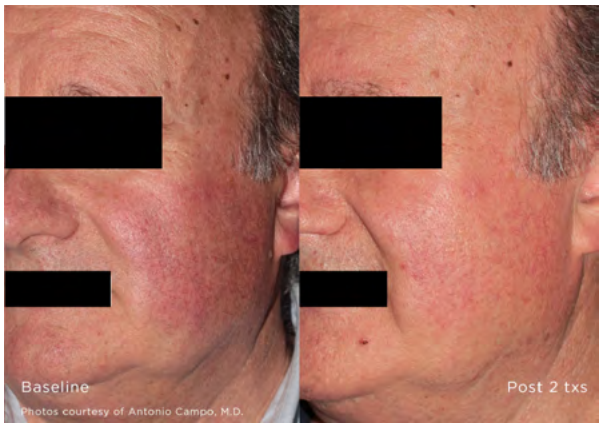


**Figure 3.**

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Stellar M22

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# A **Stellar Solution** for **Rosacea**

## With Stellar M22™ treatments, the sky is the limit

Internationally renowned as one of the most advanced, intelligent skincare innovations in the world, the Stellar M22™ is fully equipped with four leading technologies that give operators the ability to treat vascular lesions such as rosacea as well as 30 other skin conditions – all in the one modular platform.

### MultiSpot Nd:YAG

Stellar M22™ features a long-Pulse Multi-Spot™ Nd:YAG laser for precise treatment of vascular lesions such as rosacea and leg veins, on all skin types.

### Multiple Sequential Pulsing (MSP™)

MSP™ technology allows cooling between pulses, reducing risk of skin damage when treating rosacea. The series of sub-pulses enables deeper penetration and an overall longer pulse duration, which is crucial during treatment.

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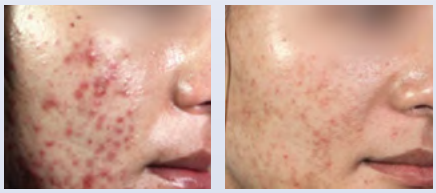
Deliver precise and comfortable treatments with three SapphireCool™ lightguides that are interchangeable in seconds and provide continuous contact cooling of the treatment area.

### Reproducible Results

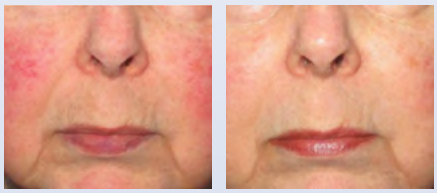
Stellar M22's unique algorithm for controlled non-sequential pulsing ensures precise, homogenous and safe energy delivery for reproducible results at every treatment.


Before After



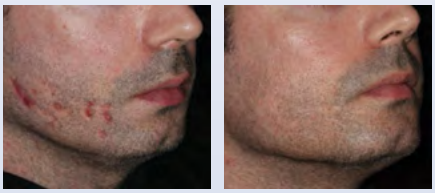
Acne treatment with IPL Courtesy of Li Yuanhong, MD

Before After



Rosacea treatment with IPL Courtesy of Gilly Munavalli, MD

Before After



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# A Stellar IPL for Rosacea

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Sponsor: **Lumenis**


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Ross EV. A Stellar IPL for Rosacea. Opin Prog Cosmet Dermatol 2021;1(2):71-72.

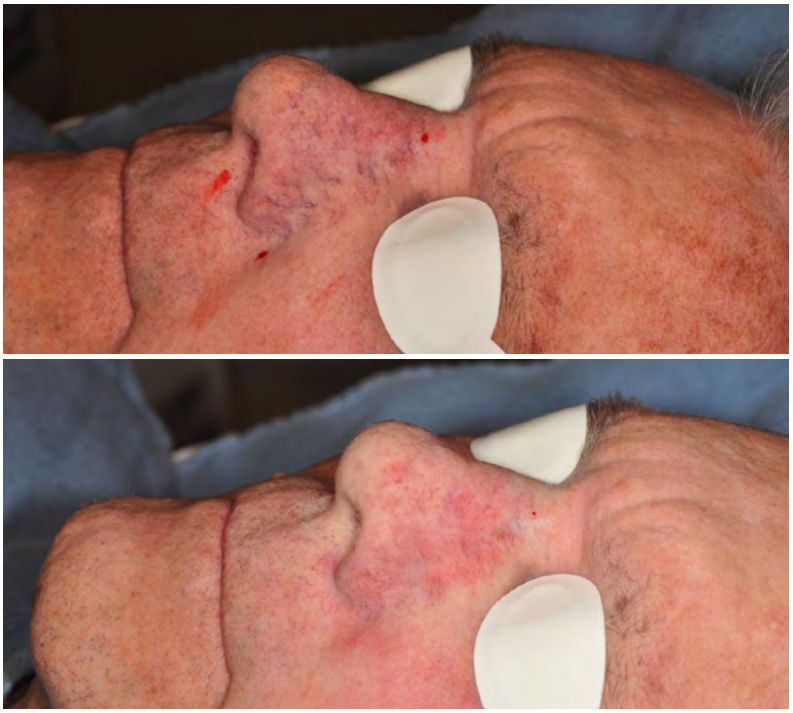
Rosacea is a vascular disorder associated with follicular inflammation. Telangiectasia are associated with the later phase of vascularization and result from a reduction in mechanical integrity of the upper dermal connective tissue, allowing a passive dilatation of capillaries. Inflammation and associated angiogenesis contribute to the telangiectasia. In the US, more than 16 million patients are affected by rosacea. Usually the diagnosis is straightforward, but one must consider alternative less common diagnoses associated with red skin and telangiectasia, such as CREST syndrome. Rosacea is now characterized by four subtypes defined as erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea.[1,2,3]

In a typical presentation, the first step in rosacea "rehabilitation" is application of topical medications, including such disparate compounds as vasoconstrictors and antibiotics. For any patient a customized approach is best and typically includes a combination of medical and light based interventions.

IPL has been found to be effective in treating rosacea. This light source has the advantage of quick vessel elimination without significant purpura or crusting (Figure 1). Scanning Doppler evaluation demonstrated a 30% decrease in blood flow after five IPL treatments. Short pulses appear to be most effective. A certain percentage of patients (20%) do not respond to the IPL and need to be treated with the PDL. Most patients need to return for retreatment once or twice a year. These observations support a role for IPL once inflammatory lesions have been suppressed.[4] A recent paper suggested the death of the Demodex occurs after IPL application. Although one paper suggested that Demodex death might exacerbate rosacea in the short term, long term IPL use has been associated with decreased Demodex counts.[5]

An optimal therapeutic approach to rosacea includes a combination of topical / oral medications and a vascular technology. There are pros and cons to the three major players, that is, intense pulsed light, frequency doubled Nd:YAG laser, and the pulsed dye laser. Why might IPL perform better than 532nm or 595nm is some cases? One potential advantage is the emission of multiple wavelengths, which are more likely to target a range of vessels sizes associated with rosacea. Larger spots also increase the ratio of dermal to epidermal damage by increasing the number of photons that penetrate deeper into the dermis, so that as a general rule larger spots are better. Other advantages of IPL include optimizing the filtering and pulse sequence for vessels versus pigment, as well enjoying a large spot. Another advantage of IPL is that devices such as the Stellar M22 are part of a multi-application platform. The operator can effortlessly proceed from one application to another, for example, if a rosacea patient is also affected by facial scaring, the non-ablative handpiece of the device can be deployed. Most modern IPLs offer a range spot sizes by changing the crystal tip. Within seconds, one can change from a larger to smaller crystal. With the Stellar M22 for lighter skinned patients, we apply the "notched" vascular filter (Figure 2) with the standard double pulse sequence with intense cooling. The filter exploits both 540nm and 940nm HgB absorption peaks, rendering robust vascular heating. For the broad areas the face, typically the 15x35 millimeter crystal. Then, for the nasal creases we use the 8x15 millimeter spot. For very small vessels or angiomas, the round 6mm spot is applied with a somewhat higher fluence. For somewhat darker patients, the 560nm filter is applied with a longer triple pulse sequence. The light spectrum is right shifted versus the vascular filter and favors a greater ratio of vessel over epidermal heating. If one examines Figure 3, the inflammatory and non-inflammatory portions of the disease are readily identified. Optimally, the condition would be better controlled medically before embarking on visible light therapy.

**Figure 1.** *Before and after telangiectaia*



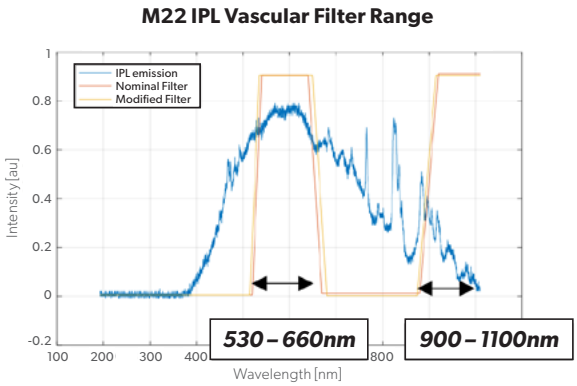



**Figure 2.** *Emission spectrum of M22 vascular filter*

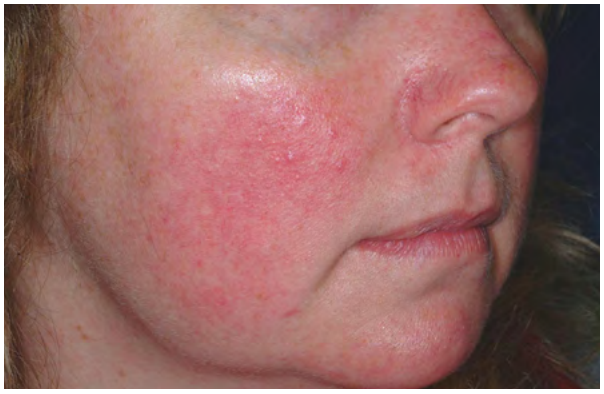


**Figure 3.** *Facial rosacea showing papules and telangiectasia*

The Stellar M22 features an easy to use graphical user interface (GUI), nine different filters, and 3 crystal sizes. The operator can apply presets or create customized pulse sequences as his/her experience increases. We advise our patients to plan on having at least 2 treatments a year to maximize control of their rosacea. A treatment session over the entire face requires only about 10 minutes. We usually apply a 5% lidocaine cream 45 minutes prior to treatment and apply ice pack postoperatively. Erythema usually recurs within 6 months of light based treatment. In short, the Stellar M22 represents a major weapon in rosacea control. The reduction in redness and flushing is a great relief for these long suffering patients.

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