Clinical Advances in ATOPIC DERMATITIS and ALOPECIA AREATA

Provided by AAPA The France Foundation

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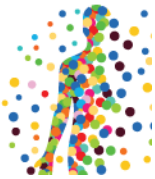

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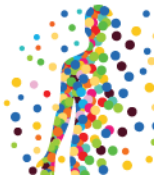


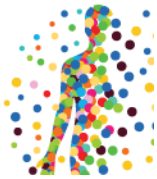
Disclosures

Activity Staff Disclosures

- The planners, reviewers, editors, staff, CME committee, or other members at the AAPA and TFF who control content have no relevant financial relationships to disclose

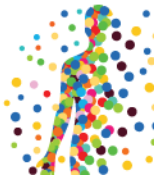
Faculty/Steering Committee

- Kimberly K. Dempsey, EdD, MPA, PA-C, DFAAPA- no relevant financial relationships to disclose
- Terri Nagy, MPAS, PA-C, DFAAPA- no relevant financial relationships to disclose
- Leigh Ann Pansch, MSN, FNP-BC, DCNP- Consultant-Novartis, Pfizer; Speaker's Bureau-Abbvie, Eli Lilly, and Sanofi-Regeneron



Learning Objectives

- Review the pathophysiologic underpinnings of atopic dermatitis (AD) and alopecia areata (AA)
- Describe the risk factors and common comorbidities associated with AD and AA
- Explain burden of disease of AD and AA from a holistic standpoint, incorporating clinical and psychosocial elements
- Summarize clinical profiles of novel and emerging therapies, including efficacy and safety



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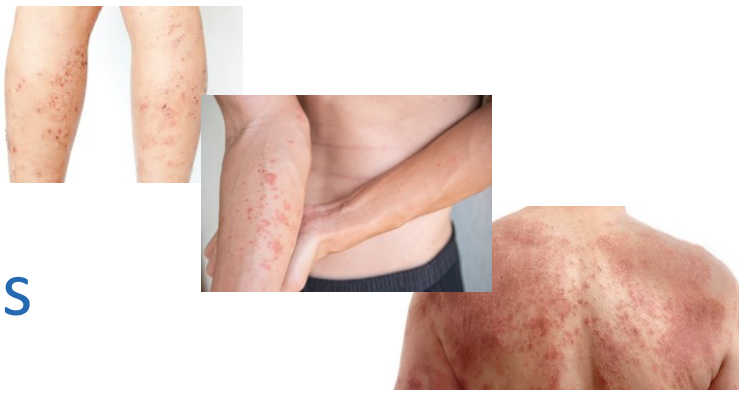
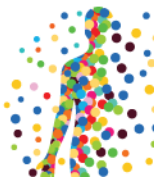
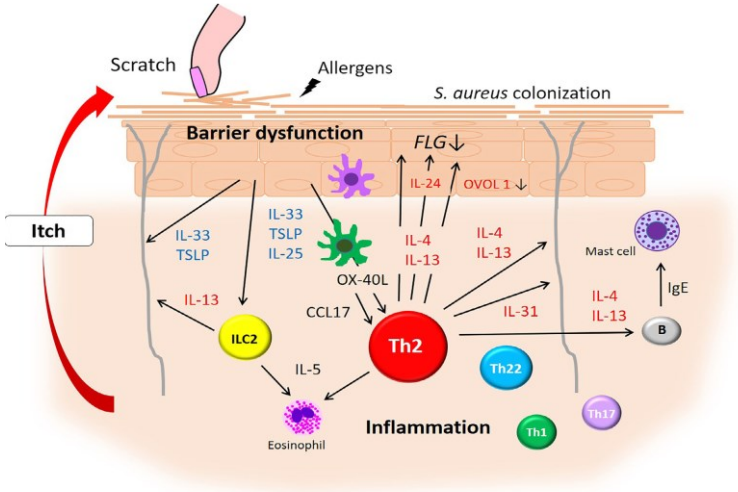
Atopic Dermatitis

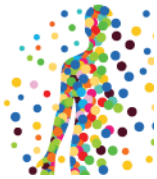




Pathophysiology

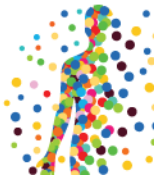


Nakahara T, et al. *J Dermatol.* 2021;48:130-139.



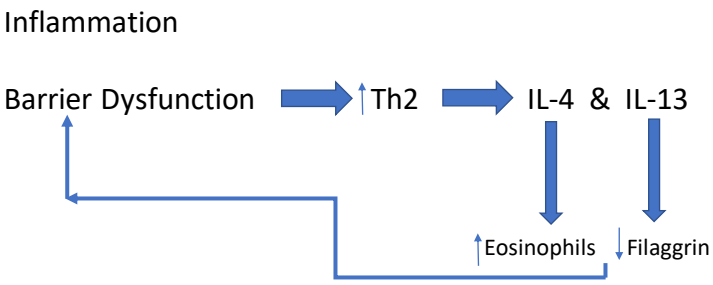
Pathophysiology

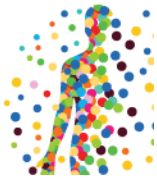
Skin Barrier Dysfunction	Result
Filaggrin	Decreased skin hydration
Ceramides	Increased penetration of allergens and microbes
Antimicrobial peptides	Increased transepidermal water loss (TEWL)
Serum protease inhibitors	Increased skin pH



Nakahara T, et al. *J Dermatol.* 2021;48:130-139.
Kim J, et al. *Allergy Athma Proc.* 2019; 40(2):84-92.

Pathophysiology

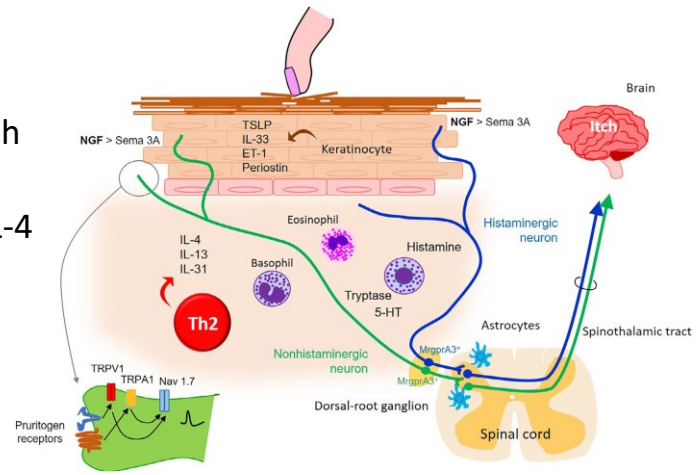


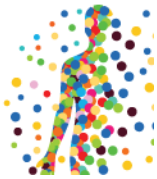


Nakahara T, et al. *J Dermatol.* 2021;48:130-139.

Pruritus

- Th2 cells produce IL-31 (itch mediator)
- Other itch mediators are IL-4 and IL-13
- ↑ Histamine
- External triggers

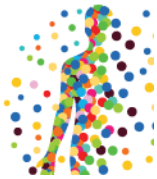




Nakahara T, et al. *J Dermatol.* 2021;48:130-139.

Risk Factors

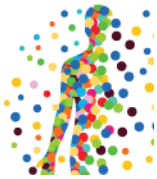
- Genetic:
  - Atopic family history
  - Loss of function variants in FLG gene
  - Other skin and allergic diseases
- Environmental Exposures:
  - Climate
  - Urban vs. rural setting
  - Early exposure to nonpathogen microorganisms



UpToDate: Atopic Dermatitis: Risk Factors

Comorbidities

- Mental Health: Depression, suicidality, and anxiety
- Atopy: Asthma, hay fever, and allergies (systemic and contact)
- Cardio-metabolic
- Infections: Cutaneous and non-cutaneous



Silverberg JI. *Ann of Allergy Asthma Immunol*. 2019;123:144-151.
Brunner PM et al. *J Invest Dermatol. 2017;*137(1):18-25.

New and Emerging Treatments for Moderate to Severe AD

Target	Route	Drug	Approval	Indication
IL-13	Injection	Dupilumab	Approved 6 yo+	Moderate to severe
	Injection	Tralokinumab	Approved for adults	Moderate to severe
	Injection	Lebrikizumab	Adult Phase III	Moderate to severe
IL-31	Injection	Nemolizumab	Adult Phase IIb	Moderate to severe
OX40	IV/Injection	GBR830	Adult Phase IIa	Moderate to severe
JAK1 and JAK2	Oral	Baricitinib	Adult Phase III	Moderate to severe
JAK 1	Oral	Upadacitinib	Approved 12 yo+	Moderate to severe
	Oral	Abrocitinib	Approved for adults	Moderate to severe

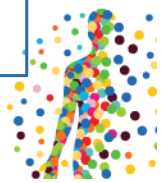
New and Emerging Treatments for Moderate to Severe AD

Dupilumab (Two phase 3 trials)

- **Efficacy** (IGA score 0 or 1 and ≥ 2 point improvement from baseline by week 16 for SOLO-1 and SOLO-2)
  - Dupilumab: 36–38%
  - Placebo: 8–10%
- **Adverse events**
  - Increased rate of idiopathic and allergic conjunctivitis in treatment groups vs placebo
  - Increase in eosinophils in dupilumab group that resolved by week 16
  - Worsening AD was the only serious AE reported in 2 + subjects

Tralokimumab (Two phase 3 trials)

- **Efficacy** (IGA score 0 or 1 and ≥ 2 point improvement from baseline by week 16 for ECZTRA 1 and ECZTRA 2)
  - Tralokimumab: 16%, 22%
  - Placebo: 7%, 11%
- **Adverse events**
  - URTI and conjunctivitis occurred more frequently with tralokinumab than with placebo
  - The frequency of SAEs was low and comparable between treatment groups in the initial treatment period



IGA, Investigator Global Assessment.
Nguyen HL et al. *Paediatr Drugs*. 2019;21(4):239-260.

URTI, upper respiratory tract infection.
Wollenberg A et al. *Br J Dermatol*. 2021;184:437-449.

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New and Emerging Treatments for Moderate to Severe AD

Abrocitinib (Two phase 3 trials)*

- **Efficacy** (IGA score 0 or 1 and ≥ 2 point improvement from baseline by week 12 for JADE MONO-1, JADE MONO-2)
  - 100 mg: 24%, 28%
  - 200 mg: 44%, 38%
  - Placebo: 8%, 7%
- **Adverse events**
  - SAEs were 1-3% in the 100 mg and 200 mg groups, and 1-4% in the placebo group
  - AEs occurring more frequently in the abrocitinib groups included nausea, nasopharyngitis, and headache

*Indicated for adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.

Simpson EL et al. *Lancet*. 2020;396(10246):255-266.
Silverberg JI et al. *JAMA Dermatol*. 2020;156(8):863-873.

Upadacitinib (Two phase 3 trials)**

- **Efficacy** (IGA score 0 or 1 and ≥ 2 point improvement from baseline by week 16 for Measure Up 1 and 2)
  - 15 mg: 48%, 39%
  - 30 mg: 62%, 52%
  - Placebo: 8%, 5%
- **Adverse events**
  - Incidence of SAEs and adverse events leading to study drug discontinuation were similar among groups
  - Aes occurring more frequently in the upadacitinib groups included acne, URTI, nasopharyngitis, and headache

**Indicated for adults and pediatric patients 12 years of age and older with refractory, moderate to severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

Guttman-Yassky E et al. *Lancet*. 2021;397(10290):2151-2168.

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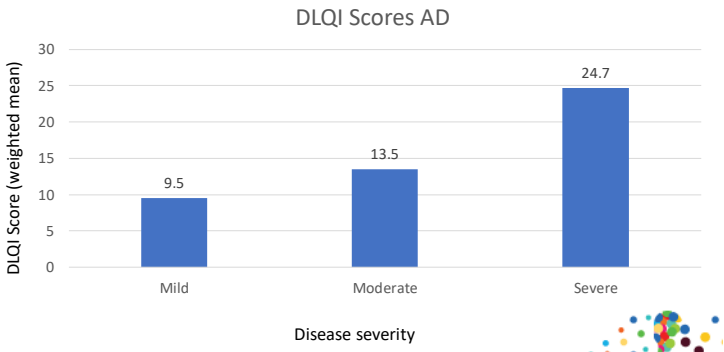
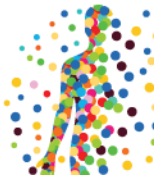
Burden of Disease

Patients with AD report significant impact on QoL

Dermatology Life Quality Index

0-1	no effect on quality of life
2-5	small effect on quality of life
6-10	moderate effect on quality of life
11-20	very large effect on quality of life
21-30	extremely large effect on quality of life

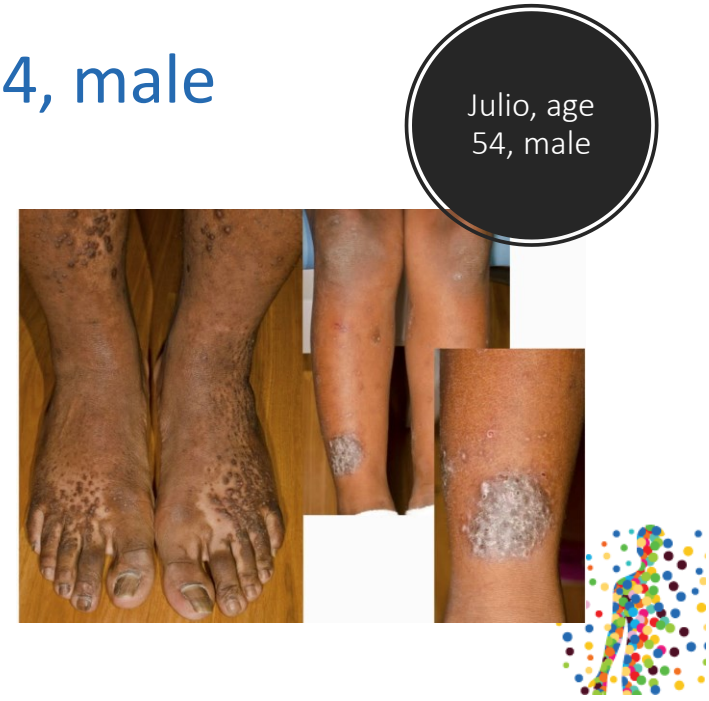




Adapted from Silverberg JI et l. *Ann Allergy Asthma Immunol. 2018;*121:340-47.

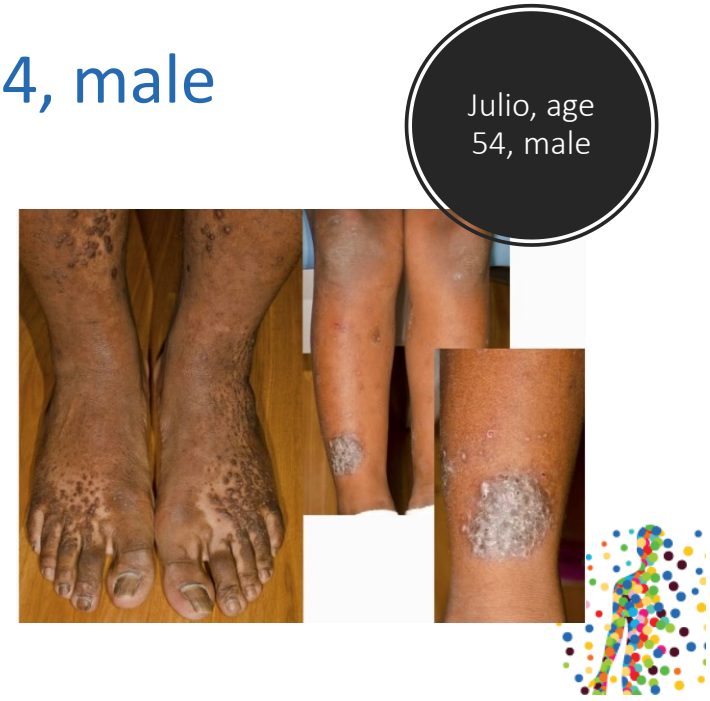
Meet Julio, age 54, male

- Julio presents to your clinic with a new-onset rash involving his arms, legs, and neck first noted 3-4 weeks ago
- He notes he has always had “sensitive skin” and, after a recent trip to Alaska, he returned to have a rash which was extremely itchy and has been keeping him up at night



Meet Julio, age 54, male

- He denies fever or change in appetite, and complains of pruritus which causes sleep disturbance at times
- He does acknowledge some medication allergies (Sulfa) as well as seasonal allergies
- His family history is positive for atopy in mom (asthma)
- There is no personal/family history of autoimmune disease



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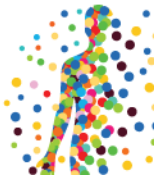
Patients Report Significant Impact on QoL

- Pruritus in AD is considered highly bothersome and has significant effect on QoL
- Patients and their families report significant burden of disease affecting sleep, irritability, poor cognitive response, and reduced performance
- Poor sleep has a direct impact on AD severity

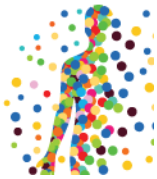


Silverberg JI et al. *Ann Allergy Asthma Immunol*. 2018;121:340-347.

Holistic Management Approaches

- Alternative fabrics
- Climate and Temperature
- Bathing
  - Bleach baths
- Moisturization
- Wet Wraps
- Allergen Avoidance
  - Immunotherapy/Desensitization
- Diet/Supplementation
- Acupuncture
- Psychological interventions, Behavioral Medicine

Kang S et al. *Science Direct.com* (2018): https://doi.org/10.1016/j.ctim.2018.08.013.
MacDonald Hull SP et al. *Br J Dermatol.* 2003;149:692-699.
Silverberg JI et al. *Ann Allergy Asthma Immunol.* 2018;121:340-347.



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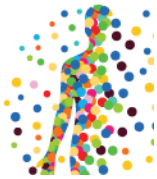
Impact of AD on Mental Health

Multiple studies have shown a significant impact of AD on psychosocial and mental health

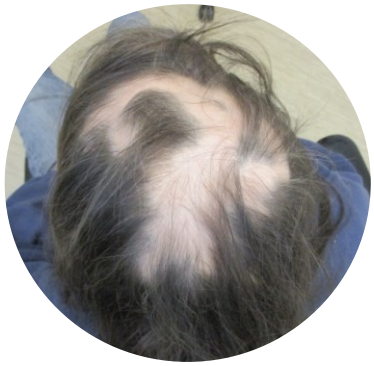
- 62% of adult patients with moderate-to-severe AD feel embarrassed or self-conscious about their skin condition[1]
- 43% feel moderately anxious or depressed[1]
- 8% feel extremely anxious or depressed[1]
- In a meta-analysis of 15 studies assessing the association between AD and suicidality[2]
  - Patients with AD were 44% more likely to have suicidal ideation
  - 36% were more likely to attempt suicide compared to patients without AD

These and other data make a strong case that patients with AD, and moderate-to-severe AD in particular, should be screened for potential mental health concerns and referrals made when necessary



1. Simpson EL et al. *J Am Acad Dermatol*. 2016;74:491-498.
2. Sadhu JK et al. *JAMA Dermatol*. 2019;155:178-187.

Alopecia Areata



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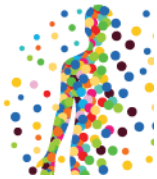
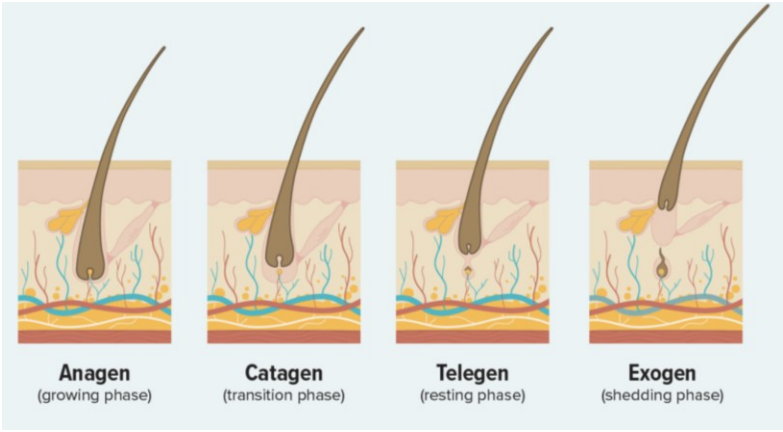
Overview

- Non-scarring form of hair loss, impacting both adults and children of all races and ethnic groups
  - Estimated to affect 1 out of every 1,000 individuals
  - Onset can occur at any age, mean age of onset is
    - 32 for males
    - 36 for females
  - If age of onset is under 10 years of age, the disease course is far more extensive
- Typically seen on the scalp, but can impact any hair bearing area
- The National Alopecia Areata Foundation identifies three different types of AA
  1. AA patchy
  2. AA totalis
  3. AA universalis

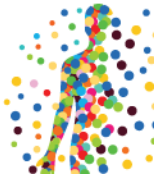


Stages of Hair Growth



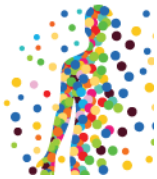
https://www.healthline.com/health/stages-of-hair-growth

- AA occurs when hair follicles in the anagen phase prematurely transition into the catagen and telogen phases
- The result is a temporary or chronic state of increased hair shedding and a suppression of hair regrowth

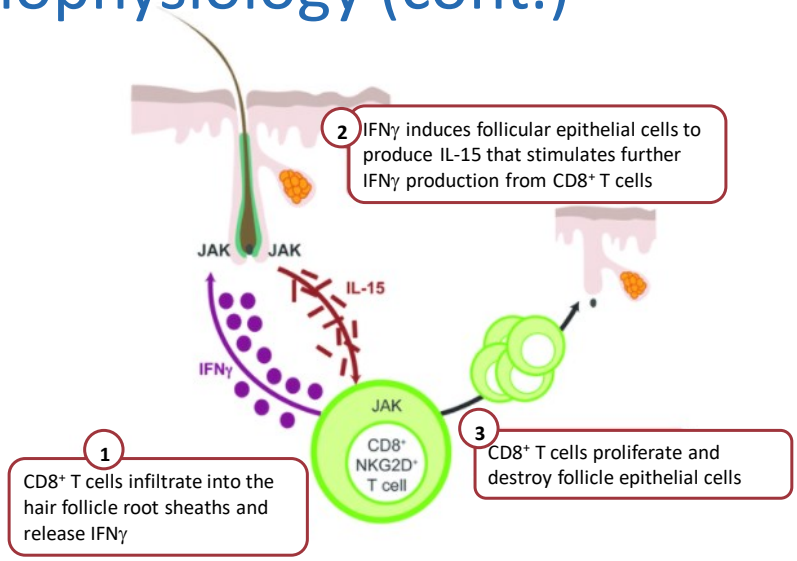


Pathophysiology

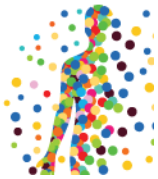
- Not completely understood, but it is believed to be driven by:
  - **Genetics**
  - **Environmental triggers**
  - **Dysfunction in the immune system**



Pathophysiology (cont.)

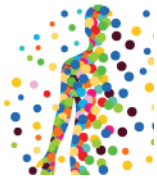


Howell MD et al. *Frontiers Immunol*. 2019;10:2432.
https://www.researchgate.net/figure/IFNg-driven-inflammation-in-alopecia-areata-is-JAK-mediated-CD8-T-cells-infiltrate_fig3_336365064



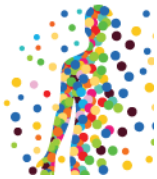
Risk Factors

- Family history of AA: Studies have shown that 20% of individuals with AA also have a first degree relative with AA
- Genetic associations have been identified with
  - HLA-DQB1*03 allele
  - ULBP gene cluster on chromosome 6q25.1
- Identical twin studies: the rate of AA in both individuals is up to 42%
- Other autoimmune disorders



Comorbidities

- Nail findings
  - Often a clinical feature of AA
  - May appear prior to onset of hair loss as a presenting complaint
- Of individuals diagnosed with AA, studies have shown a higher incidence of certain diagnoses compared to individuals without AA
- In addition:
  - Pts with Endometriosis are 5x more likely to have AA
  - AA is found in 6-8% of the patients with trisomy 21
- ***Studies have also shown that AA is associated with increased stress, unemployment, anxiety, and depression***



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Treatment

- For ~50% of cases, regardless of the treatment approach, AA will resolve in about 12 months
- Traditional treatment approaches
  - Topical
  - Intralesional and oral steroids
  - Topical minoxidil
  - Squaric acid
  - Anthralin
  - Diphencyprone
- For those with a more chronic, severe, and recalcitrant disease, there are some promising players on the horizon, **the JAK inhibitors**

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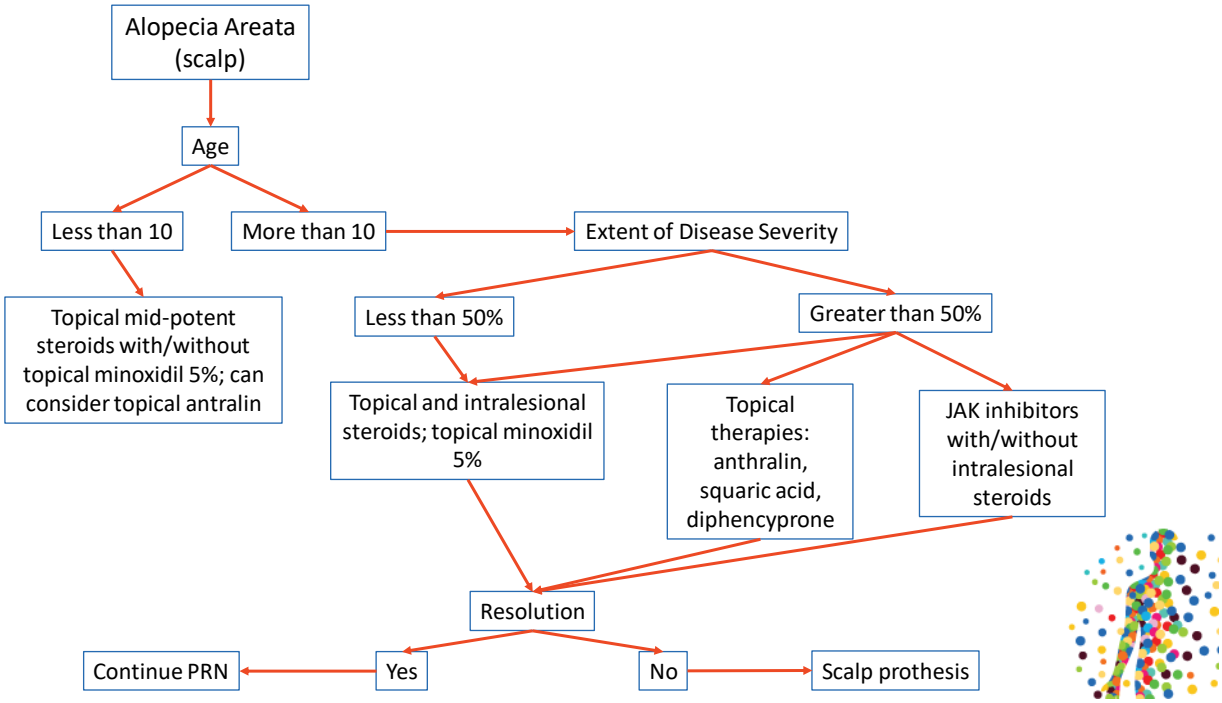
Alopecia Areata (scalp)
Age
Less than 10
More than 10
Extent of Disease Severity
Topical mid-potent steroids with/without topical minoxidil 5%; can consider topical antralin
Less than 50%
Greater than 50%
Topical and intralesional steroids; topical minoxidil 5%
Topical therapies: anthralin, squaric acid, diphencyprone
JAK inhibitors with/without intralesional steroids
Resolution
Continue PRN
Yes
No
Scalp prothesis

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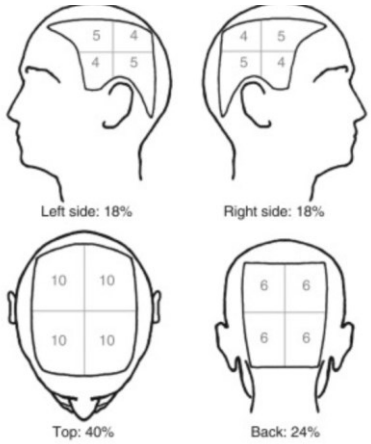
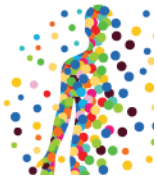
Assessing Extent of Disease Severity



- The Severity of Alopecia Tool (SALT) score is used to assess therapeutic approaches to AA
- The SALT score measures the percentage of hair loss in each of the four sections of the scalp (as shown in diagram)

Salt score			
Site:	Subject:	Visit:	Date:
Quadrant	Percentage involved	Multiplier	Score
Left side		0.18	
Right side		0.18	
Top		0.40	
Back		0.24	
Total			



Olsen EA, Canfield D. *J Am Acad Dermatol*. 2016;75(6):268-1270.

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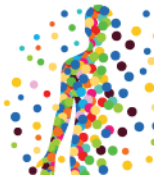
JAK Inhibitors

Target	Route	Drug	Approval	Indication
JAK1/JAK2	PO	Baricitinib	Yes	RA
JAK3	PO	Ritlecitinib	No	AA
JAK1/JAK2	PO	CTP-543	No	AA

- Presently, there are no JAK inhibitors with FDA approval to treat alopecia areata



JAK Inhibitors

Baricitinib[1]

- **Efficacy** (36 weeks, SALT scores ≤20 for BRAVE-AA1, BRAVE-AA2)
  - 4 mg daily: 39%, 36% of patients
  - 2 mg daily: 23%, 19% of patients
  - Placebo: 6%, 3% of patients
- **Adverse events**
  - Respiratory infections, urinary tract infections, headache, acne, and elevated creatinine kinase
  - No reports of thromboembolic events or death
  - SAEs 1.6-3.4% across studies and groups

Ritlecitinib[2]

- **Efficacy** (24 weeks in active treatment arms, 30 and 50 mg)
  - Significantly more participants in both treatment arms reported SALT score of < 20 vs placebo
- **Adverse events**
  - Nasopharyngitis, headaches, herpes zoster, and upper respiratory infections
  - In the 50 mg once daily arms
    - 1 participant experienced a PE
    - 2 participants diagnosed with breast cancer

CTP-543[3]

- **Efficacy** (52 weeks, SALT scores < 20)
  - 57% in treatment arm
- **Adverse events**
  - Nasopharyngitis
  - Acne
  - Headaches
  - Upper respiratory infections
  - 1 patient experienced facial cellulitis
  - No thrombotic events were reported

1. King B, et al. *N Engl J Med.* 2022 Mar 26 [online ahead of print];
2. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-results-phase-2b3-trial
3. https://www.businesswire.com/news/home/20210701005114/en/Concert-Pharmaceuticals-Presents-Update-on-CTP-543-Long-Term-Extension-Study-in-Alopecia-Areata-During-2nd-JAK-Inhibitors-Drug-Development-Summit

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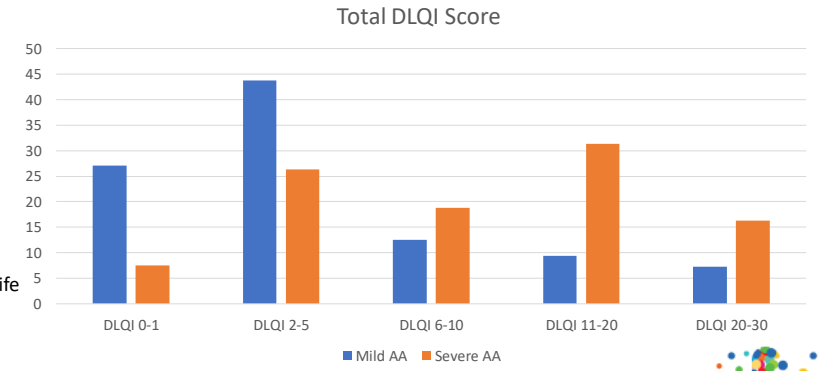
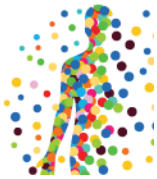
Burden of Disease

Patients with AA report significant impact on QoL

Dermatology Life Quality Index (DLQI)

0-1	no effect on quality of life
2-5	small effect on quality of life
6-10	moderate effect on quality of life
11-20	very large effect on quality of life
21-30	extremely large effect on quality of life





Liu LY et al. *J Am Acad Dermatol*. 2018;79(3):556-558.
Rencz F,et al. *Br J Dermatol*. 2016;175(3):561-571.

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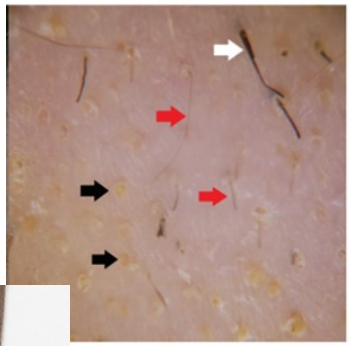
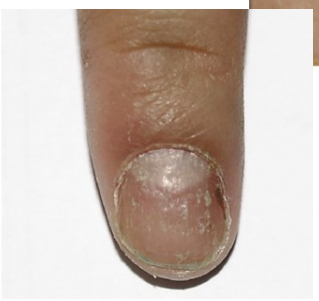
Meet Ainsley, Age 24 Years, Female

- Ainsley is a 24 year old who presents with a bald patch on her right crown and loss of eyelashes which was noted about 3-4 weeks ago
- She notes that she saw a round, ”completely bald” patch while brushing her hair one morning
- Ainsley is healthy, with no recent illnesses or surgeries
- No rashes or pruritus were noted prior

Meet Ainsley

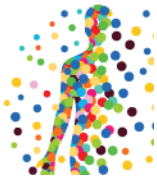
- She is very concerned that she will 'go completely bald‘
- PE reveals
  - A solitary, 2.5 cm patch of alopecia on the right crown
  - Trichoscopy reveals short hairs of even length and “yellow dots”
  - Nail pits located in 10/10 fingernails
  - No lymphadenopathy noted
- Her thyroid labs are normal
  - TSH: 1.5 mIU/L
  - FT4: 1.2 ng/dL





Holistic Management Approaches

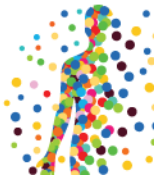
- Ensure eyes are covered when eyelashes are lost
- Sunscreen
- Wigs/hairpieces/cosmetics
- Dermatography (tattooing)
- Emotional support, support groups, and behavioral medicine



Psychiatric Disorders are Increased in Patients with AA

Disorder	AA patients, %	General population, %
Major depression	8.8	1.3–1.5
Generalized anxiety disorder	18.2	2.5
Social phobias	3.5	0.9–2.2
Paranoid disorder	4.4	<1

These data highlight the need for psychosocial support and therapy as important parts of disease management



Nillasante Fricke AC and Miteva M. *Clin Cosmet Investig Dermatol*. 2015;8:397-403.

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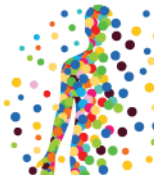
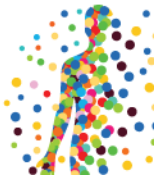
Summary

- Pathophysiology for AD and AA include genetic predisposition, environmental triggers, and immune dysfunction
- New therapies are emerging for the treatment of both AD and AA as a result of our increased understanding of pathophysiology
  - New JAK inhibitors target autoimmune-induced inflammation, skin barrier and hair follicle damage, and pruritus
  - Treatment reduces pruritus, and increases skin clearance (AD) and hair regrowth (AA)
- Pharmacological treatments should be part of a holistic regimen of bathing, moisturizing, infection control, and addressing the psychosocial aspects of both AD and AA



Questions?



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