Rosacea

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- December 2023

To the CHI Original Rosacea Clinical Guidance- Issued December 2019

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

AARS	American Acne and Rosacea Society
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
FRR	Future Research Recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorite de Sante
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IPL	Intense Pulsed Light
IVM	Ivermectin
MTZ	Metronidazole
Nd YAG	Neodymium-doped Yttrium Aluminum Garnet
NRS	National Rosacea Society
PDL	Pulsed Dye Laser
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of Life
ROSCO	ROSsacea COnsensus
SFDA	Saudi Food and Drug Authority
UV	Ultraviolet

Executive Summary

Rosacea is a chronic disorder that predominantly affects the central areas of the face (nose, forehead, cheeks, and chin). It is characterized by frequent flushing, persistent erythema and telangiectasia, and episodes of inflammation during which swelling, papules and pustules are evident. These symptoms are frequently accompanied by periocular inflammation and are sometimes associated with the later development of cutaneous swellings known as phymas[1].

Rosacea is a common condition characterized by symptoms of facial flushing and a spectrum of clinical signs, including erythema, telangiectasia, coarseness of skin, and an inflammatory papulopustular eruption resembling acne[2].

Based on specific clinical signs and symptoms, an expert committee assembled by the National Rosacea Society (NRS) explicitly defined and classified rosacea into the following subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular[2].

The erythematotelengiectatic subtype, which presents with persistent erythema with intermittent flushing of nose and cheeks, is usually the first clinical manifestation of rosacea. In the papulopustular form, patients present with eruptions of papules and pustules on the affected area on the face. This subtype is sometimes called “adult acne” due to the similarity in the appearance of lesions. Notably, rosacea lacks comedones, helping to differentiate it from true acne[3].

In 2016, the global rosacea consensus panel recommended a new classification: at least one diagnostic or two major phenotypes are required for the diagnosis of rosacea. A diagnosis of rosacea may be considered in the presence of one of the following diagnostic cutaneous signs[2]:

- Fixed centrofacial erythema in a characteristic 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).

A diagnosis of rosacea may be considered in the presence of one of the following diagnostic cutaneous signs: Fixed centrofacial erythema in a characteristic 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)[2].

Major phenotypes

Without a diagnostic phenotype, the presence of two or more of the following major features may be considered diagnostic: Papules and pustules, Flushing: Frequent and typically prolonged, Telangiectasia: Predominantly centrofacial in phenotypes I-IV, rarely seen in darker phenotypes, ocular manifestations[2].

Secondary phenotypes

The following secondary signs and symptoms may appear with one or more diagnostic or major phenotypes: Burning and stinging. Edema: Facial edema. Dry appearance: Central facial skin may be rough and scaly[2].

Ocular rosacea: Major features of ocular rosacea are as follows: Lid margin telangiectasia. Interpalpebral conjunctival injection. Spade-shaped infiltrates in the cornea. Scleritis and sclerokeratitis[2].

Secondary features of ocular rosacea are as follows: "Honey crust" and collarette accumulation at the base of the lashes. Irregularity of the lid margin. Evaporative tear dysfunction (rapid tear breakup time)[2]

A rosacea like syndrome (including perioral dermatitis) can result from the indiscriminate use of potent corticosteroids on the face. Several aggravating factors may be recognized. Excess wind and UV light (weathering) exposure may accelerate the disease process[2].

Rosacea keratitis and keratoconjunctivitis sicca are recognized complications. Rosacea fulminans is a rare complication. Scarring generally does not occur[2].

Lymphoedema is a relatively rare complication of rosacea that can develop over the face and ears. In time, this may develop into a coarsening of the features known as leonine facies. A characteristic pattern of lymphoedema of the upper half of the face developing as a complication of chronic rosacea has been termed chronic upper facial erythematous oedema or Morbihan disease. The orbital skin is often affected, resulting in severe eyelid swelling and sometimes ectropion. Malignancy, most frequently basal cell carcinoma, may be seen as a complication of rhinophyma. This can be difficult to diagnose owing to the phymatous distortion of normal skin contours, so it is important to be alert to this risk[1].

Before the initiation of therapy, the triggering factors that exacerbate the patient's rosacea should be identified and avoided if possible. These factors may be unique to each individual patient. Common triggering factors include hot or cold temperatures, wind, hot drinks, caffeine, exercise, spicy food, alcohol, emotions, topical products that irritate the skin and decrease the barrier, or medications that cause flushing. Some patients find that regular facial massage reduces lymphedema. Rosacea fulminans is treated with moderately high doses of prednisolone (30-60 mg/d) followed by oral isotretinoin.[2]

1. The use of daily broad-spectrum sunscreen is recommended for all patients with rosacea.
2. Laser: Nonablative laser is effective against rosacea by remodeling the dermal connective tissue and improving the epidermal barrier.
3. Surgical care: Permanent telangiectasia may be treated by electrosurgery or the 585-nm pulse dye laser.
4. Diet: Dietary modulation should aim at avoidance of triggers.

The global prevalence of rosacea is based on published data and found that 5·46% of the adult population is affected. However, the prevalence of rosacea depended on the diagnostic method, with higher estimates in questionnaire studies of rosacea symptoms and lower estimates in health registries with International Classification of Diseases codes[4].

The exact prevalence of rosacea in the Middle East is not known. A study conducted in Saudi Arabia by Al-Hoqail looking for common conditions in dermatology found a 1.59% prevalence of rosacea in Saudi Arabia[5].

CHI issued Rosacea guidelines in Dec 2019 updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI Rosacea clinical guidance and seeks to offer guidance for the effective management of Rosacea. It provides an **update on the Rosacea Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the updated guidelines added to the report such as** 2020 Recommendations for rosacea diagnosis, classification, and management: update from the global Rosacea Consensus 2019 panel[4] and **the new guidelines added to the report** such as the **British Association of Dermatologists** (BAD) guidelines for the management of people with rosacea (**2021**), the **German Dermatological Society** S2k guideline on rosacea (**2022**), the guidelines for the diagnosis and treatment of rosacea in **China** (**2021**), and the **Spanish** consensus document on the treatment algorithm for rosacea (**2019**).

After carefully examining clinical guidelines and reviewing the SFDA drug list, there are new SFDA registered drugs to include in the CHI formulary: Carvedilol, Propranolol while removing GLYCERIN, SODIUM CARBOXYMETHYLCELLULOSE, as it is no longer registered on the SFDA Drug List of November 2023. There has been a new drug that received FDA approval, Epsolay, however it is not yet registered by the SFDA.

There have been no changes and updates made to the previously listed drugs in terms of drug information and prescribing edits since December 2019.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Rosacea therapeutic management.

Below is a table summarizing the major changes based on the different Rosacea guidelines used to issue this report:

Table 1. General Recommendations for the Management of Rosacea

Management of Rosacea		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
<u>Topical therapies</u> 1. Offer either ivermectin, metronidazole or azelaic acid as first-line topical treatment options to people with papulopustular rosacea. Discuss the potential for irritancy of different products and formulations prior to prescribing the topical agent. 2. Consider topical minocycline foam in people with papulopustular rosacea. 3. Consider topical brimonidine in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment. 4. Consider topical oxymetazoline in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may	(↑↑) (↑) (↑) (↑)	British Association of Dermatologists guidelines, 2021

flare after discontinuation of treatment.		
<u>Systemic therapies</u> • Offer an oral antibiotic as a first-line treatment option for more severe papulopustular rosacea. Options (in alphabetical order) include azithromycin, clarithromycin, doxycycline 40 mg (modified release) daily, doxycycline 100 mg daily, erythromycin, lymecycline and oxytetracycline. These antibiotics (especially tetracyclines) are considered safe and have been prescribed for rosacea for decades. There is insufficient evidence to establish the superiority of one over another, especially in the absence of head-to-head trials or a network meta-analysis.	(↑↑)	British Association of Dermatologists guidelines, 2021
Avoid minocycline in people with rosacea due to potential side-effects unless there are no other treatment options.	(↑↑)	British Association of Dermatologists guidelines, 2021
Consider intermittent courses of low-dose isotretinoin (e.g., 0.25 mg kg–1) in people with persistent and severe rosacea. Discuss the potential side-effects and teratogenicity.	(↑)	British Association of Dermatologists guidelines, 2021
Consider oral propranolol in people with rosacea where the main presenting feature is transient facial erythema (flushing).	(↑)	British Association of Dermatologists guidelines, 2021
Offer over-the-counter ocular lubricants or liposomal sprays to alleviate symptoms in people with ocular rosacea, ensuring preservative-free preparations are used if using > 6 times daily. Increasing humidity using	(↑↑)	British Association of Dermatologists guidelines, 2021

humidifiers can help to reduce tear evaporation.		
Refer people with ocular rosacea to an ophthalmologist if they are (i) experiencing eye discomfort, sticky eye discharge persisting for > 12 months despite frequent (> 6 times daily) topical lubricant use and adequate lid hygiene; or (ii) experiencing symptoms such as reduced vision, pain on eye movement and pain that keeps the patient awake at night.	(↑↑)	British Association of Dermatologists guidelines, 2021
<u>Phymatous changes</u> Oral isotretinoin capsules are the recommended first-line treatment option. For patients with papules and pustules, oral clarithromycin, and other antimicrobial drugs (such as topical metronidazole, azelaic acid, ivermectin cream, clindamycin, and erythromycin) can be taken simultaneously with other topical preparations. The treatment options for telangiectasia are PDL therapy, long-pulse width Nd YAG laser therapy, IPL therapy, or surgical scratching. CO2 and erbium lasers or surgical ablation and resection are used to treat nodular hypertrophy.	Not graded	Guidelines for the Diagnosis and Treatment of Rosacea in China, 2021
<u>General measures</u> • It is recommended to avoid individual provocation factors (trigger factors) as far as these can be recognized based on disease progression. <u>UV protection</u> • It is recommended to protect affected areas (such as skin or eyes) from UV exposure, on the	(↑↑)	S2K guideline, Rosacea. *JDDG - Journal of the German Society of Dermatology*, 2022

one hand by avoiding direct sunlight and on the other hand by wearing hats or sunglasses as well as sunscreen. Topical treatment • It is recommended to choose the most appropriate active substance, concentration, and base for the individual patient according to the phenotypic characteristics of the rosacea, acuity, and skin type. • For treatment-refractory and severe forms of papulopustular rosacea it is recommended to combine topical treatment with systemic treatment.		
Ocular rosacea Treatment 1. Eyelid margin hygiene is recommended as a general practice. 2. *Ciclosporin eye drops* as well as azithromycin are suggested for the topical treatment of inflammation on the ocular surface (off label). Ivermectin or metronidazole (skin cream) is suggested for topical application on the eyelids (off label). 3. *Doxycycline* or *Azithromycin* as well as other macrolide antibiotics is suggested for systemic treatment (off label). 4. Systemic treatment with *ivermectin*, with or without *metronidazole* and *omega-3 fatty acids*, may be considered for ocular rosacea (off label).	(↑↑) (↑) (↑) (0) (0)	S2K guideline, Rosacea. *JDDG - Journal of the German Society of Dermatology*, 2022

5. Ocular Rosacea's clinical changes are dominated by Meibomian gland dysfunction (MGD) with various degrees of inflammation on the surface of the eye. Intense Pulsed Light treatment may be considered for ocular rosacea to treat dry eye disease (DED) symptoms and signs by decreasing symptoms due to MGD, tear film abnormality, and tear inflammatory markers.		
<u>Cleansing</u> • Gentle cleansing is recommended (tepid water, synthetic detergents adapted to the pH of healthy skin, patting the skin dry). • It is recommended to avoid irritation when cleansing, such as scrubbing, peelings, substances that promote blood circulation, or adstringents. <u>Skin care</u> • Light/hydrophilic skin care preparations are recommended for patients with rosacea. • Cosmetics with active ingredients to improve complaints in rosacea are suggested. • It is recommended to avoid irritating cosmetics and those promoting blood circulation. <u>Sunscreen</u> • Daily use of a broad-spectrum sunscreen with both UV-A and UV-B protection is recommended.	(↑↑) (↑↑) (↑↑) (↑) (↑↑) (↑↑)	German guidelines - S2k guideline: Rosacea 2022

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **the clinical and therapeutic management of rosacea.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Rosacea report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the December 2019 CHI Rosacea Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
Section 1.1 **Canadian** Clinical Practice Guidelines for Rosacea (**2016**)	N/A*
Section 1.2 Rosacea: Diagnosis and Treatment. **American Academy of Family Physicians** (**2015**)	N/A
Section 1.3 Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments (Br J Dermatol., **2019**)	N/A
Section 1.4 Rosacea treatment update: recommendations from the global Rosacea Consensus (**ROSCO**) panel (**2017**)	Section 1.1.1 Recommendations for rosacea diagnosis, classification, and management: update from the global Rosacea Consensus (**ROSCO**) **2019** panel

*****: *No updated versions available*

1.1.1 Recommendations for Rosacea Diagnosis, Classification, and Management: Update from the Global Rosacea Consensus (2019)

Please refer to **Section 1.4** of CHI Rosacea original clinical guidance.

The global ROSacea COnsensus (ROSCO) project comprises an international expert panel with dermatologists and ophthalmologists from Africa, Asia, Europe, North America, and South America. The 2017 ROSCO consensus recommended

transitioning from a subtype to a phenotype approach for rosacea diagnosis, classification, and management, which aligns with those of the NRS and American Acne and Rosacea Society (AARS). Delphi statements on which the panel achieved consensus of ≥ 75% voting 'Agree' or 'Strongly agree' are presented[6].

CUTANEOUS ROSACEA

Diagnosis, classification, and assessment

To aid diagnosis and assessment of cutaneous rosacea, feature descriptions (table 3) and considerations for assessing severity of minor features (table 4) are provided, which build on similar considerations for diagnostic and major features in the ROSCO 2017 recommendations.

Table 3. Description of Cutaneous Rosacea Features. Adapted from the ROSCO 2019 Guidelines.

Cutaneous rosacea features	Description
Diagnostic features	
Phymatous changes	Facial skin thickening due to fibrosis and/or sebaceous glandular hyperplasia. Most commonly affects the nose, where it can impart a bulbous appearance (n=19/20)
Persistent erythema	Background ongoing centrofacial redness. May periodically intensify in response to variable triggers. In darker skin phototypes, erythema may be difficult to detect visually (n=19/20)
Major features	
Flushing/transient erythema	Temporary increase in centrofacial redness, which may include sensations of warmth, heat, burning and/or pain (n=20/20)
Papules and pustules	Red papules and pustules, usually in the centrofacial area. Some may be larger and deeper (n=18/20)
Telangiectasis	Visible vessels in the centrofacial region but not only in the alar area (n=19/20)
Minor features	
Burning sensation of the skin	An uncomfortable or painful feeling of heat, typically in the centrofacial region (n=19/20)

Stinging sensation of the skin	An uncomfortable or painful sharp, pricking sensation, typically in the centrofacial region(n=19/20)
Dry sensation of the skin	Skin that feels rough. May be tight, scaly and/or itchy (n=19/20)
Edema	Localized facial swelling. Can be soft or firm (nonpitting) and may be self-limited induration or persistent (n=20/20)

Table 4. Considerations for Severity Assessment of Minor Cutaneous Rosacea Features. Adapted from the ROSCO 2019 Guidelines.

Cutaneous rosacea features	Considerations when assessing severity
Burning sensation of the skin	Duration; frequency; intensity; extent (areas involved); associations with flushing; triggers; and impact on daily life (n=19/19)
Stinging sensation of the skin	Duration; frequency; intensity; extent (areas involved); triggers; characteristic of the sensation; and impact on daily life (n=19/19)
Dry sensation of the skin	Duration; frequency; intensity; extent (areas involved); pruritus; roughness; scale; tightness; peeling; how often moisturizers need to be applied; and impact on daily life(n=20/20)
Edema	Duration; frequency; degree of swelling (depth, pitting and distortion); extent (areas involved); daily fluctuation; and impact on daily life (n=19/19)

Treatment

- **Topical alpha-adrenergic modulating agents and oral beta blockers** have been **removed**, as there is limited evidence to support their use **for treatment of flushing/transient erythema** (n = 16/17 and n = 17/18, respectively). However, clinical experience suggests that these agents could be considered in certain situations.
- **Topical alpha-adrenergic modulating agents** (n = 20/20), **intense pulsed light** (IPL; n = 15/ 15) and **vascular lasers** (e.g., pulsed-dye laser and 532-nm potassium titanyl phosphate laser; n = 18/18) have been **added** as treatment options for **persistent centrofacial erythema**. Use of IPL and vascular lasers in darker skin phototypes requires consideration by a healthcare provider with experience in this situation (n = 16/18), as it can result in dyspigmentation.

- **Combination treatment could benefit some patients with more severe rosacea** (n = 20/20) and those presenting with multiple rosacea features (n = 20/21). • The benefits of combining treatments in rosacea include helping achieve skin clear of rosacea (n = 19/20); helping some patients achieve treatment goals more quickly (n = 19/20); maximizing remission periods (n = 19/20); and minimizing burden of disease (n = 19/20).
- While the availability of new evidence for combining treatment in patients with multiple rosacea features can help to improve patient outcomes (n = 21/21), there remains an ongoing need for more studies to support combination treatment use in rosacea (n = 21/21).

Monitoring

- Rosacea is a chronic disease that requires long-term management (n = 21/21) and, as such, requires ongoing dialogue between patient and physician.
- When monitoring treatment satisfaction, the highest priority factors for discussion during consultations are tolerability (n = 21/21), cost (n = 20/21) and primary efficacy (n = 19/21)
- To maximize treatment adherence, the highest priority factors for discussion during consultations are expectations of treatment duration (n = 21/21); time to onset of efficacy (n = 19/21); additional requirements (e.g. general skincare, trigger avoidance, camouflage) (n = 17/21); need for maintenance therapy (n = 17/21); chances of achieving clear skin (n = 17/21); and potential for side-effects (n = 17/21).

OCULAR ROSACEA

Table 5. Description of Ocular Rosacea Features. Adapted from the ROSCO 2019 Guidelines.

Ocular rosacea features	Description
Lid margin telangiectasia	Visible vessels around the eyelid margins. May be difficult to detect visually in darker skin phototypes
Blepharitis	Inflammation of the eyelid margin, most commonly arising from Meibomian gland dysfunction
Keratitis	Inflammation of the cornea that can lead to defects and, in the most severe cases, vision loss
Conjunctivitis	Inflammation of the mucous membranes lining the inner surface of the eyelids and bulbar conjunctiva.

	Typically associated with injection or vascular congestion and conjunctival oedema
Anterior uveitis	Inflammation of the iris and/or ciliary body

- Optimal diagnosis of ocular rosacea (n = 21/21) and description of its features (n = 20/21) remain unmet needs.
- The following ocular rosacea features require referral by a dermatologist to an ophthalmologist for treatment: blepharokeratoconjunctivitis (n = 20/21); sclerokeratitis (n = 20/21); anterior uveitis (n = 19/21); and blepharoconjunctivitis (n = 16/21).
- Systematic, evidence-based guidelines for ocular rosacea are still required (n = 16/16)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Rosacea report, along with their recommendations.

Table 6. List of Additional Guidelines

Additional Guidelines
Section 1.2.1. British Association of Dermatologists (BAD) Guidelines for the Management of People with Rosacea (2021)[1]
Section 1.2.2. German Dermatological Society S2k Guideline: Rosacea (2022)[7]
Section 1.2.3. Guidelines for the Diagnosis and Treatment of Rosacea in China (2021)[8]
Section 1.2.4. Spanish Consensus Document on the Treatment Algorithm for Rosacea (2019)[9]

1.2.1 British Association of Dermatologists (BAD) Guidelines for the Management of People with Rosacea (2021)

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of rosacea. The document aims to: (i) offer an appraisal of all relevant literature up to February 2020 focusing on any key developments; (ii) address important, practical clinical questions relating to the primary guideline objective; and (iii) provide guideline recommendations and, if appropriate, research recommendations. The BAD guideline was developed using the BAD's recommended methodology, with reference to the Appraisal of

Guidelines Research and Evaluation (AGREE II) instrument and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[1].

Table 7. Strengths of Recommendations

Strength	Wording	Symbols	Definition
Strong recommendation for the use of an intervention	'Offer' (or similar, e.g., 'use', 'provide', 'take', 'investigate', etc.)	↑↑	Benefits of the intervention outweigh the risks; most patients would choose the intervention, while only a small proportion would not; for clinicians, most of their patients would receive the intervention; for policy makers, it would be a useful performance indicator
Weak recommendation for the use of an intervention	'Consider'	↑	Risks and benefits of the intervention are finely balanced; most patients would choose the intervention, but many would not; clinicians would need to consider the pros and cons for the patient in the context of the evidence; for policy makers it would be a poor performance indicator where variability in practice is expected
No recommendation θInsufficient evidence to support any recommendation Strong recommendation against the use	'Do not offer'	θ ↓↓	Insufficient evidence to support any recommendation Strong recommendation against the use of an intervention 'Do not offer' ↓↓ Risks of the intervention outweigh the benefits; most patients would not choose the intervention, while only a small proportion would; for

of an intervention			clinicians, most of their patients would not receive the intervention

General recommendations

- Advise people with rosacea to limit exposure to known aggravating factors such as alcohol, sun exposure, hot drinks, and spicy food.
- Provide a patient information leaflet to people with rosacea.
- When characterizing the clinical subtypes and symptoms of rosacea, classify the patient according to the phenotypes identified by Gallo et al. This approach encompasses the objective clinical signs and the subjective symptoms experienced by the patient with rosacea. Diagnostic phenotypes include characteristic fixed centrofacial erythema or phymatous changes. Other features include flushing, papules or pustules, telangiectasia, ocular changes, burning or stinging sensations, oedema, and dryness.
- Consider the older classification system for rosacea, which was based on clinical signs: erythematotelangiectatic, papulopustular, phymatous or ocular. Characterize the clinical subtypes and symptoms of rosacea affecting the person according to these clinical signs.
- Whenever possible, avoid long-term use of oral antibiotics in people with rosacea (i.e., antibiotic stewardship). The optimal duration of antibiotic therapy is not known. In acne, a lack of response after 2–3 months of antibiotic therapy is usually regarded as treatment failure, and a similar duration to establish benefit may be appropriate in rosacea. When antibiotics are working, the pros and cons of longer-term treatment need to be evaluated carefully.
- Advise that some people with rosacea find it beneficial to wash their skin with emollients, moisturize regularly and use appropriate sun protection. Soaps and washing products that contain detergent are irritant in some people and should be avoided if they worsen the symptoms.
- Consider skin camouflage in people with rosacea ‘whose main clinical feature is’ OR who are ‘presenting with’ intractable erythema.
- Consider the need for psychological support or psychiatric interventions in people with rosacea who experience anxiety or depression. Initial assessment in primary care is often appropriate.

Topical therapies

- (↑↑): Offer either **ivermectin**, **metronidazole** or **azelaic acid** as first-line topical treatment options to people with papulopustular rosacea. Discuss the potential for irritancy of different products and formulations prior to prescribing the topical agent.
- (↑): Consider topical **minocycline** foam in people with papulopustular rosacea.
- (↑): Consider topical **brimonidine** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment.
- (↑): Consider topical **oxymetazoline** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment.

Systemic therapies

- (↑↑) Offer an oral antibiotic as a first-line treatment option for more severe papulopustular rosacea. Options (in alphabetical order) include **azithromycin**, **clarithromycin**, **doxycycline 40 mg** (modified release) daily, **doxycycline 100 mg** daily, **erythromycin**, **lymecycline** and **oxytetracycline**. These antibiotics (especially tetracyclines) are considered safe and have been prescribed for rosacea for decades. There is insufficient evidence to establish the superiority of one over another, especially in the absence of head-to-head trials or a network meta-analysis. Currently, only the modified-release formulation of doxycycline is licensed specifically for papulopustular rosacea in the UK.
- (↑↑) Avoid minocycline in people with rosacea due to potential side-effects unless there are no other treatment options.
- (↑) Consider intermittent courses of low-dose **isotretinoin** (e.g., 0.25 mg kg–1) in people with persistent and severe rosacea. Discuss the potential side-effects and teratogenicity.
- (↑) Consider **oral propranolol** in people with rosacea where the main presenting feature is transient facial erythema (flushing).

Procedural therapies

- (↑) Consider pulsed dye laser, neodymium-doped yttrium aluminum garnet (Nd:YAG) laser or intense pulsed light in people with rosacea where the main presenting feature is persistent facial erythema. An appropriately qualified laser practitioner should be consulted to ensure safe and high-quality practice.

- (↑) Consider nasal debulking by laser ablation or surgical intervention (dependent on local expertise) in people with significant rhinophyma.

Ocular therapies

- (↑↑) Advise people with ocular rosacea to minimize exposure to aggravating factors such as air conditioning, excessive central heating, smoky atmospheres, and periocular cosmetics.
- (↑↑) Identify and modify/eliminate systemic medications that could be triggering eye dryness in people with ocular rosacea (e.g., antidepressants and anxiolytics).
- (↑↑) Offer warm compresses using proprietary lid-warming devices and lid hygiene with homemade bicarbonate solution or commercially available lid wipes.
- (↑↑) Offer over-the-counter **ocular lubricants or liposomal sprays** to alleviate symptoms in people with ocular rosacea, ensuring preservative-free preparations are used if using > 6 times daily. Increasing humidity using humidifiers can help to reduce tear evaporation.
- (↑↑) Refer people with ocular rosacea to an ophthalmologist if they are (i) experiencing eye discomfort, sticky eye discharge persisting for > 12 months despite frequent (> 6 times daily) topical lubricant use and adequate lid hygiene; or (ii) experiencing symptoms such as reduced vision, pain on eye movement and pain that keeps the patient awake at night.

Summary of future research recommendations

The following list outlines future research recommendations (FRRs):

- FRR1 A prospective randomized controlled trial (RCT) investigating the effect of topical ivermectin on ocular rosacea.
- FRR2 A prospective RCT investigating various interventions (topical/systemic/procedural) for transient erythema (flushing).
- FRR3 A study investigating the psychological impact of rhinophyma, the effect of treatment and the optimal choice of surgical or laser treatments.
- FRR4 A study investigating other acaricidal drugs currently used in veterinary practice, such as **moxidectin** and **afoxolaner** against Demodex.
- FRR5 A cost-effectiveness analysis of treatments for people with rosacea within a UK setting.

- FRR6 Investigations of the aetiology, pathophysiology and psychological issues of rosacea, and treatment of the sensory symptoms of rosacea, sometimes referred to as neurogenic rosacea.

1.2.2 German Dermatological Society S2k Guideline: Rosacea (2022)

This updated and upgraded S2k guideline deals with the diagnosis and treatment of rosacea, which is a common, chronic inflammatory skin disease mostly affecting the face[7].

Table 8. S2k Guideline Strengths of Recommendation: Wording, Symbolism, and Interpretation

Strength of Recommendation	Wording	Symbols	Definition
Strong recommendation in favor of a procedure	"is recommended"	↑↑	In our opinion, all or nearly all informed people would decide in favor of this procedure. Clinicians need to spend less time with the patient when deciding on this procedure. In most clinical situations, this procedure can be considered a general recommendation.
Weak recommendation in favor of a procedure	"is suggested"	↑	In our opinion, most informed people would decide in favor of this procedure, but a substantial minority would not. Clinicians and other health professionals need to take more time with the patient to make sure that choosing this procedure with its possible consequences reflects the individual patient's values and preferences. Decision procedures in the health care system require in-depth discussion and inclusion of many persons involved in the process.

No recommendation regarding a procedure	"may be considered"	0	At this point in time, no recommendation for or against a certain procedure can be given due to certain circumstances – for example lack of evidence, unclear or unfavorable benefit-risk balance, etc.)
Recommendation against a procedure	"is not recommended"	↓	In our opinion, all or nearly all informed people would decide against this procedure.

General measures

- (↑↑) It is recommended to avoid individual provocation factors (trigger factors) as far as these can be recognized based on disease progression.

<u>UV protection</u>

- (↑↑) It is recommended to protect affected areas (such as skin or eyes) from UV exposure, on the one hand by avoiding direct sunlight and on the other hand by wearing hats or sunglasses as well as sunscreen.

<u>Food</u>

- (↑↑) Avoidance of food leading to vasodilation (such as alcohol, spicy food, very hot food, or beverages) is recommended.

Topical treatment

- (↑↑) It is recommended to choose the most appropriate active substance, concentration, and base for the individual patient according to the phenotypic characteristics of the rosacea, acuity, and skin type.
- (↑↑) For treatment-refractory and severe forms of papulopustular rosacea it is recommended to combine topical treatment with systemic treatment.
- (↑↑) The vasoconstrictor **brimonidine** (0.33 % gel) is recommended for a purely symptomatic topical treatment of rosacea with persistent centrofacial erythema (erythematous rosacea).
- (↑) The vasoconstrictor **oxymetazoline** (1 % cream) is suggested for a purely symptomatic topical treatment of rosacea with persistent centrofacial erythema (erythematous rosacea) (off label).
- (↑↑) **Metronidazole** is recommended for topical treatment of rosacea.
- (↑↑) **Azelaic acid** is recommended for the topical treatment of rosacea.

- (↑↑) **Ivermectin** is recommended for the topical treatment of rosacea.

Patient information before starting topical rosacea treatment:

- Method of use (once or twice a day, always after removal of decorative cosmetics)
- Increased sensitivity of facial skin in most rosacea patients (higher rates of hypersensitivity reactions, irritation)
- Duration of treatment (usually many weeks or months)
- Therapeutic goal (absence of symptoms)
- Chronicity of the disease with potential long-term treatment or proactive subsequent treatment
- Known trigger factors such as UV radiation, heat, alcohol, spicy food)
- Various phenotypes of the disease and the possible transition into other phenotypes (such as the phyma stage)

Systemic treatment

- (↑↑) Systemic treatment is recommended for treatment-refractory and severe forms of papulopustular rosacea.
- (↑↑) Low-dose **doxycycline** is recommended as the systemic treatment of choice.
- (↑) Low-dose **isotretinoin** (0.1–0.3 mg/ kg body weight [BW] is suggested as a systemic treatment for rosacea (off label)
- (0) **Carvedilol** may be considered for systemic treatment of persistent erythema and flushing in rosacea (off label).

Dermocosmetics

Cleansing

- (↑↑) Gentle cleansing is recommended (tepid water, synthetic detergents adapted to the pH of healthy skin, patting the skin dry).
- (↑↑) It is recommended to avoid irritation when cleansing, such as scrubbing, peelings, substances that promote blood circulation, or astringents.

Skin care

- (↑↑) Light/hydrophilic skin care preparations are recommended for patients with rosacea.

- (↑) Cosmetics with active ingredients to improve complaints in rosacea are suggested.
- (↑↑) It is recommended to avoid irritating cosmetics and those promoting blood circulation.

Sunscreen

- (↑↑) Daily use of a broad-spectrum sunscreen with both UV-A and UV-B protection is recommended.

Additional practices

- (↑↑) It is recommended to use decorative cosmetics if this contributes to improved quality of life.

OCULAR ROSACEA

Clinical indications of ocular rosacea include posterior blepharitis, Meibomian gland dysfunction, and secondary inflammatory change(s) of the ocular surface.

Treatment

- The indication for treating ocular rosacea depends on the severity of ocular involvement and is frequently independent of skin symptoms.
- (↑↑) Eyelid margin hygiene is recommended as a general practice.
- (↑) **Ciclosporin eye drops** as well as azithromycin are suggested for the topical treatment of inflammation on the ocular surface (off label). Ivermectin or metronidazole (skin cream) is suggested for topical application on the eyelids (off label).
- (↑) **Doxycycline** or **azithromycin** as well as other macrolide antibiotics is suggested for systemic treatment (off label).
- (0) Systemic treatment with **ivermectin**, with or without **metronidazole** and omega-3 fatty acids, may be considered for ocular rosacea (off label).
- (0) Intense Pulsed Light treatment may be considered for ocular rosacea.

Figure 1 provides an overview of the therapeutic options for rosacea.

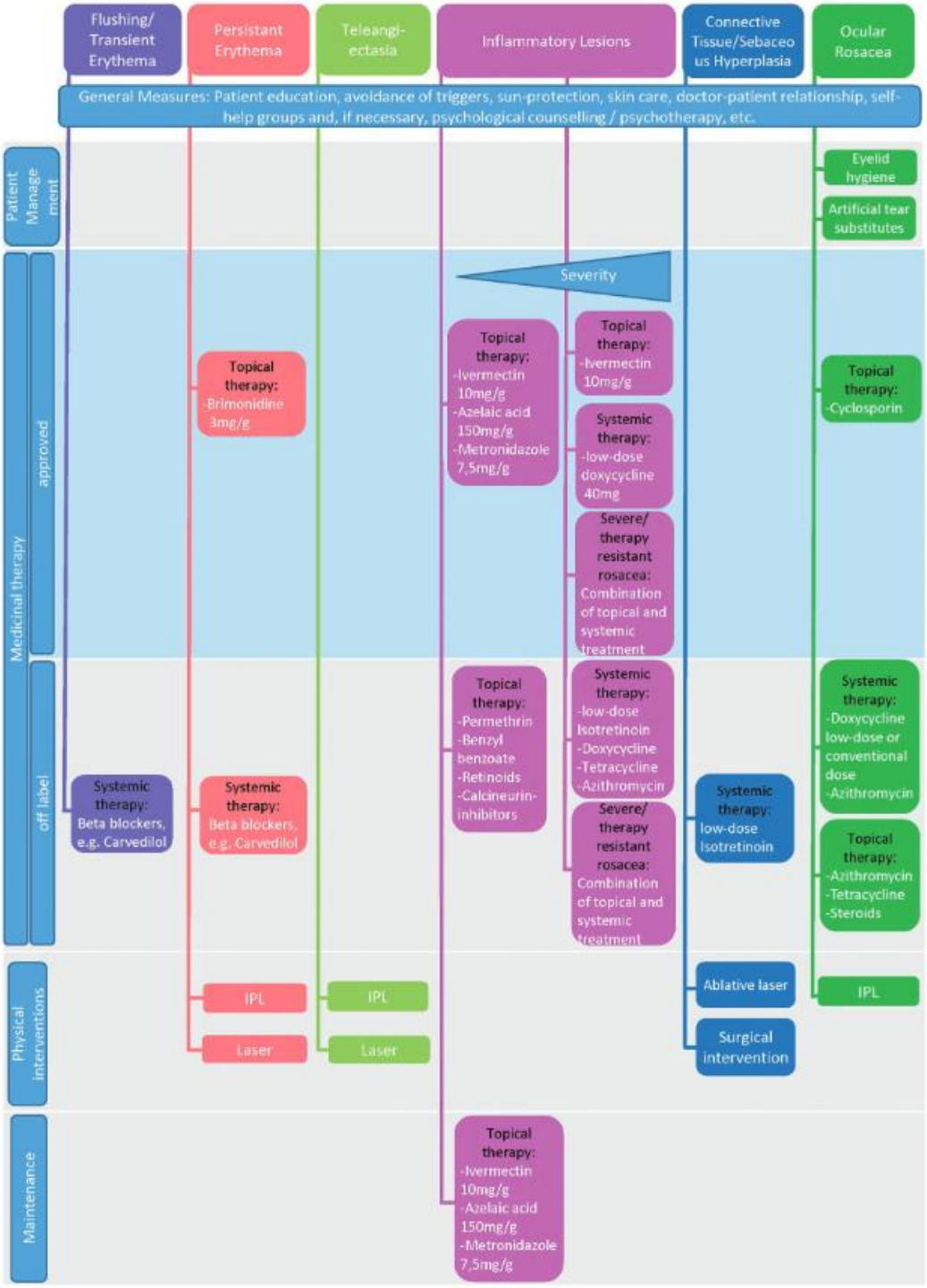

Figure 1. *Overview of Treatment Options for the Management of Rosacea. Retrieved from the S2k 2022 Guideline.*

1.2.3 Guidelines for the Diagnosis and Treatment of Rosacea in China (2021)

To standardize the diagnosis and treatment of rosacea, the subprofessional dermatology committee of the Dermatology Branch of the Chinese Medical Doctor Association formulated the first version of the expert consensus on rosacea diagnosis and treatment in China in 2016. During the past 5years, research on rosacea has made rapid progress, increasing the under-standing of rosacea in China. Therefore, the Rosacea Research Center of the Chinese Society of Dermatology and the Rosacea Professional Committee of the Chinese Dermatologist Association organized relevant experts to formulate these updated guidelines based on the 2016expert consensus and the latest local and international research, including evidence-based studies[10].

Table 9. Chinese Guidelines' Levels of Evidence and Recommendations

Quality level	Current Definition
This proposed guideline classifies treatment methods in accordance with the level of evidence	
A	One or more prospective randomized controlled clinical studies
B	Larger prospective clinical studies with ≥20 subjects, but insufficient randomized control
C	Small clinical studies with <20 subjects or retrospective studies
D	Case series with ≥ 5cases
E	Individual case reports
Level of recommendation	
The level of recommendation is classified as unanimously recommended, recommended, cautiously recommended, and not recommended.	

Topical drugs

- **Antimicrobial topical preparations: metronidazole, clindamycin, erythromycin, and ivermectin**

    1. **Metronidazole**: Metronidazole kills demodex mites in hair follicles and has anti-inflammatory and antioxidant effects. Topical metronidazole has a therapeutic effect on papules, pustules, and erythema, but is not effective for vasodilation. The usual dose is 0.75% metronidazole in a cream/gel applied one to two times daily, which usually takes several

weeks to take effect. Evidence level: A for papules and pustules; recommendation level: unanimous recommendation.

2. **Clindamycin** or **erythromycin**: Clindamycin is commonly used as a cream or gel with a concentration of 0.3% or 1%, while erythromycin is available as a cream with a concentration of 2%. Both drugs have a certain effect on papules and pustules but have poor effects on erythema and telangiectasia. These drugs are used one to two times a day as second-line treatment for papules and pustules. Evidence level: A for papules and pustules; recommendation level: recommended.
3. **Ivermectin**: 1% ivermectin cream is a new drug for rosacea treatment that eliminates anti-follicular demodex mites. Ivermectin has a good effect on papules and pustules but does not affect vasodilation. Evidence level: A for papules and pustules; recommendation level: recommended.

- **Azelaic acid:** Azelaic acid reduces the expression of kallikrein kinase-related peptidase 5 and antibacterial peptides, inhibits the release of cytokines induced by ultraviolet radiation, and improves rosacea papules and pustules. Azelaic acid is available in concentrations of 10%, 15%, or 20% in the form of a cream or gel and is applied twice a day. Azelaic acid may initially cause itching, burning, and tingling, but these symptoms are generally mild and short-lived. Evidence level: A for papules and pustules; recommendation level: recommended.
- **Benzoyl peroxide:** Benzoyl peroxide has antimicrobial effects and is used for the treatment of rosacea, but has some adverse reactions such as erythema, scaling, and local itching. Because of the increased skin sensitivity of patients with rosacea, benzoyl peroxide is only indicated for nasal or perioral papules and pustules. Evidence level: A for papules and pustules; recommendation level: cautiously recommended.
- **External vasoconstrictor drugs:** Alpha-adrenergic receptor agonists, such as brimonidine, specifically act on the surrounding smooth muscles and constrict the facial blood vessels, reducing persistent erythema in the middle of the face. Another alpha-adrenergic receptor agonist, oxymetazoline hydrochloride, constricts blood vessels by constricting the surrounding smooth muscle and exhibits an anti-inflammatory effect. In 2017, the US FDA approved 1% oxymetazoline hydrochloride cream for the treatment of persistent erythema in adults with rosacea. Evidence level: A for erythema; recommendation level: cautiously recommended.
- **Salicylic acid:** Salicylic acid has keratin-promoting, keratolytic, sterilizing, and antibacterial effects, and is effective for treating rosacea papules and pustules.

Due to the differences in the effects and adverse reactions of different concentrations, salicylic acid must be used under the guidance of a doctor. Evidence level: B; recommendation level: cautiously recommended.

Topical eye medications

- Antibiotic ointments or eye drops (e.g., tetracycline and azithromycin) can be used for local eye treatment. while immunosuppressant eye drops (such as cyclosporine) can be administered if necessary.
- Demodex blepharitis requires anti-mite treatment, including topical metronidazole. When rosacea is complicated with dry eyes, artificial tears and anti-inflammatory treatments are required. Severe symptoms require referral to an ophthalmologist for diagnosis and treatment. Evidence level: none; recommendation level: unanimously recommended for artificial tears, recommended for cyclosporine eye drops, recommended for azithromycin eye drops, and recommended for tetracycline eye drops.

Systemic therapy

1. Antimicrobials

- Antibiotics are the first-line systemic treatment for rosacea papules and pustules. The US FDA approved the use of 40mg/day doxycycline for the treatment of rosacea. For patients with rosacea who are younger than 8 years, intolerant of tetracycline antibiotics, or have other contraindications to doxycycline, macrolide antibiotics (such as 0.5 g clarithromycin once or twice a day or 0.25 g azithromycin once a day) may be used. Evidence level: A for papules, pustules, and erythema; recommendation level: unanimously recommended for papules and pustules, recommended for erythema.
- Anti-anaerobic bacteria drugs: Metronidazole has anti-demodex and anti-inflammatory effects and is used as a second-line drug for rosacea. The usual metronidazole dose is 200mg two to three times a day for approximately 4weeks. Possible adverse reactions include gastrointestinal reactions, occasional headaches, insomnia, skin rash, and leukopenia. Evidence level: B for papules and pustules; recommendation level: recommended.

2. Isotretinoin

- Isotretinoin is commonly used at doses of 10–20mg/day68 for 12–16weeks.
- Isotretinoin cannot be used simultaneously with tetracycline. Evidence level: A for hyperplasia and hypertrophy, C for papules and pustules; recommendation level: unanimously recommended for hyperplasia and hypertrophy, recommended for papules and pustules.

3. Hydroxychloroquine

- The dosage of hydroxychloroquine is 0.1–0.2 g twice a day for 8–16 weeks, but the duration can be extended in accordance with the disease condition. If hydroxychloroquine is used continuously for more than 3–6months, a fundus examination is recommended to rule out retinopathy. Evidence level: A for erythema, papules, and pustules; recommendation level: unanimously recommended for erythema, recommended for papules and pustules.

4. B-Adrenergic receptor inhibitors

- **Carvedilol** is mainly used for patients with intractable paroxysmal flushing and persistent erythema. The usual carvedilol dose is 3.125–6.25mg one to three times a day for 6–28months. Evidence level: D for erythema; recommendation level: recommended.

5. Anxiolytics

- Antidepressants such as **mirtazapine** and **paroxetine** treat menopausal hot flashes by regulating vascular function and exert anti-inflammatory effects through a variety of mechanisms. Therefore, anxiolytics are suitable for patients with rosacea with obvious symptoms, such as facial flushing, burning, and itching. Evidence level: none; recommendation level: cautiously recommended.

Phototherapy and other physical therapies

- Intense pulsed light (IPL) therapy: IPL therapy is used to treat papulopustular rosacea; however, caution should be exercised in patients in the acute swelling stage. Evidence level: A for erythematous lesions and telangiectasia; recommendation level: recommended.
- Pulsed dye lasers (PDLs) – 585 nm/595 nm: PDL therapy is used in patients with phymatous rosacea to indirectly inhibit the formation and growth of vegetation by inhibiting angiogenesis. Evidence level: B for erythematous lesions and telangiectasia; recommendation level: recommended.
- Carbon dioxide or erbium lasers: Carbon dioxide and erbium lasers target water, which is beneficial for removing skin hyperplasia tissue and softening scar tissue through gasification stripping and is suitable for patients with mild to moderate phymatous rosacea. Evidence level: E for phymatous lesions; recommendation level: recommended.
- 1064-nm neodymium-doped yttrium aluminum garnet (Nd YAG) laser therapy Nd YAG lasers target pigment, hemoglobin, and water tissues, producing a good therapeutic effect for papulopustular rosacea.86 Evidence level: B for papulopustular lesions; recommendation level: recommended.

- Radiofrequency (RF) therapy: Based on the physical properties of the eddy current electric field, the RF repair therapy instrument uses the anti-inflammatory, dermal reconstruction, and antimicrobial effects of thermal energy to treat rosacea.
- Photodynamic therapy (PDT: PDT is a superior treatment option for papules and pustules in rosacea. In addition, PDT with PDL as the light source is superior to PDL alone in terms of short-term efficacy, but there are no differences between the two therapies in terms of long-term efficacy. Evidence level: D; recommendation level: cautiously recommended.

Operative therapy

Rosacea, mainly characterized by telangiectasia or phymatous changes may be less responsive to drug treatments and may require appropriate surgical treatment.

Treatment plans for different rosacea skin lesions

Persistent erythema

- ***Mild*** persistent erythema requires only skin barrier repair, protection against sunlight, and mood stabilization.
- ***Moderate to severe*** persistent erythema is treated using oral antimicrobial drugs (such as doxycycline or minocycline) and hydroxychloroquine. The combined use of moisture-retaining skincare products that repair the skin barrier and 0.5% brimonidine tartrate gel is applied in severe cases; however, the erythema may initially be aggravated.
- Once the lesions are stabilized, IPL, PDL, or Nd YAG laser therapy can be considered to constrict the blood vessels and alleviate the erythema. RF repair treatment achieves good results and can also be used for erythema in patients with non-=swelling rosacea. Red and yellow LED therapy is used to relieve swelling in patients with obvious swelling and a burning sensation.
- For patients with moderate to severe erythema with obvious flushing and a strong burning sensation, **carvedilol can be added**. Patients with obvious anxiety, depression, and insomnia may require short-term antidepressant medication under the guidance of psychologists or psychiatrists. For patients who do not respond to local and systemic treatments, **BTX-A may be injected in the erythematous area.**

Papules and pustules

- For mild lesions, metronidazole, azelaic acid, clindamycin, erythromycin, or ivermectin topical preparations can be used. The treatment effect is evaluated after 8–12weeks. If a curative effect has been achieved, topical drugs are used

as maintenance to achieve the desired effect. Otherwise, a combination of systemic antibiotics and/or hydroxychloroquine treatment may be considered.

- For moderate and severe lesions, the first choice is oral doxycycline, minocycline, or combined oral hydroxy chloroquine, while the second choice is oral clarithromycin, azithromycin, or metronidazole. If these drugs are ineffective after 4–8weeks, clinicians should consider switching to oral isotretinoin, as it can be used in combination with external preparations.

Telangiectasia

- IPL, PDL, or Nd YAG laser therapies are used to treat telangiectasia when the inflammation control of papules or erythema is relatively stable; however, the treatment may induce or aggravate the erythema, papules, or pustules.

Phymatous changes

- **Oral isotretinoin** capsules are the recommended **first-line treatment option.** For patients with **papules and pustules, oral clarithromycin, and other antimicrobial drugs (such as topical metronidazole, azelaic acid, ivermectin cream, clindamycin, and erythromycin)** can be taken simultaneously with other topical preparations. The treatment options for **telangiectasia are PDL therapy, long-pulse width Nd YAG laser therapy, IPL therapy, or surgical scratching. CO2 and erbium lasers or surgical ablation and resection are used to treat nodular hypertrophy.**

Ocular symptoms

- For most patients with ocular symptoms, systemic treatment alleviates both the skin symptoms and the ocular symptoms.
- Systemic treatment can also be used in combination with cyclosporine eye drops but is contraindicated during the infection period.
- If there are dry-eye symptoms, high-quality artificial tears should be applied. Patients with meibomian gland-related corneal and conjunctival lesions should be referred to an ophthalmologist for appropriate treatment.

1.2.4 Spanish Consensus Document on the Treatment Algorithm for Rosacea (2019)

Recent scientific evidence and the incorporation of new drugs into the therapeutic arsenal against rosacea have made it necessary to review and update treatment criteria and strategies. To this end, a panel of 15 dermatologists, all experts in rosacea, was formed to share experiences and discuss treatment options, response criteria, and changes to treatment. Based on a critical review of the literature and a

discussion of the routine practices of Spanish dermatologists, the panel proposed and debated different options, with consideration of the experience of professionals and the preferences of patients or equality criteria. Following validation of the proposals, the final recommendations were formulated and, together with the evidence from the main international guidelines and studies, used to produce this consensus document. The goal of this consensus document is to provide dermatologists with practical recommendations for the management of rosacea[11].

The main recommendations are summarized below:

- Rosacea is a common chronic skin disease with variable symptoms that usually affect the central area of the face (expert consensus).
- The classification of rosacea into 4 subtypes is practical when applied to the results of clinical research (expert consensus).
- The clinical subtypes of rosacea are useful for classifying signs and symptoms; however, they do not clarify such aspects as chronicity or the course of disease as it is expressed in individual features of the disease (expert consensus).
- Rosacea can affect an individual's psychological and social well-being. Dermatologists should bear in mind rosacea's impact on the patient's quality of life when deciding on a treatment approach (strong recommendation, moderate quality of evidence).
- Allow time for a treatment to take effect before changing to another one, provided the treatment is tolerated (expert consensus).
- If there is no response to a first-line treatment, another first-line treatment can be prescribed or a second treatment can be added (expert consensus).
- Choice of maintenance therapy should be individualized. Give preference to the least aggressive therapy that achieves control of symptoms (expert consensus).
- Prescribe more than one treatment when the signs or symptoms of rosacea are severe (expert consensus).
- Topical **brimonidine** or **oral blockers** can be considered for treating transient erythema (flushing) (strong recommendation, high quality of evidence).
- Pulsed dye laser and IPL therapy are the first-choice treatments for non-transient erythema; brimonidine can be used for symptomatic treatment (strong recommendation, high quality of evidence).
- **IPL** and **laser** treatments are first-line choices for telangiectasia (expert consensus).

- Topical agents such as **ivermectin** and **metronidazole** are the first-line recommendations for treating rosacea with mild inflammatory lesions (papules and pustules). Oral doxycycline can be considered an alternative (strong recommendation, moderate quality of evidence)
- Topical agents such as ivermectin and metronidazole and oral **doxycycline** are the first-line recommendations for treating rosacea with moderately severe inflammatory lesions (papules and pustules) (strong recommendation, high quality of evidence).
- Treatment (**doxycycline** or **isotretinoin**) with or without associated topical therapy (ivermectin or metronidazole) or physical treatments are the first-line recommendations for rosacea with severe inflammatory lesions (papules and pustules) (strong recommendation, high quality of evidence).
- If **tetracyclines** are considered for the inflammatory lesions of rosacea, the minimum effective dose of doxycycline is recommended to minimize the risk of bacterial resistance (strong recommendation, high quality of evidence).
- Systemic treatment with doxycycline or isotretinoin is the first-line recommendation for active phymatous lesions (expert consensus).
- Surgical procedures such as dermabrasion, electrodesiccation, or laser treatments are recommended as first-line treatments for phymatous lesions without clinical inflammation. Scanned or pulsed carbon dioxide laser in continuous mode is preferred because it affords the ability to sculpt and provide hemostasis simultaneously (expert consensus).
- Dermatologists should be able to recognize the ocular manifestations of rosacea. Patients with altered vision, conjunctival involvement, or signs of corneal involvement should be referred to an ophthalmologist (expert consensus).
- The treatment of ocular rosacea depends on severity. General measures to take are adequate cleansing, the application of topical preparations (metronidazole, tetracyclines, or ciclosporin), and the use of systemic therapy (doxycycline, short-term **corticosteroids**, or isotretinoin) (expert consensus).

Section 2.0 Drug Therapy in Rosacea

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA but are not yet registered by the SFDA.

2.1 Additions

After November 2019, there have been Rosacea drugs that have received FDA approval. Nevertheless, Beta-Blocker With Alpha-Blocking Activity; ***Carvedilol,*** *and* ***a*** *Nonselective* Beta-Blocker; ***Propranolol*** *were registered in the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found below.*

2.1.1 Carvedilol

This section includes pertinent information regarding the use of ***Carvedilol in*** Rosacea[12].

Table 10. Carvedilol Drug Information

SCIENTIFIC NAME Carvedilol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	L71
Drug Class	Antihypertensive
Drug Sub-class	Beta-Blocker with Alpha-Blocking Activity
ATC Code	C07AG02
Pharmacological Class (ASHP)	Beta-Blocker With Alpha-Blocking Activity
DRUG INFORMATION	
Dosage Form	Film-coated tablet. Tablet
Route of Administration	Oral use

Dose (Adult) [DDD]*	**Carvedilol** is mainly used for patients with intractable paroxysmal flushing and persistent erythema. The usual carvedilol dose is 3.125–6.25mg one to three times a day for 6–28months. Evidence level: D for erythema; recommendation level: recommended.[10]
Maximum Daily Dose Adults*	6.25 mg three times a day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Dosing: Altered Kidney Function: Adult** **Mild to severe impairment:** No dosage adjustment necessary **Hemodialysis, intermittent (thrice weekly):** Poorly dialyzed; no supplemental dose or dosage adjustment necessary. **Peritoneal dialysis:** Unlikely to be dialyzed; no dosage adjustment necessary (expert opinion). **CRRT:** No dosage adjustment necessary. **PIRRT (e.g., sustained, low efficiency diafiltration):** No dosage adjustment necessary. **Dosing: Hepatic Impairment: Adult** **Mild to moderate impairment:** There are no dosage adjustments provided in the manufacturer's labeling; dose conservatively and interrupt therapy in the setting of hypotension (e.g., mean arterial pressure [MAP] <65 mm Hg), acute kidney injury, or hyponatremia. **Severe impairment**: Use is contraindicated per manufacturer; however, experts will use if indicated (e.g., for variceal hemorrhage prophylaxis); dose conservatively and interrupt therapy in the setting of

	hypotension (e.g., MAP <65 mm Hg), acute kidney injury, or hyponatremia.
Prescribing edits*	**MD, CU, ST**
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): For patients with moderate to severe erythema with obvious flushing and a strong burning sensation, carvedilol can be added.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Prescribed by a specialized physician (dermatologist).	
PA (Prior Authorization): N/A	
QL (Quantity Limit N/A	
ST (Step Therapy): Systemic treatment is recommended for treatment-refractory and severe forms of papulopustular rosacea. Carvedilol may be considered for systemic treatment of persistent erythema and flushing in rosacea (off label).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** • **Cardiovascular:** Hypotension (≤20%), orthostatic hypotension (≤20%) • **Endocrine & metabolic:** Hyperglycemia (5% to 12%), weight gain (10% to 12%) • **Gastrointestinal:** Diarrhea (IR: 2% to 12%; ER: 1%) • **Nervous system:** Asthenia (11%), dizziness (IR: 6% to 32%; ER: 2%), fatigue (24%) **Most serious:** • **Bradyarrhythmia** • **Bronchospasm** • **CNS effects** • **Potentiation/masking of hypoglycemia** • **Withdrawal**
Drug Interactions	**Category X** • **X**Albuterol *Depends on International labeling*

	• XArformoterol *Depends on International labeling* • XBambuterol *Depends on International labeling* • XBilastine *Depends on Renal Function* • XBromperidol • XClenbuterol *Depends on International labeling* • XDOXOrubicin (Conventional) • XEtofylline • XFenoterol *Depends on International labeling* • XFexinidazole • XFormoterol *Depends on International labeling* • XIndacaterol *Depends on International labeling* • XLevalbuterol *Depends on International labeling* • XMetaproterenol *Depends on International labeling* • XOlodaterol *Depends on International labeling* • XPAZOPanib • XProcaterol *Depends on International labeling* • XRitodrine *Depends on International labeling* • XRivastigmine • XSalmeterol *Depends on International labeling* • XSirolimus (Protein Bound) • XTerbutaline *Depends on International labeling* • XTopotecan *Depends on Route* • XTulobuterol *Depends on International labeling* • XVilanterol *Depends on International labeling*

- **X**VinCRIStine (Liposomal)
- **X**White Birch Allergen Extract

Category D

- **D**Afatinib
- **D**Amifostine
- **D**Berotralstat
- **D**Brimonidine (Ophthalmic) *Depends on Comorbidity and Dosage Form*
- **D**Ceritinib
- **D**CloNIDine *Depends on Comorbidity and Dosage Form*
- **D**Colchicine *Depends on Additional drug/group, Brand Name, Hepatic Function, Indication, International labeling, and Renal Function*
- **D**DexmedeTOMIDine *Depends on Comorbidity and Dosage Form*
- **D**Dronedarone
- **D**Fingolimod
- **D**Grass Pollen Allergen Extract (5 Grass Extract) *Depends on International labeling*
- **D**GuanFACINE *Depends on Comorbidity and Dosage Form*
- **D**Lefamulin *Depends on Route*
- **D**Lofexidine *Depends on Comorbidity and Dosage Form*
- **D**Methyldopa *Depends on Comorbidity and Dosage Form*
- **D**Moxonidine *Depends on Comorbidity and Dosage Form*
- **D**Obinutuzumab
- **D**Patiromer
- **D**Ponesimod
- **D**Pralsetinib *Depends on Additional drug/group*
- **D**Relugolix *Depends on Route*

	• **D**Relugolix, Estradiol, and Norethindrone • **D**Rilmenidine *Depends on Comorbidity and Dosage Form* • **D**Rimegepant • **D**Siponimod • **D**Sirolimus (Conventional) • **D**Talazoparib *Depends on Indication* • **D**Tasimelteon • **D**TiZANidine *Depends on Comorbidity and Dosage Form* • **D**Ubrogepant • **D**Venetoclax
Special Population	**Older adult:** Bradycardia may be observed more frequently in elderly patients (>65 years of age); dosage reductions may be necessary.
Pregnancy	Exposure to beta-blockers during pregnancy may increase the risk for adverse events in the neonate. If maternal use of a beta-blocker is needed, monitor fetal growth during pregnancy; monitor the newborn for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression.
Lactation	It is not known if carvedilol is present in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Use of a beta-blocker other than carvedilol may be preferred in lactating patients.
Contraindications	Serious hypersensitivity to carvedilol or any component of the formulation; decompensated cardiac failure

	requiring intravenous inotropic therapy; bronchial asthma or related bronchospastic conditions; second- or third-degree AV block, sick sinus syndrome, or severe bradycardia (except in patients with a functioning artificial pacemaker); cardiogenic shock; severe hepatic impairment. *Canadian labeling:* Additional contraindications (not in US labeling): Severe hypotension; primary obstructive valvular heart disease; mental incapacity (e.g., severe Alzheimer disease, alcoholism, drug abuse), unless closely supervised by an appropriate caregiver.
Monitoring Requirements	ECG, heart rate, blood pressure; kidney function; liver function; blood glucose in patients with diabetes; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; mental alertness.
Precautions	***Concerns related to adverse effects:*** • Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (e.g., epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects. • Bradycardia: May occur; reduce dosage if heart rate drops to <55 beats/minute. • Hypotension/syncope: Symptomatic hypotension with or without syncope may occur with carvedilol (usually within the first 30 days of therapy); close monitoring of patient is required especially with initial dosing and dosing increases; blood

	pressure must be lowered at a rate appropriate for the patient's clinical condition. Initiation with a low dose, gradual up-titration, and administration with food may help to decrease the occurrence of hypotension or syncope. Advise patients to avoid driving or other hazardous tasks during initiation of therapy due to the risk of syncope.
Black Box Warning	**N/A**
REMS	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including the National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC), on the use of carvedilol for the management of rosacea yielded no results.

Conclusion Statement – Carvedilol

Carvedilol may be considered for systemic treatment of persistent erythema and flushing in rosacea (off label). It is mainly used for patients with intractable paroxysmal flushing and persistent erythema. No HTA recommendations about the use of Carvedilol in patients with Rosacea.

2.1.2 Propranolol

This section includes pertinent information regarding the use of ***Propranolol*** *in* Rosacea[12].

Table 11. Propranolol Drug Information

SCIENTIFIC NAME Propranolol	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes

PMDA	No
Indication (ICD-10)	L71
Drug Class	Antihypertensive
Drug Sub-class	Beta-Blocker, Nonselective
ATC Code	C07AA05
Pharmacological Class (ASHP)	Beta-Blocker, Nonselective
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Consider **oral propranolol** in people with rosacea where the main presenting feature is transient facial erythema (flushing)[1]. Dose: 40 mg 2 or 3 times daily[13].
Maximum Daily Dose Adults*	40 mg 3 times daily
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Dosing: Altered Kidney Function: Adult** **Altered kidney function:** No dosage adjustment necessary for any degree of kidney dysfunction; use with caution, particularly in patients with more advanced kidney impairment, as decreased hepatic extraction has been reported and patients may be more prone to adverse effects when initiating therapy. **Hemodialysis, intermittent (thrice weekly):** Not significantly dialyzed: No supplemental dose or dosage adjustment necessary; use with caution. **Peritoneal dialysis:** Unlikely to be significantly dialyzed (large V_d): No dosage adjustment necessary; use with caution. **CRRT:** No dosage adjustment necessary.

	PIRRT (e.g., sustained, low-efficiency diafiltration): No dosage adjustment necessary **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling. However, hepatic impairment increases systemic exposure to propranolol. Use with caution.
Prescribing edits*	**MD, ST**
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Prescribed by a specialized physician (Dermatologist).	
PA (Prior Authorization): N/A	
QL (Quantity Limit N/A	
ST (Step Therapy): Systemic treatment is recommended for treatment-refractory and severe forms of papulopustular rosacea. Consider oral propranolol in people with rosacea where the main presenting feature is transient facial erythema (flushing).	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** • Nervous system: Sleep disorder (infants: 16% to 18%) • Respiratory: Bronchiolitis (infants), bronchitis (infants: 8% to 13%) **Most serious:** • Bradyarrhythmias • Bronchospasm • CNS effects • Potentiation/masking of hypoglycemia • Withdrawal
Drug Interactions	**Category X** • XAlbuterol *Depends on International labeling*

- **X**Arformoterol *Depends on International labeling*
- **X**Bambuterol *Depends on International labeling*
- **X**Bromperidol
- **X**Clenbuterol *Depends on International labeling*
- **X**Etofylline
- **X**Fenoterol *Depends on International labeling*
- **X**Fexinidazole
- **X**Fezolinetant
- **X**Formoterol *Depends on International labeling*
- **X**Indacaterol *Depends on International labeling*
- **X**Levalbuterol *Depends on International labeling*
- **X**Metaproterenol *Depends on International labeling*
- **X**Olodaterol *Depends on International labeling*
- **X**Procaterol *Depends on International labeling*
- **X**Ritodrine *Depends on International labeling*
- **X**Rivastigmine
- **X**Salmeterol *Depends on International labeling*
- **X**Terbutaline *Depends on International labeling*
- **X**Thioridazine
- **X**Tulobuterol *Depends on International labeling*
- **X**Vilanterol *Depends on International labeling*
- **X**White Birch Allergen Extract

Category D

- **D**Amifostine

	• **D**Brimonidine (Ophthalmic) *Depends on Comorbidity and Dosage Form* • **D**Ceritinib • **D**CloNIDine *Depends on Comorbidity and Dosage Form* • **D**DexmedeTOMIDine *Depends on Comorbidity and Dosage Form* • **D**Dronedarone • **D**Fingolimod • **D**FluvoxaMINE • **D**Grass Pollen Allergen Extract (5 Grass Extract) *Depends on International labeling* • **D**GuanFACINE *Depends on Comorbidity and Dosage Form* • **D**Lofexidine *Depends on Comorbidity and Dosage Form* • **D**Methyldopa *Depends on Comorbidity and Dosage Form* • **D**Moxonidine *Depends on Comorbidity and Dosage Form* • **D**Obinutuzumab • **D**Ponesimod • **D**Rilmenidine *Depends on Comorbidity and Dosage Form* • **D**Rizatriptan *Depends on Age and Dosage Form* • **D**Siponimod • **D**Tasimelteon • **D**TiZANidine • **D**Viloxazine
Special Population	**Reproductive Considerations** Propranolol is approved for prevention of migraines. In general, preventive treatment for migraine in patients trying to become pregnant should be avoided. Options for patients planning a pregnancy should be considered as part of a shared decision-making process.

	Nonpharmacologic interventions should be considered initially. When needed, preventive treatment should be individualized considering the available safety data and needs of the patient should pregnancy occur. A gradual discontinuation of preventive medications is generally preferred when the decision is made to stop treatment prior to conception
Pregnancy	Propranolol crosses the placenta. Exposure to beta-blockers during the third trimester of pregnancy may increase the risk for bradycardia, hypoglycemia, hypotension, and respiratory depression in the neonate. Newborns should be monitored and managed accordingly. If maternal use of a beta-blocker is needed, fetal growth should be monitored during pregnancy and the newborn should be monitored for 48 hours after delivery for bradycardia, hypoglycemia, and respiratory depression.
Lactation	In general, propranolol may be compatible with breastfeeding when used at usual doses. Breastfeeding infants should be monitored for bradycardia, cyanosis, and hypoglycemia.
Contraindications	Hypersensitivity to propranolol, beta-blockers, or any component of the formulation; uncompensated heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol); cardiogenic shock; severe sinus bradycardia, sick sinus syndrome, or heart block greater than first-degree (except in patients with a functioning artificial pacemaker); bronchial asthma.

	Canadian labeling: Additional contraindications (not in US labeling): Bronchospasm; right ventricular failure secondary to pulmonary hypertension; allergic rhinitis during pollen season; patients prone to hypoglycemia; hypotension (BP parameters not specified in labeling); metabolic acidosis; vasospastic angina (also referred to as Prinzmetal angina or variant angina); severe peripheral arterial circulatory disturbance; untreated pheochromocytoma; hereditary problems of galactose intolerance, glucose-galactose malabsorption, or congenital lactase deficiency (lactose-containing products only).
Monitoring Requirements	Acute cardiac treatment: ECG, heart rate, and blood pressure. Hypertension: Blood pressure, heart rate. Mental alertness; signs and symptoms of bronchospasm in patients with existing bronchospastic disease; serum glucose (in patients with diabetes). Proliferating infantile hemangioma (Hemangeol): Monitor heart rate and blood pressure for 2 hours after initiation or dose increases.
Precautions	Concerns related to adverse effects: Arthralgia: Arthralgia, including gait disturbances or decreased mobility associated with joint symptoms, has been reported, sometimes requiring hospitalization. May occur within days to months following initiation of therapy and has resolved with or without therapy discontinuation; report new-onset or worsening joint symptoms to health care provider.

	Renal impairment: Use with caution in patients with advanced renal impairment during initiation of therapy, as decreased hepatic extraction may result in elevated propranolol concentrations and increase the risk of side effects
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

A thorough review of various HTA bodies including the National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC), on the use of propranolol for the management of rosacea yielded no results.

Conclusion Statement – Propranolol

Oral propranolol can be considered in people with rosacea where the main presenting feature is transient facial erythema (flushing). No HTA recommendations about the use of Propranolol in patients with Rosacea.

2.2 Modifications

No modifications to prescribing edits in the drug summary spreadsheet since the publication of the previous CHI report.

2.3 Delisting

The medications below are no longer SFDA registered[14], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI Rosacea original clinical guidance*

- GLYCERIN, SODIUM CARBOXYMETHYLCELLULOSE

2.4 Other Drugs

On April 25, 2022, benzoyl peroxide 5% cream became the newest FDA-approved treatment for mild-to-moderate rosacea under the brand name EPSOLAY®, a collaboration between Sol-Gel Technologies and Galderma. EPSOLAY® contains a proprietary encapsulated cream formulation of benzoyl peroxide 5%. Its silica-based

shell ensures the medication is released slowly over time, which contributes to its favorable safety and efficacy profile for sensitive skin affected by rosacea[15].

In two double-blinded phase III randomized clinical trials with approximately 733 participants, the EPSOLAY® treatment group experienced a nearly 70% reduction in their inflammatory lesions over 12 weeks of use. In comparison, the placebo group only experienced a reduction of 38-46% during this time. In the open-label extension study, 73% of 547 participants demonstrated Investigator's Global Assessment scores of 0 (clear) or 1 (almost clear) after 52 weeks of use[15].

Section 3.0 Key Recommendations Synthesis

General Recommendations

- **Combination treatment could benefit some patients with more severe rosacea** (n = 20/20) and those presenting with multiple rosacea features (n = 20/21). • The benefits of combining treatments in rosacea include helping achieve skin clear of rosacea (n = 19/20); helping some patients achieve treatment goals more quickly (n = 19/20); maximizing remission periods (n = 19/20); and minimizing burden of disease (n = 19/20)[6].
- British Advise people with rosacea to limit exposure to known aggravating factors such as alcohol, sun exposure, hot drinks, and spicy food[1].
- When characterizing the clinical subtypes and symptoms of rosacea, classify the patient according to the phenotypes identified by Gallo et al. This approach encompasses the objective clinical signs and the subjective symptoms experienced by the patient with rosacea. Diagnostic phenotypes include characteristic fixed centrofacial erythema or phymatous changes. Other features include flushing, papules or pustules, telangiectasia, ocular changes, burning or stinging sensations, oedema, and dryness[1].
- Advise that some people with rosacea find it beneficial to wash their skin with emollients, moisturize regularly and use appropriate sun protection. Soaps and washing products that contain detergent are irritant in some people and should be avoided if they worsen the symptoms[1].
- (↑↑) It is recommended to avoid individual provocation factors (trigger factors) as far as these can be recognized based on disease progression[7].
- (↑↑) It is recommended to protect affected areas (such as skin or eyes) from UV exposure, on the one hand by avoiding direct sunlight and on the other hand by wearing hats or sunglasses as well as sunscreen[7].
- Rosacea can affect an individual's psychological and social well-being. Dermatologists should bear in mind rosacea's impact on the patient's quality

of life when deciding on a treatment approach (moderate quality of evidence, strong recommendation[11].

Treatment plans for different rosacea skin lesions

Persistent erythema

- ***Mild*** persistent erythema requires only skin barrier repair, protection against sunlight, and mood stabilization[10].
- ***Moderate to severe*** persistent erythema is treated using oral antimicrobial drugs (such as doxycycline or minocycline) and hydroxychloroquine. The combined use of moisture-retaining skincare products that repair the skin barrier and 0.5% brimonidine tartrate gel is applied in severe cases; however, the erythema may initially be aggravated[10].
- Once the lesions are stabilized, IPL, PDL, or Nd YAG laser therapy can be considered to constrict the blood vessels and alleviate the erythema. RF repair treatment achieves good results and can also be used for erythema in patients with non-=swelling rosacea. Red and yellow LED therapy is used to relieve swelling in patients with obvious swelling and a burning sensation[10].
- For patients with moderate to severe erythema with obvious flushing and a strong burning sensation, **carvedilol can be added**. Patients with obvious anxiety, depression, and insomnia may require short-term antidepressant medication under the guidance of psychologists or psychiatrists. For patients who do not respond to local and systemic treatments, **BTX-A may be injected in the erythematous area**[10].

Papules and pustules

- For mild lesions, metronidazole, azelaic acid, clindamycin, erythromycin, or ivermectin topical preparations can be used. The treatment effect is evaluated after 8–12weeks. If a curative effect has been achieved, topical drugs are used as maintenance to achieve the desired effect. Otherwise, a combination of systemic antibiotics and/or hydroxychloroquine treatment may be considered[10].
- For moderate and severe lesions, the first choice is oral doxycycline, minocycline, or combined oral hydroxy chloroquine, while the second choice is oral clarithromycin, azithromycin, or metronidazole. If these drugs are ineffective after 4–8weeks, clinicians should consider switching to oral isotretinoin, as it can be used in combination with external preparations[10].

Telangiectasia

- IPL, PDL, or Nd YAG laser therapies are used to treat telangiectasia when the inflammation control of papules or erythema is relatively stable; however, the treatment may induce or aggravate the erythema, papules, or pustules[10].

Phymatous changes

- **Oral isotretinoin** capsules are the recommended **first-line treatment option.** For patients with **papules and pustules, oral clarithromycin, and other antimicrobial drugs (such as topical metronidazole, azelaic acid, ivermectin cream, clindamycin, and erythromycin)** can be taken simultaneously with other topical preparations. The treatment options for **telangiectasia are PDL therapy, long-pulse width Nd YAG laser therapy, IPL therapy, or surgical scratching. CO2 and erbium lasers or surgical ablation and resection are used to treat nodular hypertrophy**[10].

Topical treatment

- (↑↑) It is recommended to choose the most appropriate active substance, concentration, and base for the individual patient according to the phenotypic characteristics of the rosacea, acuity, and skin type.[7]
- (↑↑) For treatment-refractory and severe forms of papulopustular rosacea it is recommended to combine topical treatment with systemic treatment.[7]
- (↑↑): Offer either **ivermectin**, **metronidazole** or **azelaic acid** as first-line topical treatment options to people with papulopustular rosacea. Discuss the potential for irritancy of different products and formulations prior to prescribing the topical agent[1].
- Topical agents such as ivermectin and metronidazole and oral doxycycline are the first-line recommendations for treating rosacea with moderately severe inflammatory lesions (papules and pustules). Evidence based, High quality Strong recommendation[11].
- (↑): Consider topical **minocycline** foam in people with papulopustular rosacea[1].
- (↑): Consider topical **brimonidine** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment[1].
- (↑): Consider topical **oxymetazoline** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment[1].

Systemic therapies

- (↑↑) Offer an oral antibiotic as a first-line treatment option for more severe papulopustular rosacea. Options (in alphabetical order) include **azithromycin**, **clarithromycin**, **doxycycline 40 mg** (modified release) daily, **doxycycline 100 mg** daily, **erythromycin**, **lymecycline** and **oxytetracycline**. These antibiotics (especially tetracyclines) are considered safe and have been prescribed for rosacea for decades. There is insufficient evidence to establish the superiority of one over another, especially in the absence of head-to-head trials or a network meta-analysis[1].
- (↑↑) Avoid minocycline in people with rosacea due to potential side-effects unless there are no other treatment options[1].
- (↑) Consider intermittent courses of low-dose **isotretinoin** (e.g., 0.25 mg kg–1) in people with persistent and severe rosacea. Discuss the potential side-effects and teratogenicity[1].
- (↑) Consider **oral propranolol** in people with rosacea where the main presenting feature is transient facial erythema (flushing)[1].

Ocular rosacea

- (↑↑) Advise people with ocular rosacea to minimize exposure to aggravating factors such as air conditioning, excessive central heating, smoky atmospheres, and periocular cosmetics[1].
- (↑↑) Identify and modify/eliminate systemic medications that could be triggering eye dryness in people with ocular rosacea (e.g., antidepressants and anxiolytics)[1].
- (↑↑) Offer warm compresses using proprietary lid-warming devices and lid hygiene with homemade bicarbonate solution or commercially available lid wipes[1].
- (↑↑) Offer over-the-counter **ocular lubricants or liposomal sprays** to alleviate symptoms in people with ocular rosacea, ensuring preservative-free preparations are used if using > 6 times daily. Increasing humidity using humidifiers can help to reduce tear evaporation[1].
- (↑↑) Refer people with ocular rosacea to an ophthalmologist if they are (i) experiencing eye discomfort, sticky eye discharge persisting for > 12 months despite frequent (> 6 times daily) topical lubricant use and adequate lid hygiene; or (ii) experiencing symptoms such as reduced vision, pain on eye movement and pain that keeps the patient awake at night[1].
- (↑↑) Eyelid margin hygiene is recommended as a general practice[7].

- (↑) ***Ciclosporin eye drops*** as well as azithromycin are suggested for the topical treatment of inflammation on the ocular surface (off label). Ivermectin or metronidazole (skin cream) is suggested for topical application on the eyelids (off label)[7].
- (↑) ***Doxycycline*** or ***Azithromycin*** as well as other macrolide antibiotics is suggested for systemic treatment (off label)[7].
- (0) Systemic treatment with ***ivermectin***, with or without ***metronidazole*** and ***omega-3 fatty acids***, may be considered for ocular rosacea (off label)[7].
- (0) Intense Pulsed Light treatment may be considered for ocular rosacea[7].
- For most patients with ocular symptoms, systemic treatment alleviates both the skin symptoms and the ocular symptoms[10].
- Systemic treatment can also be used in combination with cyclosporine eye drops but is contraindicated during the infection period[10].
- If there are dry-eye symptoms, high-quality artificial tears should be applied. Patients with meibomian gland-related corneal and conjunctival lesions should be referred to an ophthalmologist for appropriate treatment[10].
- Topical brimonidine or oral blockers can be considered for treating transient erythema (flushing) (high quality of evidence, strong recommendation)[11].
- Pulsed dye laser and IPL therapy are the first-choice treatments for no transient erythema; brimonidine can be used for symptomatic treatment (high quality of evidence, strong recommendation)[11].
- Treatment (doxycycline or isotretinoin) with or without associated topical therapy (ivermectin or metronidazole) or physical treatments are the first-line recommendations for rosacea with severe inflammatory lesions (papules and pustules) (high quality of evidence, strong recommendation)[11].
- If tetracyclines are considered for the inflammatory lesions of rosacea, the minimum effective dose of doxycycline is recommended in order to minimize the risk of bacterial resistance (high quality of evidence, strong recommendation)[11].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Rosacea report** and aims to provide recommendations to aid in the management of Rosacea. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Rosacea.

Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Rosacea Scope

Section	Rationale/updates
Section 1.1 Canadian Clinical Practice Guidelines for Rosacea (**2016**)	**N/A**
Section 1.2 Rosacea: diagnosis and treatment. American family physician (2015)	**N/A**
Section 1.3 Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments (2019)	**N/A**
Section 1.4 Rosacea treatment update: recommendations from the global Rosacea Consensus (ROSCO) panel (2017)	**2020 Recommendations for rosacea diagnosis, classification, and management: update from the global Rosacea Consensus 2019 panel**[6] • To aid diagnosis and assessment of cutaneous rosacea, feature descriptions (Table 1) and considerations for assessing severity of minor features (Table 2) are provided, which build on similar considerations for diagnostic and major features in the ROSCO 2017 recommendations. Updated recommendations on treatment and monitoring:

	• ***Topical alpha-adrenergic modulating agents and oral beta blockers*** have been **removed**, as there is limited evidence to support their use for treatment of flushing/transient erythema (n = 16/17 and n = 17/18, respectively). However, clinical experience suggests that these agents could be considered in certain situations. • **Topical alpha-adrenergic modulating agents** (n = 20/20), intense pulsed light (IPL; n = 15/ 15) and vascular lasers (e.g. pulsed-dye laser and 532-nm potassium titanyl phosphate laser; n = 18/18) have been added as treatment options for **persistent centrofacial erythema**. Use of IPL and vascular lasers in darker skin phototypes requires consideration by a healthcare provider with experience in this situation (n = 16/18), as it can result in dyspigmentation. • **Combination treatment could benefit some patients with more severe rosacea** (n = 20/20) and those presenting with multiple rosacea features (n = 20/21). • The benefits of combining treatments in rosacea include helping achieve skin clear of rosacea (n = 19/20); helping some patients achieve treatment goals more quickly (n = 19/20); maximizing remission periods (n = 19/20); and minimizing burden of disease (n = 19/20). Ocular rosacea • Optimal diagnosis of ocular rosacea (n = 21/21) and description of its features (n = 20/21) remain unmet needs. • The following ocular rosacea features require referral by a dermatologist to an ophthalmologist for treatment: blepharokeratoconjunctivitis (n = 20/21); sclerokeratitis (n = 20/21); anterior uveitis (n = 19/21); and blepharoconjunctivitis (n = 16/21). • Systematic, evidence-based guidelines for ocular rosacea are still required (n = 16/16)
N/A	**British Association of Dermatologists guidelines for the management of people with rosacea 2021**[1] • General recommendations on the management of Rosacea • Topical and systemic therapies to consider: (↑↑): Offer either **ivermectin**, **metronidazole** or **azelaic acid** as first-line topical treatment options to people with papulopustular rosacea. Discuss the potential for irritancy of different products and formulations prior to prescribing the topical agent.

	(↑): Consider topical **minocycline** foam in people with papulopustular rosacea (minocycline foam is currently not available in the UK). (↑): Consider topical **brimonidine** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment. (↑): Consider topical **oxymetazoline** in people with rosacea where the main presenting feature is facial erythema. Warn patients that there are reports that redness may flare after discontinuation of treatment (oxymetazoline is currently not available in the UK) *Systemic therapies* (↑↑) Offer an oral antibiotic as a first-line treatment option for more severe papulopustular rosacea. Options (in alphabetical order) include **azithromycin**, **clarithromycin**, **doxycycline 40 mg** (modified release) daily, **doxycycline 100 mg** daily, **erythromycin**, **lymecycline** and **oxytetracycline**. These antibiotics (especially tetracyclines) are considered safe and have been prescribed for rosacea for decades. There is insufficient evidence to establish the superiority of one over another, especially in the absence of head-to-head trials or a network meta-analysis. Currently, only the modified-release formulation of doxycycline is licensed specifically for papulopustular rosacea in the UK. (↑↑) Avoid minocycline in people with rosacea due to potential side-effects unless there are no other treatment options. (↑) Consider intermittent courses of low-dose **isotretinoin** (e.g. 0.25 mg kg–1) in people with persistent and severe rosacea. Discuss the potential side-effects and teratogenicity. (↑) Consider **oral propranolol** in people with rosacea where the main presenting feature is transient facial erythema (flushing). Ocular therapies (↑↑) Advise* people with ocular rosacea to minimize exposure to aggravating factors such as air conditioning, excessive central heating, smoky atmospheres, and periocular cosmetics. (↑↑) Identify* and modify/eliminate systemic medications that could be triggering eye dryness in people with ocular rosacea (e.g. antidepressants and anxiolytics). (↑↑) Offer* warm compresses using proprietary lid-warming devices and lid hygiene with

	homemade bicarbonate solution or commercially available lid wipes. (↑↑) Offer* over-the-counter **ocular lubricants or liposomal sprays** to alleviate symptoms in people with ocular rosacea, ensuring preservative-free preparations are used if using > 6 times daily. Increasing humidity using humidifiers can help to reduce tear evaporation. (↑↑) Refer* people with ocular rosacea to an ophthalmologist if they are (i) experiencing eye discomfort, sticky eye discharge persisting for > 12 months despite frequent (> 6 times daily) topical lubricant use and adequate lid hygiene; or (ii) experiencing symptoms such as reduced vision, pain on eye movement and pain that keeps the patient awake at night. • Summary of future research recommendations
N/A	**German guidelines - S2k guideline: Rosacea 2022**[7] This updated and upgraded S2k guideline deals with the diagnosis and treatment of rosacea, which is a common, chronic inflammatory skin disease mostly affecting the face. • Recommendations on general measures, UV protection, food, topical treatment. • Topical treatment recommendations ➔ Brimonidine and oxymetazoline ➔ Metronidazole ➔ Azelaic acid ➔ Ivermectin • Systemic treatment is recommended for treatment-refractory and severe forms of papulopustular rosacea. ➔ Low-dose doxycycline is recommended as the systemic treatment of choice. ➔ Low-dose isotretinoin (0.1–0.3 mg/ kg body weight [BW] is suggested as a systemic treatment for rosacea (off label). ➔ Carvedilol may be considered for systemic treatment of persistent erythema and flushing in rosacea (off label). • Ocular Rosacea management recommendations. • Dermocosmetics measures (cleansing, sunscreen, skincare)

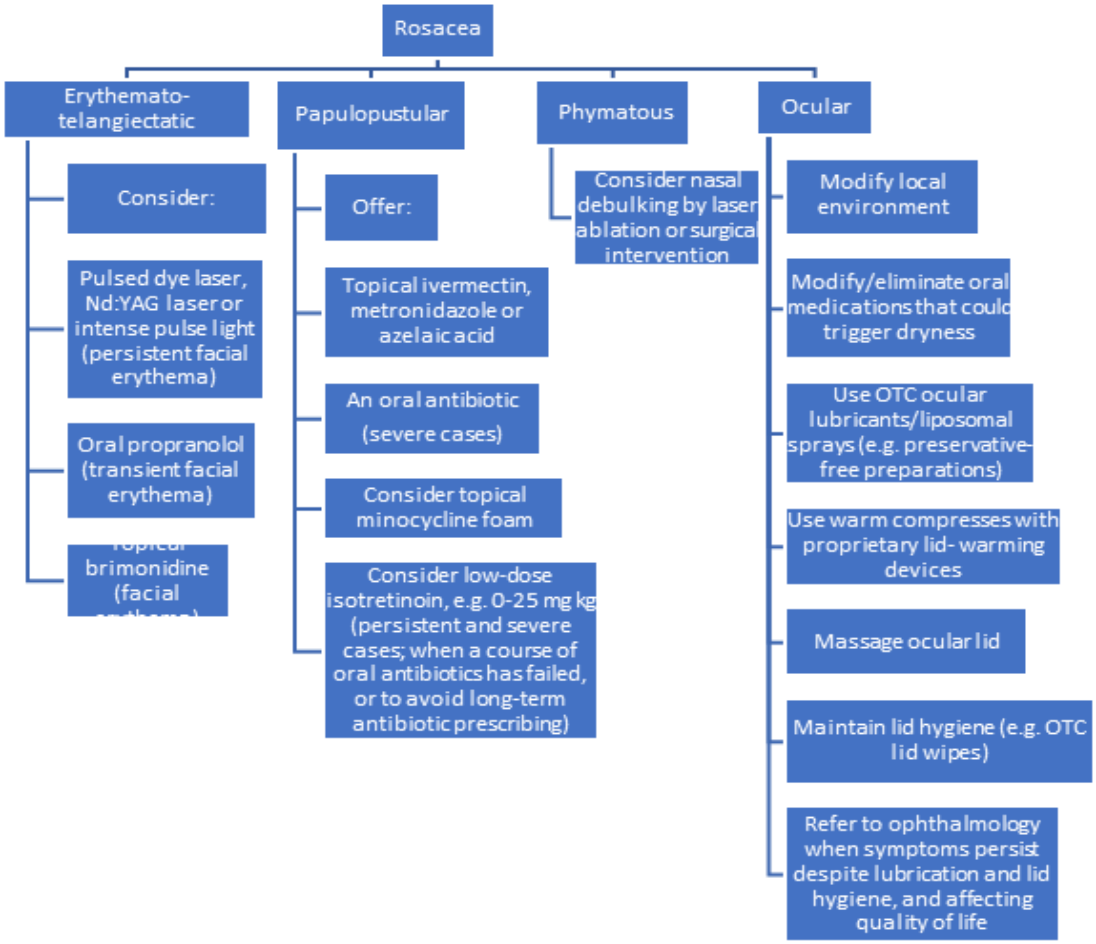
N/A	**Guidelines for the Diagnosis and Treatment of Rosacea in China 2021**[8] • Antimicrobial topical preparations: metronidazole, clindamycin, erythromycin, and ivermectin • Azelaic acid: Azelaic acid reduces the expression of kallikrein kinase-related peptidase 5 and antibacterial peptides, inhibits the release of cytokines induced by ultraviolet radiation, and improves rosacea papules and pustules.55 Azelaic acid is available in concentrations of 10%, 15%, or 20% in the form of a cream or gel, and is applied twice a day. Azelaic acid may initially cause itching, burning, and tingling, but these symptoms are generally mild and short-lived. Evidence level: A for papules and pustules; recommendation level: recommended. • Recommendations on the use of Benzoyl peroxide, external vasoconstrictor drugs and salicylic acid - Benzoyl peroxide: Benzoyl peroxide has antimicrobial effects and is used for the treatment of rosacea,56 but has some adverse reactions such as erythema, scaling, and local itching. Because of the increased skin sensitivity of patients with rosacea, benzoyl peroxide is only indicated for nasal or perioral papules and pustules. Evidence level: A for papules and pustules; recommendation level: cautiously recommended. - Salicylic acid has keratin-promoting, keratolytic, sterilizing, and antibacterial effects, and is effective for treating rosacea papules and pustules. Due to the differences in the effects and adverse reactions of different concentrations, salicylic acid must be used under the guidance of a doctor. Evidence level: B; recommendation level: cautiously recommended. • Recommendations on the use of Topical eye medications and systemic therapy • Treatment plans for different rosacea skin lesions; persistent erythema, papules and pustules, telangiectasia, phymatous changes • Ocular symptoms management
N/A	Spanish Consensus Document on the Treatment Algorithm for Rosacea **2019**[9] • Topical **brimonidine** or **oral blockers** can be considered for treating transient erythema (flushing). Evidence based. Expert consensus High quality Strong recommendation NA • Pulsed dye laser and IPL therapy are the first-choice treatments for nontransient erythema; brimonidine can be used for symptomatic treatment. Evidence based, High quality Strong

	recommendation. • **IPL** and **laser** treatments are first-line choices for telangiectasia. Expert consensus NA • Topical agents such as **ivermectin** and **metronidazole** are the first-line recommendations for treating rosacea with mild inflammatory lesions (papules and pustules). Oral doxycycline can be considered an alternative. Evidence based Moderate quality Strong recommendation. • Topical agents such as ivermectin and metronidazole and oral **doxycycline** are the first-line recommendations for treating rosacea with moderately severe inflammatory lesions (papules and pustules). Evidence based, High quality Strong recommendation. • treatment (**doxycycline** or **isotretinoin**) with or without associated topical therapy (ivermectin or metronidazole) or physical treatments are the first-line recommendations for rosacea with severe inflammatory lesions (papules and pustules). Evidence based, High quality Strong recommendation. • If **tetracyclines** are considered for the inflammatory lesions of rosacea, the minimum effective dose of doxycycline is recommended in order to minimize the risk of bacterial resistance. Evidence based, High quality Strong recommendation. • Systemic treatment with doxycycline or isotretinoin is the first-line recommendation for active phymatous lesions. Expert consensus NA • Surgical procedures such as dermabrasion, electrodesiccation, or laser treatments are recommended as first-line treatments for phymatous lesions without clinical inflammation. Scanned or pulsed carbon dioxide laser in continuous mode is preferred because it affords the ability to sculpt and provide hemostasis simultaneously. Expert consensus NA • Dermatologists should be able to recognize the ocular manifestations of rosacea. Patients with altered vision, conjunctival involvement, or signs of corneal involvement should be referred to an ophthalmologist. Expert consensus NA • The treatment of ocular rosacea depends on severity. General measures to take are adequate cleansing, the application of topical preparations (metronidazole, tetracyclines, or ciclosporin), and the use of systemic therapy (doxycycline, short-term **corticosteroids**, or isotretinoin). Expert consensus NA

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
((((((((((Rosacea[MeSH Terms]) OR (Rosacea[Title/Abstract])) OR (Acne Rosacea[Title/Abstract])) OR (Phymatous Rosacea[Title/Abstract])) OR (Rosacea, Phymatous[Title/Abstract])) OR (Ocular Rosacea[Title/Abstract])) OR (Rosacea, Ocular[Title/Abstract])) OR (Papulopustular Rosacea[Title/Abstract])) OR (Rosacea, Papulopustular[Title/Abstract])) OR (Erythematotelangiectatic Rosacea[Title/Abstract])) OR (Rosacea, Erythematotelangiectatic[Title/Abstract])) OR (Granulomatous Rosacea[Title/Abstract])) OR (Rosacea, Granulomatous[Title/Abstract])	Guideline, in the last 5 years	("Rosacea"[MeSH Terms] OR "Rosacea"[Title/Abstract] OR "acne rosacea"[Title/Abstract] OR "phymatous rosacea"[Title/Abstract] OR "rosacea phymatous"[Title/Abstract] OR "ocular rosacea"[Title/Abstract] OR "rosacea ocular"[Title/Abstract] OR "papulopustular rosacea"[Title/Abstract] OR "rosacea papulopustular"[Title/Abstract] OR "erythematotelangiectatic rosacea"[Title/Abstract] OR "rosacea erythematotelangiectatic"[Title/Abstract] OR "granulomatous rosacea"[Title/Abstract] OR "rosacea granulomatous"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	2

Appendix D. Treatment Algorithms



Nd:YAG, neodymium-doped yttrium aluminum garnet; OTC, over the counter.

Figure 2. *Management Pathway for People with Rosacea*

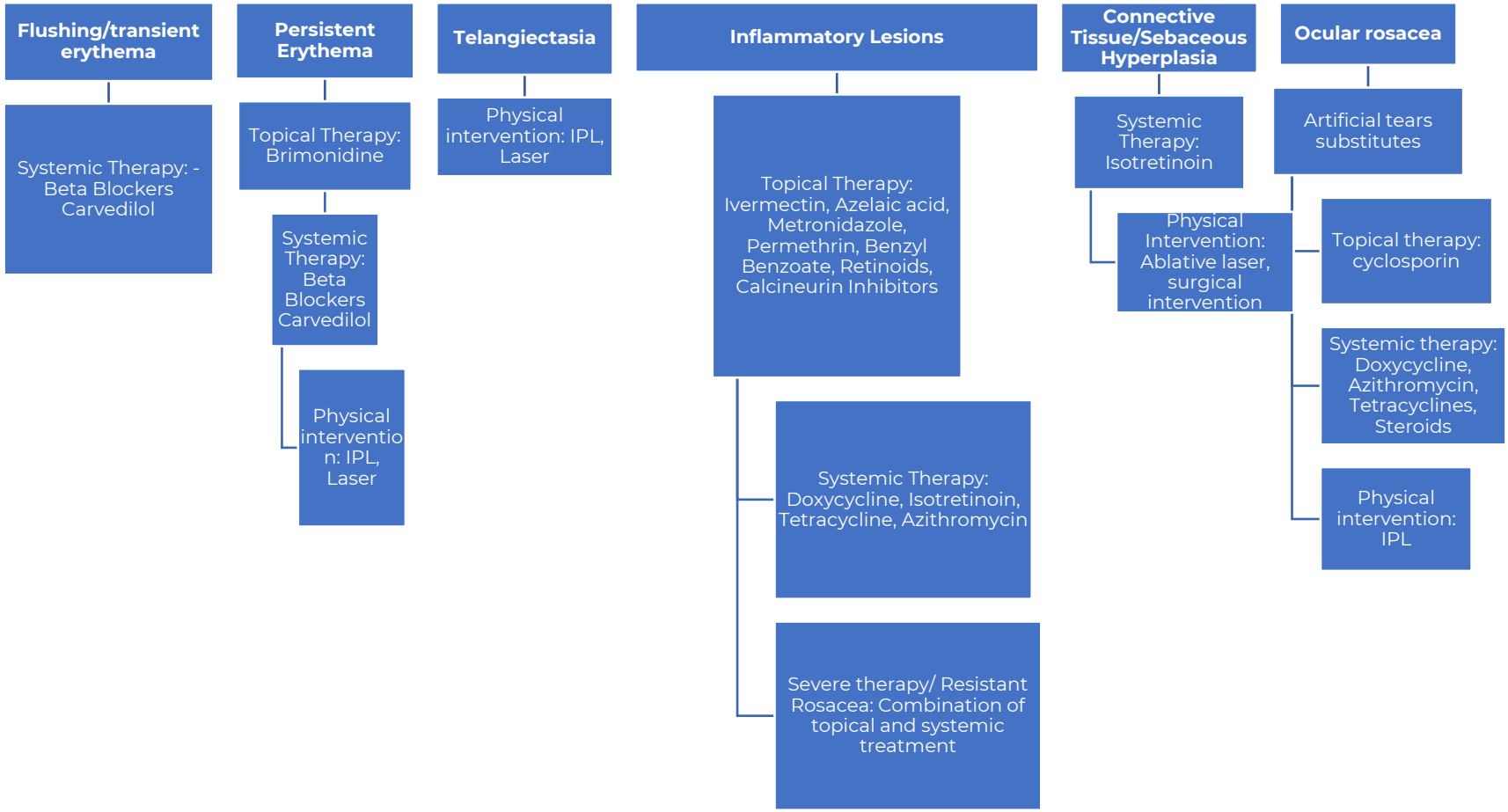


Figure 3. *Overview of Treatment Options for the Management of Rosacea*