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Cutaneous Biometrics

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Preface

In the nineteenth century, dermatology developed into a rich and highly efficient clinical specialty—on the basis of history and morphology.

In the twentieth century, the clinical laboratory provided enormous strength in refining the science.

The twenty-first century will be remembered as the century of cutaneous biometrics.

Our clinical judgments are now going to be based upon evidence-based medicine highly buttressed by metrics.

This slim textbook is our first attempt to pull together some of the rapidly building database on these metrics.

We welcome your comments and suggestions.

San Francisco, CA, USA

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Rosacea Severity Assessment: Review of Evaluation Methods Used in Clinical Trials

Kritika Joshi, Leah A. Cardwell, Sarah L. Taylor, Hossein Alinia, and Steven R. Feldman

Abstract

The pathophysiology underlying rosacea has not been fully elucidated. The therapeutic approach targets symptoms and is often fraught with suboptimal patient satisfaction and clinical results. Clinical trials have been executed to provide evidence-based support for the efficacy of novel rosacea treatment options. The current assessment tools used to classify the severity of rosacea in clinical trials are not standardized, limiting our ability to compare the efficacy of various treatments. A valid and reliable assessment methodology is merited to define the efficacy of newer rosacea treatments and provide a common ground for

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treatment comparisons. We review various rosacea severity assessment methodologies used in clinical trials, discussing findings of previous reviews and supplementing those findings with methodology used in 25 additional clinical trials published since 2014. Rosacea severity assessment is most commonly measured specifically through changes in facial erythema, followed by papules and pustular count and then telangiectasia. Visual inspection by a clinician is the most common modality of assessment of erythema, with a four-point scale as the most frequent methodology. Lesion count over the entire face is the primary mode of assessment for measuring papules and pustules, and telangiectasia measurement varied. The vast array of measurement tools and variability among numeric scales, clinical observation, and patient reports of subjective symptoms leaves the researcher and clinician without a standardized method to assess rosacea treatment and assess efficacy of novel treatments.

Keywords
Classification · Erythema · Ocular rosacea · Papules and pustules · Phymatous rosacea · Scale · Severity · Telangiectasia · Treatment

Introduction

Rosacea is a common inflammatory skin condition which tends to be relapsing and remitting in nature. The condition has higher prevalence among adults of Northern European heritage and fair skin types. There is role of family history and genetics in rosacea development, though exact genes have not been elucidated (Tan and Berg 2013). The distribution of rosacea is typically along the convexities of the face. Areas such as the cheeks, chin, forehead, and nose are affected, while perioral and periocular regions are typically spared. There are also instances of rosacea occurring outside of the facial regions, termed extrafacial rosacea.

The focus of rosacea treatment is symptomatic and aimed at reducing the primary manifestations to preserve quality of life, prevent disease progression, and sustain remission. Management of rosacea may include several steps including confirmation of diagnosis and severity of the disease, noting patient treatment history and exacerbating factors, screening for rosacea risk factors and comorbidities, addressing concerns regarding quality of life and psychosocial impact, providing general recommendations pertaining to the chronicity and relapsing/remitting nature of the disease, educating about trigger avoidance, and encouraging a gentle skin care regimen and sunscreen use. These steps encompass a strong rosacea management plan and are essential to optimal patient care (Rainer et al. 2017). Rosacea may be treated using topical medications, oral agents, laser therapy, or surgical modalities. Due to the complexities of the condition, patients are often left with unsatisfactory treatment results.

Rosacea pathophysiology involves dysregulation of the immune system resulting in increased levels of antimicrobial peptides, neuropeptides, nitric oxide radical

species, proteases, cytokines, chemokines, and vascular endothelial growth factor (VEGF). These pathways may be activated by the *Demodex* mite or by ultraviolet radiation. No diagnostic laboratory test is available; diagnosis and classification are based on clinical assessment (Tan et al. 2017). The role of the *Demodex* mite in rosacea pathogenesis has been extensively studied. *Demodex* mites are obligatory parasites of the human pilosebaceous units; they feed on epidermal cells and sebum. This parasitic feeding process may lead to disruption of the epithelial barrier that may allow for intradermal penetration of the mite resulting in cell injury via mechanical follicle blockage or triggering of foreign body immune reaction through shedding of the *Demodex* exoskeleton and waste products. A gram-negative bacterium, *Bacillus oleronius*, which is present on the *Demodex* mite is capable of proinflammatory protein production that can induce peripheral blood mononuclear cell proliferation (Tan and Berg 2013). Our growing understanding of the pathogenesis of rosacea is leading to development of new treatments, but clinical trials to assess the efficacy of new treatments require the availability of accurate measures of rosacea severity.

The primary features of rosacea include transient erythema, non-transient erythema, papules, pustules, and telangiectasia. Secondary features include burning, stinging, dryness, edema, ocular manifestations, and phymatous changes including skin thickening and a bulbous appearance. Four rosacea subtype designations were developed based off the most common groupings of these symptoms. These subtypes include erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, and ocular rosacea. The erythematotelangiectatic rosacea subtype is the most prevalent and is characterized by transient facial flushing and persistent central facial erythema with telangiectasias. This subtype may be mistaken for dermatoheliosis, or photoaging, as chronic actinic damage can cause facial telangiectasias with an erythematous background particularly in fair-skinned individuals. Papulopustular rosacea is characterized by persistent central facial erythema and a variable number of centrally located papules and/or pustules. This subtype may be misdiagnosed as acne vulgaris, but the absence of comedones and truncal lesions and predominance in older age groups differentiate papulopustular rosacea from acne vulgaris. Phymatous rosacea is characterized by thickened skin due to tissue hypertrophy, irregular nodules, and sebaceous hyperplasia. The nose is commonly affected, termed rhinophyma. Ocular rosacea is characterized by water or bloodshot eyes, foreign body sensation, burning or stinging sensation, dryness, itchiness, photosensitivity, blurred vision, conjunctival or marginal telangiectasia, lid or periocular erythema, blepharitis, conjunctivitis, chalazion, hordeolum, corneal infiltrates, corneal ulcers, or keratitis (Tan and Berg 2013). The complexity and variation of these factors make simple assessment of rosacea difficult. Within clinical trials, no single assessment methodology has been consistently used to measure rosacea severity in response to treatment (Hopkinson et al. 2015). These assessment tools are not standardized, limiting our ability to draw sound conclusions when comparing efficacy of rosacea treatment options. Previous authors have reviewed measures for rosacea, including Gessert and Bamford in 2003 and Hopkinson et al. in 2015 (Hopkinson et al. 2015; Gessert and Bamford 2003). We discuss their

findings, supplemented with additional search of the literature encompassing 25 rosacea clinical trial research articles published since 2014.

Grading System for Rosacea Severity

A standard provisional classification system of rosacea was first developed in April 2002 by the National Rosacea Society (NRS) describing the condition's primary and secondary features and delineating four subtypes based on the most common groupings of these features. This development immensely aided clinicians and researchers in grading and classification (Gallo et al. 2018).

Several established deficiencies of this classification scheme have been noted. Flushing as a primary diagnostic factor for erythematotelangiectatic rosacea is an area of debate in the field since it overlaps with the criteria for papulopustular rosacea. As flushing is subjective, may be subject to recall bias and inaccurate histories, its use may not be as useful from a diagnostic standpoint. It can be particularly difficult to establish a baseline of flushing and erythema in darker-skinned individuals possibly due to genetic differences in susceptibility, abundance of melanin masking the redness, or ultraviolet (UV)-protective effects of melanin inhibiting rosacea development as UV radiation is an aggravating factor for rosacea.

Nearly 15 year later, newer research findings have led to an update to the initial classification system. Since individual features of rosacea can span multiple subtypes or advance between subtypes, a phenotype-led approach was suggested. In 2017, there was an international consensus to change the classification system to a phenotype-led approach that aims to facilitate patient-centered management based off identification of major elements of the disease process (Gallo et al. 2018). This system describes individuals' observable characteristics that can be influenced by genetic or environmental factors, or phenotypes. Persistent, centrofacial erythema associated with periodic intensification and phymatous changes was independently considered diagnostic for rosacea. Flushing, telangiectasias, inflammatory lesions, and ocular manifestations were not considered to be individually diagnostic (Tan et al. 2017). At least one diagnostic phenotype or two major phenotypes are required for the diagnosis of rosacea (Table 1).

Severity Assessment Scales

A variety of assessment scales are used to measure rosacea severity. Validity and reliability are two important features of a scale. Validity indicates whether the scale measures what it is intended to measure. Reliability indicates whether the scale measures what it is intended to measure in a fashion that is reproducible. The three components to validity include content, construct, and criterion. Content refers to whether the scale appears to be assessing all of the relevant content or domains based on the judgment of experts. Construct refers to whether the scale agrees with other related variables and measures of the same construct with which it should agree.

Table 1 Rosacea phenotypes. Phenotypes of rosacea based on 2017 National Rosacea Society classification

Diagnostic[a]	Major[b]	Secondary
Fixed centrofacial erythema in a characteristic pattern that may periodically intensify Phymatous changes	Flushing Papules and pustules Telangiectasias Ocular manifestations Lid margin telangiectasias Interpalpebral conjunctival injection Spade-shaped infiltrates in the cornea Scleritis and sclerokeratitis	Burning sensation Stinging sensation Edema Dryness Ocular manifestations "Honey crust" and collarette accumulation at the base of the lashes Irregularity of the lid margin Evaporative tear dysfunction (rapid tear breakup time)

[a]These features by themselves are diagnostic of rosacea
[b]Two or more major features may be considered diagnostic

Criterion refers to whether the scale correlates with some other measure of the disease, ideally a gold standard, that has been used and accepted in the field. The components of reliability include inter-observer reliability, intra-observer reliability, and internal consistency. Inter-observer reliability determines whether two measurements made by two or more observers produce the same or similar results. Intra-observer reliability determines whether two measurements made by the same observer on two or more occasions produce the same or similar results. Internal consistency pertains to whether the scores from different item scales correlate with each other and with the total scale score (Schmitt 2000).

Despite advancements and recent efforts in the field, larger-scale studies and validated scales are still required for precise and dependable severity assessment of individual rosacea features. Objective and clinically practical tools are invaluable when assessing treatment targets and monitoring progress in patients with rosacea (Tan et al. 2017). Validated scales exist for the measurement of erythema, flushing, and papules/pustules. We found no validated scales for phymatous changes, telangiectasias, or ocular rosacea (Table 2). Potentially, these individual scales could be amalgamated to create one clinical score that measures response to treatment in rosacea severity (Tan et al. 2017).

Features of Rosacea Used for Assessment

The main feature of rosacea assessed in clinical trials was erythema, as this is the most common presenting sign for the majority of patients. Erythema was assessed in 29 of 32 clinical trials. The second most commonly assessed features of rosacea were papules and pustules, assessed in 23 trials, followed by telangiectasias which were assessed in 22 trials. Most often, the severity of erythema was assessed on a four-point scale, but no single methodology was used (Hopkinson et al. 2015).

Table 2 Scales in the assessment of rosacea. Scales to assess rosacea phenotypes

Phenotype	Scale
Flushing	FAST, GFSS
Persistent erythema	IGA, CEA, PSA
Telangiectasias	None
Papules/pustules	Lesion counts, IGA
Phymatous changes	None
Ocular changes	None
Psychosocial effects	RosaQoL

CEA clinician erythema assessment, *FAST* flushing assessment tool, *GFSS* global flushing severity score, *IGA*, Investigator's Global Assessment, *PSA* patient self-assessment, *RosaQoL* Rosacea quality of life index

Secondary signs and symptoms of rosacea studied in clinical trials include stinging, itching, edema, dryness, flushing, phymatous changes, ocular lesions, scaling, extrafacial signs, plaques, nodules, overall skin sensitivity, and quality of life. The most common of these being burning, as noted in nine trials, followed by stinging in seven trials. Flushing and edema were most commonly measured on a four-point scale, though none utilized the Flushing Assessment Tool (FAST). Visual analog scales were used in one trial (Neuhaus et al. 2009). One study used a seven-point scale to assess dryness (Dahl et al. 1998). Visual analog scales are sensitive for pain intensity assessment; however, they have not been validated for the assessment of erythema (Tan et al. 2014).

Erythema

Erythema, whether transient or permanent, is the main characteristic observed in rosacea. Its initial presentation is likely the beginning of an inflammatory continuum originating from a blend of neurovascular dysregulation and the innate immune system (Gallo et al. 2018). In one study, erythema was measured, not discriminating between transient and permanent, using a four-point scale defined as zero points for no perceptible erythema, one as mild to slight erythema, two as moderate to pronounced erythema, and three as severe erythema or purple hue (Tirnaksiz et al. 2012). Twenty-one studies utilized a similar four-point scale, and two studies used a five-point scale. Six-, seven-, ten-, and eleven-point scales were each used by one study.

There are several concerns that arise with the use of such scales. Inter-rater reliability may be limited by subjectivity and error. The studies that assessed erythema did not discriminate between background erythema, an expression of vascular reactivity, and perilesional erythema, an expression of the inflammatory response (Hopkinson et al. 2015).

Flushing/Transient Erythema Scales

Flushing Assessment Tool (FAST)

The Flushing Assessment Tool (FAST) was developed to assess flushing symptoms in response to niacin therapy in patients with dyslipidemia (Kawata et al. 2009). The components of flushing are cutaneous warmth, redness, itching, or tingling. The FAST is administered through an electronic patient diary that is used to measure the flushing experienced by patients on a daily basis. It assesses the severity of flushing and impact of flushing on daily activities and sleep. No rosacea clinical trials utilized this method as a means to measure flushing (Hopkinson et al. 2015).

Global Flushing Severity Score (GFSS)

The Global Flushing Severity Score (GFSS) is an item within the Flushing Symptom Questionnaire that assesses overall flushing on a scale from one to ten. This was developed to assess the flushing symptoms associated with niacin use. Scoring is on a scale of 0 (none) to 10 (extreme). The Flushing Symptom Questionnaire was validated in a randomized, double-blind, placebo-controlled trial of extended-release niacin versus placebo and was deemed to be a reliable and valid tool to assess niacin-induced flushing (Norquist et al. 2007).

Persistent Erythema

Investigator's Global Assessment (IGA)

This scale is a simple subjective measurement of a patient's condition and typically ranges from zero to four. It is widely used among researchers for evaluating rosacea and psoriasis severity in clinical trials. These scales have been used in clinical trials for at least 35 years, initially with mental health studies on anxiety and dementia, and then in immunoinflammatory diseases. There are variations of this scale ranging from 4 points to 13 points; no single version has been accepted as the standard scale (Langley et al. 2015).

In analyzing the strengths and weaknesses of the five-point IGA scale as a measurement tool for psoriasis, the scale was noted to be relatively simple and intuitive but not well validated and including a small number of ordinal point scores, leaving room for improper severity classification (Langley et al. 2015).

Clinician Erythema Assessment (CEA)

The Clinician Erythema Assessment scale is a five-point grading scale for facial erythema severity commonly used as a measurement for rosacea severity. In a study

assessing the inter-rater and intra-rater agreement of this grading scale, it was noted to be a reliable measure of the facial erythema associated with rosacea. The rating process involved each dermatologist evaluating the patients twice using photographs accompanying the CEA scale. The inter-rater reliability showed a weighted kappa of 0.74 for the first session and 0.673 for session two. For intra-rater reliability, the overall weighted kappa score between the two sessions was 0.692, indicating good results. To improve the scale, authors suggested the addition of a "very severe" grade to complete the spectrum (Tan et al. 2014).

Patient Self-Assessment (PSA)

The Patient Self-Assessment (PSA) tool mirrors the CEA in that it is based on a five-point scoring system but instead assesses the patients' level of satisfaction with their facial redness. In a study assessing the validity of the PSA tool through the use of test-retest reliability, construct validity, and known-group validity based on data collected for a rosacea clinical trial evaluating the efficacy of brimonidine gel in the treatment of erythema associated with rosacea, the scale was determined to be appropriate for use though the results were most generalizable to moderate to severe erythema (Tan and Leoni 2015).

Telangiectasia Scales

There is no designated scale for telangiectasia assessment. No single method was primarily used among the clinical trials. Of the 32 trials, 22 utilized telangiectasias as a means of severity assessment. Seventeen of the 22 utilized a four-point scale, with five-, seven-, and ten-point scales also used once each. Only four of the studies that utilized the four-point scale used a scale from 0 (absence of telangiectasias) to 3 (severe, or many fine vessels and large vessels covering greater than 30% of the face) to clearly define telangiectasias based on the size of the vessels and the percentage of the face that is covered by the vessels. One study used a simple two-point scale, either presence or absence of telangiectasias. Two of the studies that used a four-point scale initially began with a numerical count of the vessels visibly seen on the face but then converted to a four-point scale.

Papules and Pustules

Lesion Counts

Counting the lesions on the entire face by the clinician is the most common approach to evaluating papules and pustules. Twenty-three of the 32 studies utilized this method. Half used clinician counts, and the other half used a four-point (14 studies)

or five-point (2 studies) scale. Four trials did not measure papules or pustules at all when assessing rosacea severity.

IGA Scales

Global assessment scales, as discussed previously, are also an option to assess for papule and pustules on a more subjective level.

Quality of Life Scales

Rosacea Quality of Life Index (RosaQoL)

The patient burden of rosacea can be significant; however, few tools exist to measure the psychosocial burden of rosacea. Seventy-five percent of rosacea patients have low self-esteem, 70% feel embarrassed, and 69% feel frustrated due to their rosacea (Rainer et al. 2017). The Rosacea Quality of Life Index (RosaQoL) is a quality of life assessment tool which is specific to rosacea. RosaQoL has a 21-item scale, but does not cover phymatous changes. The outcome scores also lack an indication of clinical relevance. These limitations may reduce the usefulness of RosaQoL in clinical practice. Relative to the Skindex-29 quality of life survey, the RosaQoL was more sensitive (Palubin and Chen 2005).

Walsgrave Hospital Rosacea Scoring System

A separate scoring system developed in England was named the Walsgrave Hospital Scoring system. According to this method, rosacea involvement of the face was measured in seven different areas including the forehead, nose, right cheek, left cheek, chin, right paranasal, and left paranasal. Each of these areas was assessed for erythema, telangiectasia, papules, pustules, edema, and scaling. A score of one was given if less than half of each area was involved and a score of two if half or more was involved. If there were areas of rosacea outside of the face, this was noted as well. Total and inflammatory lesion scores were calculated separately, and total scores were the sum of the scores given to each parameter for each area. For inflammatory lesion scores, only the score of two parameters (papules and pustules) was used for evaluation. Only one study has used this system; there have not been any validation or analyses performed on the strength of this system (JTM 1998; Bakar et al. 2004).

Advanced Methods

Spectrophotometry

Advanced methods such as spectrophotometry have been in existence since 1940, though their use in dermatology is relatively new. This device may be used to measure erythema and melanin pigment concentration in skin and serves as a method to potentially diagnose melanoma and provide an objective measure of erythema. Use of this measurement tool may provide an impartial assessment of treatment response to rosacea therapies with respect to erythema severity. The various spectrophotometric devices available include the Chromameter CL-200A (Minolta, Osaka, Japan), the DermaSpectrometer (Cortex Technology, Hadsund, Denmark), and the Mexameter M X16 (Courage-Khazaka Electronic, Ko¨ln, Germany).

The Mexameter M X16 consists of 16 light-emitting diodes arranged circularly that emit light at three defined wavelengths of 568 nm, 660 nm, and 880 nm, corresponding to green, red, and infrared, respectively. A photodetector measures the light reflected by the skin. With this information, the melanin and erythema indices can be computed. The skin measurement area is 5 mm in diameter, and the probe is applied on the skin surface with a constant pressure of 91 g/cm^2. Measurements are either discrete, up to a total of 8, with average values of two through eight or continuous (Clarys et al. 2000). There is now a newer version of this device, the M X18, which is more sensitive to color changes than the previous version.

The DermaSpectrometer's light-emitting diodes emit light at two defined wavelengths of 568 nm (green) and 655 nm (red), and a photodetector measures the light reflected by the skin. It measures the absorbed and reflected light at wavelengths in the green and red for hemoglobin and melanin, respectively. A melanin index and an erythema index are computed from the intensity of the absorbed and the reflected light at 568 and 655 nm, similar to the Mexameter. The skin measuring area is 6 mm in diameter, and the probe is applied on the skin surface with a pressure of 158 g/cm^2 (Clarys et al. 2000).

The Chromameter illuminates the skin's surface via a pulsed xenon arc lamp. The light reflected perpendicular to the surface is collected for a tristimulus color analysis at 450, 560, and 600 nm, using the L*a*b* color system. L* represents the relative brightness from total black (L* = 0) to total white (L* = 100), a* represents the balance between red and green, and b* represents the balance between yellow and blue. The a* parameter is the most fitting to assess the redness of skin and its progression over time. Unlike the other two devices, the Chromameter does not give information about the substances that generate the color. The skin measurement area is 8 mm in diameter, and the probe is applied on the skin surface at a pressure of 368 g/cm^2 (Clarys et al. 2000).

The tristimulus colorimeter, or the Chromameter, is qualified to measure all colors, whereas the simple reflectance meters, Mexameter and DermaSpectrometer, are created to measure the concentration of erythema- and melanin-induced pigmentation. These instruments are discriminative and sensitive in measuring normal skin colors for both fair and darker skin types (Clarys et al. 2000). Eight clinical trials have utilized spectrophotometry as a means to assess erythema.

Computer Analysis of Digital Photograph

Computer analysis of a digital photograph is another method used to assess and provide an objective record of treatment response over time. Though not as popular as clinical evaluation through the use of scales or spectrophotometry, it is still a viable option. Three trials used computer analysis of a color digital photograph as a means to assess erythema. In one particular study, a photograph album of six photographs varying in rosacea severity served as a visual reference marker for erythema progression to treatment response throughout the course of the trial (Rigopoulos et al. 2005). A third trial used cross-polarized photographs to analyze skin redness. Their software analyzed L*, a*, and b* parameters from the red, green, and blue components of the digital images. L* represents the relative brightness from total black (L* = 0) to total white (L* = 100), a* represents the balance between red and green, and b* represents the balance between yellow and blue. The a* parameter is the most fitting to assess the redness of skin, and its progression over time was used to record the effectiveness of the treatment being tested in the trial (Dupont et al. 2012). There was variance in methodology even among these three trials. Though the measurements may be objective and statistically significant, there is no consistency in between trials, thus, leaving the researcher to question which treatment is of most benefit to patients.

As of 2017, there have been 25 additional clinical trials testing various treatment methods for rosacea management. Only one utilized the DermaSpectrometer, while the rest utilized various methods, namely, erythema scales and global assessment scales. The trends were similar to the findings by Hopkinson et al.

Future Developments

Assessment of rosacea severity is critical to guiding disease management and evaluating the efficacy of a particular treatment during clinical trials. There are various methodologies which assess the severity of rosacea, but these tools are not standardized. This lack of standardization hinders our ability to compare the utility of particular treatments in the management of rosacea. In an effort to stratify the major phenotypes of rosacea, a new scale idea has been proposed (Tan et al. 2017).