5 MOST COMMON SKIN DISEASES IN PRIMARY CARE

URTICARIA
ECZEMA
PSORIASIS
IMPETIGO
ROSACEA

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Question & Answer from an Allergist's Perspective

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Chapter 1: URTICARIA

Urticaria is characterized by hives, which typically develop over a short period of time and are accompanied by pruritus.[1] Angioedema, which can be painful, accompanies the wheals in approximately half of cases. Angioedema typically occurs in rich neurovascular areas such as fingers, lips, and around the eyes. The erythematous hives typically appear as raised pale often plaque-like lesions on an erythematous background. They can appear on essentially any part of the skin and in patients of any age.

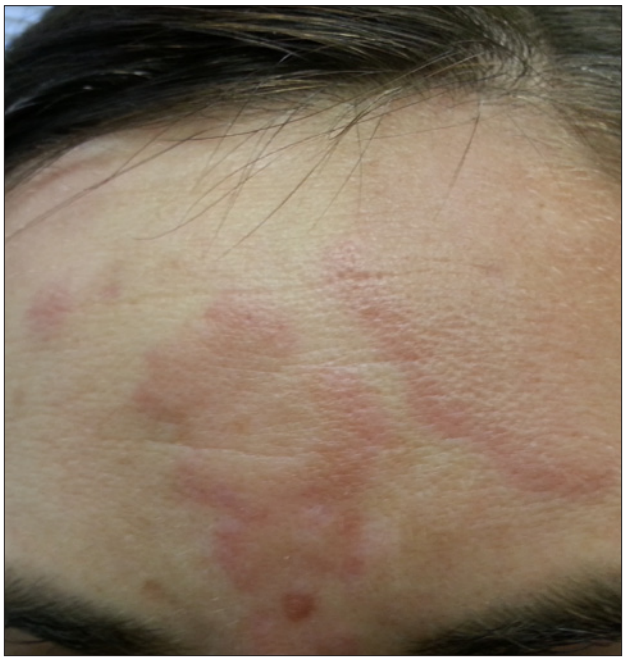
The lifetime prevalence of all urticaria is 20%, but this skin disease is classified into two major types by duration.[2] Chronic urticaria, which has a much lower prevalence and is more common in adults of middle age or older, refers to persistent lesions for periods of more than six weeks. Acute urticaria refers to a presentation of a shorter duration. Acute urticaria which denotes hives occurring for under 6 weeks may be triggered by medications, infections, insect stings, food allergies, and other acute factors. Chronic spontaneous urticaria is typically idiopathic without known or consistent triggers but can co-exist with inducible triggers such as physical triggers.[3] For example, in physical pressure induced urticaria, it typically occurs in areas of increased pressure due to clothing.

Pathophysiology

Degranulation of mast cells in the skin is the primary driver of urticaria. Mast cells and basophils release histamine and other mediators, such as cytokines and lipid mediators, to induce an inflammatory reaction that underlies the characteristic rash and pruritus. Immunoglobulin E through the FcERI receptor is one mediator of activation and degranulation of mast cells , but non-IgE activation also commonly occurs to physical triggers, tachykinins, complements, toll like receptors, and autoimmune mechanisms.[3] Angioedema accompanies the hives when degranulation includes mast cells deeper in the dermis. The inflammatory activity excites sensory nerves, promotes vasodilation, and increases the permeability of postcapillary venules.

On histology, wheals demonstrate an inflammatory perivascular infiltrate that might include neutrophils, eosinophils, basophils, macrophages and T cells. Endothelial cell adhesion molecules, neuropeptides, and T cells are also often present. Although skin adjacent to lesions may also contain upregulation of cytokines, eosinophils, and adhesion molecules, urticaria is a condition localized to the skin without systemic involvement (Figure 1). Rarely, urticaria may be a symptom of serious anaphylaxis or a major underlying disease.

FIGURE 1 | Chronic Spontaneous Urticaria



Diagnosis

Neither acute nor chronic urticaria requires an extensive diagnostic workup. Rather, the diagnosis of urticaria is one of exclusion that is reached with history to rule out alternative pathologies, particularly systemic diseases.[4] At initial examination, the history should document the time of onset as well as the location, severity, and impact of the symptoms. Other important aspects of history include potential environmental triggers, medication use such as non-steroidal anti-inflammatory medications and allergies. A diagnosis of urticaria is appropriate in those with characteristic features and no systemic or vasculitic symptoms, such as fever, gastrointestinal complaints, arthralgias or myalgias. Extensive laboratory testing or biopsies in the absence of such symptoms are not recommended. Many dermatologic conditions can be confused with urticaria; it crucial to rule out anaphylaxis which has systemic consequences and involves other organ systems.[2]

For acute urticaria, there is a long list of potential triggers, including heat, cold, sun exposure, foods, alcohol, drugs, stress, pressure on the skin, and prescription drugs. Repeated episodes of urticaria that occur in a temporal relationship to triggers provide both a diagnosis and a potential strategy for removing the cause. Although the identification of triggers is helpful in the diagnosis of acute urticaria, urticaria remains idiopathic in more than half of patients who meet the definition of chronic disease.

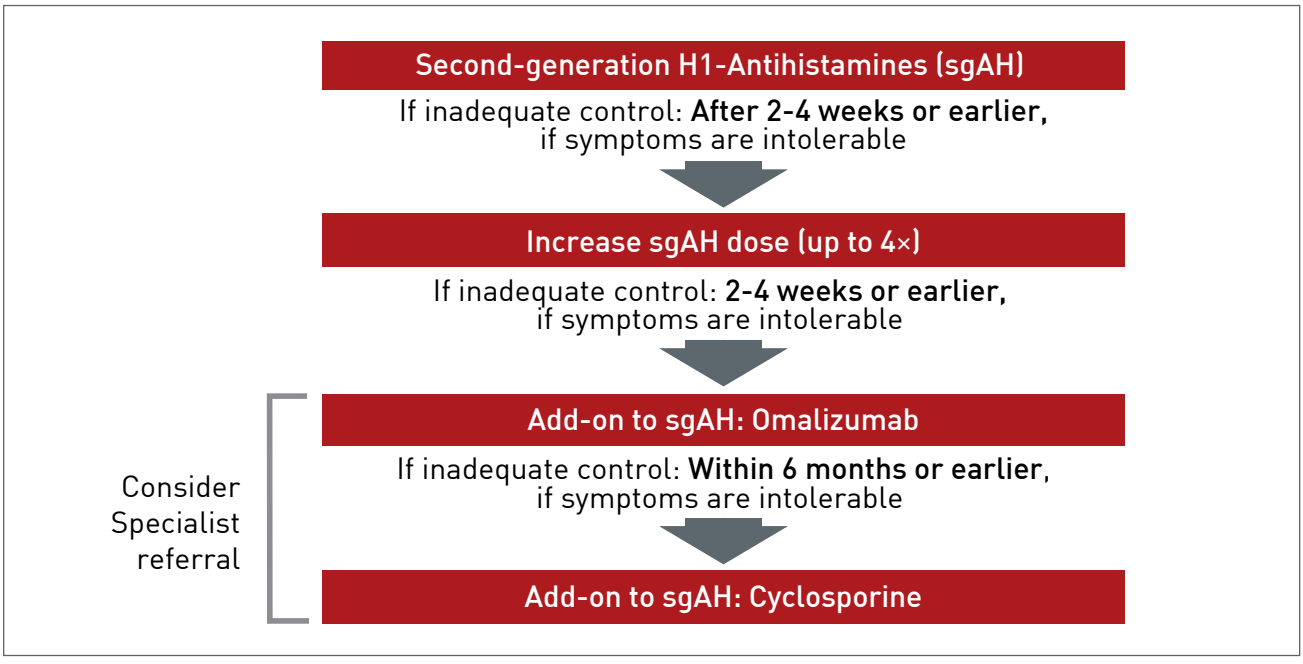
When chronic urticaria is idiopathic, which accounts for 80% to 90% of cases,[1] an entity now commonly referred to as chronic spontaneous urticaria (CSU), autoantibodies for IgE can be commonly identified, but the absence of autoantibodies does not rule out CSU or guide therapy, so it is not considered a routine diagnostic procedure. Although the presence of angioedema should increase attention to potential drug triggers, such as antihypertensive medications, it does not necessarily justify biopsy or more extensive laboratory studies when symptoms remain localized to the skin.

Treatment

The single most important goal of treatment for urticaria, which imposes a large adverse impact on quality of life through its symptoms and appearance, is to improve quality of life. Urticaria poses a low risk of serious complications. In cases of acute urticaria, trigger avoidance may adequately address symptoms. In cases where avoidance is problematic, tolerance induction should be considered.

Second-generation antihistamines represent the first-line of pharmacologic therapy for acute or chronic urticaria (Figure 2). Recent guidelines specifically recommend avoiding first-line antihistamines due to their sedative effects and adverse impact on sleep.[4] When selecting among agents, relative risk for drug-drug interactions should be considered for patients taking antibiotics or other drugs with a potential to compete on pathways of drug metabolism.

FIGURE 2 | Recommended Treatment Algorithm for Urticaria



Adapted from Zuberbier T, et al. The EAACI/GA² LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69:868-887; Zuberbier T, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification,diagnosis and management of urticaria. *Allergy* 2018;73:1393–1414

For acute urticaria, symptom control with antihistamines can be expected with a short course of therapy. H_2 antihistamines such as cimetidine, famotidine, and ranitidine may be added if symptoms continue, and corticosteroids such as prednisone may be added for three to ten days in severe cases.[2] For chronic urticaria, recent guidelines recommend a stepwise care approach, moving from a conventional dose of a second-generation antihistamine as a first-line therapy to high doses of antihistamines as the next step when adequate symptoms control is not achieved. Escalations up to four times the conventional dose are recommended. With these two steps, more than 50% of patients can anticipate adequate symptom control.

For those still uncontrolled, the next step in treatment is to add the anti-IgE antibody omalizumab to the antihistamines. The phase 3 trial found omalizumab resulted in a high degree of efficacy for the primary endpoint of pruritus control as well as for key secondary endpoints involving control of angioedema and resolution of lesions. The drug was well tolerated with low rates of serious adverse events.

In those who remain uncontrolled, alternative agents are appropriate, but cyclosporine is listed first among alternatives in the current guidelines, which delisted H2-receptor antagonists and leukotriene receptor antagonists due to the weak quality of available evidence. The guidelines do acknowledge corticosteroids as efficacious but conclude that cyclosporine has a better benefit-to-risk ratio despite the concern for potential side effects.

In an outline of therapies specifically for children, the guidelines reemphasized the importance of relying on second- rather than first-generation antihistamines due to a more favourable side effect profile. The authors further recommended second-generation antihistamines that have been tested in children. The agents on this list are cetirizine, desloratadine, fexofenadine, levocetirizine, rupatadine, bilastine, and loratadine.

Summary

Urticaria is a common condition characterized by hives and itching and can be accompanied by angioedema. It is non-life-threatening with a low risk of significant complications, but it imposes a major adverse impact on quality of life. In the majority of cases, the diagnosis is easily reached by a careful history that rules out systemic involvement. Laboratory testing and biopsy are not routinely employed in patients without alarm features of symptoms that suggest an alternative diagnosis. Consistent with a pathophysiology that is characterized by mast cell degranulation and histamine release, antihistamines are the main stay of pharmacologic therapy. In those with chronic urticaria, which is typically spontaneous, additional steps may be required to achieve adequate symptom control. Initial workup and first-line therapies for urticaria are appropriate at the level of primary care. The simple goal is relief of symptoms in order to improve quality of life. ●

Q&A

Urticaria: The Allergist's Perspective

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1. Should urticaria be considered an allergic or dermatologic disease?

Short answer is both. Urticaria can be a dermatologic manifestation of a type I Gell and Coombs hypersensitivity reaction, which defines an allergic process. However, the manifestations primarily by definition are occurring in the skin terminally differentiated mast cells which are distinct from GI mast cells and other visceral mast cells in the body. Due to the recent evolution of the understanding of CSU having an underlying type I or type II autoimmune mechanism (anti-IgG to FcERI or IgE vs an autologous allergen) it simply represents the degranulation of mast cells irrespective of the trigger. In fact the most common form of chronic inducible urticaria (CINDU) is triggered through baroreceptors that sense pressure on the mast cell. While it shares some pathophysiology to atopic conditions such as atopic dermatitis or allergic rhinitis, it is mediated by a different population of mast cells as mast cells are terminal organ differentiators. There is some recent thought that CSU really represents another type II inflammatory condition due to the prevalence of autoimmune mechanism as an etiology.

2. When is it appropriate to refer a patient with urticaria to a specialist?

A specialist consult is not normally required either to make the diagnosis or to initiate treatment. Adequate symptom control can be achieved in the majority of cases with secondary antihistamines and trigger avoidance where found. Contrary to popular misconception, CSU is not caused by food allergies or inhalant allergies. This risk of serious complications is low. A specialist consultation becomes appropriate when an adequate quality of life cannot be achieved with up titration of antihistamines to four times the dose. Anyone requiring omalizumab or cyclosporine should be referred to an experienced specialist familiar with biologics and or cytotoxic immunosuppressants that require monitoring.

3. If patients do not respond to first- or second-line treatment for urticaria, what is the most appropriate specialist referral, a dermatologist or an allergist?

In cases where the response to antihistamines is inadequate, the anti-IgE monoclonal antibody omalizumab has been shown to be effective. Although this drug is typically well tolerated, clinicians experienced with this agent, which requires in some cases reconstitution of the medication with subcutaneous dosing, might be more comfortable with administration. In patients who do not respond to high doses of antihistamines, a detailed workup for an alternative diagnosis might be appropriate. Either a dermatologist or an allergist are reasonable choices provided they are experienced with cytotoxic immunosuppressants that require monitoring for cyclosporine or have critical number of experience using biologics. In addition, in those rare cases when a patient does not respond to omalizumab or cyclosporine, a specialist familiar with adjunct therapies is helpful.

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Chapter 2: **ECZEMA**

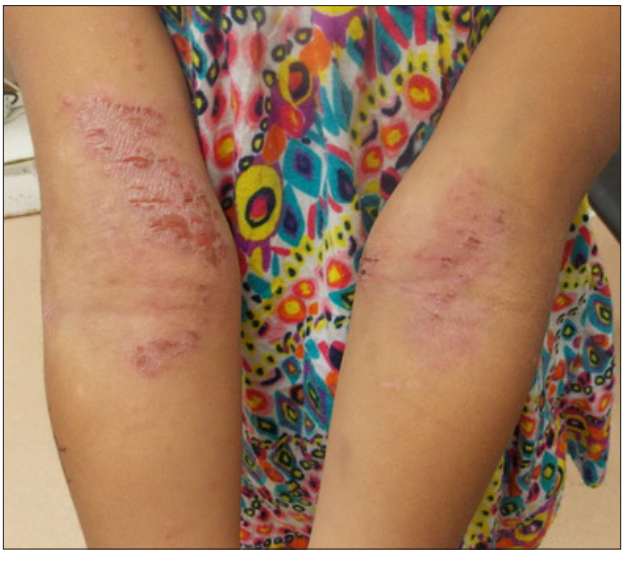
Eczema, also called atopic dermatitis (AD), is an inflammatory and pruritic condition of the skin with a variable presentation frequently involving some combination of vesicles, papules, and oedema.[1] Guidelines differ on the necessity of a history of atopy as prerequisite for a diagnosis of eczema but agree that the diagnosis is made clinically.[2,3] Most cases of eczema involve childhood onset with up to 60% of cases developing within the first year of life. In Canada, approximately 10% of children develop atopic dermatitis during childhood,[4] but higher rates have been reported elsewhere.[5] Adult cases are less common but not rare. In the event of childhood onset, spontaneous remissions prior to adolescence are observed in up to 70% of cases but can re-emerge in some patients.[6]

Eczema, often first observed on the scalp, face, or flexure areas of the limbs, is characterized by a relapsing course.[7] Most cases are of mild to moderate involvement, but approximately 10% are severe,[8] involving frequent flares and an extensive lesion burden. Other atopic conditions, such as bronchial asthma and allergic rhinoconjunctivitis, are common in those who develop eczema at an early age.[9] Although infection can complicate eczema, the largest burden of this condition is physical and psychological discomfort.

Pathophysiology

Immune dysregulation and defects in skin barrier function are both implicated in the pathogenesis of eczema, but this interaction is not completely understood. Although the concordance rate for atopic dermatitis among monozygotic twins is 77%, suggesting a high degree of heritability, studies of genetic variants suggest that environmental triggers may be important for disease development in at least some patients.[7] Both immune dysregulation and disturbances in skin barrier function are implicated in disease expression, but it is unclear which comes first. On histopathology, eczematous skin includes a perivascular infiltrate of T cells, lymphocytes, macrophages, dendritic cells, and eosinophils, which might be a driver of disease or an immunologic response to a loss of the epidermal barrier function (Figure 1).

FIGURE 1 | Atopic Eczema



Although IgE-mediated sensitization is a common feature of many patients with atopic dermatitis, this is not uniformly observed and it is uncommon in the early stages of disease.[6,10] Overall, the factors involved in the pathogenesis of eczema are likely to include genetic susceptibility, environmental allergens, infectious agents, and resident skin bacteria, initiating and then driving inflammation. Pruritic-driven scratching of the skin is also a factor in formation of lesion inflammatory activity.

It has been argued that non-atopic eczema might be a useful term to distinguish non-IgE-mediated disease from a true atopic form,[11] but others have rejected this as an unhelpful division that does not account for transient IgE upregulation.[7] Although anti-inflammatory therapy is a cornerstone of eczema treatment, treatments designed to augment epidermal barrier function through topical moisturization also have a potential role in mitigating and attenuating disease processes.

Diagnosis

There is no biomarker or single test to establish a diagnosis of eczema.[12] Rather, the diagnosis is made on the basis of multiple criteria. The set of Hanifin and Rajka criteria, published in 1980, remain widely cited.[13] These include pruritic chronic or relapsing dermatitis and a family history of atopy without other known aetiology. Accompanying characteristics, such as erythema, cheilitis, recurrent conjunctivitis, and frequent cutaneous infections may be helpful in supporting a diagnosis of eczema. There is general agreement that face and neck involvement is more common in infants and young children while lesions on flexural surfaces of the extremities and on the hands and feet are more common in adolescents and adults.[14]

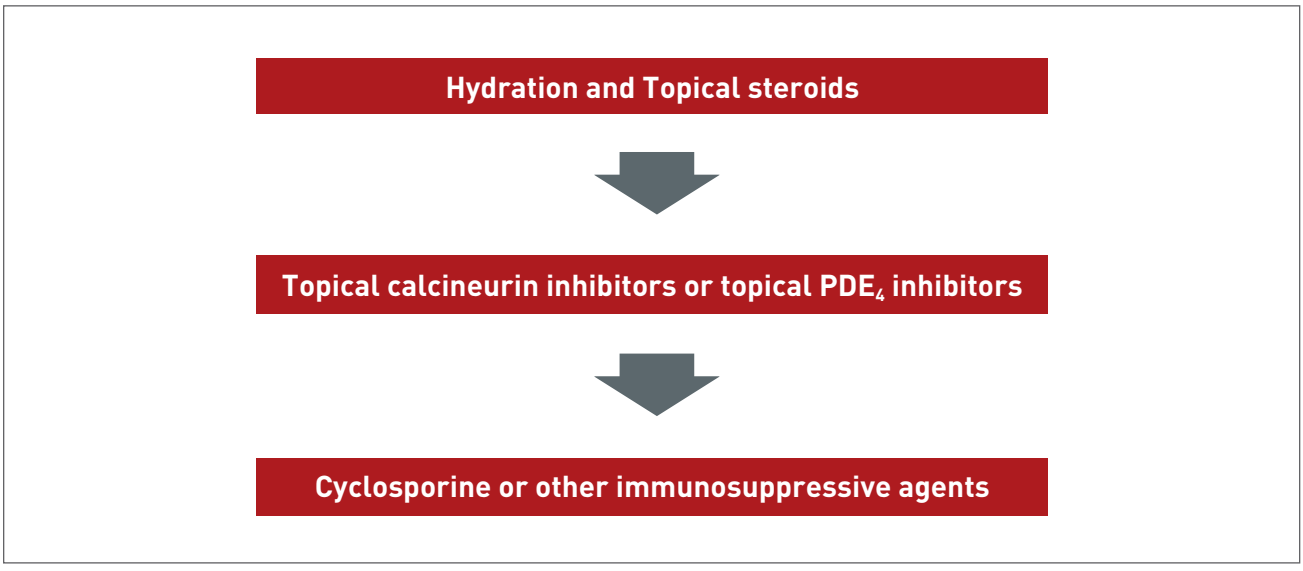
History or presentation plays a critical role when differentiating eczema from other types of dermatitis or other skin conditions. In the absence of a family or personal history of atopy, scabies, impetigo, seborrheic dermatitis, contact dermatitis, and lichen simplex are among alternative diagnoses to consider.[15] However, these differ in general appearance and are not typically expressed in the same areas as eczema. Diagnostic work-ups utilize patient history, skin and blood tests, and challenge tests to investigate exacerbating factors as well as to prescribe treatment regimens and avoidance recommendations.

Treatment

Guidelines from the American Academy of Dermatology (AAD),[2] the joint task force (JTF) of the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma & Immunology,[3] and a panel of European organizations[12] identify non-pharmacologic therapies as the first-line intervention for mild eczema. This basic therapy should comprise optimal skin care, addressing the skin barrier dysfunction and avoiding triggering factors. This includes bathing to remove irritants and bacteria followed by moisturizers to maintain skin hydration. Hydrophilic ointments without fragrance and preservatives are preferred in AAD and JTF guidelines. Although food allergies are more common in patients with eczema, food allergies are not the driver of eczema. Moreover, although dust mite and mould sensitization is common and dust mites have protease activity, it is a minor contributor to eczema flares.

In the European guidelines, treatment recommendations are listed separately for adults and children, but are compatible. For both, topical class II steroids are considered first-line for those with mild disease inadequately controlled with non-pharmacologic interventions. Topical calcineurin inhibitors are listed as an alternative. Wet wrap

FIGURE 2 | Recommended Treatment Algorithm for Eczema



therapy and ultraviolet light were identified as adjunctive therapies to topical steroids or calcineurin inhibitors for those with moderate to severe disease. In severe disease, systemic immunosuppression with such therapies as cyclosporine A, methotrexate, mycophenolate mofetil are recommended in children and are off label in adults. In adults, dupilumab, an anti-IL-4 and IL-13 monoclonal antibody, is currently the only approved systemic therapy specifically for eczema (Figure 2).

The AAD and JTF guidelines discuss the same pharmacologic interventions in the same order. Relative to the European guidelines, which offer limited advice on how to identify provocation factors, the JTF and AAD guidelines encourage control of atopic-related triggers, such as food and contact allergens. The JTF guidelines, in particular, endorse steps such as avoiding clothing with irritating fabrics and washing clothes with non-allergenic soaps.

Even though all of the guidelines acknowledge that randomized trials of eczema treatments are limited, recognizing that current guidelines are largely guided by expert opinion, the treatment strategies are largely compatible among the published guidelines. For optimal disease management, consistent medical supervision, education of the patient or the person who provides care to the patient, and a strong psychological support system are needed.[16]

Summary

Eczema is a common relapsing pruritic dermatitis associated with atopy. Face and neck involvement is more common in infants and young children while involvement of the flexures, hands, and feet is more common in adolescents and adults. There is no definitive diagnostic test, but an adequate history and examination is sufficient to reach a diagnosis of eczema in most cases. By reducing skin damage from scratching, moisturizers are an important, non-pharmacological first step to control of lesions. Topical steroids are regarded as a first-line pharmacologic therapy. Eczema resolves before adolescence in the majority of patients who develop eczema in early childhood. ●

Q&A

Eczema: The Allergist's Perspective

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1. What is the pathophysiology of atopic dermatitis?

Eczema, which is interchangeable with AD, is a type II inflammatory condition and, as such, other atopic comorbidities are often observed in patients such as allergic rhinitis, nasal polyps, and asthma. The underlying cascade of release of inflammatory mediators is a similar but not identical process related to Gell and Coombs type I hypersensitivity. Patients with AD are at increased risk of having contact dermatitis which is a type IV Gell and Coombs hypersensitivity. Although commonly mistakenly identified as "allergens" these are in fact technically antigens that trigger a T cell initiated response with different effectors than mast cells. IL-33 (found mainly in the skin on keratinocytes and not in other organs), IL-4, and IL-13 are important in the start and propagation of the itch, scratch, and lichenification cycle. Contact dermatitis testing requires patch testing and not skin prick testing, as it is not an IgE mediated reaction.

2. When is it appropriate to refer a patient with eczema to a specialist?

Patients with eczema or other atopic diseases can typically be diagnosed on the basis of symptoms and history. There is an extensive differential but careful examination for typical patterns and signs such as lichenification and xerosis in areas typical for AD points one in the right direction. Control of mild involvement is often achieved with topical treatments, but a specialist consultation becomes appropriate if the symptoms do not respond to first-line therapies. Both a dermatologist and clinical immunologist and allergist are typically familiar with non-steroidal topical therapies such as calcineurin inhibitors and PDE inhibitors.

3. If patients do not respond to first- or second-line treatment for eczema, what is the most appropriate specialist referral, a dermatologist or an allergist?

Primary care physicians who have limited experience with administration of potent systemic immunosuppressive agents, such as cyclosporine and topical and systemic calcineurin inhibitors, might prefer to refer patients with atopic dermatitis who do not respond to topical agents. Likewise, not all specialists in dermatology or allergy are familiar or experienced with the use of biologics such as dupilumab and a referral should be made in severe atopic dermatitis. For a patient with atopic comorbid conditions, including those affecting the respiratory tract, an allergist might be a better first choice.

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Chapter 3: **PSORIASIS**

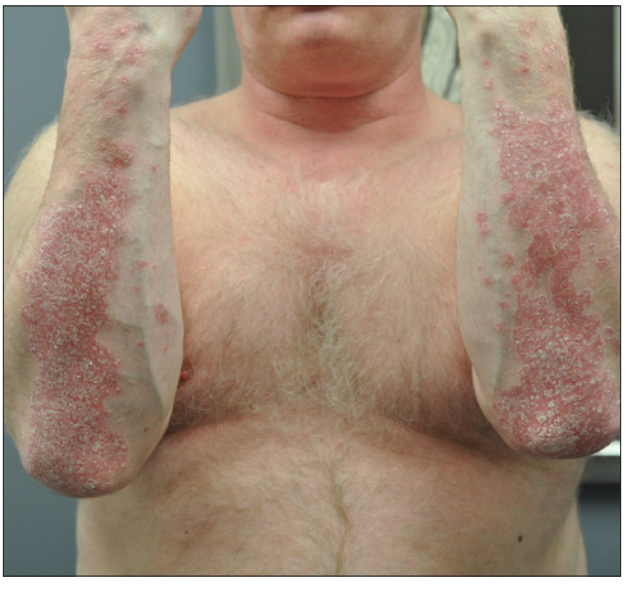
Psoriasis is a chronic disease characterized by well-demarcated scaly plaques driven by a hyperproliferative epidermis.[1,2] Although it most commonly involves the scalp, elbows, and knees, it can develop on most skin surfaces, including the palms, soles, and genitalia. Nail involvement is observed in nearly 50% of patients.[3] Total body involvement provides an objective measure of psoriasis severity, but it may not reflect the disease burden for patients self-conscious about lesions or who have persistent pruritus. Common phenotypes include guttate, pustular, annular, erythematous, and palmoplantar forms. The adverse impact of psoriasis on quality of life, including diminished self-esteem, is a well-documented feature.

In Canada, the estimated prevalence of psoriasis is 1.7%,[4] but higher rates have been reported elsewhere.[5] Psoriasis is considered an autoimmune inflammatory process. The most common age of onset is between the ages of 20 and 30 years, although psoriasis can develop in children.[4] Up to 30% of patients also develop inflammation of the joints. Although many of the anti-inflammatory medications effective for psoriasis also reduce disease activity in the joints, psoriatic arthritis is typically managed separately. A variety of disease phenotypes classified by appearance or predominant site of involvement have been described, but psoriasis vulgaris is the most common form of the skin disease.[6]

Pathophysiology

Psoriasis is driven by a dysregulated immune system. Based on the frequency with which psoriasis occurs in related individuals, genetic susceptibility appears to be important. Association studies suggest that the PSORS1 gene may account for up to half of psoriasis heritability, although other genes have been implicated in linkage studies.[1] Genetic heterogeneity among psoriasis subtypes supports the involvement of multiple pathways. For many patients, this might involve a disturbance in the sentinel function of dendritic cells, altering the innate immune defense mechanisms and inducing proliferation of T cells and proinflammatory cytokines.[7]

FIGURE 1 | Psoriasis



On histopathology, the macrophages, dendritic cells, and T cells are prominently represented in the dermis. The erythematous appearance is attributed to capillaries reaching close to the surface of the skin due to a thinned epithelium (Figure 1). The efficacy of anti-inflammatory drugs including biologics targeted at inflammatory cytokines has provided an important demonstration that an upregulated immune system drives disease and is an important target of therapy.

Diagnosis

The diagnosis of psoriasis is made on the basis of clinical examination and history. This should include a characterization of lesion distribution and appearance during an examination that includes the scalp and nails. Although there is no definitive test or biomarker for psoriasis, suspicion should increase in those with a family history of psoriasis. The Auspitz sign, which is pinpoint bleeding when psoriatic scales are removed, and the Koebner phenomenon, which is the appearance of new lesions at sites of trauma, may provide additional confidence in the diagnosis but have limited independent sensitivity.[8]

From the Canadian Psoriasis Guidelines Committee, disease severity is judged to be mild, moderate, or severe based on body surface area coverage and effect on quality of life. The Psoriasis Area and Severity Index similarly measures the disease severity using body surface area affected, erythema, induration, and scaling.[4]

There are different clinical types of psoriasis, but the most common is chronic plaque psoriasis, which affects 80% to 90% of psoriasis patients.[4] The differential diagnosis of psoriasis includes seborrheic dermatitis, pityriasis rosea, and mycosis fungoides.[9] The risk of confusion with other skin diseases is low when psoriasis includes involvement of the trunk, but skin biopsies are useful when features overlap with other conditions. Diagnosis may be particularly challenging in cases when psoriatic lesions are confined to the scalp or hands. KOH examination is useful for ruling out dermatophyte infection masquerading as psoriasis in these locations.

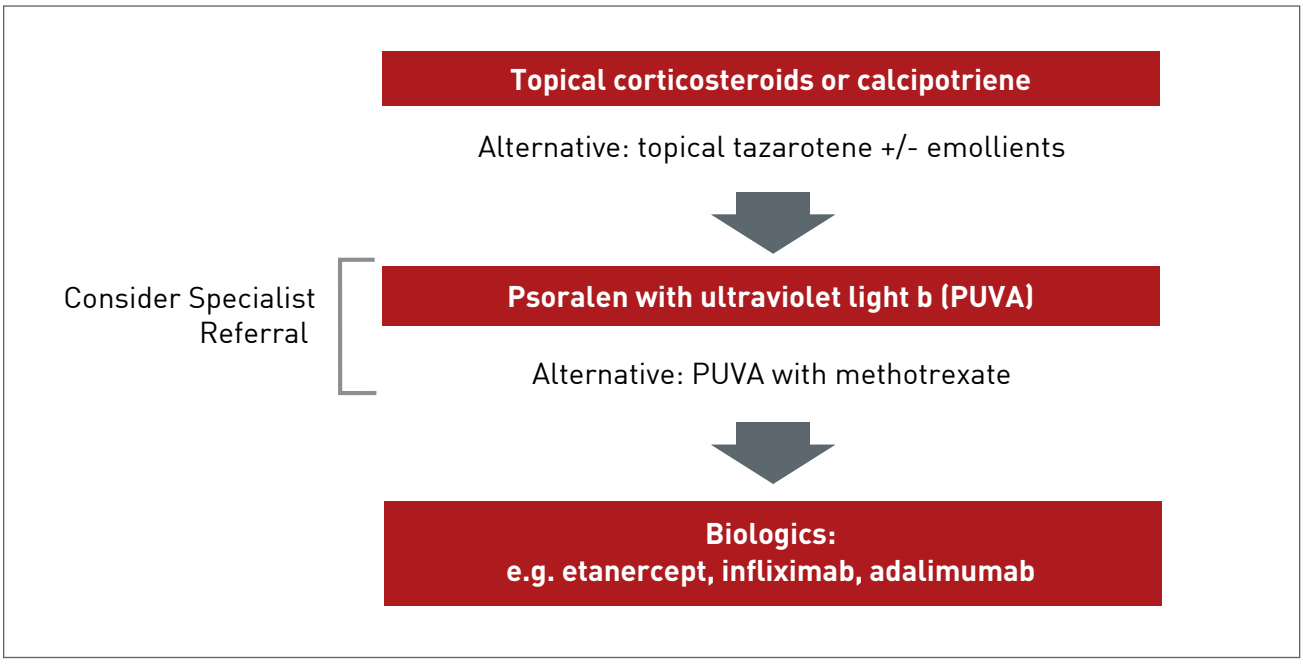
Treatment

Although there is no cure for psoriasis, there are several effective treatment options. In patients with mild psoriasis, topical corticosteroids, topical calcipotriene, or calcipotriol-steroid combination products may be sufficient as a first-line therapy to reduce lesion burden and pruritus. Topical tazarotene, a retinoid, has also demonstrated efficacy in mild disease.[10] Emollients might be useful as adjunctive therapy. For more severe disease, systemic therapies or ultraviolet (UV) light are appropriate. Of systemic therapies, once-weekly methotrexate, alone or combined with UVB or photochemotherapy (PUVA), has been in use for decades. However, concern about side effects has reduced the clinical application of other once commonly used immunosuppressants, such as cyclosporine (Figure 2).

Biologics, such as etanercept, infliximab, adalimumab, and secukinumab, are now commonly introduced relatively early in the course in patients with moderate to severe disease because of their relative efficacy in lesion clearing. However, referral to specialists is appropriate. Biologics, which are expensive, pose significant clinical risks, including increased propensity for malignancy. Despite these risks, biologics are perceived to have a favourable risk-to-benefit ratio when lesions are inadequately controlled with alternative treatment strategies. Non-biologics such as acitetrin and apremilast have also been used, but are not considered the mainstream treatment from the current literature.[4]

Overall, the goal of therapy in psoriasis is to control disease activity to improve quality of life. Even

FIGURE 2 | Psoriasis Treatment Algorithm



severe psoriasis is rarely life threatening, but the physical distress induced by lesions is complicated by the psychological burden of visible lesions, which can cause patients to limit activities of daily living. These can include constraints on social interaction and employment.

Summary

Psoriasis is a chronic, multisystem, autoimmune disorder characterized by pruritic plaques. Nail and scalp involvement are common. Apart from skin and joint involvement, the disease is associated with various psychiatric and medical comorbidities. Topical therapies are a first-line therapy in patients with mild disease, particularly when control of pruritus can limit skin damage from excoriation. Many of the most effective therapies, including ultraviolet light and immunosuppressants, are associated with significant risks, including malignancy, when utilized chronically. Primary caregivers are uniquely positioned to offer timely diagnosis and treatment of mild to moderate cases. In cases of extensive involvement on visible skin surfaces, patients should participate in a detailed discussion with specialists of the risk-to-benefit ratio regarding available therapies. ●

Q&A

Psoriasis: The Allergist's Perspective

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1. Should psoriasis be considered an allergic or dermatologic disease?

Psoriasis is a type I autoimmune inflammatory disorder affecting the skin with systemic symptoms that involve joints or other organs (rarely the lungs). No strong associations have been made between development of psoriatic lesions and hypersensitivity reactions. Some patients with psoriasis do have some type II atopic conditions and it has been found that there is a regulatory T cell (Treg) that may be the culprit.

2. When is it appropriate to refer a patient with psoriasis to a specialist?

Except in mild cases, suspected psoriasis should be referred to a dermatologist for evaluation and the initiation of treatment. Psoriasis is a chronic and often challenging condition for which a comprehensive treatment plan may be important for an optimal outcome. An experienced dermatologist will likely screen for systemic involvement.

3. If patients do not respond to first- or second-line treatment for psoriasis, what is the most appropriate specialist referral, a dermatologist or an allergist?

Psoriasis that is inadequately controlled with topical therapies and appropriate skin care can be challenging. Second- and third-line therapies, such as PUVA and biologics, are associated with significant risks that are best administered by physicians familiar with the benefit-to-risk ratio of these treatments. In most cases, this will be a dermatologist.

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Question & Answer from an Allergist's Perspective

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Chapter 4: IMPETIGO

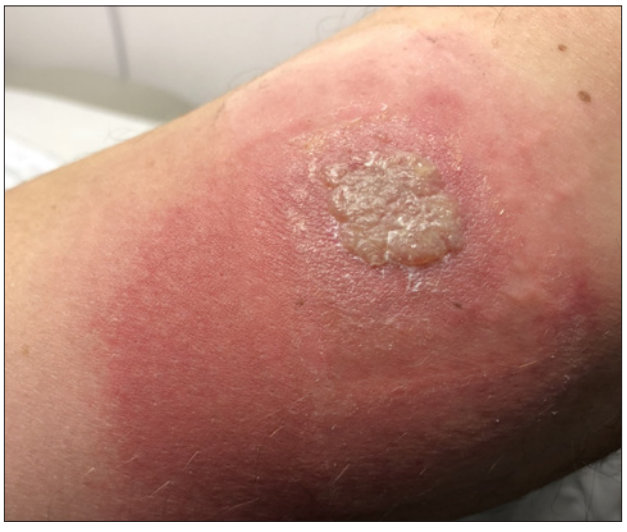
Impetigo is a common bacterial infection of the superficial skin that most commonly occurs among children.[1] Cases in adolescents and adults are commonly observed with some type of skin lesions, such as an abrasion or dermatitis. Non-bullous impetigo, or impetigo contagiosa, is the more common of the two types and is characterized by yellowish crusty lesions. In children, these often include perioral involvement but can appear anywhere on the skin. Bullous impetigo, as the name suggests, is characterized by large, flaccid bullae that are prone to rupture and ooze yellow fluid. These develop most commonly on the trunk, the extremities, or in intertriginous areas, such as the axilla or buttocks.[2]

Impetigo is extremely common in young children, with an average estimated global prevalence of 12.3%.[3] Generally, the prevalence is higher in tropical and low-income areas of the world than in areas with temperate climates, but prevalence rates near 20% have been reported among underprivileged children living in high-income countries, including Canada.[3] Although impetigo readily resolves without scarring even in the absence of treatment, topical antibiotics can speed healing and reduce risk of transmission. In general, systemic involvement and complications are rare, but impetigo caused by methicillin-resistant *Staphylococcus aureus* (MRSA) is potentially serious without prompt intervention.[4]

Pathophysiology

Highly contagious, impetigo is associated with overgrowth of bacteria introduced from the environment which transiently colonize healthy skin. For nonbullous impetigo, Group A streptococcus is the most common pathogen. For bullous impetigo, *S. aureus* infection accounts for most cases.[1,2] There are several risk factors for bacterial overgrowth, including poor hygiene, diminished immune defenses, high temperature or humidity, comorbid dermatoses, and young age. In older individuals, transmission is typically observed only in those with some additional factor compromising the skin barrier function, such as an insect bite or wound, which allows bacterial invasion and overgrowth. In cases where the epidermis is compromised, the condition is known as secondary impetigo.

FIGURE 1 | Impetigo



Nonbullous impetigo, which accounts for approximately 70% of cases,[5] is characterized by thin-walled vesicles. The honey-coloured crusting of the nonbullous lesions is produced by the contents of these ruptured vesicles[2] (Figure 1). The lesion formation of the less common bullous impetigo (30% of cases) is attributed to the exfoliative toxins produced by the invading bacteria.[6] The pathophysiology of the two subtypes is believed to be similar. In most cases, hygiene plays a role in acquiring and transmitting impetigo.[7]

Diagnosis

The diagnosis of impetigo is based on clinical examination. Although bacteria are the cause of impetigo, skin swabs are considered unhelpful in diagnosis because they do not reliably distinguish between infectious and resident organisms.[8] Based on a probable diagnosis, treatment can be initiated without steps to identify the pathogen. However, if first-line therapy fails, culture of the pus or bullous fluid is a reasonable step to identify the infecting pathogen and its susceptibilities.

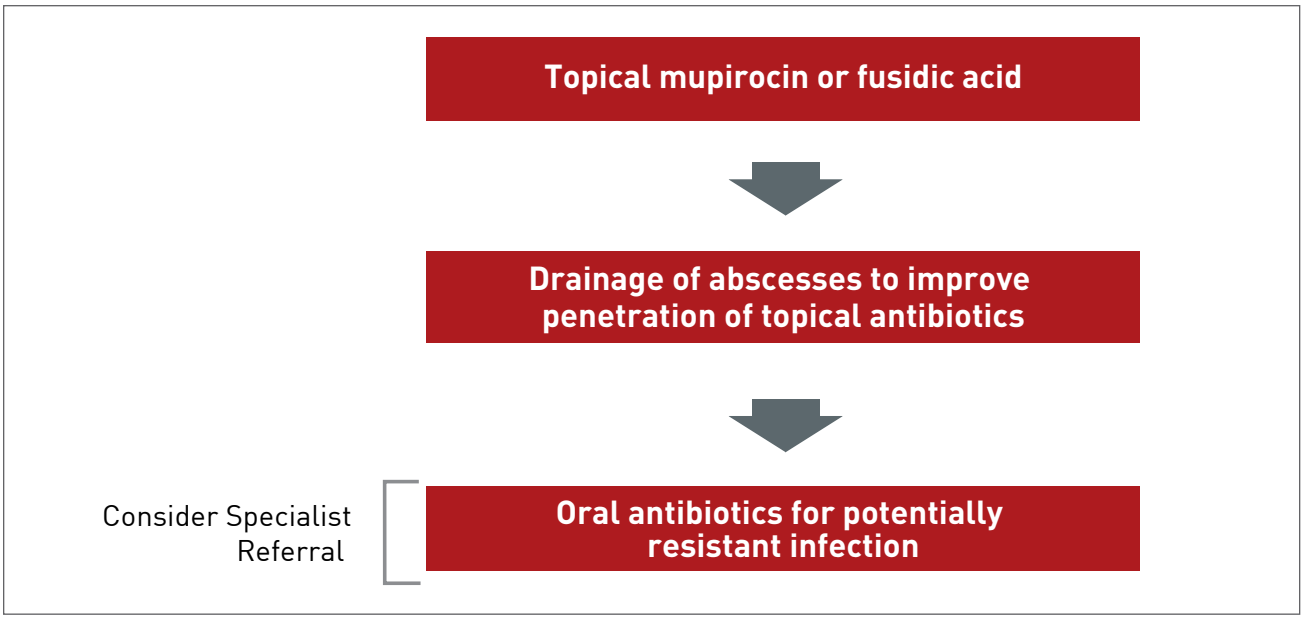
The differential diagnosis is specific to the nonbullous and bullous presentations. For nonbullous lesions, the list includes inflammatory conditions, such as atopic dermatitis and contact dermatitis, along with other types of infection, including herpes simplex virus, cutaneous candidiasis, and scabies. Of these conditions, scabies, which shares poor hygiene as a risk factor, is the most likely to produce pruritic lesions with a similar distribution and appearance when excoriation has been extensive, but the characteristic mite burrows are pathognomonic.[9] For bullous lesions, the list includes various other bullous dermatoses as well as other types of infections or skin wounds, such as insect bites, necrotizing fasciitis, and Stevens' Johnson syndrome.[2]

Treatment

There are no recent guidelines for impetigo management, but the non-profit Canadian Agency for Drugs and Technologies in Health (CADTH) has published a review of the role of topical antibiotics as first-line therapy.[10] Based on a survey of published systematic reviews and meta-analyses, it was concluded that topical mupirocin and fusidic acid are similarly effective in the treatment of impetigo, but that the evidence for the efficacy of bacitracin is insufficient. This review also found topical mupirocin to be at least as effective as erythromycin, dicloxacillin, cephalexin, and ampicillin. A Cochrane Review also concluded that mupirocin and fusidic acid are similarly effective, but more effective than oral antibiotics.[11] Although incision and drainage of abscesses is recommended to improve antibiotic penetration in patients with impetigo,[12] topical antibiotics have the additional advantage of a low risk of systemic side effects (Figure 2).

Oral antibiotics appear to be reserved for situations in which topical therapy is impractical or in the event of extensive disease.[2] Oral agents or alternatives to first-line topical agents may also be appropriate when the presence of resistant organisms is suspected. Rising rates of MRSA, macrolide-resistant streptococcus, and mupirocin-resistant streptococcus, have been reported.[13] In patients who do not respond to first-line antibiotics or who develop fever or other systemic symptoms, agents with relative broad coverage, such as doxycycline, trimethoprim-sulfamethoxazole (TMP/SMX), and clindamycin, can be considered.[2] All offer at least modest coverage of MRSA, but TMP/SMX has limited efficacy for staphylococcal bacteria. Local antibiotic resistance patterns may be useful for guiding therapeutic decisions when resistance is a concern. Systemic antibiotics may also be used in combination with topical antibiotics for both global and local coverage.

FIGURE 2 | Impetigo Treatment Algorithm



Topical antibiotics, regardless of specific choice, should be applied three times daily for seven to 12 days, but treatment response should be evaluated after three to five days, switching treatments if lesions have not begun to resolve. Oral antibiotics should be offered in their usual doses and schedules for seven days.

Outbreaks of impetigo are common in daycare or other settings where young children are in close contact, and community-acquired MRSA has become widespread in recent years as well.[14] Emphasizing the importance of early diagnosis, treatment, and isolation of children with impetigo is an important step for community health professionals for reducing transmission.

Summary

Even though impetigo is a self-limited superficial bacterial infection of the skin in most cases, early diagnosis and treatment facilitate healing and reduce risk of transmission. The nonbullous form of impetigo most commonly involves vesicular lesions with honey-coloured crusts on the face and extremities. It is typically due to overgrowth of *S. aureus* or *S. pyogenes*. The less common bullous form of impetigo is more typically caused by streptococcus. In patients with either form, topical antibiotics are the preferred therapy. Oral antibiotics are employed when topical antibiotics are impractical, the disease is extensive, and there is systemic involvement, particularly if an antibiotic-resistant pathogen is suspected. ●

Q&A

Impetigo: The Allergist's Perspective

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1. Should impetigo be considered an allergic or dermatologic disease?

Impetigo is caused by bacterial infection. In general, the crusting lesions are not easily confused with pruritic hypersensitivity reactions of the skin. Rather, the differential diagnosis more typically involves other infectious dermatologic diseases, such as herpes. Patients with AD are more at risk for superficial skin infections such as impetigo in general due to a dysregulation of skin immunity.

2. When is it appropriate to refer a patient with impetigo to a specialist?

Topical antibacterial agents are effective for most cases of impetigo, which resolve readily with treatment. Referrals are most appropriate when the diagnosis is uncertain or the lesions do not resolve readily with appropriate treatment.

3. If patients do not respond to first- or second-line treatment for impetigo, what is the most appropriate specialist referral, a dermatologist or an allergist?

Impetigo is an infectious disease readily managed by primary care physicians. Although it is important to consider resistant organisms, including MRSA, in patients who do not respond to first-line therapies, the referral in serious and progressive infections should be made to an infectious disease specialist or a dermatologist or allergist when there is diagnostic uncertainty.

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Chapter 5: **ROSACEA**

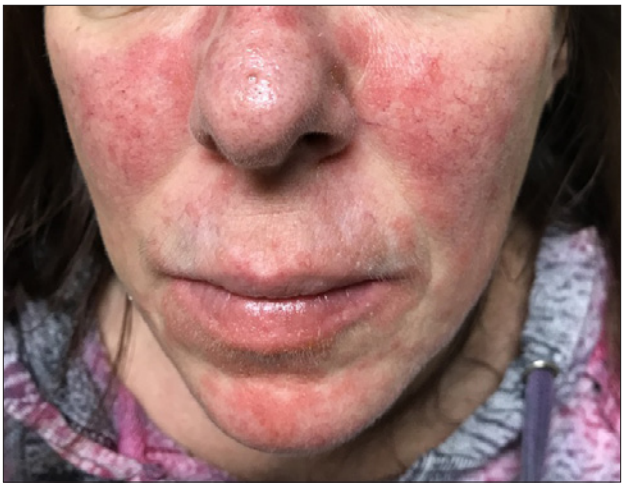
Rosacea is a chronic erythematous inflammatory condition with a relapsing-remitting course that primarily involves facial skin. Generalized flushing often accompanies the papules, pustules, telangiectasia, coarse skin, and hyperplasia that are characteristic of this condition.[1] These episodes of pimply red rash may be transient, but chronic hypertrophy of the sebaceous glands, called phyma, can produce persistent and sometimes irreversible skin changes, such as a bulbous nose in rhinophymatous rosacea.[2] Burning, stinging, and facial edema often accompany active lesions. Vision impairment can occur in those with ocular involvement, but serious complications are uncommon. Rather, the disease burden derives largely from psychosocial consequences of facial lesions, which have been associated with negative effects on quality of life due to depression and anxiety.[3,4]

The variable estimated prevalence of rosacea, which typically first develops in individuals between 30 and 50 years of age,[5] ranges from 2% to 22% in predominantly fair-skinned populations.[6] It is more common in women than in men.[5] It has been estimated that more than three million Canadians have rosacea when extrapolated from an expected prevalence rate of 10%.[7] The underlying causes of rosacea are unclear, but many patients associate the onset of flares with triggers such as stress, spicy food, hot beverages, ultraviolet light, and alcohol. Avoidance of triggers is a foundation of intervention. Although a long list of medications offer potential benefit based on empiric reports of efficacy, controlled trials with pharmacologic agents remain limited.

Pathophysiology

The U.S. National Rosacea Society has identified erythematotelangiectatic, papulo-pustular, phymatous, and ocular subtypes of rosacea.[8] These may be useful for predicting course and guiding therapy, but it is unclear whether they differ by underlying mechanisms, and more than one type can occur in the same individual.[2] The underlying inflammatory component of all forms of rosacea are most often attributed to alterations in innate immune function,[9] but changes in adaptive immunity have also been reported.[10] There is a variety of evidence supporting a genetic predisposition for rosacea.[11] The importance of this predisposition relative to environmental factors remains incompletely defined. Overall, several factors may influence the development of rosacea, including facial vasculature traits, microbial organisms, exposure to chemical agents, dermal matrix degeneration, environmental trauma, physiology of nerve innervation, high density of facial sebaceous glands, reactive oxygen species, and under- or overexpression of certain signaling factors and proteins.[12]

FIGURE 1 | Rosacea



Several comorbidities have been associated with risk of rosacea as well. Rosacea has been associated with other inflammatory conditions, such as inflammatory bowel disease (IBD), suggesting a link to other types of immunologic dysfunction.[12] It is also more common in patients with neurologic disorders, including migraine and complex regional pain syndrome.[13] An upregulation of matrix metalloproteinases (MMPs), which has been seen in both rosacea and neurologic disorders, is a potential link.[14] Increased colonization of facial skin by *Demodex folliculorum* mites has been reported, which alone or in association with genetic susceptibility might provoke an immune response leading to rosacea. Once the immune function is disturbed, triggers, such as heat or sun exposure, may drive disease through alterations in the skin's microenvironment.[15] Skin peeling and increased skin sensitivity may be due to water loss when scratching impairs the skin barrier function.[16]

Diagnosis

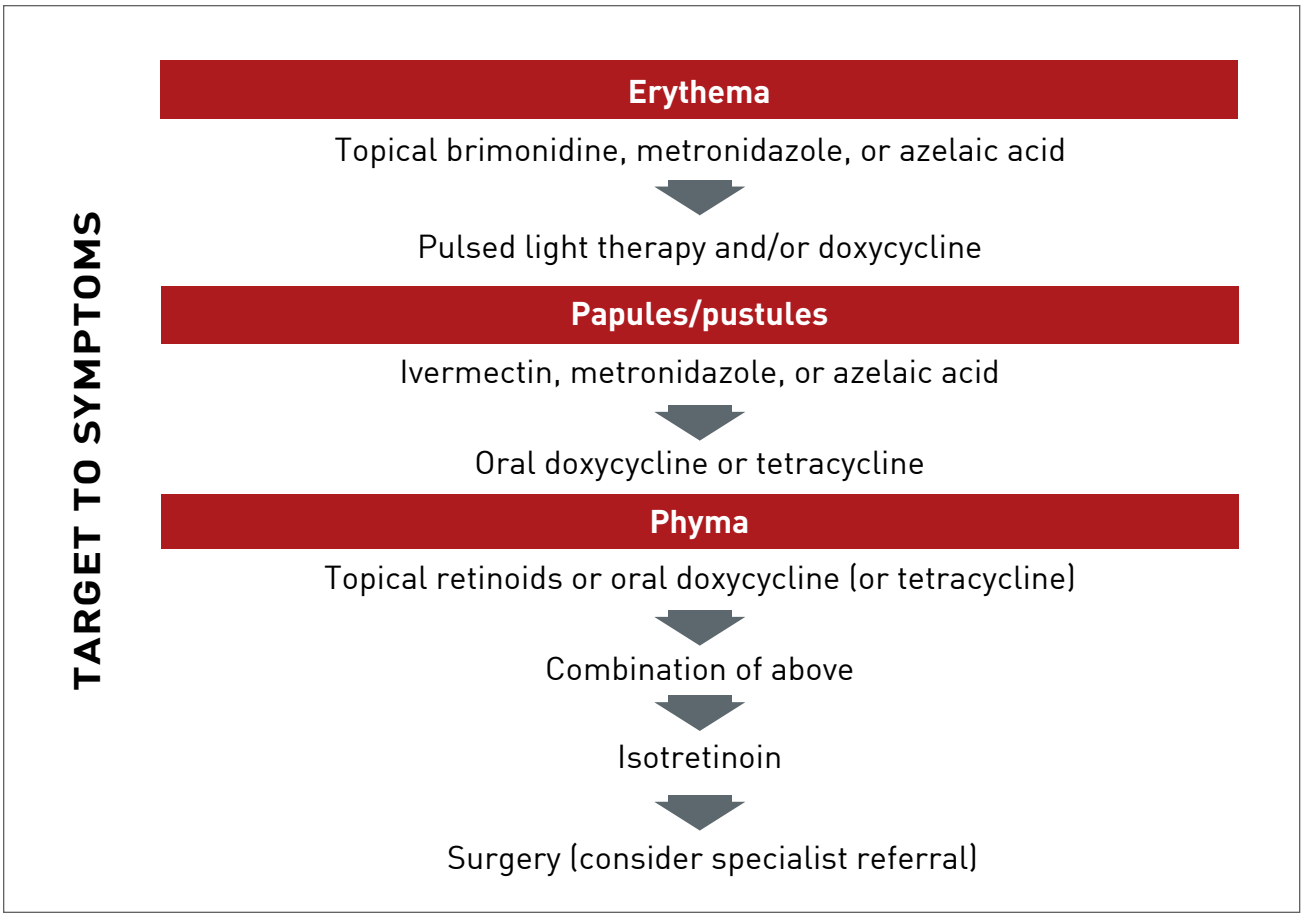
The diagnosis of rosacea is based on clinical features and history alone.[7] Although a skin biopsy might be helpful to exclude differential diagnoses when clinical signs are ambiguous, the histopathology of rosacea is not unique and can be similar to that of other inflammatory skin diseases.[1] When accompanied by transient flushing, a history of episodic rash in the central part of the face with papules, pustules, and/or telangiectasia supports a diagnosis of rosacea in the absence of another explanation for these symptoms (Figure 1). Involvement can include the eyes and the neck in some individuals. Other features, such as burning or stinging and enlargement of the sebaceous glands are also consistent with the diagnosis.

The conditions most likely to be confused with rosacea include acne vulgaris, any of several forms of dermatitis affecting the face, such as contact dermatitis or seborrheic dermatitis, and steroid-induced acneiform eruption.[17] Potentially more serious but less common conditions in the differential diagnosis include lupus erythematosus, sarcoidosis, drug reactions, and dermatomyositis. A family history of skin rash associated with the common triggers of rosacea, such as exposure to sunlight or alcohol, is common. The diagnosis may be easier to reach in those with long-standing symptoms because of the phymatous changes and more extensive erythema that develop when persistent rosacea is poorly controlled. Rosacea presents in a multitude of ways, and has been subclassified into four categories: erythematotelangiectatic, papulopustular, phymatous, and ocular.

Treatment

Avoidance of dietary, medicinal, and environmental triggers is reasonably considered the first-line therapy for rosacea. Common triggering factors include extreme temperatures, spicy food, caffeine, physical exertion, emotions, topical irritants, and medications that cause flushing.[19] To identify triggers, patients are advised to journalize/document exposures, diet consumption, and activities leading up to flare-ups. According to guidelines issued by an expert panel of Canadian dermatologists, available pharmacologic therapies are best directed at individual symptoms. There is no pharmacologic therapy that addresses the underlying pathophysiology. For most symptoms, the Canadian guidelines make recommendations

FIGURE 2 | Rosacea Treatment Algorithm



stratified by mild versus moderate-to-severe involvement. For example, the options for mild erythema are listed as topical brimonidine, metronidazole, and azelaic acid. Response should be evaluated after eight weeks. For severe erythema, intense pulsed light therapy or oral doxycycline can be added to the first-line agents, but specialist care might be appropriate. For papules and pustules, the options listed for mild involvement are topical ivermectin, metronidazole, or azelaic acid. Oral doxycycline or tetracycline can be added for moderate to severe disease if topical agents provide inadequate relief (Figure 2).

For phyma, topical retinoids or an oral antibiotic (doxycycline or tetracycline) are recommended as a first step for mild involvement followed by the combination if adequate control is not achieved after at least eight weeks. Isotretinoin is an additional second-line option. For severe phyma, some form of surgery may be required. Ocular involvement, which typically requires some combination of lid care and artificial tears, should be referred to a specialist. In general, patients should also use daily broad-spectrum sunscreen to protect against UV-A and UV-B light, ideally with protective silicones and green-tinted for erythema.

Due to the chronicity of rosacea, patients should be considered for maintenance therapy and re-evaluated regularly in order to adjust treatment. When used for maintenance, several of the topical agents recommended for acute control, including metronidazole,[18] ivermectin,[19] and brimonidine,[20] have been associated with a reduced risk of relapse.

Summary

Rosacea is a chronic inflammatory skin disease most often involving the cheeks, nose, chin, and forehead. The relapsing-remitting features, which include erythema, papules, pustules, and telangiectasia, are often associated with triggers, such as exposure to UV light, spicy foods, psychological stress, and alcohol consumption. Avoidance of triggers is the first step to reduce risk and severity of flares. The same topical therapies used to control acute symptoms can be considered in maintenance regimens to reduce risk of relapses. For severe or ocular involvement, specialist care is appropriate. Due to the risk of irreversible skin changes from persistent erythema and phyma, early diagnosis and aggressive symptom control is appropriate. Although serious complications are uncommon, the facial involvement that is typical of rosacea imposes psychological distress and reduces quality of life for many affected individuals. ●

Q&A

Rosacea: The Allergist's Perspective

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1. Should rosacea be considered an allergic or dermatologic disease?

Rosacea is an inflammatory condition, but its relationship to hypersensitivity is uncertain. Although skin mite colonization is considered a potential etiologic factor, the inflammatory pathways typically upregulated in an atopic response are not closely associated with rosacea. It is therefore largely regarded as a dermatologic condition. There is some connection to immune dysregulation and a microbiome imbalance that causes an aberrant immune shift to commensal organisms such as Malassezia furfur but these are typically not type II inflammatory issues.

2. When is it appropriate to refer a patient with rosacea to a specialist?

As the underlying pathophysiology of rosacea remains incompletely understood, current treatments focus on avoiding known triggers and topical therapies that ameliorate the skin manifestations. Patients with significant and persistent phyma are at risk of permanent skin changes. Such patients and those with ocular involvement are candidates for specialist care. Although some foods such as chocolate and alcohol are known to flare up rosacea, these are not mediated through an IgE reaction and as such are not allergies. Patients with rosacea can get flares of contact dermatitis like anyone else which may sometimes cause diagnostic confusion.

3. If patients do not respond to first- or second-line treatment for rosacea, what is the most appropriate specialist referral, a dermatologist or an allergist?

In cases of rosacea refractory to first-line therapies, particularly in cases of progressive phyma, dermatologists typically have more experience with third-line interventions, such as retinoids or phototherapy, than other specialists. Although demodex mites are among suspected triggers, in suggesting an inflammatory, allergic-like underlying pathophysiology, dermatologists are generally consulted before allergists for difficult cases.

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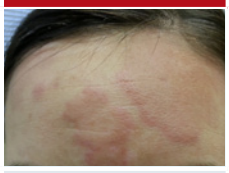
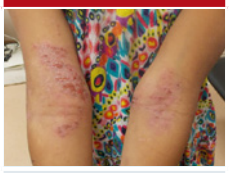
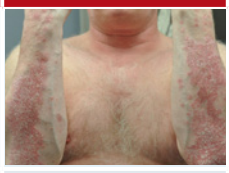
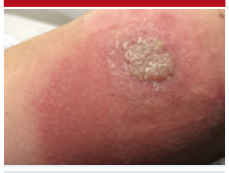
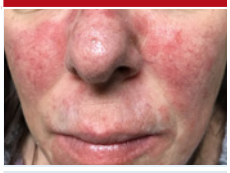
CHEAT SHEET ON THE **5 MOST COMMON SKIN DISEASES**

	Chronic Spontaneous Urticaria	Atopic Eczema	Psoriasis	Impetigo	Rosacea
Example					
Key Features	Pruritic Hives, angioedema	Papules, vesicles and erythema, squames	Scaly plaques, erythema	Crusted yellowish lesions or bullae	Flushing, papules, pustules, telangiectasia on the face
Peak Ages	Acute: mostly young Chronic: middle age	Early childhood	≥20 years old but can occur in children	Young children	Middle age or older
Mechanism	Inflammatory	Immune dysregulation	Immune dysregulation	Infection	Immune dysregulation
Diagnosis	Physical exam and history	Physical exam and history	Physical exam and history	Physical exam and history	Physical exam and history
1st Line Rx	Antihistamines	Hydration and topical steroids	Topical steroids or calcipotriene	Topical mupirocin or fusidic acid	Avoid triggers, topical agents targeted at symptoms
IF UNCONTROLLED					
2nd Line	High dose antihistamines and then anti-IgE antibody omalizumab	Topical calci-neurin inhibitors and then immu-nosuppressive agents such as cyclosporine	Phototherapy or immunosuppres-sive therapies and then biolog-ics such as infliximab	Oral antibiotics for seven days but consider MRSA if infection does not readily resolve	Oral antibiotics or pulsed light therapy for erythema, topical retinoids for phyma