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Peeking Beneath the Surface of Atopic Dermatitis:

Testing Your Skills from Pathogenesis to Treatment

Supported by an educational grant from Sanofi Genzyme and Regeneron Pharmaceuticals

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This event is not a part of the official Internal Medicine Meeting 2018 Education Program.

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#ADskills

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#ADskills

Learning Objective 1

Apply knowledge of the pathogenesis of atopic dermatitis (AD) to make better informed treatment decisions.

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Learning Objective 2

Increase identification of signs and symptoms of AD by 25% to improve differential diagnosis.

#ADskills

Learning Objective 3

Integrate data from recent clinical trials on novel treatment strategies into clinical practice to optimize patient outcomes.

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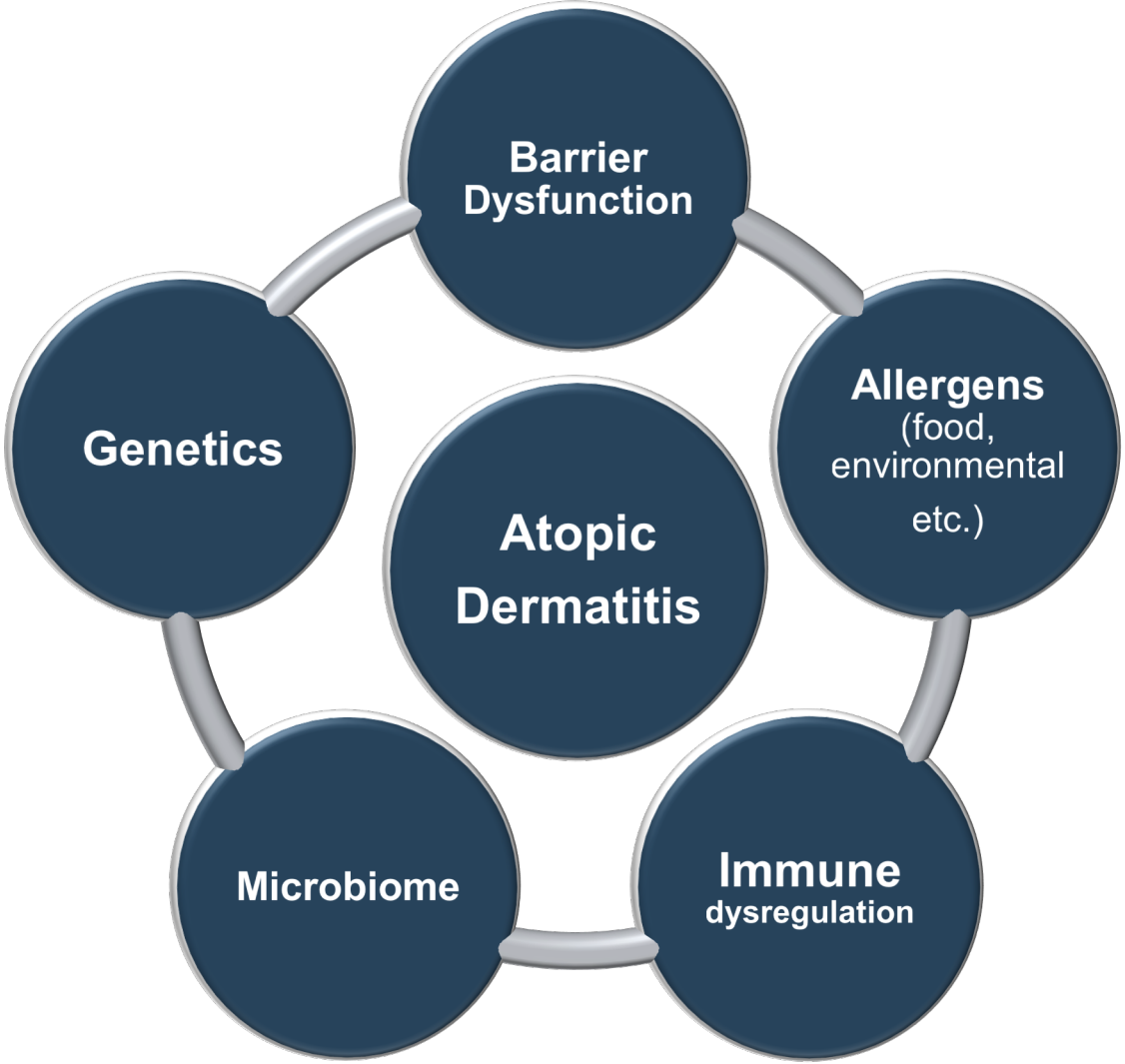
Under the Surface of AD

Understanding Disease Pathogenesis

Audience Response

Which statement regarding atopic dermatitis is true?

A. It presents the same in adult and children patients
B. Systemic corticosteroids are adequate for long-term disease control
C. Most patients can be managed effectively with once daily corticosteroids
D. Most patients with AD have a FLG mutation

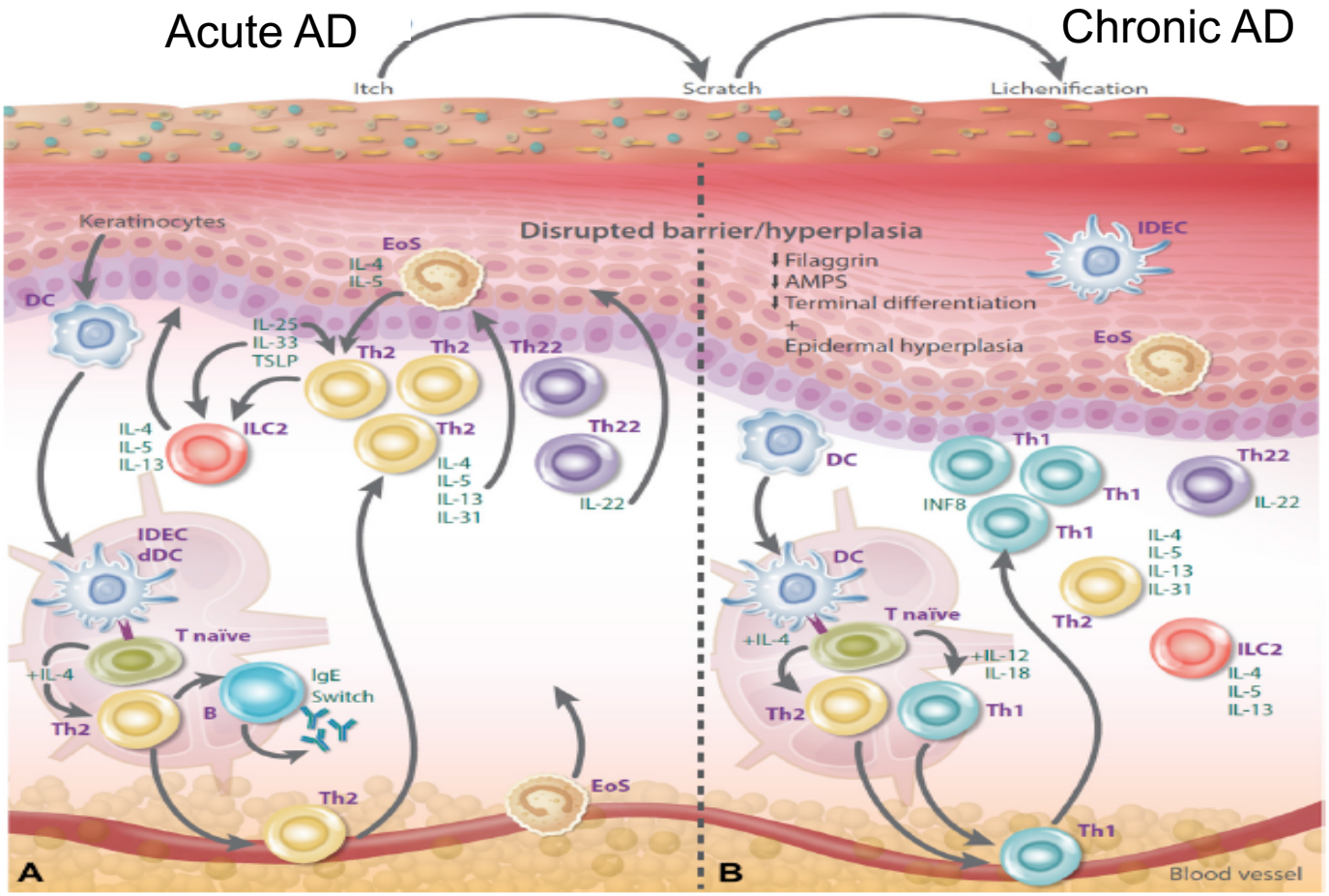

Barrier Dysfunction
Allergens (food, environmental etc.)
Immune dysregulation
Microbiome
Genetics
Atopic Dermatitis

AD Pathogenesis Basics

- Outside-in: Epidermal barrier disruption
  - Filaggrin, proteases
  - Allows antigens and irritants in
- Inside-out: Th2 inflammatory cytokines (IL-4, IL-13, IL-22, IL-25, IL-31)…
  - Suppress epidermal structure protein synthesis
  - Induce proteases

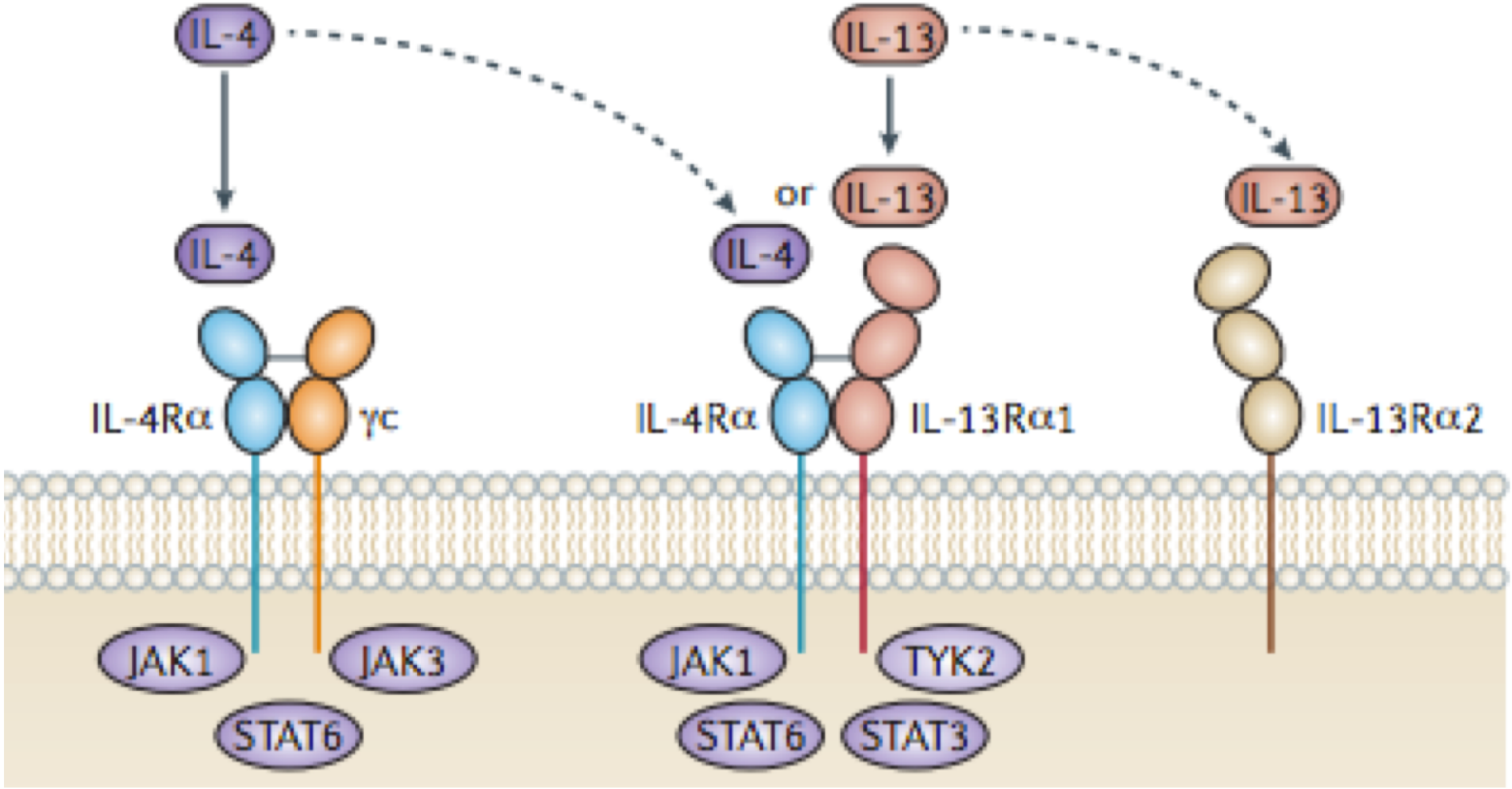
Malajian D, Guttman-Yassky E. *Cytokine*. 2015;73(2):311-8.

Atopic Dermatitis: Under the Skin

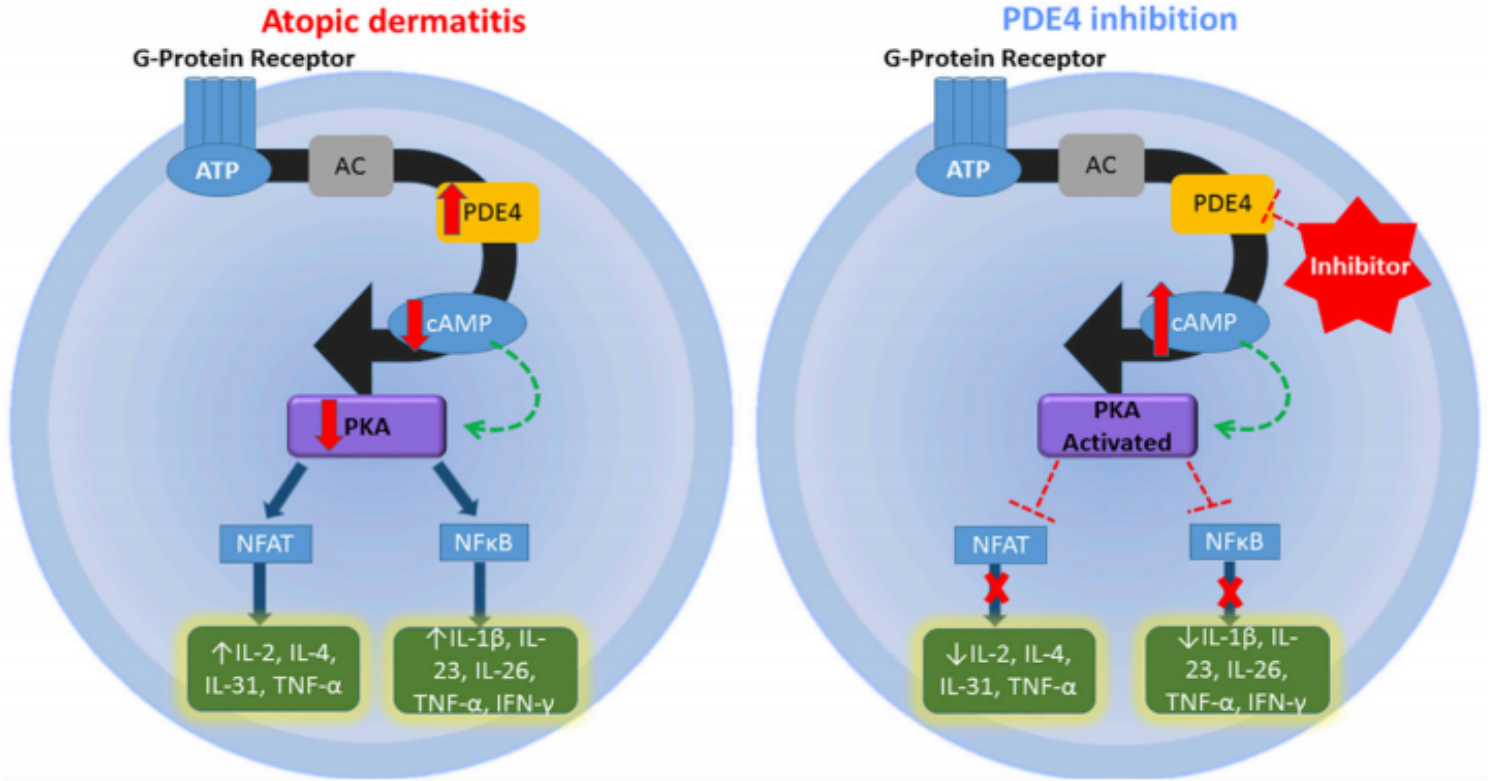


Gooderham MJ, et al. *J Am Acad Dermatol*. 2018 ;78:S28-S36.

Key Inflammatory Pathways in AD



Gandhi NA, et al. *Nat Rev Drug Discov*. 2016;15:35-50.



cAMP, cyclic adenosine monophosphate; PKA, protein kinase A ; NFAT, nuclear factor of activated T cells ; NFkB, nuclear; AC, Adenylyl cyclase; ATP, adenosine triphosphate; IL, interleukin; IFN-g, interferon gamma; TNF-a, tumor necrosis factor-a.

Zebda R, et al. *J Am Acad Dermatol*. 2018;78:S43-S52.

Strategies for Diagnosing AD

Improving Accuracy and Timeliness

Myths

- AD is a disease primarily affecting children and that they will eventually outgrow
- Presentation in children is the same as in adults
- Eczema is a mild skin condition and does not have a significant impact on patients' QOL
- Eczema is caused by allergies

Clinical Phenotypes in AD

Infants/early childhood:
face, scalp, trunk and extensor surfaces

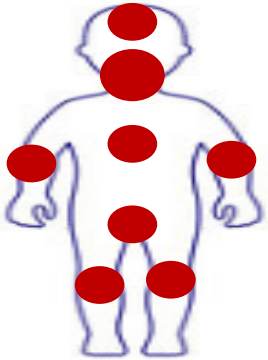
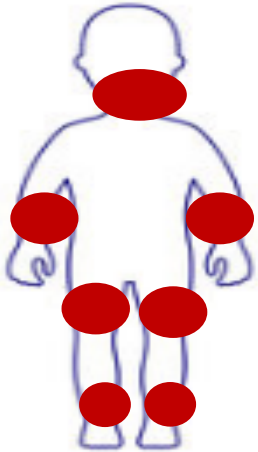
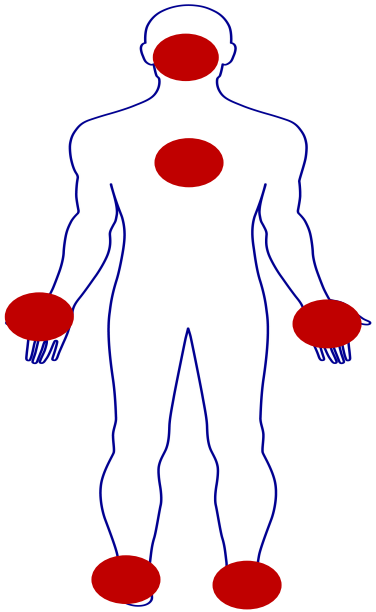


Image courtesy of Dr. Chiesa Fuxench

Childhood:
neck, flexors, feet



Adults:
face, neck, hands, feet, trunk (back)



Differential Diagnosis of Atopic Dermatitis

INFANCY	CHILDHOOD	ADULTHOOD
Seborrheic dermatitis	Scabies	Seborrheic dermatitis
Scabies	Contact dermatitis	Contact dermatitis
Immunodeficiency syndromes: • Wiskott-Aldrich syndrome • Hyper-IgE syndrome • Omenn syndrome • Netherton syndrome	Tinea corporis	Scabies
	Pityriasis Lichenoides/PLEVA	Insect bites
	Psoriasis	Photoallergic or photoirritant dermatitis
	CTCL	HIV-related dermatitis
Langerhan's cell histiocytosis		Psoriasis
Acrodermatitis enteropathica		CTCL
Metabolic disorders		Drug-induced dermatitis

Simpson EL, et al. *J Am Acad Dermatol*. 2017;77:623-633

Case Presentation: JC

- JC is a 36 y/o black male with an itchy rash
- Duration: Has had intermittent symptoms throughout his entire life. Feels as if these have been getting progressively worse in recent years
- Location: Rash is primarily located on the chest, arms, and legs
- Symptoms: Extremely itchy, feels as if he cannot stop scratching, results in waking up from sleep almost every night.

Audience Response

Based on what you know so far, what would be your next step in managing JC?

A. Prescribe a topical corticosteroid
B. Do a skin biopsy
C. Refer for patch testing
D. Refer for skin prick testing
E. I am not sure

Making the Diagnosis

Diagnostic Criteria

- Clinical diagnostic criteria core sets[1,2]
  - Hanifin and Rajka criteria
  - UK Working Party
  - American Academy of Dermatology (AAD) consensus criteria[1]

1. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;70:338-351.
2. Napolitano M, et al. *G Ital Dermatol Venereol*. 2016;151:403-411.

UK Working Party Diagnostic Criteria for Atopic Dermatitis

Must have an itchy skin condition plus 3 or more of:
• Onset below age 2 (criterion not used in children under 4 years)
• History of flexural involvement
• History of generally dry skin
• Personal history of other atopic diseases (in children aged under 4 years, history of atopic disease in a first degree relative may be included)
• Visible flexural dermatitis

Williams HC, et al. *Br J Dermatol.* 1994;131(3):406-416.

Assessment of Disease Severity, Clinical Outcomes and Impact on Quality of Life

- Most common severity scales:
  - SCORAD—SCORing Atopic Dermatitis index
  - EASI—Eczema Area and Severity Index
  - IGA—Investigator's Global Assessment
  - BSA-% Body Surface Area Involvement

Assessment of Disease Severity, Clinical Outcomes and Impact on Quality of Life

- Symptom specific:
  - Pruritus Numerical Rating Scale
- PRO
  - Dermatology Life Quality Index
  - Patient Oriented Eczema Measure (POEM)

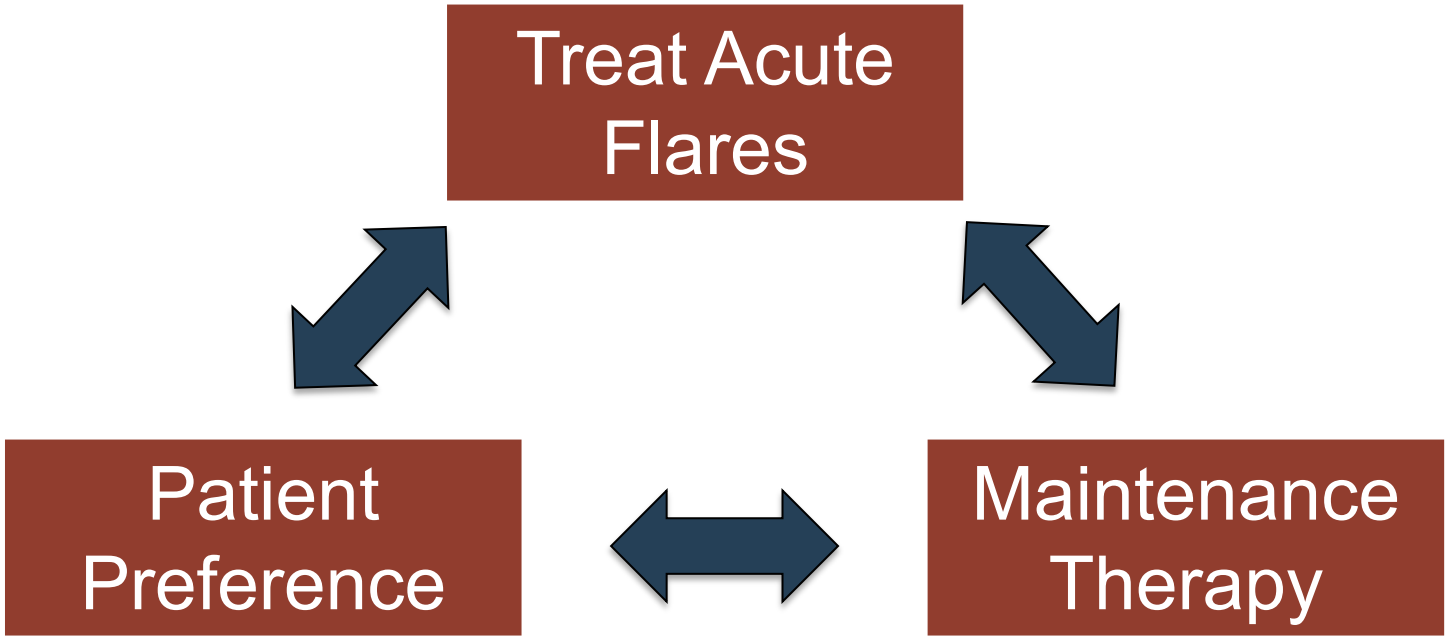
Symptoms that Impact Quality of Life

- Ask about itching
- Ask about sleep
- Ask about depression and anxiety
- Document QOL and disease severity at each visit
  - Also being requested by some payors

Optimizing Outcomes in Patients with Moderate-to-Severe AD

Integrating the Latest Evidence Into Clinical Practice

Considerations for Treatment



Wang D, Beck LA. *Am J Clin Dermatol.* 2016;17:425-443.; Saeki H, et al. *J Dermatol.* 2016;43:1117-1145.; Ring J, et al. *J Eur Acad Dermatol Venereol.* 2012;26:1045-1060.; Ring J, et al. *J Eur Acad Dermatol Venereol.* 2012;26:1176-1193.

Goals for Treatment

- Maintain a state in which symptoms are mild with minimal impact on quality of life
- Decrease the rate of acute flares or disease exacerbation
- Manage acute flares quickly and effectively

AAD Guidelines

- Most patients can be managed with topical moisturizers, topical corticosteroids, and other nonpharmacologic interventions
- Patients with moderate-to-severe disease require more complex strategies
  - Phototherapy
  - Systemic medications

Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132.

Moisturizers

- Topical emollients
  - Petroleum jelly
  - White petrolatum
- Lotions or creams that contain ceramides or lipid formulations
- Patient preference is the most important factor in selecting moisturizer

Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132.

Prescription Topical Treatments

- Cornerstone for treatment of moderate to severe disease
- Topical corticosteroids
  - Effective
  - Side effects are rare
    - Steroid induced cutaneous atrophy, striae
    - Systemic absorption VERY rare
    - Steroid phobia-specifically in pediatric populations
- Topical calcineurin inhibitors
- Topical PDE4 inhibitors

Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):116-132.

Role of Proactive Treatment

Reactive approach

Relies on anti-inflammatory therapies administered to active lesions that are then discontinued once visible skin lesions are cleared

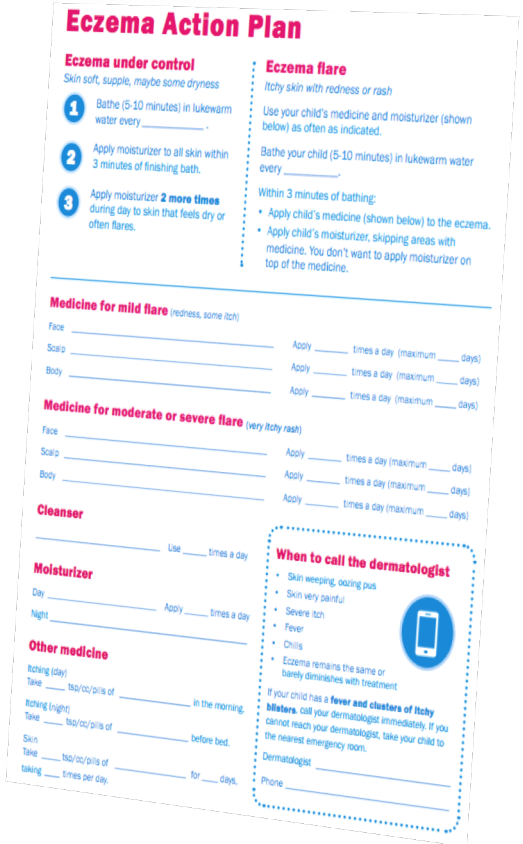
Proactive approach

A combination of predefined, long-term, low-dose, anti-inflammatory treatments applied to previously affected areas of the skin on a regular schedule, in addition to emollients on the entire body

Wollenberg A, et al. *J Eur Acad Dermatol Venereol.* 2016;30:729-747.; Torrelo A, et al. *Actas Dermosifiliogr*. 2013;104:409-417.; Thaci D, et al. *J Eur Acad Dermatol Venerol.* 2010;24:1040-1046.; Sidbury R, et al. *J Am Acad Dermatol.* 2014;71:1218-1233.

Adherence to Treatment in AD

- Lack of adherence can result in:
  - Worse clinical outcomes
  - Lack of treatment efficacy
  - Poor adherence may be misconstrued as a poor treatment response
- Strategies:
  - Frequent follow-up appointments
  - Educational patient workshops
  - Written eczema actions plans/electronic reminders



Eczema Action Plan

Eczema under control

Skin soft, supple, maybe some dryness

1. Bathe (5-10 minutes) in lukewarm water every _____.
2. Apply moisturizer to all skin within 3 minutes of finishing bath.
3. Apply moisturizer **2 more times** during day to skin that feels dry or often flares.

Eczema flare

Itchy skin with redness or rash

Use your child's medicine and moisturizer (shown below) as often as indicated.

Bathe your child (5-10 minutes) in lukewarm water every _____.

Within 3 minutes of bathing:

- Apply child's medicine (shown below) to the eczema.
- Apply child's moisturizer, skipping areas with medicine. You don't want to apply moisturizer on top of the medicine.

Medicine for mild flare (redness, some itch)

Face _____ Apply _____ times a day (maximum ____ days)

Scalp _____ Apply _____ times a day (maximum ____ days)

Body _____ Apply _____ times a day (maximum ____ days)

Medicine for moderate or severe flare (very itchy rash)

Face _____ Apply _____ times a day (maximum ____ days)

Scalp _____ Apply _____ times a day (maximum ____ days)

Body _____ Apply _____ times a day (maximum ____ days)

Cleanser

_____ Use ____ times a day

Moisturizer

Day _____ Apply ____ times a day

Night _____

Other medicine

Itching (day) Take ____ tsp/cc/pills of _____ in the morning.

Itching (night) Take ____ tsp/cc/pills of _____ before bed.

Skin Take ____ tsp/cc/pills of _____ for ____ days, taking ____ times per day.

When to call the dermatologist

- Skin weeping, oozing pus
- Skin very painful
- Severe itch
- Fever
- Chills
- Eczema remains the same or barely diminishes with treatment

If your child has a **fever and clusters of itchy blisters**, call your dermatologist immediately. If you cannot reach your dermatologist, take your child to the nearest emergency room.

Dermatologist _____

Phone _____

Bass AM, et al. *J Clin Med.* 2015;4:231-242.; Snyder A, et al. *Cutis.* 2015;96:397-401. Ellis RM, et al. *Pediatr Dermatol.* 2011;28:242-244.; Smith SD, et al. *Med J Aust.* 2013;199:467-469.

What do you take into account when considering whether to start systemic therapy for atopic dermatitis?

Audience Response

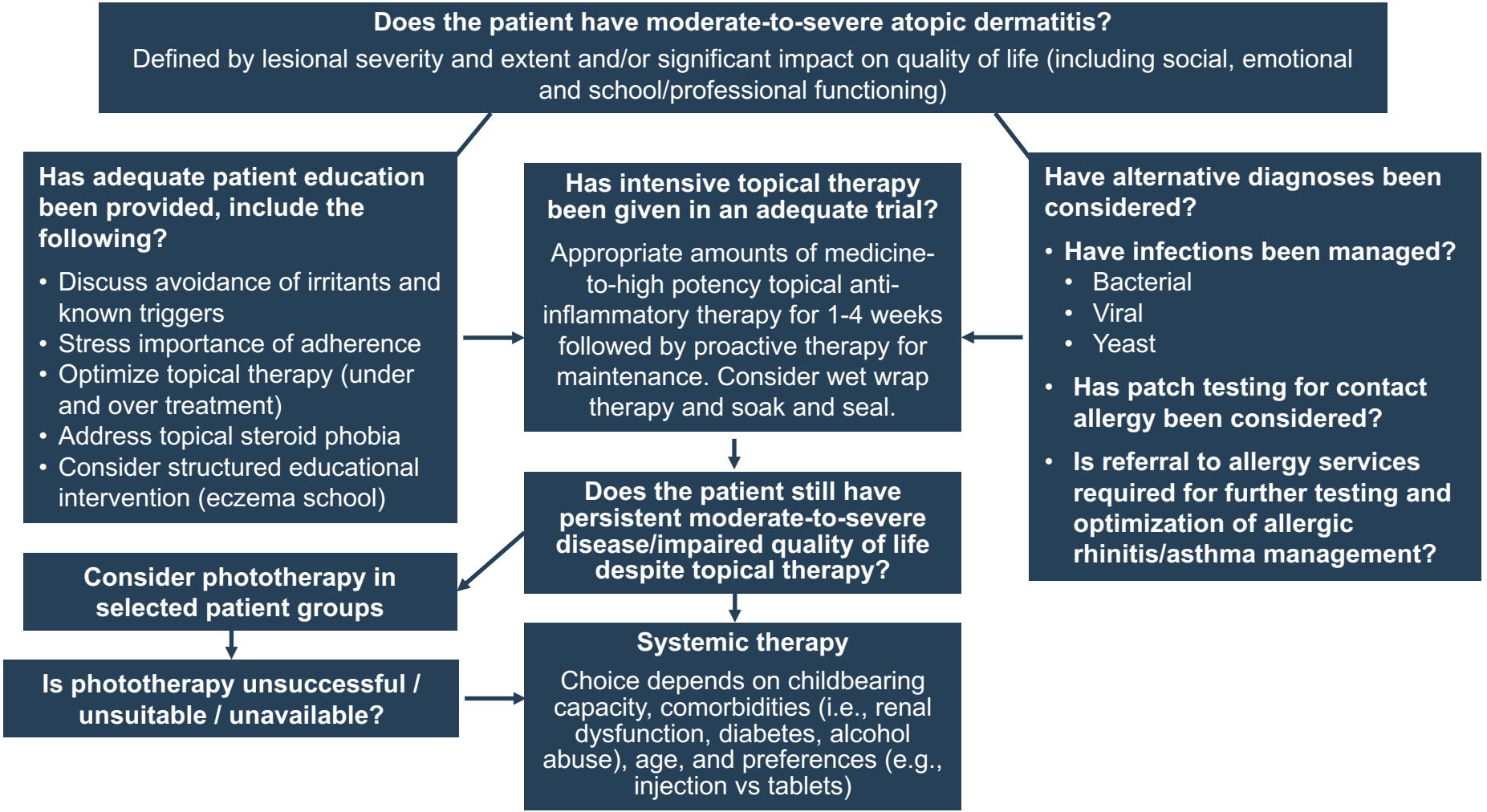
Our patient JC has been adherent to regular moisturizer and topical corticosteroid use but continues to flare, what is your next step?

A. Refer for skin prick testing
B. Prescribe a course of systemic steroids
C. Refer to a dermatologist
D. I don’t know
E. None of the above

Audience Response

What information would you like to receive from the dermatologists after referring a patient with AD?

A. Information related to diagnosis
B. Drugs/interventions that have been prescribed
C. Follow-up plan
D. Is there anything that I should be monitoring?

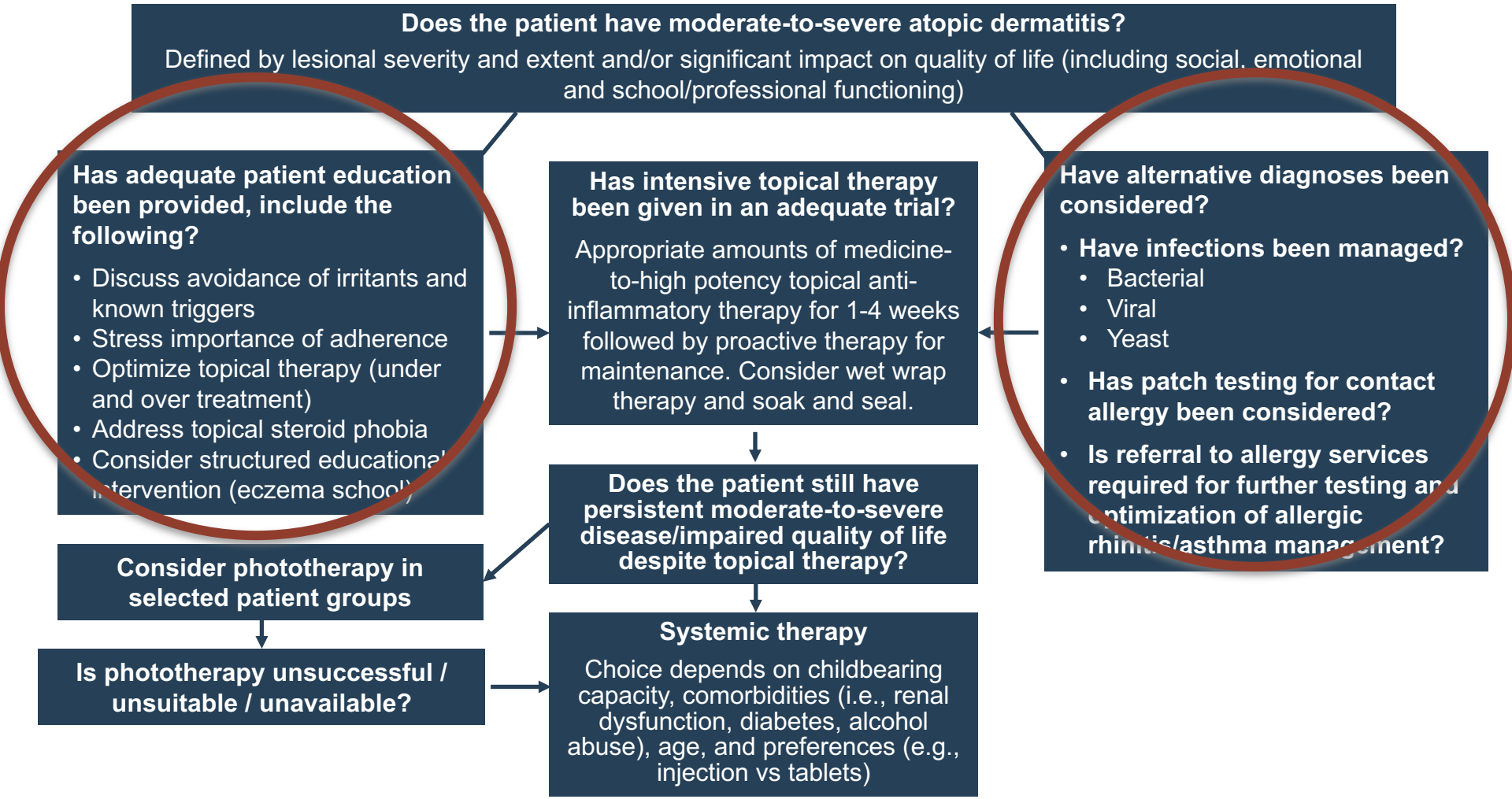


Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

Does the patient have moderate-to-severe atopic dermatitis?

Defined by lesional severity and extent and/or significant impact on quality of life (including social, emotional and school/professional functioning)

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.
Chopra R, et al. *Br J Dermatol*. 2017;177(5):1316-1321.



Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

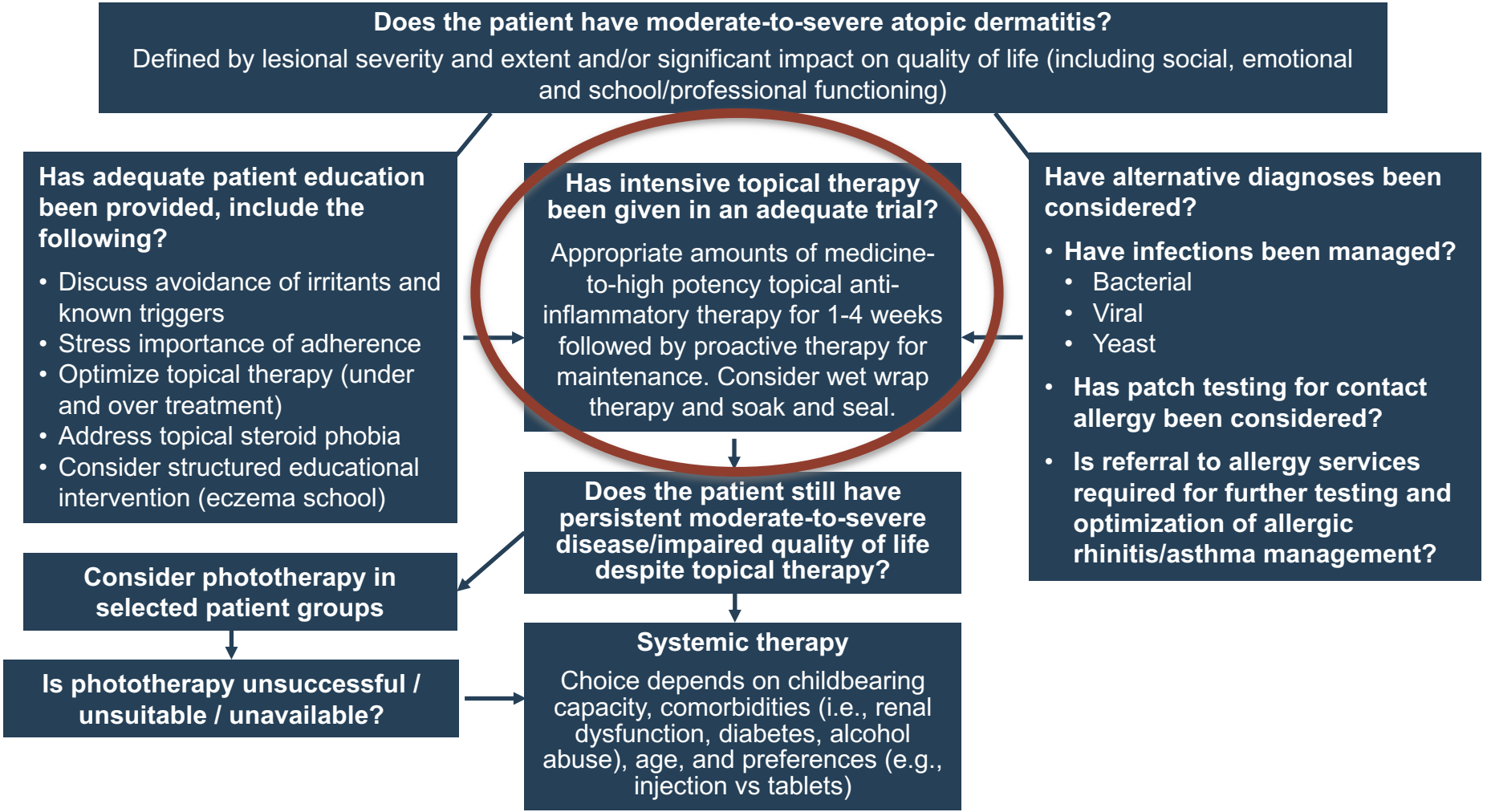
Has adequate patient education been provided, including the following?

- Discuss avoidance of irritants and known triggers
- Stress importance of adherence
- Optimize topical therapy (under and over treatment)
- Address topical steroid phobia
- Consider structured educational intervention (eczema school)

Have alternative diagnoses been considered?

- **Have infections been managed?**
  - Bacterial
  - Viral
  - Yeast
- **Has patch testing for contact allergy been considered?**
- **Is referral to allergy services required for further testing and optimization of allergic rhinitis/asthma management?**

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

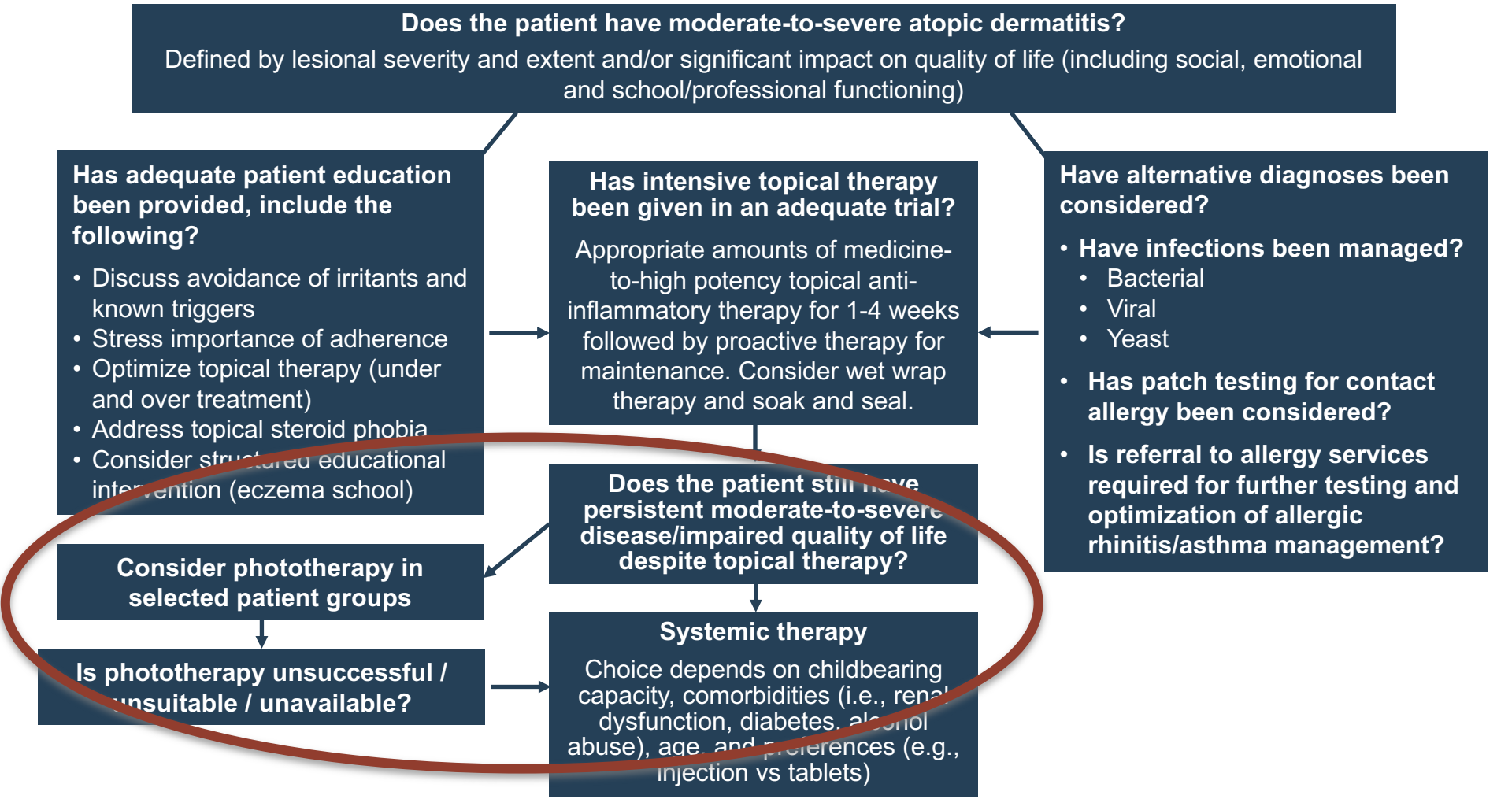


Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

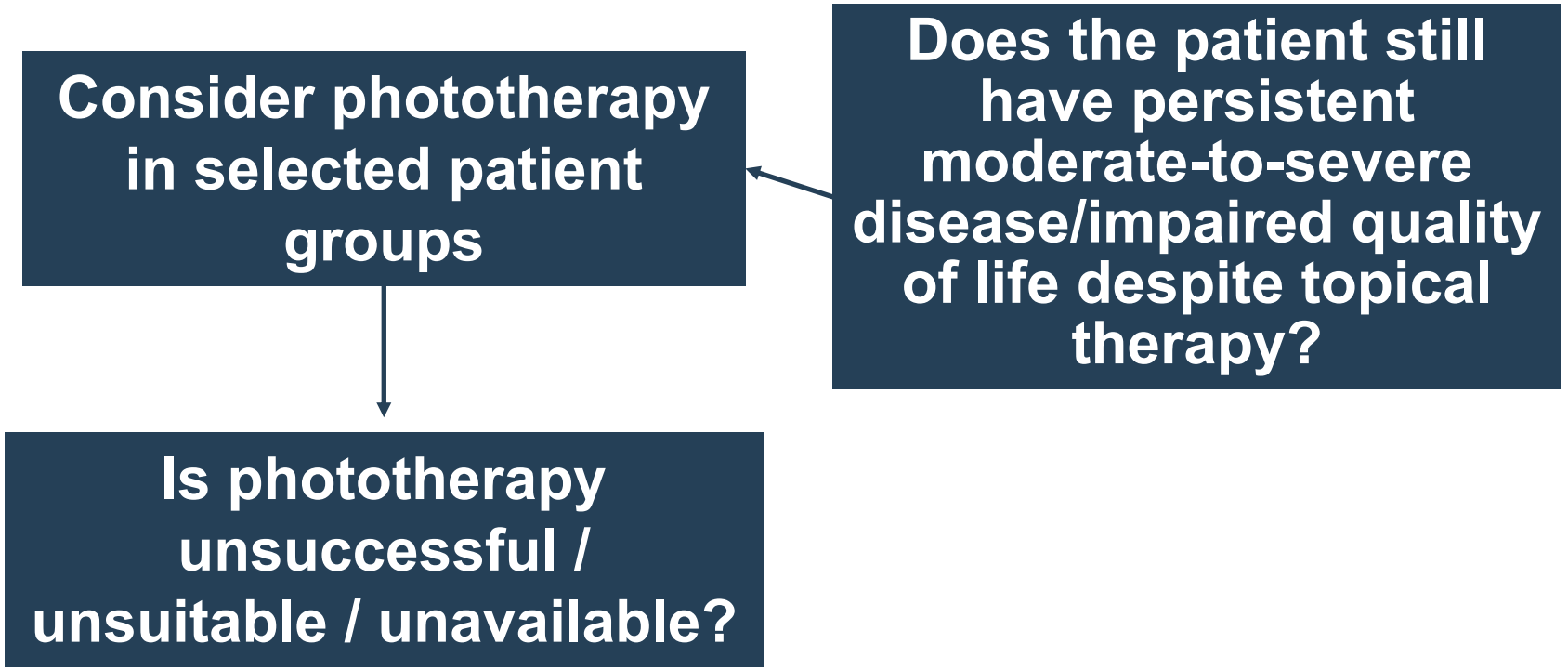
Has intensive topical therapy been given in an adequate trial?

Appropriate amounts of medium-to-high potency topical anti-inflammatory therapy for 1-4 weeks followed by proactive therapy for maintenance. Consider wet wrap therapy and soak and seal.

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.



Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.



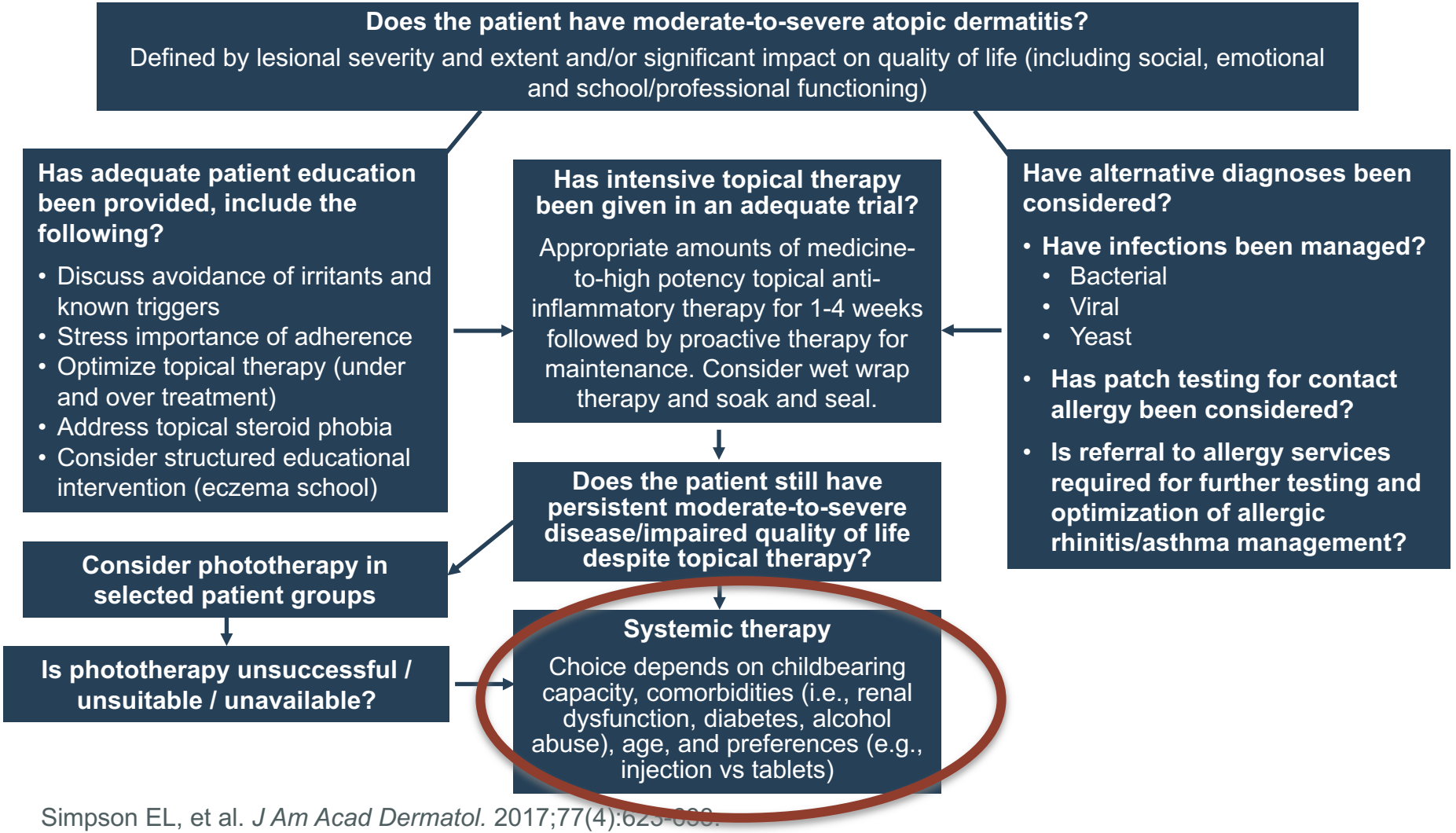
Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

Phototherapy for AD

- Types of phototherapy
  - Broad band UVB
  - PUVA
  - Narrow band UVB has better safety profile
- Efficacious in pediatric population, but long-term risk of skin cancer not fully understood
- Optimal benefit requires prolonged course (~24 treatments) to induce sustained remission
- Adherence is a challenge
- Discontinue if systemic therapy is initiated

PUVA = psoralen ultraviolet A.

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.



Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

Systemic Therapy

Choice depends on childbearing capacity, comorbidities (ie, renal dysfunction, diabetes, alcohol abuse), age, and preferences (eg, injection vs tablets)

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

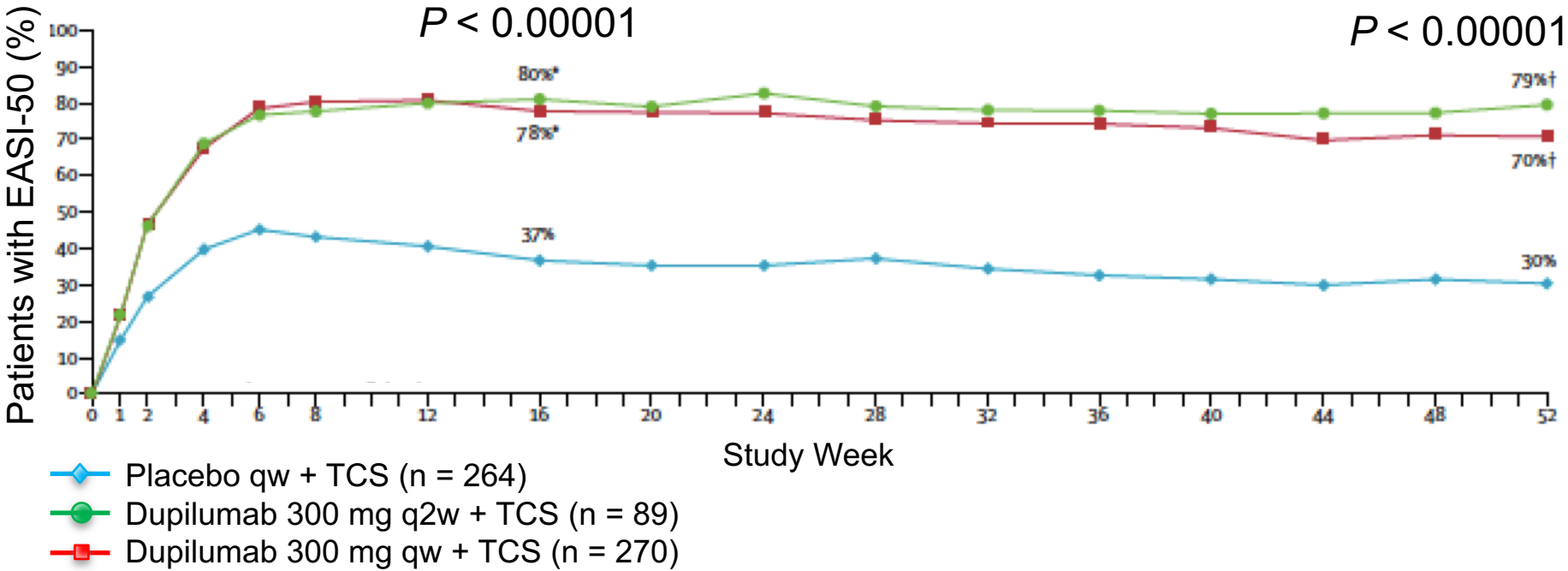
Most Common Systemic Medications for AD

Drug	Monitoring Required	Common or Serious Side Effects
Azathioprine*	CBC, CMP, thiopurine methyltransferase	Nausea, vomiting, hematologic abnormalities, skin malignancies, hepatosplenic lymphoma, CNS infection
Cyclosporine*	CBC, CMP, magnesium, uric acid, lipids, and blood pressure	Renal insufficiency, hypertension, drug interactions
Dupilumab	None	Injection site reactions, conjunctivitis
Methotrexate*	CBC, CMP	Hepatoxicity, hematologic abnormalities, teratogen, GI intolerance, nausea, fatigue
Mycophenolate mofetil*	CBC, CMP	Gastrointestinal, teratogen

***Not FDA approved for the treatment of AD.**

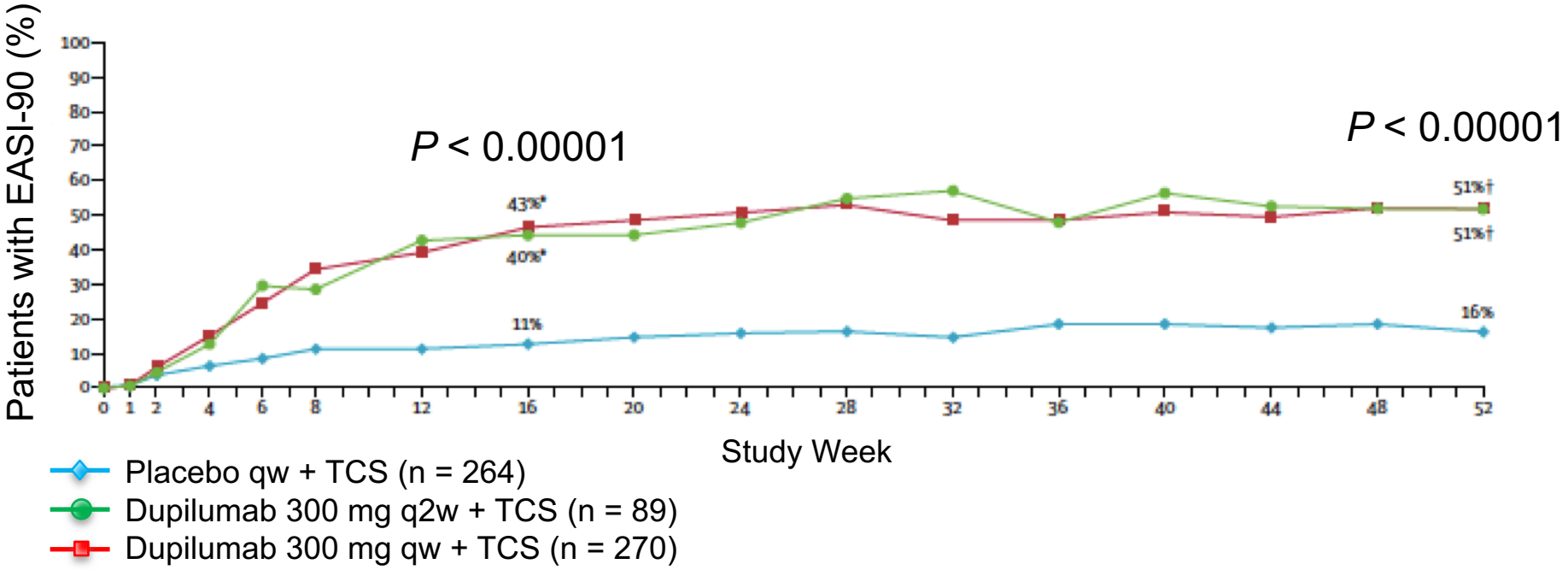
Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

Dupilumab: One Year Efficacy EASI-50



Blauvelt A, et al. *Lancet* 2017;389:2287–303.

Dupilumab: One Year Efficacy EASI-90



Blauvelt A, et al. *Lancet* 2017;389:2287–303.

52-Week Reported Adverse Events

Drug	Injection site pain	Conjunctivitis
Placebo + TCS	8%	8%
Dupilumab 300 mg q2w + TCS	15%	14%
Dupilumab 300mg qw + TCS	19%	19%

Blauvelt A, et al. *Lancet* 2017;389:2287–303.

Biologics Pipeline

Target	Compound	Phase
TSLP	Tezepelumab	2a →
IL-4	Pitrakinra	2a → ?
IL-13	Tralokinumab	3
IL-13	Lebrikizumab	3
IL-5	Mepolizumab	2a
IgE	QGE031/ligelizumab	2a → ?
IL-12/IL-23	Ustekinumab	2a →
IL-17A	Secukinumab	2a →
IL-31	BMS-981164	1b → ?

Adapted from Paller AS, et al. *J Allergy Clin Immunol.* 2017;140(3):633-643.

Oral Therapy Pipeline

Target	Compound	Phase
CRTH2 (Th2 marker)	OC000459	2a → STOP
CRTH2 (Th2 marker)	QAQ 039	2b → STOP
PDE4	Apremilast	2a → STOP
Histamine 4 Receptor	ZPL389	2a →
JAK 1/2	Baricitinib	2b →
JAK 1	Pf-04965842	2a →
JAK 1	Upadacitinib (ABT 494)	2a →
NK1R (substance P receptor)	VLY-686/tradipitant	2a →
NK1R (substance P receptor)	Serlopitant	2a →

Adapted from Paller AS, et al. *J Allergy Clin Immunol.* 2017;140(3):633-643.

Topical Therapy Pipeline

Target	Compound	Indication	Phase
Aryl hydrocarbon receptor	Tapinarof/benvitimod	Moderate-severe	2a →
PDE4	Roflumilast	Moderate	2a → ?
PDE4	RVT-501	Mild-moderate	2a →
JAK 1, JAK 3	Tofacitinib	Moderate-severe	2a → STOP
JAK 1, JAK 2	INCB18424	Mild-moderate	2a →
JAK 1, JAK 3	LEO 124249/JTE-052	Mild-moderate	2a
S. aureus	R mucosa bacteria	Antecubital AD	1/2
S. aureus	Coag negative staph	Moderate-severe	1/2

Adapted from Paller AS, et al. *J Allergy Clin Immunol.* 2017;140(3):633-643.

Summary: When to Consider Systemic Therapy

- Moderate or severe disease
- Poor quality of life
- Adequate trial of topical therapy
- Considered aggravating factors
  - infection, allergic contact dermatitis
- Phototherapy not possible / not appropriate / already failed

Simpson EL, et al. *J Am Acad Dermatol.* 2017;77(4):623-633.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- AD presents differently in children vs adults
- Recognize the impact of AD on patients' quality of life
- Educate patients to improve adherence
- Employ treatment strategies that consider:
  - Clinical efficacy and patient safety
  - Individual patient characteristics and patient preference
- Patients with moderate-to-severe disease require more complex strategies

Questions & Answers

#ADskills

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Thank you!

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