Biologic Therapy For Your Asthma Patients

Dr. Ashwin K. Shankar
Pediatric & Adult Allergist/Immunologist

Disclosures

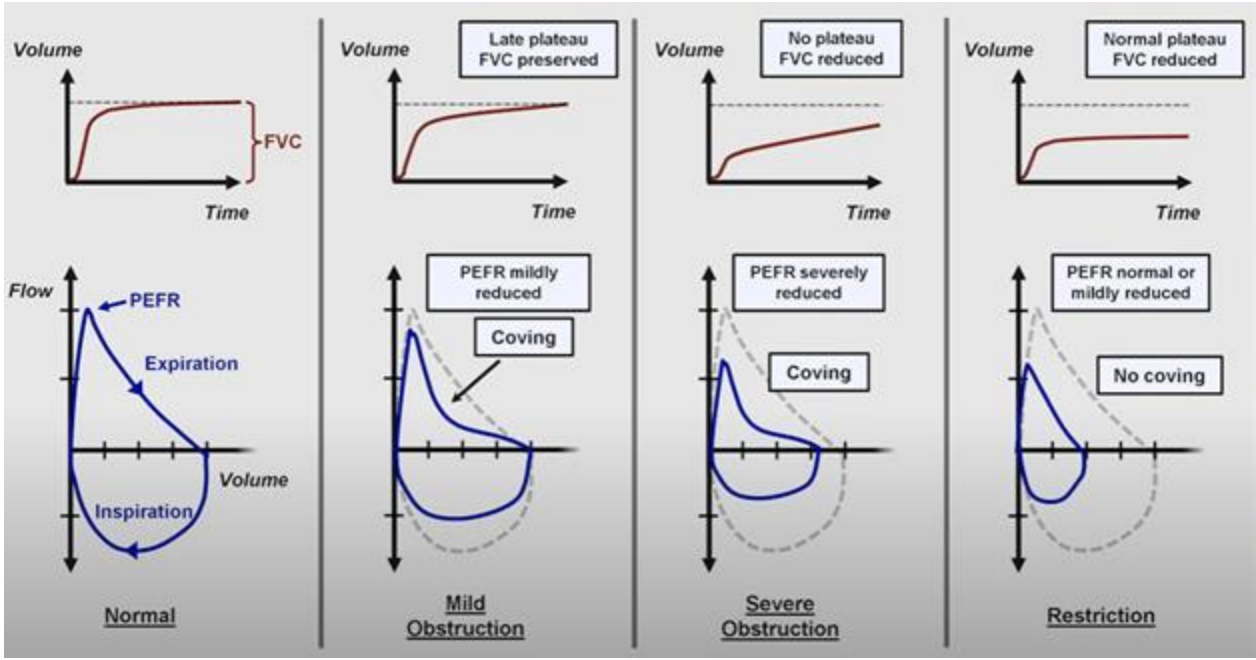
- Sanofi Pharmaceuticals - Medical Consultant and Advisory Board
- AAAAI - Board Member of Division Directors Committee and DEI Committee
- ACAAI - Board Member of Food Allergy Committee and Population Health Committee

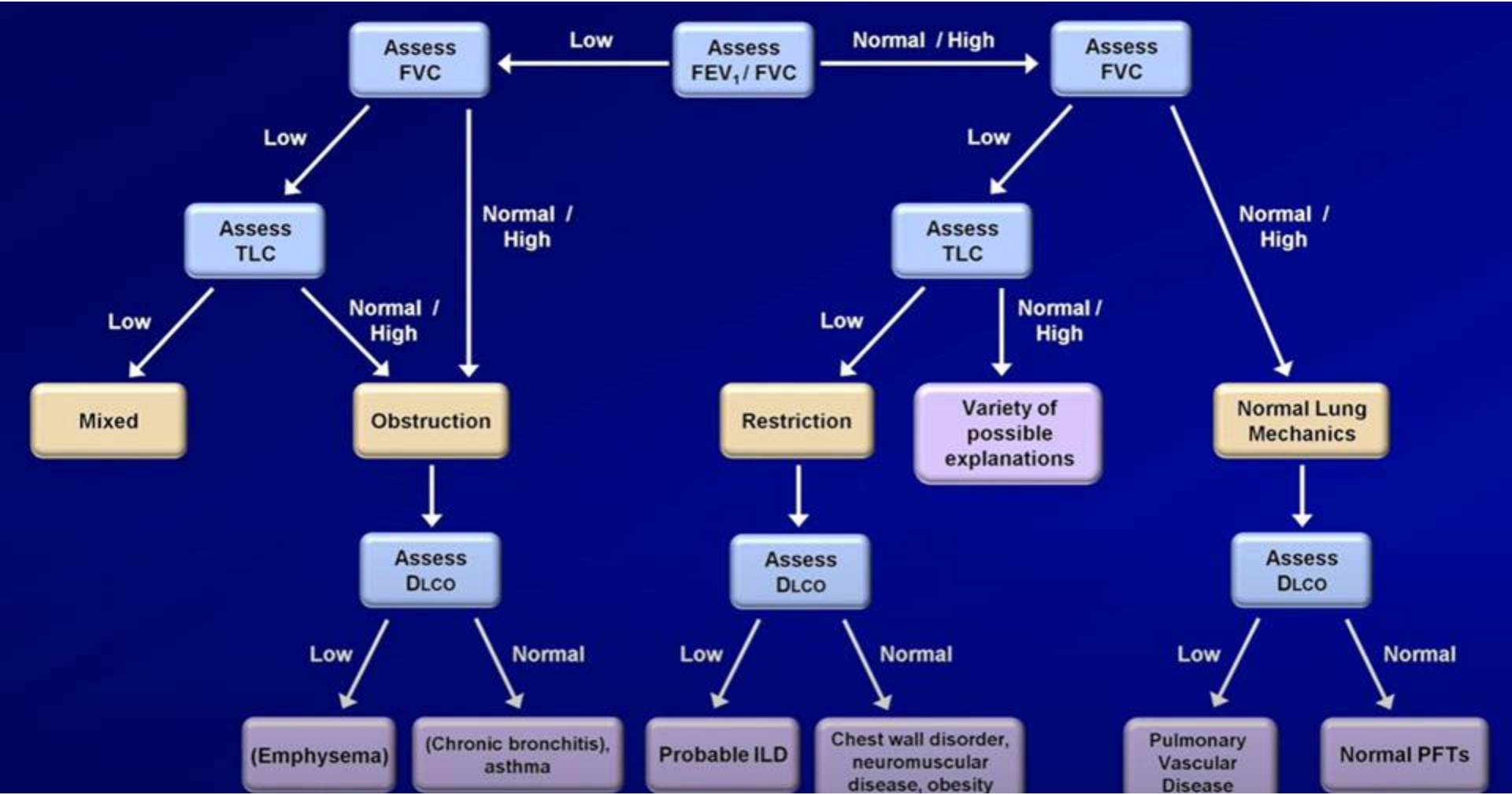
Objectives

- Review and interpret spirometry
- Characterizing different types of asthma
- Review mechanism of action for biologics
- Pairing patient's clinical history and lab work with mechanism of action for biologics

Spirometry

- Review with medical assistants
- Before interpretation
  - Acceptability
  - End of Test
  - Repeatability
  - Loop Shape




Assess FEV1 / FVC
Low
Assess FVC
Normal / High
Assess FVC
Low
Assess TLC
Normal / High
Low
Assess TLC
Normal / High
Low
Mixed
Normal / High
Obstruction
Low
Restriction
Normal / High
Variety of possible explanations
Normal / High
Normal Lung Mechanics
Assess DLCO
Assess DLCO
Assess DLCO
Low
Normal
Low
Normal
Low
Normal
(Emphysema)
(Chronic bronchitis), asthma
Probable ILD
Chest wall disorder, neuromuscular disease, obesity
Pulmonary Vascular Disease
Normal PFTs

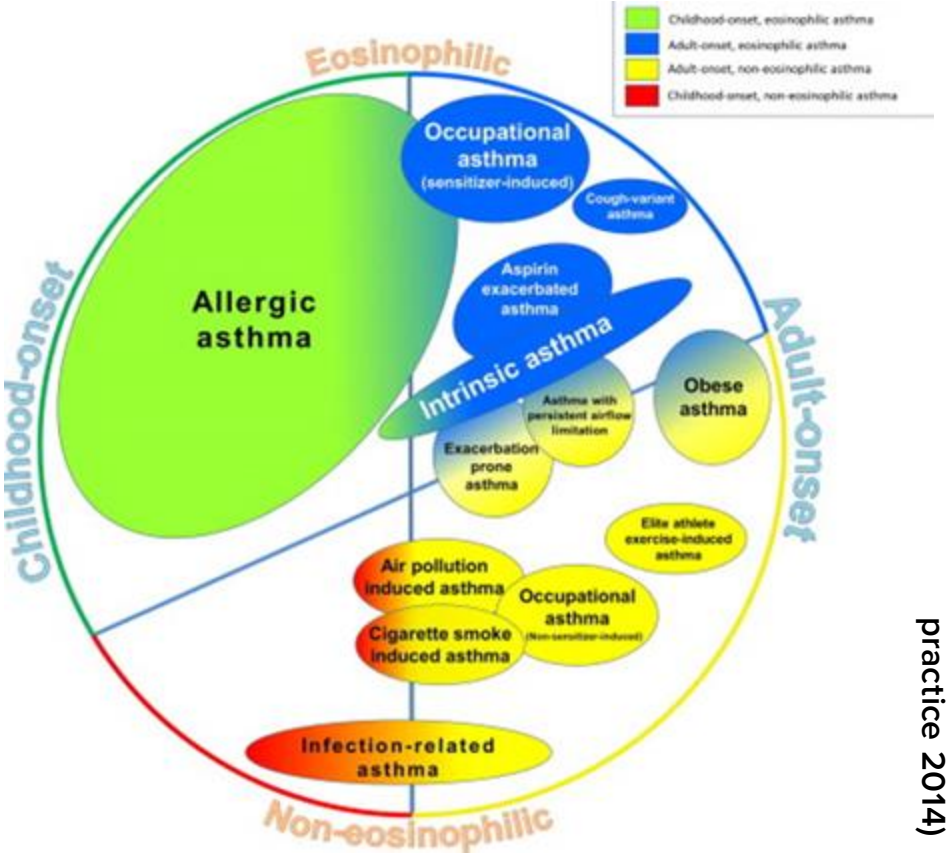
Spirometry Interpretation

- Spirometry interpretation for asthma severity uses FEV_1 (percent predicted) and sometimes FEV_1/FVC (to show obstruction). The cutoffs differ slightly for adults and children
- FEV1 and FEV1/FVC vs. Z-Scores of FEV1

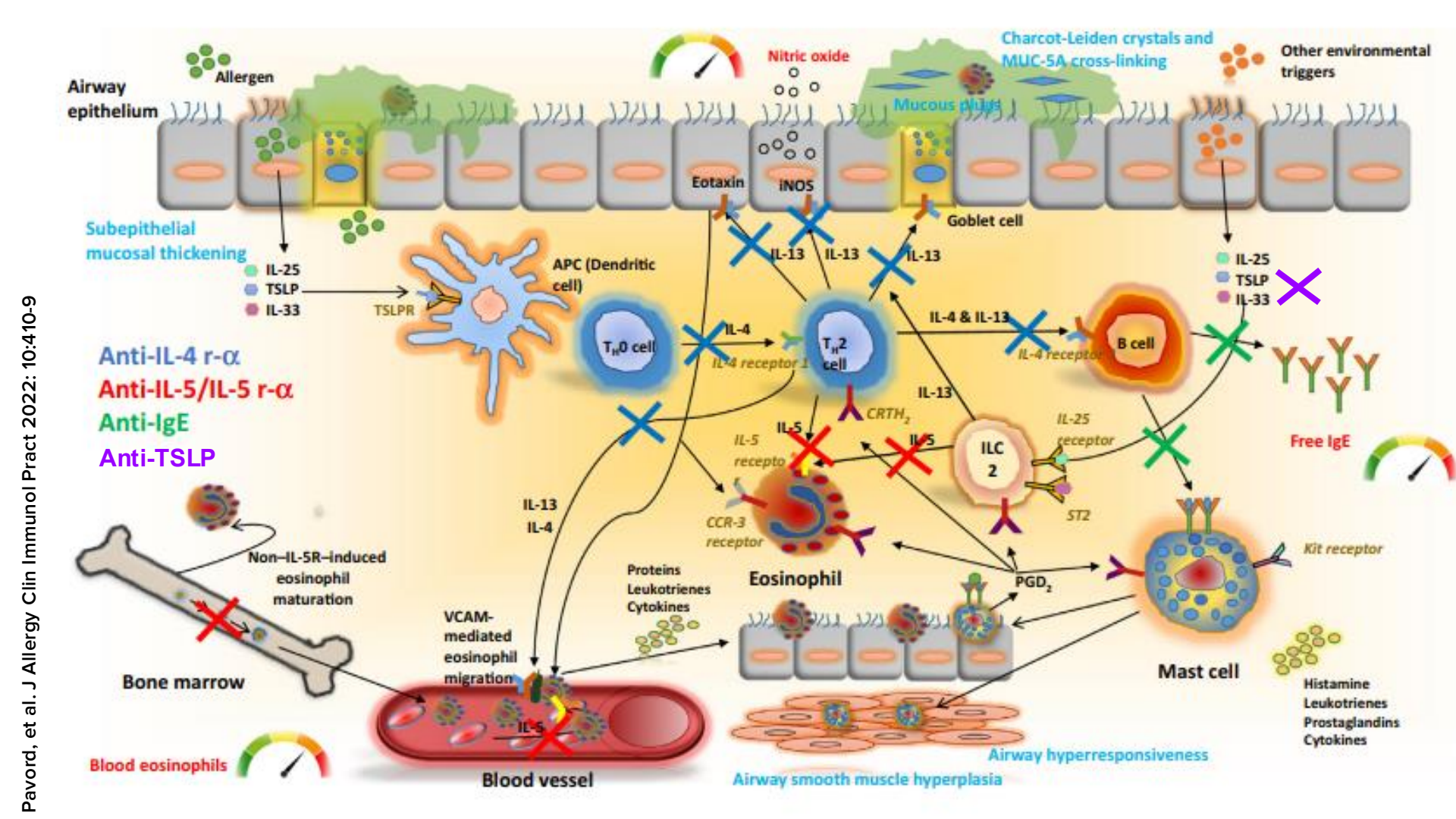
Spirometry Interpretation

	Adults (≥12 yrs)	Children (5–11 yrs)
Intermittent	FEV_1 ≥ 80% predicted, FEV_1/FVC normal	FEV_1 ≥ 80% predicted, FEV_1/FVC > 85%
Mild persistent **Z-Score** **FEV1/FVC** **-1.645 to -2.5**	FEV_1 ≥ 80% predicted, FEV_1/FVC reduced (but ≥70%)	FEV_1 ≥ 80% predicted, FEV_1/FVC 75–80%
Moderate persistent **Z-Score** **FEV1/FVC** **-2.5 to -4**	FEV_1 60–79% predicted	FEV_1 60–79% predicted, FEV_1/FVC 70–75%
Severe persistent **Z-Score** **FEV1/FVC** **<-4**	FEV_1 < 60% predicted	FEV_1 < 60% predicted, FEV_1/FVC < 70%

Different Types of Asthma



(Hekking & Bel, JACI: In practice 2014)



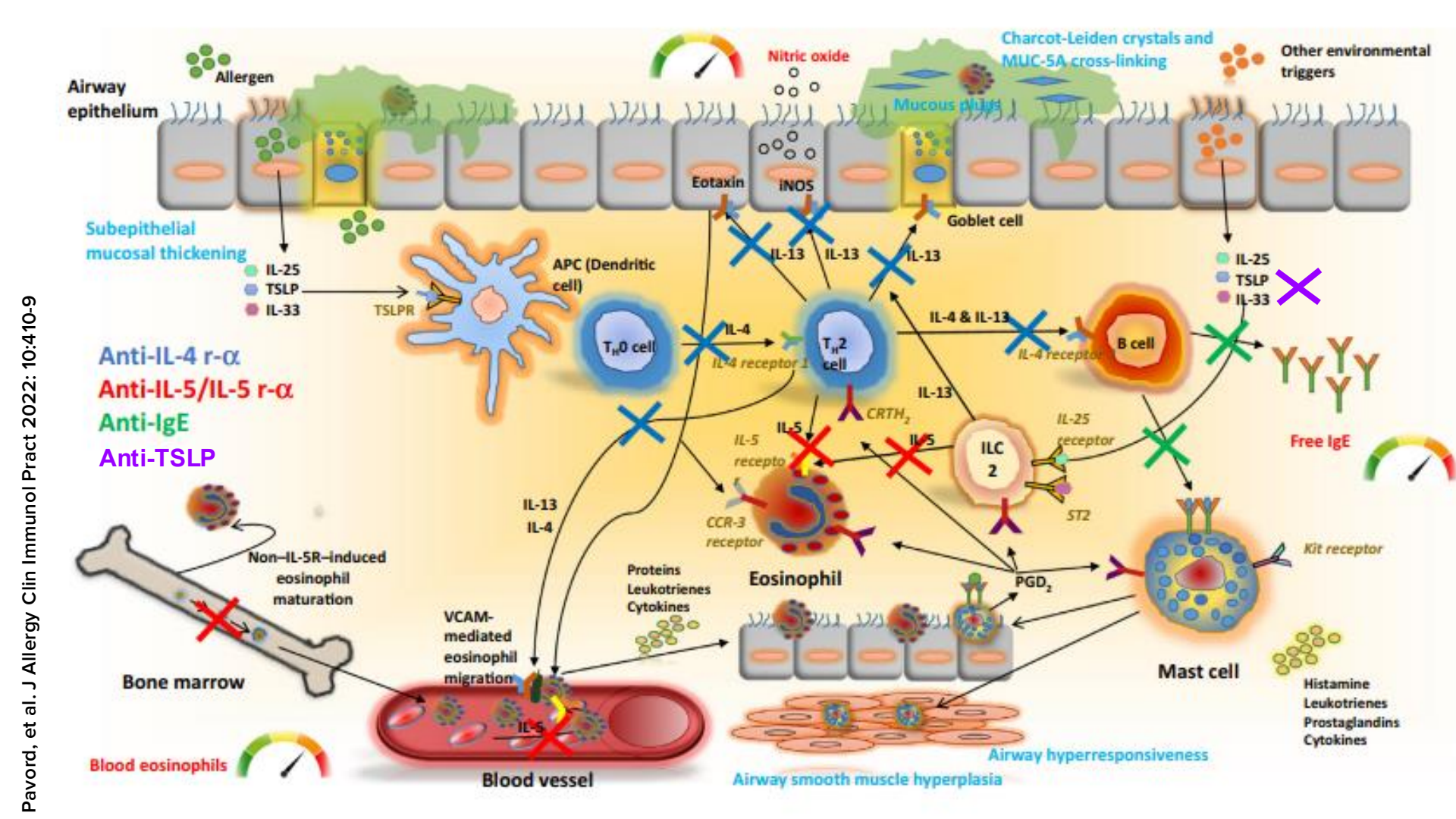
Pavord, et al. J Allergy Clin Immunol Pract 2022; 10:410-9

Biologics - Omalizumab

- Inhibits the binding of IgE to high affinity IgE Receptor (FcκRI) on mast cells and basophils
- Approved in 6+ YO for Asthma
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
  - Patients with 2 or more of the following characteristics:
    - History of emergency treatment of asthma in the past year.
    - Taking ≥800 µg of inhaled beclomethasone dipropionate (BDP) per day
    - FEV1 ≤65% of the predicted value or lower (Bousquet et al., 2004)
  - In patients ≥12 years of age, more severe asthma and absolute eosinophil count (AEC) ≥300 cells/µL asthma exacerbation rate reduction was more pronounced (Casale et al., 2018)
  - +skin test or in vitro reactivity to a perennial aeroallergen (eg, dust mites, pet dander, cockroach debris)

Biologics - Omalizumab (Safety & Dosing)

- Local reactions
- Risk of anaphylaxis
- Thrombocytopenia
- Alopecia
- Risk of helminthic infections
- Risk of malignancy, not statistically significant and has not been shown in post-approval surveillance
- Dosing
    - 75 to 375mg SC every 2-4 weeks



Pavord, et al. J Allergy Clin Immunol Pract 2022; 10:410-9

Biologics - Dupilumab

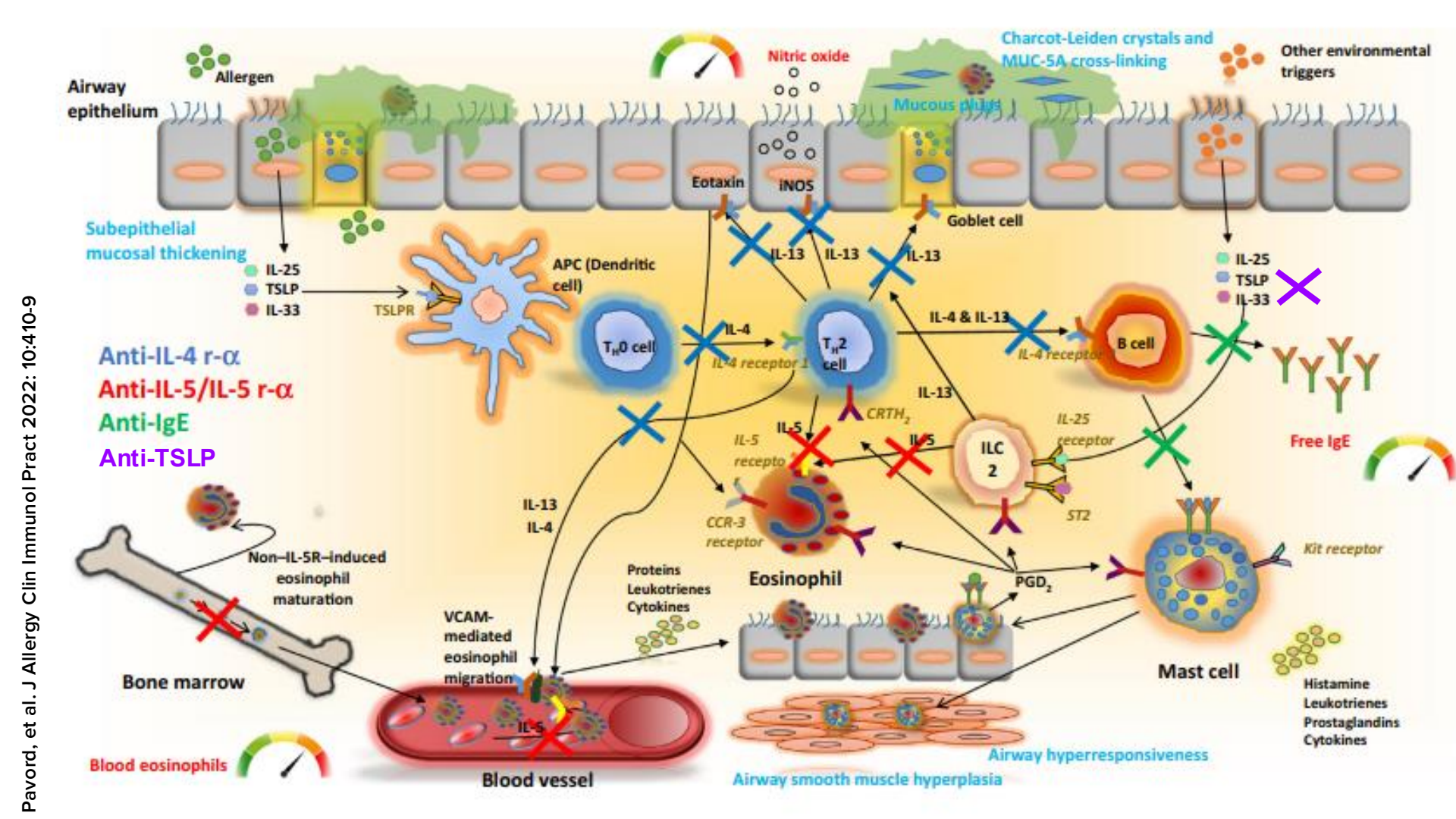
- Targets the IL-4 receptor subunit alpha (IL-4Ra) and blocks intracellular signaling of IL-4 and IL-13
- Approved in 6+ YO for Eosinophilic/OCS-Dependent Asthma
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
  - Patients with (AEC) ≥300 cells/µL (Castro et al., 2018):
    - In the overall study population with no exclusion for AEC, the asthma exacerbation rate was 47.7% lower with dupilumab than with placebo
    - Among patients with AEC ≥300 cells/µL:
      - The asthma exacerbation rate was 65.8% lower with dupilumab than with placebo
    - Among patients with ≥150 cells/µL, but <300 cells/µL:
      - The asthma exacerbation rate was 35.6% lower with dupilumab than with placebo.
  - With an eosinophilic phenotype (AEC ≥150 cells/µL), but has also had efficacy in those without biomarkers (Regeneron Sanofi Genzyme, 2019)

Biologics - Dupilumab

- Targets the IL-4 receptor subunit alpha (IL-4Ra) and blocks intracellular signaling of IL-4 and IL-13
- Approved in 18+ YO for COPD (Gold Criteria for Diagnosis)
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
    - Patients with (AEC) ≥300 cells/µL had fewer exacerbations, better lung function, improved quality of life, and less severe respiratory symptoms (Bhatt et al., 2023)

Biologics - Dupilumab (Safety & Dosing)

- +/- Administration of live vaccines to patients receiving dupilumab
- Avoid co-administration of dupilumab that with medications that are metabolized by CYP450 enzymes
- Risk of helminthic infections
- Risk of conjunctivitis in patients with atopic dermatitis
- Risk of eosinophilia
- Risk of anaphylaxis
- Risk of autoimmune or malignant skin manifestations (ie. CTCL)
- Dosing
    - Asthma: 6-11YO - Weight Tiered, 12+ YO - 2 Dose Regimen
    - COPD: 18YO - 300mg every 2 weeks (no initial loading dose)



Pavord, et al. J Allergy Clin Immunol Pract 2022; 10:410-9

Biologics - Mepolizumab

- IL-5 antagonist monoclonal antibody (IgG1κ) which inhibits IL-5 signaling
- Approved in 6+YO for Asthma, 18+YO for COPD
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
  - Exploratory modeling has shown that patients with more exacerbations in the year prior to starting mepolizumab are more likely to benefit from mepolizumab (Pavord et al., 2012)
  - The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline blood eosinophil count of ≥150 cells/μL to 70% in patients with a baseline count of ≥500 cells/μL
  - At a baseline count <150 cells/μL, predicted efficacy of mepolizumab was reduced (Ortega et al., 2014)

Biologics - Mepolizumab (Safety & Dosing)

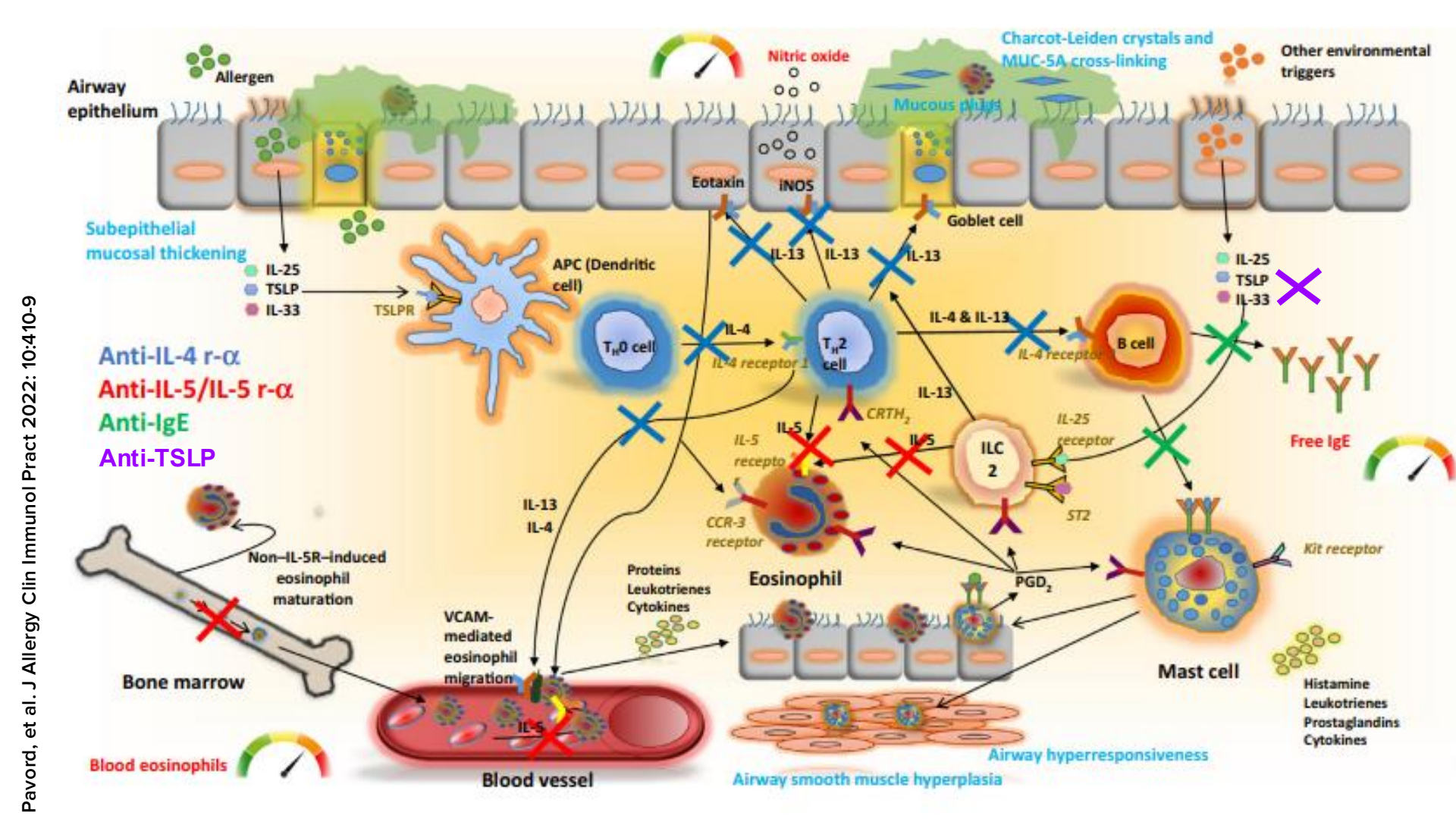
- Anaphylaxis
- Herpes zoster infections (shingles)
- Inject site reactions
- Headache
- Back Pain
- Fatigue
- Dosing
  - 6-11YO: 40mg every 4 weeks, 12-17YO: 100mg every 4 weeks
  - 18+YO: 100mg every 4 weeks

Biologics - Reslizumab

- IL-5 antagonist monoclonal antibody (IgG4κ) which inhibits IL-5 signaling
- Approved in 18+YO for Asthma
- IV-Based
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
  - The efficacy trials for reslizumab used a higher AEC of ≥400 cells/µL in efficacy trials examining annual frequent of clinical asthma exacerbations (Castro et al., 2015)
  - Subgroup analyses in patients with an AEC ≥400 cells/µL had significant improvements in FEV1 compared to placebo (Corren, Weinstein, Janka, Zangrilli, & Garin, 2016)

Biologics - Reslizumab (Safety & Dosing)

- Oropharyngeal Pain
- Anaphylaxis
- Dosing
  - 18+YO: 3 mg/kg IV q4 weeks; infuse over 20-50 minutes
  - Do not administer as an IV push or bolus. Treat patients with pre-existing helminth infections before therapy



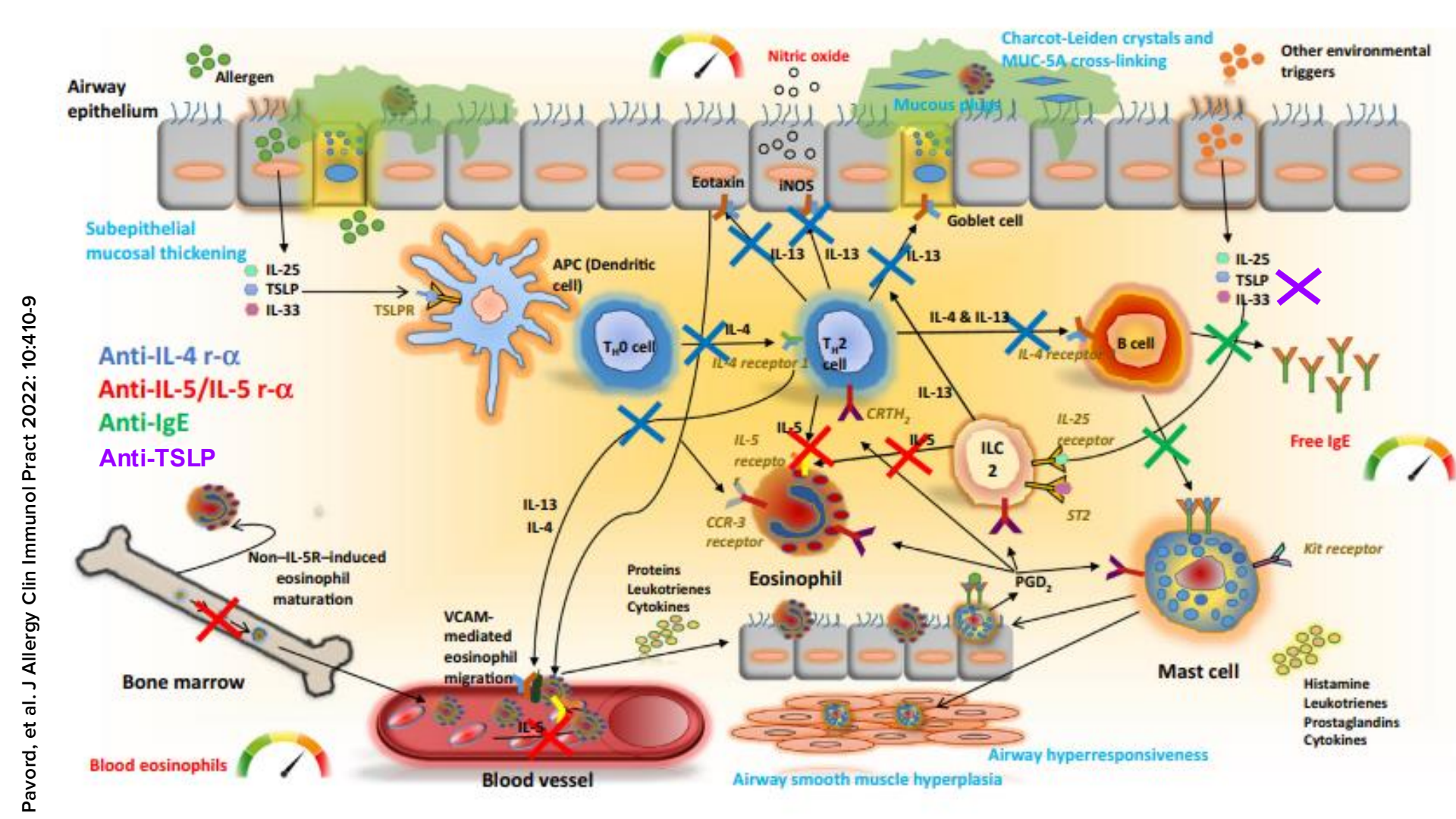
Pavord, et al. J Allergy Clin Immunol Pract 2022; 10:410-9

Biologics - Benralizumab

- IL-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1κ) which binds to alpha subunit of IL-5R and inhibits IL-5 signaling
- Approved in 6+YO for asthma
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History)**
  - In post-hoc analyses by Bleecker et al., patients with the following characteristics had greater reduction in annual exacerbation rate:
    - With an AEC of ≥300 cells/μL
    - With oral corticosteroid use
    - With concurrent nasal polyps (Bleecker et al., 2018)

Biologics - Benralizumab (Safety & Dosing)

- Anaphylaxis
- Headache
- Pharyngitis
- Parasitic (Helminth) Infection
- Dosing
  - 6-11YO <35kg: 10mg every 4 weeks (first 3 doses), then 10mg every 8 weeks
  - 6-11YO 35+kg: 30mg every 4 weeks (first 3 doses), then 30mg every 8 weeks
  - 12+YO: 30mg every 4 weeks (first 3 doses), then 30mg every 8 weeks



Pavord, et al. J Allergy Clin Immunol Pract 2022; 10:410-9

Biologics - Tezepelumab

- TSLP antagonist monoclonal antibody (IgG2κ). Inhibits TSLP signaling, decreasing release of downstream mediators
- Approved in 12+YO for asthma
- **Decision Criteria (CBC w/Diff, Total IgE, and Clinical History):**
  - Reduction of exacerbations from baseline by 77% to 79% respectively in AEC 150-300+ cells/uL with positive aeroallergen skin testing (PATHWAY/NAVIGATOR Data, Amgen AstraZenica, 2021)
  - Reduction in exacerbation by 71% seen in patients with an allergen exposure (PATHWAY/NAVIGATOR Data, Amgen AstraZenica, 2021)

Biologics - Tezepelumab (Safety & Dosing)

- Pharyngitis
- Arthralgia
- Back Pain
- Helminthic Infection
- Risk of Malignancy (further examination found the rate of malignancy similar in treatment and control groups)
- Dosing
    - 12+YO: 210mg every 4 weeks

All Biologics for Asthma

- **Decision Criteria**
  - Age of Patient
  - Clinical History (oral corticosteroid use, exacerbation frequency)
  - CBC w/Diff (Absolute Eosinophil Count)
  - Total IgE
  - Dosing and convenience of administration
  - Allergy to perennial and seasonal Allergies
  - Insurance coverage
  - Comorbidities
    - Omalizumab: CSU, CRSwNP, Food Allergies
    - Dupilumab: AD, PN, CSU, CRSwNP, EoE, BP
    - Mepolizumab: EGPA, CRSwNP, HES
    - Benralizumab: EGPA
    - Tezepelumab: +/-CRSwNP
  - Treatment goals (Reduce asthma exacerbation rate? Reduce oral corticosteroid dose? Improve lung function? Improve quality of life?)

When to re-evaluate?

- If no response on re-assessment of biologic in 6 months, you can consider other biologic agents

Resources for Patients and Providers

- American College of Allergy, Asthma, and Immunology [ACAAI] (https://www.acaai.org)
- American Academy of Allergy, Asthma, and Immunology [AAAAI] (https://www.aaaai.org/tools-for-the-public)