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Dupilumab As Add On Therapy For Chronic Spontaneous Urticaria: A Single Center Retrospective Review

ISAAI Spring Meeting

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Disclosures

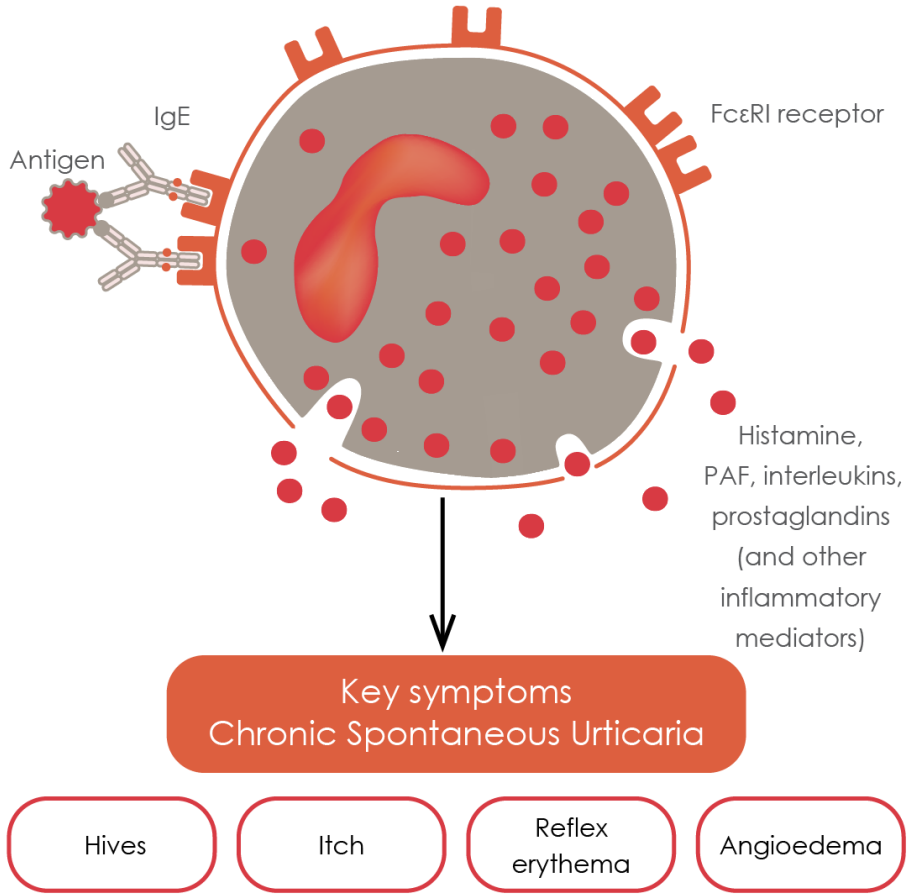
- None

Urticaria and Chronic Spontaneous Urticaria

- Urticaria: well-circumscribed area of non-pitting edema associated with pruritus and erythematous wheals, last <24hrs
- Can occur with or without angioedema
- F>>M predominance, most common in the 3rd and 5th decades of life
- Classification of urticaria
  - Acute <6 weeks
  - Chronic >6 weeks
    - Chronic spontaneous urticaria (CSU)
    - Chronic inducible (CIndU or CIU)

Old Paradigm of CSU

- Canonically type 2 inflammatory disease
- Main mediator→ mast cell
- Activation of mast cell→ **histamine**,** leukotrienes, prostaglandins, cytokines→
  - Local vasodilation
  - Sensory nerve activation
  - Recruitment of other inflammatory cells
    - Cellular infiltrate of CSU similar to late phase allergen mediated skin reaction (CD4+, CD8+ T cells, eosinophils, basophils, mast cells, neutrophils, macrophages).
- Autoimmune mast cell activation
  - Auto-IgE binding to high affinity FCER1 receptor, cross linking leads to mast cell degranulation
    - Omalizumab (anti-IgE)



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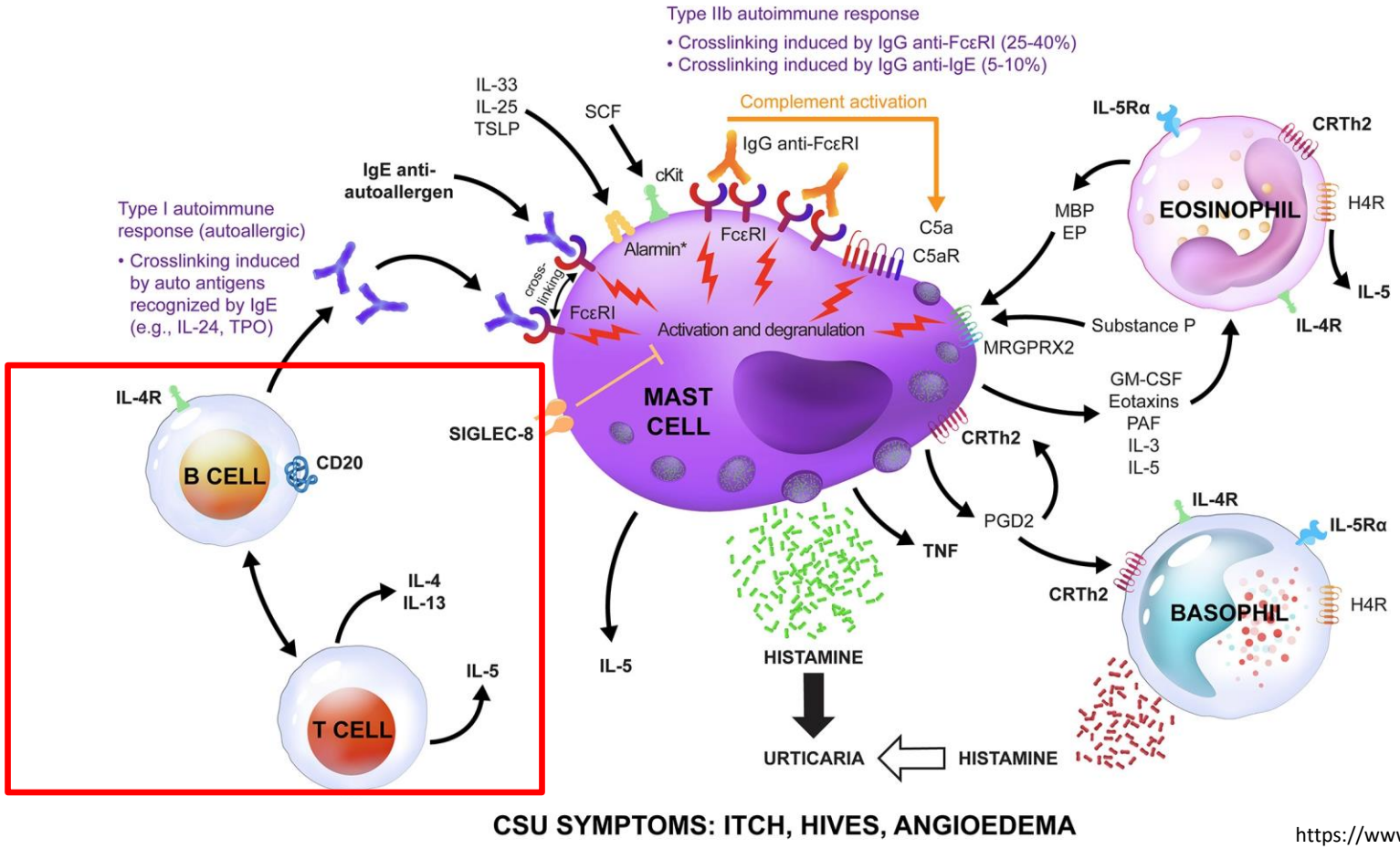
Emerging View of CSU Pathophysiology



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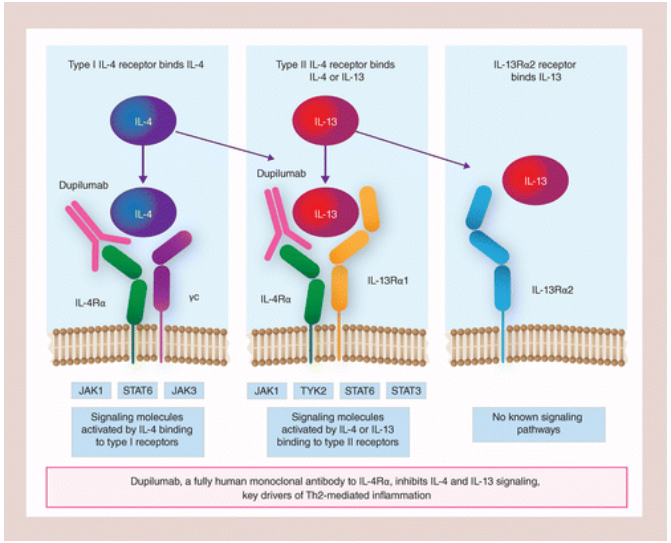
Background: Dupilumab

- Dupilumab (dupixent) is an injectable monoclonal antibody that targets the IL-4R alpha present in both IL-4 and IL-13 receptors
  - Current clinical indications:
    - Moderate to Severe AD, adults, children >6+ months
    - Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), adults
    - Moderate/ Severe Asthma or eosinophilic asthma, Adults, children >6
    - Eosinophilic Esophagitis, children 12+, at least 40kg
    - Prurigo Nodularis, adults (as of Sept 2022)



https://www.futuremedicine.com/doi/10.2217/imt.15.69

CSU: Dupilumab What's Currently Known

- **Dupilumab as a novel therapy for difficult to treat CSU.** Lee and Simpson, JACI in Practice. 2018.
- **Long Term Follow up Of Patients Treated with Dupilumab for CSU: a case report.** Abadeh and Lee, SAGE Open Med Case Rep. 2022.
  - 6 patients (3 M, 3F) previously failed omalizumab (300mg-600mg qmonthly), prospective clinical trial, followed urticaria activity score over 7 days (UAS7)
  - Initial UAS 34.7 +/- 4.04
  - All patients had concomitant AD (BSA 5-70% involvement), on other controller meds
  - All pts had improved in UAS or reported clinical symptoms at 3-month follow up
  - Subsequent, 34 month follow up period
  - 4 pts w/ UAS of 0 at 14-22 months follow up
  - 1 with refractory CSU, required add-on omalizumab
  - 1 unable to afford med relapsed CSU

CSU and Dupilumab: LIBERTY-CUPID A

- **Methods:**
  - Phase 3, 24 week, Randomized control trial
  - Population: >=6 y.o. with CSU, symptomatic despite treatment with H1 antihistamines at standard or >=4 x dose
  - Randomized to receive either dupilumab 300mg (n=70, adults/adolescents >60k) or 200mg (adolescents <60kg, or children >30kg) or placebo (n=68) Q2week
- **Primary/ secondary endpoint:**
  - Change from baseline at week 24 itch severity score over 7 days (ISS7) and UAS7
- **Results:**
  - Baseline mean dupilumab/ placebo, ISS7: 16.1/15.7, UAS7 31.9/30.8
  - Week 24 least squares change dupilumab/ placebo, ISS7 -10.2/-6.0, (p=0.0005), UAS7 -20.5/-12.0 (p=0.0003).
  - Treatment related adverse events similar between groups

CSU and Dupilumab: LIBERTY-CUPID B

- Randomized control trial evaluating dupilumab in patients refractory to omalizumab
- Halted in Feb 12, 2022 due to futility on interim analysis
- Improvement in itch/ hives, not going to reach statistical significance for primary endpoints (reduction in hive scores)

- **Dupilumab improves objective measures of urticarial disease activity as compared to placebo, but not in patients refractory to omalizumab**

To Summarize…

- CSU is a chronic condition with complex pathophysiology; canonically Type 2 inflammatory condition
- Dupilumab has been shown to be effective at treating select CSU patients
- Dupilumab improves itch and urticaria scores relative to placebo, but appears to have limited benefit in patients refractory to omalizumab
- Does dupilumab have clinical utility for patients with CSU who have other comorbid allergic conditions?

Hypothesis

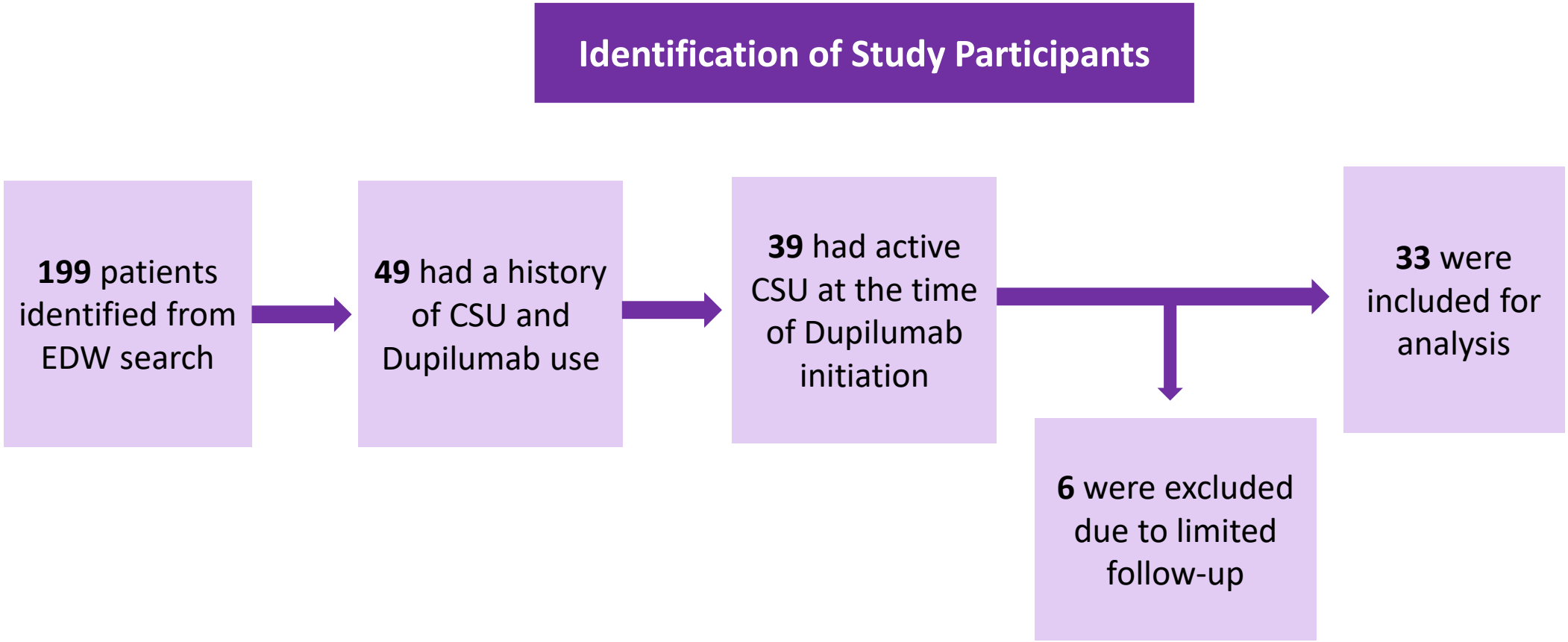
Dupilumab when used as add on therapy for patients with CSU has clinical benefit in a real-world clinical setting

Dupilumab when used for other allergic indications has benefit in treating concomitant CSU

Study Design

- A single center retrospective review
- We identified patients using our tertiary academic care center electronic health record (EHR) by querying for all patients with ICD-9 (708.1, 708.8, 708.9) and ICD-10 codes (L50.1, L50.8, L50.9) for CSU and a history of dupilumab use between 1/1/2010-6/30/2022.
- Retrospective chart review manually performed to confirm:
  - CSU diagnosis
  - Dupilumab use
  - Patient demographics
  - Medical comorbidities
  - CSU treatment
- Outcomes (physician global assessment of change, use of H1 blockers pre- vs. post dupilumab)
- Data were evaluated using summary/ descriptive stats, paired t-test, Fisher's exact test, McNemar's test

Results


Identification of Study Participants
199 patients identified from EDW search
49 had a history of CSU and Dupilumab use
39 had active CSU at the time of Dupilumab initiation
33 were included for analysis
6 were excluded due to limited follow-up

Demographics and Disease History

Variables	Frequency (%)
Sociodemographics (n=33)	
Age (yrs), mean±SD	46 +/- 15.4
BMI, mean±SD	28.8 +/- 6.8
Sex	
Female	28 (84.8%)
Race	
White	18 (54.5%)
Black	5 (15.2%)
Asian	4 (12.1%)
Other/Declined	3 (9.1%)

Variables	Frequency (%)
Comorbidities (n=33)	
Angioedema	7 (21.2%)
AD	21 (63.6%)
Asthma	20 (60.6%)
CRSwNP	3 (9.1%)
EoE	2 (6.1%)
AD Severity (n=21)	
Mild	2 (9.5%)
Moderate	9 (42.9%)
Severe	8 (38.1%)
Not available	2 (6.1%)

AD: atopic dermatitis
CRSwNP (chronic rhinosinusitis with nasal polyps)
EoE: eosinophilic esophagitis

Documented Indication for Dupilumab

Indication (n=33)	Frequency (%)
AD	19 (57.6%)
Moderate-Severe Persistent Asthma	9 (27.3%)
CRSwNP	1 (3%)
Asthma/CRSwNP	2 (6.1%)
EoE	2 (6.1%)

Medication Use Pre- and Post-Dupilumab

Medication Use (n=33)	Pre-Dupilumab, Frequency (%)	Post-Dupilumab, Frequency (%)	P-value
Daily H1 antagonist	27 (81.8%)	20 (60.1%)	**0.03**
Total # of daily Antihistamines, mean ±SD	1.95 +/- 2.0	0.13 +/- 0.20	**0.01**
Daily Oral Corticosteroids	2 (6%)	1 (3%)	0.32
LTRA	11 (33.3%)	9 (27.3%)	0.8
H2 antagonist	5 (15.2%)	3 (9.1%)	0.32
Cyclosporine	1 (3%)	1 (3%)	1.0
Omalizumab*	6 (18.2%)	3 (9.1%)	0.18

*Omalizumab within 30 days of starting Dupilumab
LTRA: leukotriene receptor antagonist

H1 Blocker Use by Disease Severity

H1 Blocker Use	Mild (n=20)			Moderate/Severe (n=13)		
	Pre-Dupilumab	Post-Dupilumab	P-value	Pre-Dupilumab	Post-Dupilumab	P-value
Daily H1 antagonist	15 (75%)	10 (50%)	0.13	12 (92.3%)	10 (76.9%)	0.32
Daily # of H1 antagonists	1.1 +/-0.8	0.13 +/-0.2	**0.02**	3.31 +/- 2.50	2.0 +/- 1.74	0.07

Moderate/ Severe CSU: >= 4 H1 antihistamines daily or concurrent omalizumab

Physician Global Impression of Change

Physician Global Impression of Change	Mild (n=20)	Moderate/Severe (n=13)	P value
Worse	1 (5.0%)	1 (7.9%)	**0.02**
Unchanged	13 (65.0%)	2 (15.4%)	
Somewhat or Significantly Improved	6 (30%)	10 (77%)	

Moderate/ Severe CSU: >= 4 H1 antihistamines daily or concurrent omalizumab

Treatment-Emergent Adverse Events

Adverse Event (n=33)	N (%)
None	26 (78.8%)
Severe TEAE*	1 (3%)
Arthralgias	3 (9.1%)
Conjunctivitis	2 (6.1%)
CSU recurrence on Dupilumab	1 (3%)
Injection Site Redness/ Irritation	0 (0%)

*documented ?anaphylaxis

Limitations

- Single-center, retrospective study design with limited number of patients
- Limited subjective and objective measures of disease response

Conclusions

- Dupilumab reduces need for controller therapy in patients on H1 antagonists and improves disease control when utilized as add on therapy
- Dupilumab when used for other allergic indications improves CSU disease control in select patients
- Adds to limited body of evidence for benefit of dupilumab as off-label therapy for CSU
- Adverse events consistent with known safety profile of dupilumab
- Prospective studies are needed to better understand the role of dupilumab in mono- and combination therapy for CSU

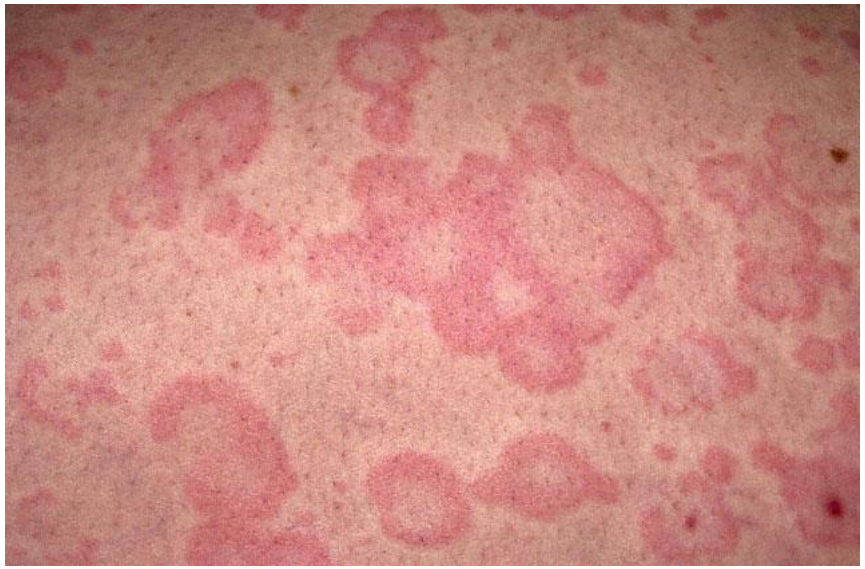
Acknowledgements

- Raj Chovatiya, MD, PhD
- Phoebe Newell, BS

Questions?

CSU

- 0.5-5% prevalence, although not great estimates
- Common co-morbid conditions
  - (AWARE study, Thomsen et al. 2017)
    - Allergic rhinitis 16.5%
    - Atopic dermatitis 6.3%
    - Asthma 19.6%
    - Food allergy 8.2%
- Significant disease burden (Maurer et a. 2017)
  - Pruritus
  - Sleep interference
  - Productivity impairment, personal relationships, leisure
  - Missed work, physician visits



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