Review

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The Pathophysiology, Diagnosis and Management of Chronic Inflammatory Skin Diseases

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Atopic dermatitis, psoriasis, rosacea, seborrheic dermatitis, allergic contact dermatitis, and irritant contact dermatitis comprise a large proportion of chronic inflammatory dermatoses. This paper reviews the clinical presentations, pathophysiology, and therapeutics of inflammatory dermatoses, highlighting recent drug developments such as lebrikizumab for atopic dermatitis as well as deucravacitinib and spesolimab for psoriasis. Chronic inflammatory dermatoses significantly impact patient quality of life and contribute to substantial healthcare costs. Effective management of severe cases often requires systemic therapies and biological therapies. A thorough clinical evaluation with a tailored therapeutic approach is essential for delivering optimal care to individuals with chronic inflammatory skin diseases.

Keywords: atopic dermatitis; psoriasis; rosacea; seborrheic dermatitis; allergic contact dermatitis; irritant contact dermatitis

Introduction

Inflammatory dermatoses are the most common chronic skin conditions in the field of dermatology. They are characterized by persistent inflammation and lead to significant psychosocial burdens and high healthcare costs [1]. Due to their widespread prevalence and profound impact, a solid understanding of chronic inflammatory skin disease is essential to providing quality patient care. While a dysfunction of skin barrier integrity underlies most chronic inflammatory dermatoses, some have a primarily genetic etiology while others are more influenced by external triggers. Depending on the disease type, inflammation could be mediated by the innate or adaptive immune system, or both. Furthermore, differences in pathogenesis directly guide directions in pharmacological therapy. This review synthesizes our current understanding of the basic pathophysiology, diagnostics, and management of six common chronic inflammatory skin diseases. We will first review the most prevalent chronic inflammatory diseases such as atopic dermatitis and psoriasis, then discuss other common conditions such as rosacea, seborrheic dermatitis, and contact dermatoses.

Atopic Dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. It is an immune-mediated disease characterized by intensely pruritic eruptions with an increasing worldwide prevalence, ranging from 13.5% to 41.9% in children and 1.5% to 4.9% in adults [2,3]. Typically, AD onset occurs within the first five years of life, though 25% of adults report onset during adulthood [2–4]. Many patients with infant-onset AD see complete resolution by adulthood, though some cases persist. Along with asthma and allergic rhinitis, AD is part of the "atopic triad" [5,6]. This term refers to the common progressive succession or co-occurrence of three related atopic conditions. Prevalence appears to be increasing particularly in industrializing populations in Africa, East Asia, Western Europe, and Northern Europe [4,7]. This phenomenon supports the hygiene hypothesis, which states that lower microbial exposures early in life are associated with autoimmune diseases and may explain the increasing prevalence of AD in industrializing nations [8].

Clinical Features

Clinical features include intensely pruritic, erythematous, ill-defined patches and plaques, often with xerosis and lichenification. Acute flares often consist of crusting papules with exudates, while chronic AD may exhibit more scale, excoriation, lichenification, and fissuring. Affected areas in infants and young children often include the cheeks, scalp, and extensor surfaces [6]. Although the distribution in adults varies widely, affected areas often include the face, neck, hands, and flexor surfaces of the skin [9].

Etiology

Atopic dermatitis (AD) is a clinically diverse and complex disease of epidermal barrier dysfunction triggered by environmental factors in genetically susceptible individu-

als. The two main theories in AD pathogenesis are the "outside-in" hypothesis, which states that the breaching of skin barrier integrity drives immune system malfunction, and the "inside-out" hypothesis, which states that cytokine and immune dysregulation drive skin barrier malfunction [8].

The modern definition of AD integrates the two paradigms and describes it as a heterogeneous disease with T helper (Th) cells playing a central role [10]. The fate of Th differentiation is primarily regulated by Janus kinase (JAK) signaling [11]. Classically, the immune response in AD is an acute proliferation of Th2 in the early phase and a mixed Th2, Th1, and Th17 response in the chronic phase. Activated Th2 release interleukins (IL), especially IL-4, which induces a positive feedback loop for Th2 differentiation and immunoglobulin E (IgE) production [11,12]. Overproduction of IgE is associated with type 1 hypersensitivity and is the hallmark of atopy. While most cases of AD are interleukin-4 (IL-4) and IgE-mediated, about 20% are non-IgE-mediated [13]. Other cytokines produced by Th2 include IL-13, which promotes inflammation and alteration of skin microbiome, and IL-31, which promotes pruritus [14]. Alteration of the skin microbiome is now identified as a major component of AD pathogenesis. In particular, studies have shown that overgrowth of Staphylococcus aureus is associated with AD flares. S. aureus also alters the cutaneous microbiome environment and results in a feed-forward loop of IL-4, IL-13, and IL-31 secretion that contribute to AD severity [15].

As mentioned, AD is genetically predisposed in susceptible individuals. Most commonly, AD is associated with a mutation on chromosome 1q21 of Filaggrin, which is a structural protein in the stratum corneum [16]. Fillaggrin maintains the epidermal barrier and hydration of the skin, and mutations in this protein lead to earlier onset of AD, more severe disease course, and increased infection risk due to physical barrier disruption [17]. Other genetic predispositions of AD include an imbalance between protease and antiprotease activity in the stratum corneum, resulting in desquamation and cytokine activation, further damaging the epidermal barrier [18]. Disruption of the claudin-1 protein in tight junctions in the epidermis may also influence atopic dermatitis and contribute to the damaging of skin barrier integrity [19].

Making the Diagnosis

AD is primarily a clinical diagnosis based on patient history and physical examination. Several diagnostic criteria are available: the 1980 Hanifin and Rajka criteria, the UK Working Party's Diagnostic Criteria, and the American Academy of Dermatology criteria (Table 1, Ref. [20–22]. Disease severity can be assessed with the SCORing AD (SCORAD) index and the Eczema Area and Severity Index (EASI). Several conditions present similarly to AD and should be ruled out. These include conditions such as seborrheic dermatitis, allergic/irritant contact dermatitis, psoriasis, and cutaneous T-cell lymphoma [22].

Testing Overview

There is no recommended testing regimen for the diagnosis or treatment of AD; however, clinicians may request histologic confirmation. Although AD is often an IgE-mediated disease, obtaining serum IgE levels is not recommended as this test is nonspecific.

Management

The goals for the management of AD involve the avoidance of aggravating factors, restoration of the skin barrier, and pharmacologic treatment of skin inflammation [22–25]. Barrier protection with topical emollients (i.e., lotions, creams, and ointments) and topical corticosteroids (TCSs) (e.g., triamcinolone, clobetasol) are considered first-line therapy for mild to moderate AD. Alternative agents include topical medications involving calcineurin inhibition (e.g., tacrolimus and pimecrolimus), phosphodiesterase 4 inhibition (crisaborole), JAK inhibition (ruxolitinib), and an aryl hydrocarbon receptor agonist (tapinarof) [26]. These agents are particularly useful in sensitive areas at risk for skin atrophy secondary to the use of potent topical steroid use (e.g., face, genitalia).

For moderate to severe disease, therapies such as phototherapy, biologic agents, and JAK inhibitors may be considered [24]. Currently, two Food and Drug Administration (FDA)-approved biologic therapies are available in the United States. Dupilumab, a monoclonal antibody targeting interleukin-4 (IL-4) receptor alpha (shared by the receptors for both IL-4 and IL-13), was the first biological medication approved by the FDA for the treatment of AD [27]. It is approved for adults and children aged 6 months and older and is administered via subcutaneous injections. Tralokinumab, which targets IL-13, is approved for the treatment of AD in adults and children aged 12 years and older [28]. Lebrikizumab also targets IL-13 and could potentially be approved for AD in the United States soon [29]. Another new biologic, nemolizumab, is approved to treat AD in Japan [30]. It works by targeting IL-31 and is currently under FDA review for AD treatment in the United States.

Oral JAK inhibitors are significantly changing the management of atopic dermatitis by offering a new mechanism of action that directly targets the immune pathways responsible for the disease. JAK inhibitors target the JAK/Signal Transducer and Activator of Transcription (STAT) pathway, which is critical for transmitting signals from these cytokines and other immune mediators.

In randomized clinical trials involving the oral JAK inhibitors upadacitinib and abrocitinib, 67% and 55% of patients, respectively, experienced significant itch reduction compared to placebo [31–35]. A study comparing upadacitinib with dupilumab demonstrated that upadacitinib provided superior itch relief within one week, with a 31.4% reduction compared to 8.8% [31].

Table 1. Comparison of the diagnostic criteria for atopic dermatitis

Diagnostic criteria	1980 Hanifin and Rajka criteria [20]	UK Working Party's Diagnostic criteria [21]	American Academy of Dermatology criteria [22]
	Original diagnostic criteria Requires ≥3 of 4 basic features and ≥3 of 19 minor features.	Requires having an itchy skin condition and ≥3 of 5 additional features. Most abbreviated criteria Intended to take under 2 minutes per patient to assess. Can be used to assess patients without a physical exam.	Newest criteria Requires ≥3 of 5 essential features and ≥2 of 3 important features and ≥1 of 16 associated features. Higher specificity than the 1980 Hanifin-Rajka criteria Optimal for pediatric patients.

Systemic medications with serious side effects, such as methotrexate, upadacitinib, or abrocitinib, which require laboratory monitoring, should be reserved for patients with a clear underlying cause or those whose quality of life is severely affected and have not responded to topical treatments.

Preventative Measures and Lifestyle Modifications

Since inadequate barrier hydration contributes to and is exacerbated by AD, preventative measures and lifestyle modifications are recommended [25]. Although the literature has shown that the frequency of showers or baths does not contribute to AD, avoiding hot water can prevent dehydration of the epidermis. The use of fragrance-free products, including soaps, perfumes, detergents, and cleaning products, may help prevent or attenuate AD flares. Rough clothing can also exacerbate the condition and should be avoided. Environmental allergens are also a potential contributory factor for AD, particularly in the context of the atopic triad [5]. Lastly, hypersensitivity to mold, pollen, house dust mites, and animal dander can be associated with AD, although a causal relationship is not well-supported.

Psoriasis

Psoriasis is a common, chronic, inflammatory skin disease typically characterized by well-demarcated, erythematous plaques with overlying scales. Subtypes include chronic plaque psoriasis, inverse psoriasis, guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, and palmoplantar psoriasis [36]. Although psoriasis is primarily considered a dermatologic disease, associations with comorbid conditions such as diabetes mellitus, cardiovascular disease, and cancer have been demonstrated. In particular, psoriatic arthritis is essential to distinguish from other causes of arthritis (e.g., osteoarthritis) as proper management can potentially lead to attenuation of the joint destruction process [37].

The prevalence of psoriasis is estimated at 3% of the U.S. population and between 0.5–11.4% of adults worldwide [38,39]. There is a bimodal distribution of the age of onset, with the first peak between the ages of 16 and 22 years and the second between the ages of 57 and 60 years.

Clinical Features

The most common subtype, chronic plaque psoriasis, often presents with sharply demarcated, symmetric plaques with silvery scales on the extensor surfaces, trunk, and/or scalp [36,40]. Pinpoint bleeding following the debridement of scale (Auspitz sign) and lesions in areas of skin trauma (koebnerization) may be observed [41]. Plaques presenting in intertriginous areas, such as the inguinal folds, axillae, and interdigital spaces, characterize inverse (intertriginous) psoriasis [42]. These lesions are often aggravated or worsened by sweat and friction. Guttate psoriasis typically presents with the sudden onset of many small erythematous, scaly papules in a characteristic “drop-like” pattern on the proximal extremities and trunk [36,40]. This presentation often follows a streptococcal infection. Generalized pustular psoriasis is a potentially life-threatening type of psoriasis, characterized by widespread pustules on erythematous skin. A sub-type of pustular psoriasis, palmoplantar psoriasis, is isolated to the palms and soles and often causes severe pain [43]. Lastly, erythrodermic psoriasis is a potentially fatal form of psoriasis characterized by generalized erythema covering over 80 percent of the entire body surface. The erythematous lesions are often followed by subsequent desquamation, fever, hypothermia, and sepsis.

Nail involvement is common, with pitting, subungual hyperkeratosis, onycholysis, discoloration, and splinter hemorrhages constituting the most frequent nail findings. Additionally, about 1 in 4 psoriasis patients will develop psoriatic arthritis [37]. Symptoms consistent with psoriatic arthritis include pain, tenderness, and swelling of the joints, ligaments, or tendons (e.g., enthesitis). Psoriatic arthritis is typically managed by a rheumatologist with systemic medications [44].

Etiology

Psoriasis is a chronic inflammatory disease characterized by accelerated epidermal proliferation in patients with a genetic predisposition [45]. The immune dysregulation in psoriasis involves both innate and adaptive immune systems including dendritic cells, T-lymphocytes, and cytokines. Dendritic cells secrete IL-12 and IL-23, which activate T-helper (Th) proliferation, especially the Th1 and Th17 subtypes [46]. Th1 and Th17 release major inflammatory cytokines such as tumor necrosis factor (TNF), IL-6, and IL-17, leading to abnormal keratinocyte differentiation that manifests as the characteristic scaly psoriatic plaques. IL-17 increases neutrophil recruitment in the dermis, dilating and elongating the dermal blood vessels, which causes the erythema of psoriatic lesions. IL-17 also induces the nucleotide oligomerization domain (NOD)-like receptor-containing protein 3 (NLRP3) inflammasome in keratinocytes, producing cathelicidin LL-37 autoantigens that maintain chronic dermal inflammation. While the mechanism is not fully clear, dysregulated secretion of IL-36 by keratinocytes and other innate immune cells can increase neutrophil-mediated pustule formation in generalized pustular psoriasis [47].

Genetically, the psoriasis-susceptibility (PSORS1) locus and Human Leukocyte Antigen (HLA)-Cw6 gene in the major histocompatibility complex (MHC) region of chromosome 6p21 have been associated with psoriasis [48]. Genetic mutations at loci associated with IL-12 and IL-23 signaling–and thus immune modulation–have also been implicated due to the inflammatory nature of the disease [49].

Well-known environmental inciting factors of psoriasis include stress, infection, hypocalcemia, and medica-

tions such as lithium or non-steroidal anti-inflammatory drugs (NSAIDs) [50]. Abrupt cessation of systemic corticosteroids may also incite pustular or erythrodermic psoriasis. Lastly, palmoplantar psoriasis has been associated with environmental factors like smoking and mechanical friction or trauma [43].

Making the Diagnosis and Testing Overview

Since psoriasis is a clinical diagnosis, testing is often not required. However, skin biopsies may be done to confirm the diagnosis, particularly in cases with uncertain etiology such as erythroderma [50]. Histologic findings typically include epidermal thickening, elongated rete ridges, diminished granular layer, neutrophil infiltration, and dilation of dermal vasculature [45]. A potassium hydroxide (KOH) test or culture of lesional tissue/fluid may help rule out dermatophytes or other pathogens [40].

The differential diagnosis of psoriasis vulgaris includes lichen planus, atopic dermatitis, nummular eczema, pityriasis lichenoides chronica, dermatomyositis, pityriasis rubra pilaris, and tinea corporis. More dangerous conditions that may present similarly to psoriasis vulgaris include secondary syphilis, cutaneous T-cell lymphoma, and subacute cutaneous lupus erythematosus [51]. Due to the diffuse, rapidly progressive rash common with pustular and erythrodermic psoriasis, the differential diagnosis should include Stevens-Johnsons syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis [40,51]. Since palmoplantar psoriasis is located mainly on the palms and soles, it can be mistaken for several similarly presenting conditions. Dyshidrotic eczema, particularly when scarred or lichenified, can appear similar. Irritant dermatitis, folliculitis, and allergic contact dermatitis should also be considered.

Management

For mild psoriasis, topical corticosteroids (e.g., triamcinolone) and topical emollients are considered first-line therapies [36]. Topical vitamin D analogs (e.g., calcipotriene) and calcineurin inhibitors (e.g., tacrolimus) are effective, particularly in sensitive skin areas. In moderate to severe disease, oral systemic agents and injectable biologic medications are indicated [50]. Methotrexate and cyclosporine have traditionally been the most common oral systemic medications for the treatment of moderate to severe psoriasis. Other systemic oral medications include apremilast and acitretin [52]. In 2022, Deucravacitinib, an oral TYK2 inhibitor, was approved for the management of moderate to severe plaque psoriasis. In clinical trials, deucravacitinib demonstrated significant efficacy compared to both placebo and apremilast [53].

Since the 2000s, many biologic agents have been approved for the treatment of psoriasis (Table 2, Ref. [36,54,55]). These biologic medications are often grouped based on their mechanism of action. Tumor necrosis factor-alpha (TNF-α) inhibitors include adalimumab, certolizumab, etanercept, adalimumab, infliximab, and golimumab [54]. IL-17 inhibitors include bimekizumab, secukinumab, brodalumab, and ixekizumab. IL-23 inhibitors include tildrakizumab, risankizumab, guselkumab, and ustekinumab, which also have IL-12 inhibitor activity. Another approved therapeutic agent is spesolimab (IL-36 inhibitor), which significantly improves and prevents generalized pustular psoriasis flares in a randomized control trial [55]. In general, biologics are administered anywhere from weekly to every 3 months, with patient preference leaning towards longer intervals [56]. Overall, biologic agents have a high efficacy in treating moderate to severe psoriasis. The newer drugs risankizumab, guselkumab, ixekizumab, and brodalumab have achieved more than 90% reduction in the Psoriasis Area Severity Index (PASI) within 70%–80% of patients at 16 weeks in randomized controlled trials [44]. Furthermore, the complete clearance rate of psoriasis ranges from 50–60% of patients at 52 weeks. Lastly, phototherapy is an option for moderate-to-severe psoriasis that is unresponsive to topical medications [36].

Table 2. List of FDA-approved psoriatic biologics.

Mechanism of action	FDA approved medications [36,54,55]
IL-17 inhibitors	bimekizumab secukinumab brodalumab ixekizumab
IL-12/23 inhibitors	ustekinumab
IL-23 inhibitors	tildrakizumab risankizumab guselkumab
IL-36 inhibitors	spesolimab
TNF-α inhibitors	certolizumab etanercept adalimumab infliximab golimumab

FDA, Food and Drug Administration; IL, interleukin; TNF-α, Tumor necrosis factor-alpha.

Rosacea

Rosacea is a chronic, inflammatory skin disorder that predominantly affects the face and eyes. The true prevalence of rosacea is difficult to assess but global prevalence is estimated to be 5.5% [57]. Historically, rosacea has been reported to be more prevalent in fair-skinned individuals; however, the masking of rosacea with skin pigmentation may result in underdiagnosis in darker-skinned individuals. Rosacea becomes more prevalent with age and peaks during the 45-to-60-year age group. The condition is more common in females, but males may develop a more severe disease [58]. Rosacea is associated with systemic inflamma-

tory disorders (e.g., inflammatory bowel disease), malignancies, autoimmune disorders, and neurological disorders (e.g., Alzheimer's, migraines) [59].

Clinical Features

While guidelines have changed over time, the National Rosacea Society (NRS) previously described 4 subtypes and 1 variant of rosacea: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PhR), ocular rosacea, and granulomatous rosacea (GR) [60]. The most common subtypes, ETR and PPR, represent 57% and 43% of all rosacea in a meta-analysis [61]. ETR and PPR primarily involve the convexities of the cheek, nose, chin, and forehead. ETR presents with centrofacial erythema, persistent facial flushing, and limited papule or pustule formation. PPR is characterized by papules, pustules, erythema, and telangiectasias in the centrofacial area. PhR is characterized by the progressive hyperplasia of connective tissue and sebaceous glands, predominantly involving the nasal dermis [62]. Clinically, it often presents as a bulbous, erythematous, and nodular deformity of the nose, often with telangiectasia and sebaceous hypertrophy. Ocular rosacea is characterized by chronic eye irritation, erythema, and dryness [63]. GR, previously described by the NRS as a variant subtype of rosacea, is characterized by centrofacial papulonodular lesions that are typically hard, yellow, red, or brown [64]. The GR subtype of rosacea is more common in African American or African individuals. Other disorders related but not classified as rosacea include pyoderma faciale, neurogenic rosacea, and Morbihan disease.

The classification of rosacea by the NRS has since been updated in 2017 with recommendations from the global Rosacea Consensus (ROSCO) panel to focus on a phenotype-based approach (see "Making the Diagnosis" section below).

Etiology

The pathogenesis of rosacea remains imperfectly understood. However, current literature describes rosacea as a disorder of skin barrier and immune dysfunction that can be exacerbated by environmental triggers [65–67]. Anecdotal triggers of rosacea are well documented, including but not limited to stress, emotional events, hot and spicy foods, ultraviolet (UV) light, heat, alcohol, exercise, bacterial overgrowth, microorganisms, as well as drugs and topical products. Demodex mite infection is associated with papulopustular lesions. Alcohol consumption is a known risk factor for phymatous rosacea in males while smoking is a known risk factor in females [68,69]. While Helicobacter pylori infection is associated with rosacea, the link is weak, and targeted treatment results in little to no substantial therapeutic difference [70]. Genetic predisposition to rosacea may be due to single nucleotide polymorphisms [66].

Early-stage rosacea is characterized by neurovascular dysregulation with increased innate immunity activity. Mast cell density is generally increased in all types of rosacea. Neurovascular dysregulation in ETR is thought to be mediated by increased local vasoactive factors such as transient receptor potential vanilloid channel receptors (TRPV), calcitonin, substance P, neurokinin-1, and vascular endothelial growth factor-A (VEGF-A) [65,67]. UV light or Demodex infection can increase the activity of Toll-like-receptor-2 and keratinocyte protease kallikrein 5, generating abnormal production of the neutrophil-associated antimicrobial peptide cathelicidin LL-37. Altered cathelicidin causes angiogenesis and chronic inflammation through the NLRP3 inflammasome. Papulopustular development is associated with increased mast cell density, IL-8 release, Th1/Th17, and perifollicular neutrophil recruitment. Late and severe rosacea activate B cells and plasma cells, particularly in PPR and PhR subtypes. Other mediators of rosacea pathogenesis include increased MMP, decreased TGF-beta, and altered dermis elastotic content [64].

Making the Diagnosis

Rosacea diagnosis is usually made from clinical observation and patient history. According to the most updated NRS criteria, at least one diagnostic phenotype or two major phenotypes must be present to diagnose rosacea [71]. The diagnostic phenotypes of rosacea include (1) persistent centrofacial erythema with periodic intensifications and (2) phymatous changes. Centrofacial erythema is the most common sign of rosacea and is associated with periodic intensifications and blushing in phototypes I to IV. Phymatous changes are defined by phymas, which are enlarged glandular follicles frequently affecting the nose (less often the chin, forehead, ears, or eyelids) that are accompanied by fibrosis and a bulbous appearance. The major phenotypes of rosacea include (1) flushing, (2) telangiectasias, (3) papules or pustules, and (4) ocular manifestations. While not used in making a definitive diagnosis, secondary phenotypes can help guide the clinical assessment of rosacea. They include (1) skin burning or stinging, (2) dry appearance, (3) edema, and (4) ocular manifestations nonspecific to rosacea.

Papules and pustules may be the only clinical manifestations of rosacea in darker skin types as erythema and telangiectasia can be subtle or difficult to detect. However, a history of burning and tingling symptoms, and hyperpigmentation can be helpful in diagnosis [57,71]. Skin biopsy is rarely indicated and only performed to rule out other skin disorders or to diagnose granulomatous rosacea [64]. Differential diagnoses include actinic damage, seborrheic dermatitis, acute cutaneous lupus erythematosus, dermatomyositis, acne vulgaris, drug-induced eruptions, and perioral dermatitis.

Several validated scales exist for grading severity and quality of life in rosacea patients, including the Flushing Assessment Tool, the Global Flushing Severity Scale for flushing, the Clinician's Erythema Assessment, the Patient's Self-Assessment for persistent erythema, the Rosacea Quality of Life Index (RosaQoL), and the Dermatology Life Quality Index [72].

Testing Overview

Rosacea is a clinical diagnosis with no definitive laboratory test. However, patients with rosacea often exhibit significantly elevated levels of systemic inflammation, such as erythrocyte sedimentation rate and C-reactive protein [73]. Other laboratory findings may include an increased systemic immune inflammation (SII) index, monocyte count, and platelet count. A slit-lamp examination may be useful in detecting keratitis and scleritis in ocular rosacea [71].

Histopathological examination of rosacea reveals blood vessel and lymphatic proliferation, accompanied by perivascular mast cells and macrophage infiltrate [74]. In cases of ETR, perivascular and perifollicular lymphohistiocytic infiltrate with vascular changes and solar elastosis may be present. PPR presents with similar histology as ETR but is additionally marked by dense follicular infiltrates accompanied by spongiosis and exocytosis. PhR histological findings include sebaceous gland hyperplasia, fibrosis, lymphocytic infiltrate, and hair follicle dilation [62]. Ocular rosacea is characterized by infiltration of phagocytic cells and antigen-presenting cell infiltration in the conjunctival epithelium [63]. GR shows mixed lymphohistiocytic inflammation and noncaseating epithelioid granulomas [64].

Management

There is no definitive cure for rosacea. Management of rosacea often involves a multifaceted approach (Table 3, Ref. [75–82]). Multiple guidelines are available, including those by the National Rosacea Society (NRS), American Acne & Rosacea Society (AARS), British Association of Dermatologists (BAD), Canadian Clinical Practice Guidelines for Rosacea, and the global Rosacea Consensus (ROSCO) Panel [71,75,76]. Recent guidelines from the NRS in 2019 emphasize therapies targeting specific symptoms and phenotypes rather than focusing solely on rosacea subtypes.

Initial management for mild rosacea characterized by skin sensitivity, dryness, flushing, or centrofacial erythema alone involves conservative measures (e.g., Sun protection, avoidance of triggering factors, gentle non-soap skin cleansing, moisturization).

Persistent centrofacial erythema unresponsive to conservative therapy may be managed with topical medication, oral medication, light therapy, and/or laser therapy [76–78]. Typically, treatment begins with a combined oral and topical regimen followed by long-term use of a single agent during remission. For persistent centrofacial erythema, there is robust evidence supporting the efficacy of topical alpha agonists such as brimonidine or oxymetazoline, which reduce facial redness by causing vasoconstriction of cutaneous blood vessels. FDA-approved topical treatments for papules or pustules include ivermectin, metronidazole, azelaic acid, minocycline foam, and various sulfa formulations. Other off-label topical medications include benzoyl peroxide, clindamycin, minocycline, tacrolimus, and pimecrolimus, as well as anti-parasitic medications such as permethrin. Oral extended-release doxycycline 40 mg has a favorable safety profile with a low risk of developing resistance. It is highly effective in treating papulopustular lesions and commonly used for ocular rosacea. Off-label oral drugs for severe rosacea include antimicrobial doxycycline, azithromycin, minocycline, tetracycline, isotretinoin, trimethoprim-sulfamethoxazole, and clindamycin. Oral antibiotics are typically reserved for papulopustular lesions and are rarely used for flushing or persistent erythema alone. Beta-blockers such as carvedilol and propranolol are rarely used off-label to treat flushing and persistent erythema with moderate efficacy. Notably, botulinum toxin can help reduce erythema and flushing in rosacea [79]. Additionally, low-dose oral mirtazapine may ameliorate hot flashes [80].

Regarding non-pharmacologic therapies, intense pulsed light (IPL), pulsed dye laser, and potassium titanyl phosphate (KTP) are effective in treating persistent erythema, flushing, and telangiectasias in rosacea. Phymatous changes are particularly resistant to topical therapies and no gold standard management exists. Inflamed phymas are usually treated with oral doxycycline and isotretinoin. Surgical interventions and lasers such as neodymium, erbium laser, carbon dioxide (CO_2) laser, blade and radio excision, dermabrasion, or cryosurgery may be beneficial but carry risks of scarring [81]. Ocular rosacea is typically managed topically with Ivermectin and metronidazole, and orally with omega-3 supplements and doxycycline. Non-FDA-approved therapy includes topical cyclosporine ophthalmic emulsions, macrolide emulsions, and tacrolimus. In addition, IPL following periocular treatment can improve symptoms, and thermal pulsation may help with meibomian gland dysfunction.

No standard treatment exists for granulomatous rosacea due to a lack of randomized control trials. Mainstay therapies include oral tetracycline, isotretinoin, or dapsone [82]. CO_2 lasers and pulsed dye lasers can be used in GR but can also lead to scarring [81,82]. Pediatric rosacea is managed similarly to adults, but oral tetracyclines are contraindicated in children under 8 years of age and replaced by macrolides (e.g., azithromycin) [83]. All guidelines emphasize the importance of photoprotection, avoidance of known triggers, and use of non-irritating topical products to prevent exacerbation and flare-ups of rosacea [76–78].

Table 3. Treatment options for rosacea based on phenotypes: medications, procedures, and conservative measures [75–82].

	Persistent centrofacial erythema	Papules or pustules	Phymatous changes	Flushing	Telangiectasias	Ocular rosacea
Topical FDA approved	brimonidine* oxymetazoline*	ivermectin* metronidazole* azelaic acid* minocycline foam sulfacetamide sodium/sulfur	-	brimonidine oxymetazoline ivermectin	-	ivermectin metronidazole
Topical (off-label)	-	benzoyl peroxide clindamycin retinoids	retinoids	-	retinoids	cyclosporin, azithromycin, tacrolimus
Oral FDA approved	-	doxycycline 40 mg extended release*	-	-	-	doxycycline 40 mg extended-release
Oral (off-label)	carvedilol, doxycycline, minocycline, tetracycline	doxycycline, azithromycin, minocycline, tetracycline, isotretinoin, trimethoprim-sulfamethoxazole clindamycin	doxycycline, azithromycin, minocycline, tetracycline, isotretinoin, trimethoprim-sulfamethoxazole	low dose mirtazapine, propranolol, carvedilol	-	cyclosporin azithromycin doxycycline minocycline tetracycline trimethoprim-sulfamethoxazole
Light, laser, surgical interventions, and procedures	intense pulsed light (IPL), pulsed dye laser, potassium titanyl phosphate (KTP)	-	neodymium laser, erbium laser, CO_2 laser, blade and radio excision, dermabrasion, cryosurgery	intense pulsed light (IPL), potassium titanyl phosphate (KTP), intradermal botulinum toxin	intense pulsed light (IPL), pulsed dye laser, potassium titanyl phosphate (KTP)	intense pulsed light (IPL), thermal pulsations
Conservative measures	Avoidance of known triggers, soap cleansers, and irritating topical products. photoprotection with metal oxide sunscreen sun protection factor 30+					omega-3 supplements, sunglasses, eye lubrication

*High efficacy with strong supporting evidence from randomized clinical trials.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is a chronic, relapsing, papulosquamous dermatitis characterized by scaling, erythema, and itching [84,85]. The least severe form of SD, pityriasis capitis/pityriasis sicca, is characterized by small, dry skin flakes commonly (i.e., dandruff) and affects about half of the adult population [86]. According to a 2019 global epidemiological study, the prevalence of clinically significant SD is around 3%, with a higher incidence in males compared to females in the older population. Although SD can affect individuals of any age, its incidence follows a biphasic distribution, affecting approximately 72% of infants during the first three months and 11.6% of middle-aged and elderly people [86]. Risk factors for SD include Parkinson's Disease and various immunodeficiencies, such as human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), syphilis, and organ transplantation [85,87]. The incidence of SD in patients with HIV or AIDS is much higher and ranges from 30–83% [88].

Clinical Features

Generally, SD affects skin areas rich in sebaceous glands, such as the scalp, face, upper chest, back, and intertriginous areas. Infantile seborrheic dermatitis is a type of chronic, nonpruritic SD characterized by confluent, folliculocentric scaly papules and plaques with a yellowish-greasy crust affecting the scalp [84,85]. This condition is commonly known as "cradle cap". Infantile SD is thought to be influenced by transplacental maternal androgens and cutaneous biome alterations [89]. Additionally, it is associated with excessive shedding of the scalp (pityriasis amiantacea) and atopic dermatitis [90].

Adult seborrheic dermatitis, characterized by flaky, greasy, erythematous patches, can affect the face, scalp, and less commonly the trunk or torso [84,85]. On the face, the nasolabial folds are commonly affected and may appear scaly, erythematous, gray, or hyperpigmented, depending on skin color. Scalp SD ranges from mild pruritus to severe inflammation with patchy, salmon-colored greasy scales. SD affecting the scalp often covers the temporoparietal area and can sometimes spread to the postauricular area, with the potential for superimposed ear infections.

Truncal SD can present as the common petaloid type, marked by fine scaling with small perifollicular papules over the sternum, or the rarer pityriasiform type, marked by oval erythematous patches resembling pityriasis rosea. Other types of SD affecting the torso include the psoriasiform type with thick scaly plaques, the arcuate type with annular plaques with central clearings (seborrheic eczema in kids), and the intertriginous type with scaly erythema of the axillary, inframammary, crural, or umbilical areas. HIV-associated SD may have an acute, sudden onset with widespread, recalcitrant scaling associated with discharge [88].

Etiology

The cause of SD is presently unknown. While SD is associated with sebaceous glands, it is not a primary disease of these glands or sebum excretion. The most accepted explanation of SD pathology involves skin barrier dysfunction secondary to nonspecific immune responses, particularly to the Malassezia spp. [85,91]. Malassezia yeast is a known constituent of normal skin flora but is found at a higher density in patients with SD. It thrives in high-lipid environments such as sebaceous glands. The higher androgen levels and sebaceous gland activity in males may explain the higher prevalence of SD compared to females [89]. Malassezia-derived lipases break down sebaceous gland triglycerides and release abundant free fatty acids [92]. These fatty acids trigger inflammation and proliferation of the epidermis. Hyperproliferation of the epidermis leads to incomplete corneocyte differentiation and compromises skin barrier function, leading to the clinical presentation of scaling, redness, and itching. SD lesions also have elevated cytokine markers such as IL-1 that stimulate keratinocyte proliferation and differentiation [84,85,92]. Additionally, Malassezia spp. is a strong inducer of the NLRP3 inflammasomes when recognized by the immune system [93].

Nutritional deficiencies, drugs, and neurological disorders, (e.g., Parkinson's Disease (PD)), have also been associated with SD [85]. While the exact underlying mechanism is unclear, the connection between SD and PD might be directly related to Malassezia. Recent studies have found a higher diversity of Malassezia on the skin of patients with PD, and several studies suggest that Malassezia can survive in internal organs and parts of the central nervous system [94]. Additionally, Malassezia uses levodopa to produce melanin, suggesting it may be a direct contributor to PD [95]. More research is needed to elucidate the association between SD and PD.

Making the Diagnosis

Currently, there is no uniform clinical evaluation criterion for assessing SD. The three most tell-tale signs of SD are erythema, scalp flaking, and pruritus [85]. According to the American Academy of Dermatology Association (AAD), the diagnosis of SD is usually made based on clinical presentation alone, with the location of the lesions being an important factor in diagnosis, such as those affecting the scalp, face, or chest. Biopsies are reserved only for uncertain cases or overlapping conditions, such as sebopsoriasis.

A non-exhaustive list of differential diagnoses includes tinea amiantacea, tinea versicolor, tinea corporis, pityriasis rosea, psoriasis, rosacea, allergic contact dermatitis, systemic lupus erythematosus, and pemphigus foliaceus.

Testing Overview

Since SD is clinically diagnosed, further testing is usually not required. KOH prep, skin swabs, microscopy, or

culture can help identify Malassezia or other concurrent microorganism infections. Most affected individuals are healthy, but SD has been associated with immunodeficiencies, thus serology may present with decreased cluster of differentiation 4 (CD4+) cell counts, positive HIV, or positive Venereal Disease Research Laboratory (VDRL) markers [85,88,96]. Additional associated serology findings include zinc and other nutritional deficiencies. In a cross-sectional study assessing biological laboratory markers of SD, patients with SD had an increase in sebaceous gland secretion rate, an increase in transepidermal water loss, and a decrease in stratum corneum hydration [97].

The histology of SD presents with nonspecific spongiosis and psoriasiform hyperplasia [84,85]. Acute SD presents with shoulder parakeratosis or the buildup of scales around the follicular opening and prominent lymphocytic exocytosis. Chronic SD presents with psoriasiform hyperplasia and parakeratosis with lichenoid lymphocytic infiltrates. HIV-associated SD presents with necrotic keratinocytes in addition to widespread spongiosis and parakeratosis [96].

Management

SD is managed mainly through long-term treatment aimed at reducing symptoms of erythema, scaling, and pruritus using topical agents (Table 4, Ref. [98–106]). Scalp SD is particularly responsive to antifungal shampoos used daily initially and then maintained twice per week. Ketoconazole 2% and ciclopirox 1% are the most common formulations followed by miconazole [98,99]. For mild SD or dandruff, over-the-counter shampoos such as (e.g., selenium sulfide, zinc pyrithione) can be utilized before trying prescription-strength shampoo. Unfortunately, antifungal shampoo can rarely lose its efficacy due to Malassezia's resistance to the medication. In such cases, rotating shampoos every few weeks or months can be effective at preventing antifungal resistance.

For patients experiencing thick scales on the scalp, salicylic acid or coal tar shampoo can be helpful in exfoliation. If a patient is experiencing more severe SD or scalp pruritus, topical corticosteroids such as betamethasone or clobetasol can be incorporated into the regimen daily and then twice weekly, alternating with antifungal shampoos [98].

Depending on severity, facial SD is managed with topical antifungals alone or with concurrent topical corticosteroids. However, long-term use of steroids can cause skin atrophy, telangiectasias, and striae, which may be undesirable on the face. Other medications, such as calcineurin inhibitors tacrolimus and pimecrolimus, are sometimes used off-label to treat facial SD as an alternative to steroid medication [98]. Additionally, phosphodiesterase-4 (PDE4) inhibitors roflumilast and crisaborole have high efficacy with low adverse effects, but high costs may be a barrier to use [100,101]. Other medications, such as nonsteroidal topical device cream (NSTD), NSAIDs, and lithium sulfate ointments, may help reduce inflammation with fewer side effects [102,103]. Oral antifungals are not recommended for SD unless it is severe and recalcitrant, in which case oral itraconazole can be given for a course of seven days followed by varying intermittent therapy for maintenance [104].

Irritant Contact Dermatitis

Clinical Features

Irritant contact dermatitis (ICD) is a non-immune mediated, localized inflammatory response to a chemical or physical agent without prior sensitization or exposure [107]. Common chemical irritants include detergents, surfactants, solvents, water-soluble agents, oxidizing agents, acids, and alkalis. Irritation can occur from solvents removing lipids from the stratum corneum and detergents removing lipids and water-containing substances from the skin; both damage the protective barrier of the skin [108]. In contrast, physical irritants (such as soil, dust, and wood) cause friction or microtrauma to the stratum corneum of the skin, leading to irritation [109]. Physical and chemical irritants may work synergistically to disrupt the skin barrier.

ICD is the most common variant of contact dermatitis and the most frequent cause of hand eczema [110]. In 2021–2022, the Bureau of Labor Statistics reported 3460 cases of occupational contact dermatitis, although mild cases were likely underreported [111]. Epidemiologic data on occupational contact dermatitis is limited due to a lack of standardization of case definitions and methods [112].

Occupational contact dermatitis (OCD) (consisting of ICD and/or allergic contact dermatitis (ACD)) is estimated to impact 1700 per 100,000 workers each year [110]. Data has estimated that ICD accounts for 32–71% of OCD cases, while ACD causes 34–60% [112]. Occupations involving exposure to "wet work" (e.g., hairdressing or housekeeping) are particularly at risk of developing occupational contact dermatitis, with other risk factors including the use of occlusive gloves and exposure to fresh foods, detergents, oils, and dirt [110]. "Wet work" (defined as skin exposed to liquids, use of occlusive gloves for more than 2 hours daily, or hand washing more than 20 times daily) causes the stratum corneum to swell and disrupts intercellular lipids in the skin, making the skin more permeable and susceptible to irritants [113].

Dermatitis of the hands most frequently affects females aged 20–59, likely because many female-dominated occupations (e.g., hairdressing, cleaning, housekeeping) involve extensive wet work in addition to more frequent domestic exposures [110,114]. A study have found no gender difference regarding irritant reactivity [110].

Response to irritants is multifactorial; it varies based on the thickness of the stratum corneum in the exposed area, skin barrier function, and environmental factors. Areas most prone to ICD include the face, dorsum of the hands,

Table 4. Oral and topical treatments for seborrheic dermatitis [98–106].

	Topical agent	Frequency and duration	Potential side effects (SE)
Topical antifungals	ketoconazole 1%, 2% shampoo, foam or gel ciclopirox 1% shampoo, 0.77% gel miconazole 2% shampoo or solution	daily initially, then twice per week for at least 4 weeks, alternating if necessary	irritation, dryness, pruritus
Nonsteroidals for concurrent rosacea (off-label)	metronidazole 0.75% gel azelaic acid 15% gel	twice daily, at least 4 weeks	burning, irritation
Topical steroids	betamethasone valerate 0.12% foam clobetasol propionate 0.05% shampoo, solution fluocinolone 0.1% shampoo, 0.1% solution	twice daily during flares, then twice weekly as needed, alternating with other agents if necessary	burning, erythema, folliculitis, atrophy, striae, telangiectasia, and hypopigmentation
Calcineurin inhibitors (off-label)	tacrolimus 0.03%, 0.1% ointment pimecrolimus 1% cream	twice daily, 4 to 16 weeks	rosacea-like demodicidosis
Phosphodiesterase-4 (PDE4) inhibitors	roflumilast 0.3% foam crisaborole 2% cream	once to twice daily, from 2–8 weeks	contact dermatitis
Nonprescription agents	selenium sulfide zinc pyrithione lithium sulfate or gluconate nonsteroidal topical device cream (NSTD)	twice per week for selenium or zinc twice daily for lithium or NSTD	irritation, hair discoloration

All prescription agents are FDA-approved for SD unless otherwise noted for off-label use.

and finger webs [112]. Individuals with chronically impaired barrier function, such as those with atopic dermatitis, are particularly susceptible to developing ICD [110]. The environment also influences the skin's response to irritants. High temperatures and airflow decrease skin barrier function, increasing exposure to irritants [115]. During cold temperatures and low humidity, there is increased transepidermal water loss, making the skin more vulnerable to irritants [116]. High humidity may disrupt the skin barrier and enhance inflammatory responses to chemical or mechanical irritants [115].

Repeat exposure to irritants can lead to the "hardening phenomenon," where the skin gradually becomes less reactive to an irritant after repeated exposure [117]. Evidence of this phenomenon may include changes in skin morphology such as acanthosis and hyperkeratosis, alteration of lipids within the stratum corneum, changes in barrier permeability, and enhanced expression of inflammatory mediators.

Etiology

The initiating event of ICD involves disruption of the stratum corneum through either occlusion or chemical or physical irritants, leading to enhanced cutaneous permeability, transepidermal water loss, and reduced natural moisturization [118]. Direct epidermal injury from exposure to surfactants (i.e., sodium lauryl sulfate, used for provocative testing in many experimental ICD studies) initiates innate immune responses, resulting in the release of cytokines such as IL-1, TNF-α, and IL-6 [119]. This process induces increased vascular permeability and recruitment of CD4+ and CD8+ T cells, macrophages, and neutrophils to the site of injury.

It is unknown why ICD becomes chronic in some patients. Long-term inflammation may expose the immune system to immunogenic skin peptides, resulting in persistent recruitment of inflammatory mediators. TNF-α is regulated in an autocrine manner and may therefore maintain inflammation [120].

Making the Diagnosis

For diagnosing ICD, a complete skin examination and patient history are needed. The patient's occupation, occupational and home exposures, hobbies, hand-washing habits, and relevant medical history and/or cosmetic use are investigated. If an occupational exposure is suspected, the material safety data sheets of products are reviewed to identify potential offending irritants. Clues suggestive of ICD include pain, burning, or stinging that surpasses itching, symptom onset within minutes to hours of exposure, and a history of exposure to chemical or physical agents. Notably, the rash should improve when irritants are removed, a response commonly described as the decrescendo effect [121].

On exam, localized areas of inflammation with a glazed, parched, or scalded appearance of the epidermis may be observed, with more scaling, hyperkeratosis, or fissuring than vesicular changes [121]. Hands, especially the dorsal aspect, are the most commonly affected area, but other exposed areas such as the face and neck may also be affected [110]. Notably, it is difficult to distinguish between ICD and ACD based on morphology, especially when the condition is chronic [107].

Differential diagnoses to consider include allergic contact dermatitis, atopic dermatitis, psoriasis, hand eczema, fungal infections, and scabies.

Testing Overview

If the condition is chronic or not responding to therapy, patch testing is recommended to rule out ACD. However, it is possible for both ICD and ACD to coexist. Skin biopsies are not routinely performed unless there is a need to rule out other conditions such as psoriasis. Histologic features of ICD vary based on the stage and severity of skin lesions and histopathologic features of ICD are indistinguishable from allergic contact dermatitis and eczema [122].

Management

The first goal of ICD management is avoidance of offending substances and contact with other irritants (detergents, cleaning agents, fragrances, solvents). Next, protective measures such as moisturization and barrier cream application (especially after handwashing) may be incorporated. When appropriate, the substitution of alcohol-based hand sanitizer for traditional hand washing with a mild, fragrance-free cleanser is recommended [123].

In the workplace, patients should utilize personal protective equipment (i.e., gloves, goggles, face masks, *etc.*) as appropriate to reduce exposure to irritants. If the patient has occupational exposure to wet work or glove use, switching to a vinyl glove with a cotton lining and limiting wet work is recommended. When using gloves, patients should avoid prolonged wear and frequent glove changing.

Active treatment of ICD involves reducing inflammation and restoring the skin barrier through the use of topical corticosteroids in addition to emollients (Table 5, Ref. [123–127]) [124,125]. For mild, non-facial ICD, the application of a high-potency corticosteroid such as fluocinonide or betamethasone dipropionate for 2–4 weeks is indicated. For severe, non-facial ICD, high to very high-potency topical corticosteroid (e.g., clobetasol propionate) to the affected area for 2–4 weeks may be used. If lesions involve the face or flexure regions, a medium to low potency topical corticosteroid may be applied to the affected area for 1–2 weeks [126,127].

Allergic Contact Dermatitis

Clinical Features

Allergic contact dermatitis (ACD) is a type IV/delayed hypersensitivity response in the skin to an antigen in sensi-

tized individuals [128]. In contrast to ICD, ACD requires prior allergen exposure and sensitization. This induces the expansion of antigen-specific T-cell populations. After re-exposure to the allergen, a localized inflammatory cutaneous response occurs, which ranges from mild to intense depending on the sensitizing ability and concentration of the allergen. The most commonly ICD-affected areas are the hands, face, or eyelids [129].

In the United States and the United Kingdom, the annual incidence of contact dermatitis (including both ACD and ICD) is 13 to 34 cases per 100,000 workers [130,131]. ACD manifests most commonly during adulthood; however, the sensitization process likely begins during childhood [132]. Risk factors include occupational exposure, history of atopic dermatitis, stasis dermatitis, and venous ulcerations [133].

Common specific causes of ACD include poison ivy/oak, nickel, rubber gloves, hair dyes, preservatives, fragrances, textile chemicals, sunscreens, and photo allergens [128]. A meta-analysis of over 20,000 patch-tested individuals identified nickel as the most common allergen and 20–40% of the world population is estimated to be allergic to nickel [134–139]. Other identified allergens included fragrance mix, cobalt, and Myroxylon pereirae (also known as balsam of Peru) [140]. Common occupation-related causes of ACD include resins, acrylics, soap, cleansers, rubber-related materials, or protective equipment [141].

Etiology

Upon initial exposure, an allergen penetrates the stratum corneum and is taken up by Langerhans cells. These cells migrate to lymph nodes, presenting the allergen to T cells leading to clonal expansion and creation of sensitized antigen-specific T-lymphocytes [128]. Subsequent exposure triggers T cell activation and release of inflammatory mediators, leading to characteristic skin inflammation, itching, and rash. There are multiple pathological factors involved in ACD such as the causative agent (which may have concomitant irritant actions), mode and means of exposition (cutaneous vs systemic; direct vs aero-mediated), tissue structures involved, and the anatomic properties of the cutaneous region being impacted [142]. Other factors to keep in mind are environmental (UV, temperature, humidity) which was further discussed in the ICD section, and other individual patient characteristics (preexisting dermatitis in the involved area, personal variation in itching intensity and/or sensitizing level). The individual's susceptibility can also be associated with genetic variation (single-nucleotide polymorphisms (SNPs) of genes) which may contribute to sensitization to weaker allergens such as NMDA or nickel, although the genetics of ACD is not fully understood [143].

There are some clinical patterns of noneczematous ACD linked to topical or systemic use of specific allergens. Erythema multiforme-like ACD is particularly common with exposure to exotic plants and woods (e.g., Capsicum, *Toxicodendron radicans* (poison ivy)), medicaments (e.g., neomycin, ethylenediamine), and chemicals such as formaldehyde, epoxy resin, and many more [142]. Rubber compounds (e.g., mercaptobenzothiazole), textile compounds (e.g., formaldehyde resins), plants such as d-Limonene, and many others are frequently the cause of a purpuric ACD. Lichenoid ACD is uncommon but when present, is most often linked to color-developing substances, particularly substances derived from para-phenylenediamine [142].

Making the Diagnosis

Similar to ICD, diagnosis of ACD requires a complete history and skin examination [128]. Information on the patient's occupation, hobbies, systemic and topical medications, lifestyle, fragrance and/or perfume use, cosmetics, toiletries, and relevant medical history should be obtained. Personal products such as eyeglasses, gloves, or clothing may need to be evaluated. History of long-term use or exposure to an allergen does not rule out contact allergy as the susceptibility of individuals may change over time, and multiple exposures may be required for sensitization [144]. Although pruritus is the dominant symptom of ACD, the patient may report other symptoms such as pain, burning, or stinging [145].

On examination, acute ACD lesions appear as erythematous, indurated plaques with overlying scales. If the eyelids, lips, or genitalia are involved, edema may be appreciated. In severe cases, vesiculation and bullae may occur. With continued exposure to allergens, acanthosis, hyperkeratosis, edema, and cellular infiltration in the dermis occurs, resulting in dry, scaly, and thicker skin [144].

ACD is usually localized to areas of the skin in contact with the allergen and distribution may provide clues on which allergen(s) are involved (Table 6, Ref. [129,141]). Identification of the allergen based on skin examination alone is difficult as the response to the allergen may extend beyond the site of application. It is important to keep in mind that certain allergens may be transferred to distant skin areas (e.g., rinse-off products such as hair dyes and shampoos) resulting in dermatitis of the neck, eyelids, scalp, and lateral face [146].

Testing Overview

Patch testing can support the diagnosis of ACD and is highly recommended if ACD is suspected [147].

Management

Once patch testing has been completed or when allergens are otherwise identified, avoidance of the culprit allergen is the primary objective of management [148]. The American Contact Dermatitis Society's Contact Allergen Management Program (CAMP) is a resource for the identification of personal care products free from identified allergens. Otherwise, patients are instructed to carefully

Table 5. General measures and treatments for irritant contact dermatitis [123–127].

Preventative measures		
Avoid the irritating substance(s). Frequent use of moisturizers and barrier creams. Gentle hand hygiene. Substitute alcohol-based hand sanitizer when appropriate. Use personal protective equipment to reduce exposure to irritants. Limit wet work and switch to a vinyl glove with cotton lining. Avoid prolonged glove wear or frequent glove changing.		
Treatments for irritant contact dermatitis		
Potency group	topical corticosteroid examples (non-exhaustive list)	application frequency
Severe, non-facial irritant contact dermatitis		
Super high potency	betamethasone dipropionate 0.05% ointment clobetasol propionate 0.05% ointment	1–2 times per day for 2–4 weeks
Mild, non-facial irritant contact dermatitis		
High potency	amcinonide 0.1% ointment, clobetasol propionate 0.025% cream, diflorasone 0.05% ointment, halobetasol propionate 0.01% cream, triamcinolone acetonide 0.5% ointment	1–2 times per day for 2–4 weeks
Irritant contact dermatitis involving the face or flexural regions		
Medium potency	betamethasone dipropionate 0.05% spray, fluocinolone acetonide 0.025% ointment, mometasone furoate 0.1% cream, triamcinolone acetonide 0.05% ointment	1–2 times daily for 1–2 weeks
Lower mid potency	betamethasone dipropionate 0.05% lotion, desonide 0.05% ointment, fluocinolone acetonide 0.025% cream, hydrocortisone butyrate 0.1% cream	1–2 times daily for 1–2 weeks
Low potency	alclometasone dipropionate 0.05% cream, betamethasone valerate 0.1% lotion fluocinolone acetonide 0.01% cream, triamcinolone acetonide 0.025% cream	1–2 times daily for 1–2 weeks

Table 6. Clinical features of allergic contact dermatitis [129,141].

Lesion distribution	Suspected allergen
Hands-only	may be occupational, look for occupation-specific exposures
Scalp +/- adjacent skin	product applied to the scalp (hair dyes, shampoos)
Face	cosmetic products, tools, or allergens transferred to the face such as nail polish
Periocular, perioral, or genital	fragrances, detergents, preservatives in hygiene products, or wet wipes
Trunk involvement with prominent lesions in the axillary folds	textile dyes or textiles
Lesions at the location of waistbands	rubber from the elastic waistband
Dorsal foot	shoe chemicals such as rubber accelerators or potassium dichromate
Photo-exposed areas	photoallergic contact dermatitis
Pendant-like lesions involving the neck and chest	fragrance in perfume or lotions

scalp +/- adjacent skin, Scalp with or without involvement of adjacent skin.

analyze ingredient labels on topically applied products (e.g., personal care/cosmetic products. If the patient has a nickel allergy or sensitivity, a nickel test kit may be used to identify nickel-releasing objects in home or work environments. In addition to avoidance of culprit allergens, frequent application of emollients may be used to help support healthy skin barrier function [148].

Pharmacologic treatment of ACD varies based on lesion severity and location. For the treatment of non-sensitive areas (e.g., trunk and extremities), mid-high potency topical corticosteroids (e.g., triamcinolone) are used with a frequency of 1–2 times per day and for a duration of 2–4 weeks or until symptoms resolve (Table 7, Ref. [145,148]. In areas with relatively thicker skin (e.g., palms), high-potency topical corticosteroids (e.g., clobetasol) are often required to control symptoms [145,148]. For ACD in sensitive areas (e.g., face, genitalia) a medium to low-potency topical corticosteroid or non-steroidal agent (e.g., tacrolimus) applied 1–2 times per day for 1–2 weeks is advised [149,150]. If over 20% of the total body surface area is involved or there is extensive or severe ACD of the face, hands, feet, or genitalia, systemic corticosteroids are recommended [145,148]. For example, prednisone (0.5 to 1 mg/kg per day) may be given for seven days, followed by a gradual taper and discontinuation.

If dermatitis persists despite allergen avoidance and topical therapies, it is important to explore alternative diagnoses or a concurrent diagnosis such as atopic dermatitis [150]. Some alternative therapies for chronic ACD include systemic immunosuppressive agents such as methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine, or phototherapy (bath psoralen plus ultraviolet A photochemotherapy or narrowband ultraviolet B) [151,152]. Of note, studies utilizing phototherapy were limited to patients with chronic hand eczema, and more data is needed to generalize findings to other regions of the body [152].

Discussion

Atopic dermatitis (AD), psoriasis, rosacea, seborrheic dermatitis (SD), and contact dermatoses (irritant contact dermatitis (ICD), allergic contact dermatitis (ACD)) share several constitutive similarities including immune dysregulation and microbial interactions. Discerning the subtle differences in the pathogenesis of each condition is critical for proper assessment and management.

Immune dysregulation is a common theme in inflammatory dermatoses, but the specific pathogenic mechanism behind each cutaneous pathology is different. For example, psoriasis is strongly associated with the CD4+ Th1 and Th17-driven immune response with cytokines (IL-12, IL-23, IL-17) playing a significant role in inflammatory cascade amplification and epidermal hyperplasia. A similar Th1-mediated response is demonstrated in chronic AD, whereas acute AD has a robust Th2 response with the involvement of other cytokines (IL-4, IL-13, IL-31). Rosacea and SD are a result of a maladaptive immune response to microbes, and both share common inflammatory pathways such as NLRP inflammasome and kallikrein, which is also dysregulated in psoriasis. Rosacea, particularly the papulopustular type, shares similarities to psoriasis due to the upregulation of CD4+ T lymphocytes in the Th1/Th17 mediated immune response. Interestingly, SD has a depressed T-cell response rather than the classic T-cell upregulation seen in all other inflammatory dermatoses. SD also demonstrates secretion of nonspecific inflammatory cytokines such as TNF-α and IL-1. ACD is a delayed type-4-hypersensitivity response mediated by allergen-sensitized T lymphocytes. ICD is unique compared to other inflammatory dermatoses in that the immune response is triggered by direct injury to the epidermis, leading to a localized inflammatory response to the involved irritant. Overall, the innate immune system plays a role in each of these cutaneous conditions, but the humoral immune system mainly contributes to AD and psoriasis.

Microbial overgrowth may exacerbate many inflammatory dermatoses. While Staphylococcus aureus is a part of normal skin flora, it colonizes the skin in more AD patients compared to the general population. S. aureus colonization worsens AD by promoting Th2 inflammation, while Malassezia species contribute to SD via immune depression. In rosacea, Demodex mites can trigger an exag-

Table 7. Treatment of allergic contact dermatitis [145,148].

Area involved	Medication	Frequency of application	Additional information
Acute allergic contact dermatitis (ACD)			
Localized ACD	topical corticosteroids and topical tacrolimus, plus emollients	1–2 times daily until resolved (max 4 weeks) then taper over 2 weeks	
Hands, feet, nonflexural regions	high potency topical corticosteroids	apply 1–2 times daily for 2–4 weeks or until resolved	if weeping, may add drying agent (aluminum acetate compress, calamine lotion, colloidal oatmeal compress)
Face, flexural areas	medium to low potency topical corticosteroids	apply 1–2 times daily for 1–2 weeks, then taper over 2 weeks	topical tacrolimus (0.1%) can be used as an alternative, applied twice daily until improved, then taper
Severe ACD, if >20% of total BSA involved, or if face, hands, feet, or genitalia involved	systemic corticosteroids (prednisone)	0.5–1 mg/kg per day for 7 days, then reduce dose by 50% over 5–7 days, then taper and discontinue within the following 2 weeks	
Chronic ACD			
Hands, feet, or nonflexural regions	intermittent high-potency topical corticosteroids plus, frequent use of allergen free emollients	once daily for 7–10 days initially, followed by every other day treatment	
Face, intertriginous areas, or localized areas resistant to topical corticosteroids	tacrolimus (0.1%) ointment plus, frequent use of allergen free emollients	1–2 times daily to affected areas until resolved. may repeat treatment if recurs	
Second-line therapies			
Chronic hand eczema specifically	phototherapy: bath psoralen + ultraviolet a photochemotherapy (PUVA) or narrowband ultraviolet b (NBUVB) plus, frequent use of allergen-free emollients		NBUVB has fewer side effects than PUVA
Other regions of chronic ACD that are unresponsive to topical therapies	systemic immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil, cyclosporine)		

gerated innate and adaptive immune response, leading to inflammation and vascular changes. While these pathogens are not required for the development of these dermatoses, they may worsen the clinical course and should be considered when selecting appropriate treatment.

As inflammation is the main contributing factor for all inflammatory dermatoses, the appropriate therapeutic agent(s) may be used for the treatment of multiple different cutaneous conditions. Anti-inflammatory agents, such as topical steroids and nonsteroidal agents (e.g. calcineurin inhibitors) are commonly used across these diseases. PDE-4 inhibitors are frequently used to treat psoriasis and AD. PDE-4 inhibitors are being studied as a potential treatment for rosacea. Lastly, an exploratory open-label trial of secukinumab (IL-17 inhibitor) has demonstrated reduced inflammatory lesions in the setting of papulopustular rosacea, although further investigation is needed to confirm its clinical efficacy [153].

In addition to anti-inflammatory treatment options, there are also specific targeted therapies available for many of the discussed conditions. Biologics targeting IL-17, IL-23, IL-36, and TNF-α are effective in psoriasis due to the predominance of the Th1/Th17-driven immune response [54,55]. Dupilumab, an IL-4 receptor antagonist, and tralokinumab, an IL-13 receptor antagonist, are commonly used in AD to block the Th2-mediated IL-4 pathway [27,28]. Individuals with AD are more susceptible to contact dermatoses, thus choice of treatment (systemic versus topical) may differ based on the disease severity and clinical presentation. Contact dermatitis generally does not require systemic treatment.

Immune dysregulation leads to characteristic epidermal changes which may be seen grossly and/or histologically. Both AD and psoriasis have increased epidermal proliferation. However, the histology of psoriasis will also include hyperparakeratosis, irregular acanthosis with elongated rete ridges, and tortuous vasculature. In contrast, AD demonstrates regular hyperkeratosis and irregular acanthosis. The vasculature in AD is also dilated without the presence of new angiogenesis. Of note, AD and contact dermatitis are difficult to distinguish on histology alone as they show similar histologic findings. Rosacea shows gross epidermal changes of the face, manifesting as erythema and prominent vascular changes. SD demonstrates greasy scales and erythematous plaques. Pruritus is a common symptom among all inflammatory cutaneous conditions, as a result of cytokine release and nerve sensitization.

Conclusion

Due to chronic inflammation, the first-line treatment for all inflammatory dermatoses typically involves topical or systemic anti-inflammatory agents. However, the choice of specific treatment will vary depending on which condition is involved. Although the inflammatory conditions discussed share many similarities, the underlying immunological mechanisms and approach to targeted treatment are variable. Understanding the differences between these cutaneous conditions is crucial for the effective management and treatment of these complex dermatological conditions. Continued research and understanding of the shared immune pathways will enhance the development of future therapies and improve patient outcomes, especially in cases of patients with multiple chronic inflammatory dermatoses.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: MD; Data Curation: LT, RD, RO; Formal Analysis: LT, RD, RO; Investigation: LT, RD, RO; Methodology: LT, RD, RO; Validation: LT, RD, RO, MD; Visualization: LT, RD, RO, MD; All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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