Post transplant immunologic issues: how I got to know our transplant APPs

Vanderbilt Transplant APP Symposium 2025

Yasmin Khan, MD

Assistant Professor Pediatric Allergy/Immunology

Monroe Carell Jr Children's Hospital at Vanderbilt

Monroe Carell Jr. Children's Hospital at Vanderbilt

VANDERBILT UNIVERSITY MEDICAL CENTER

Disclosures

- None

Objectives

Become familiar with the risk for secondary immunodeficiency after transplant focusing on secondary hypogammaglobulinemia

Learn about the link between immunosuppression and eosinophilia and TAFA

Think about drug allergy and delabelling for our transplant patients

Inborn errors of immunity are often inherited, but not always

- Inborn errors of immunity are defined as a group of disorders with increased infection susceptibility, immune dysregulation, autoinflammation, increased risk of malignancy, severe atopic disease and bone marrow failure
- By definition, these are caused by a specific molecular defect, either inherited or arising from a de novo mutation
- However, there are other paths to what looks like a genetic IEI and two of those are immunosuppression and solid organ transplant
  - So, what should we be doing with these patients??

Secondary hypogammaglobulinemia is common

- There have not been clear guidelines on the management of secondary antibody deficiency which has made it hard to know what to do with these patients
- Secondary antibody deficiency or secondary hypogammaglobulinemia (SHG) is defined as reduced immunoglobulin levels due to acquired causes (medication or disease process) or losses
- Much of SHG is due to immunosuppressive treatments, most notably B-cell–targeted therapy (BCTT), which is used in autoimmune rheumatologic, hematologic and neurologic conditions as well as oncologic disease.
- Chronic corticosteroid use is another common cause, although it does not appear to have the same increase in frequency or severity of infectious complications

American Academy of Allergy Asthma & Immunology

Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees

Iris M. Otani, MD,[a] Heather K. Lehman, MD,[b] Artemio M. Jongco, MD, PhD, MPH,[c] Lulu R. Tsao, MD,[a] Antoine E. Azar, MD,[d] Teresa K. Tarrant, MD,[e] Elissa Engel, MD,[f] Jolan E. Walter, MD, PhD,[g,h,i] Tho Q. Truong, MD,[j] David A. Khan, MD,[k] Mark Ballow, MD,[l] Charlotte Cunningham-Rundles, MD, PhD,[m] Huifang Lu, MD, PhD,[n] Mildred Kwan, MD, PhD,[o] and Sara Barmettler, MD[p] *San Francisco, Calif; Buffalo and Great Neck, NY; Durham and Chapel Hill, NC; Cincinnati, Ohio; St Petersburg, Fla; Denver, Colo; Dallas, Tex; and Boston, Mass*

Most common causes of secondary hypogammaglobulinemia

- Medications
- Nephrotic syndrome
- GI losses
- Significant liver disease

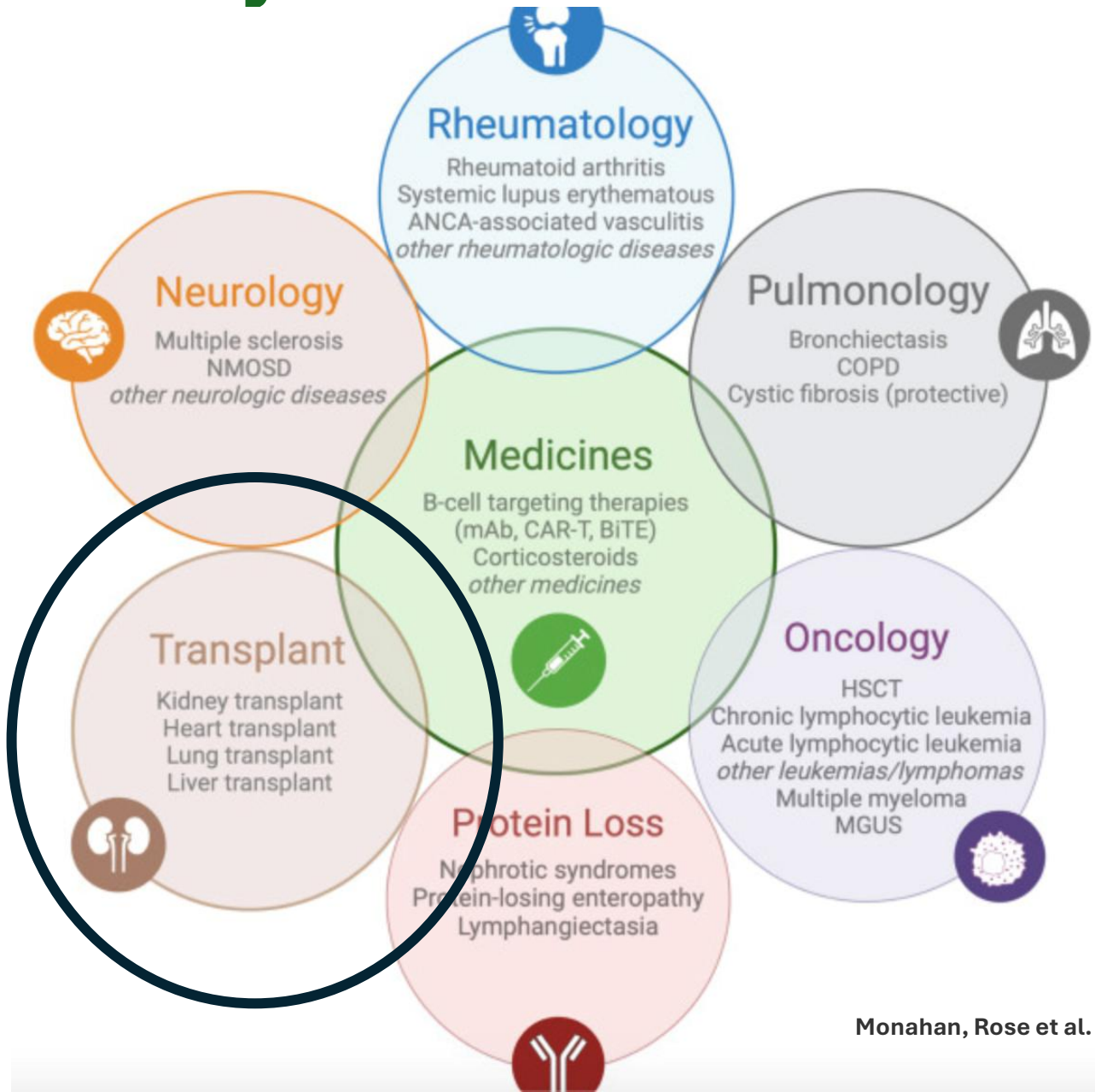
Table 2
Medications Associated With Hypogammaglobulinemia

Medications
Antimalarial
Captopril
Carbamazepine
Glucocorticoids
Fenclofenac
Gold salts
Penicillamine
Phenytoin
Sulfasalazine
Anti-CD20 mAbs (rituximab)

NOTE. Adapted from the International Consensus Document (ICON): Common Variable Immunodeficiency Disorders.[3]

Lee TK, Gereige JD, Maglione PJ. State-of-the-art diagnostic evaluation of common variable immunodeficiency. Ann Allergy Asthma Immunol. 2021 Jul;127(1):19-27. doi: 10.1016/j.anai.2021.03.005. Epub 2021 Mar 11. PMID: 33716149

Many conditions lead to SHG



Monahan, Rose et al. Annals of Allergy, Asthma & Immunology, Volume 134: 269 - 278

Secondary antibody deficiency happens in a variety of conditions

- It is important to understand if patients have antibody defects before starting immunosuppressive therapies
- Many societies advocate for baseline screening labs but this is not standard practice for all
    - Society guidelines exist for systemic lupus erythematous (SLE), ANCA-associated vasculitis, rheumatoid arthritis, chronic lymphocytic leukemia and solid organ transplant

- Adding more complexity, over the last few years, the category of primary immune dysregulatory disorders has expanded within the world of IEI
    - Disorders that present primarily with autoimmunity and lymphoproliferation rather than the classic PI presentation of severe, recurrent, and/or unusual infections.
- SHG found in patients after solid organ transplant also appears to be largely iatrogenic due to immunosuppression, plus losses in patients after kidney transplant

Seconday hypogammaglobulinemia after solid organ transplant

- Secondary hypogammaglobulinemia has been found to affect 45% of patients in the first year after solid organ transplant (both children and adults included in this study though primarily adults)
  - 26% children, 52% adults
- In this patient population, IgG <400 mg/dL has been associated in multiple studies with worse outcomes
- A meta-analysis of 18 studies looking at 1756 SOT recipients found significantly increased odds of infection, respiratory infection, cytomegalovirus infection, Aspergillus infection, other fungal infection, and mortality at 1 year
- Their IgG level is unlikely to be the only factor but may be a very important one

Florescu DF, Kalil AC, Qiu F, Schmidt CM, Sandkovsky U. What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant. 2013 Oct;13(10):2601-10. doi: 10.1111/ajt.12401. Epub 2013 Aug 6. PMID: 23919557.

Universal recommendations for cutoffs to define secondary hypogammaglobulinemia do not currently exist

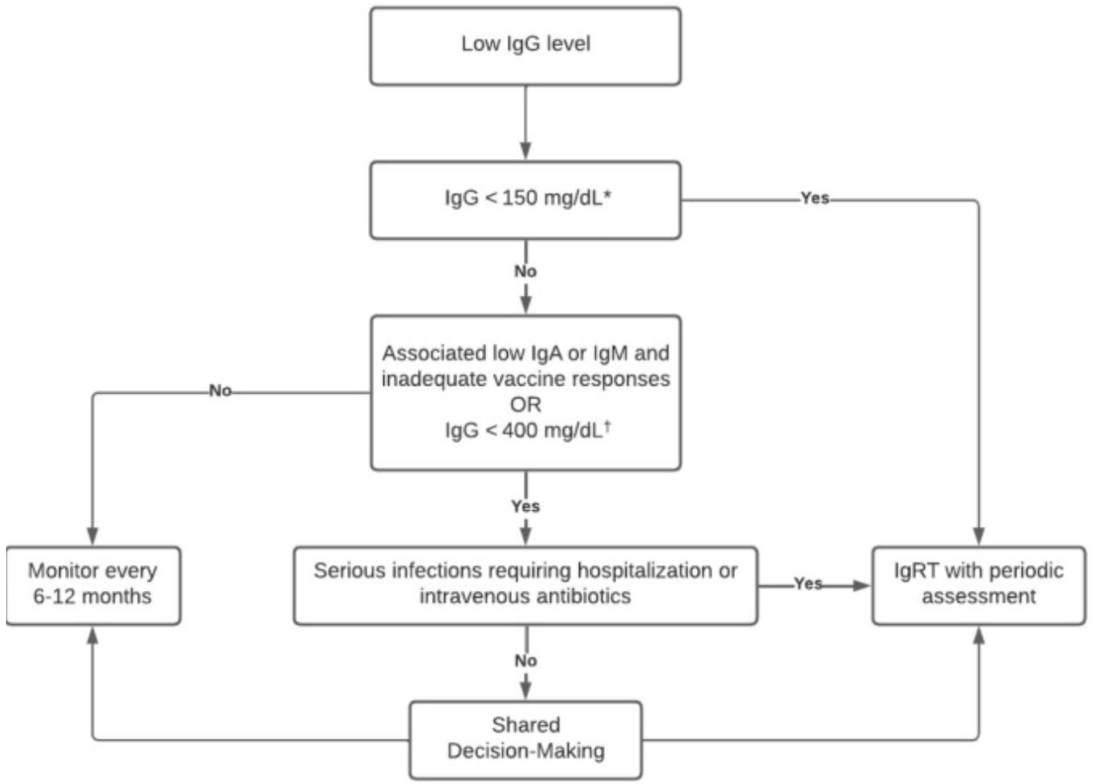
- The IgG level used to define hypogammaglobulinemia varies greatly throughout the literature and among different subspecialities
- The 2022 working group report from the AAAAI suggests the following for adults:
  - Hypogammaglobulinemia = 700 mg/dL or less in adults
  - Mild = 400-699 mg/dL
  - Moderate – 300-399 mg/dL
  - Severe 0-199 mg/dL
- They do not suggest the same brackets for pediatrics, but do stress the importance of using pediatric reference ranges
  - For example, the lower limit of normal for age 1-2 years old is 345 and the mean is 679
- It is also suggested that we think about duration to understand transient versus persistent
  - 3-6 months
  - 6-12 months
  - 12-24 months
  - More than 24 months

Infection severity is also a consideration

- We also need to think about what types of infections the patient is getting, if any
- The working group report also makes the following suggestions
  - Severe: infection requiring an ED visit or hospitalization, IV antibiotics, or antiviral or antifungal treatment for an infection (separate from prophylaxis)
  - Recurrent: following Jeffrey Modell Foundation criteria—4 or more new ear infections, 2 or more serious sinus infections, 2 or more pneumonias, 2 or more invasive infections

There are not clear guidelines on when to start IgG replacement without other abnormalities

- The authors of the working group report suggest that an IgG below 150 mg/dL should warrant starting IgRT without other functional abnormalities, based on what is accepted throughout the primary immunodeficiency literature
- The solid organ transplant and hematologic malignancy literature recommends starting at a cutoff of 400 mg/dL
- There are no guidelines on how long to follow a low IgG before starting replacement or considering additional evaluation, however many of these will be transient and recover on their own



Monahan, Rose et al. Annals of Allergy, Asthma & Immunology, Volume 134: 269 - 278

There are not clear guidelines on when to start IgG replacement without other abnormalities

- When starting IgRT, we follow the IEI literature as there are not guidelines specific to SHG
- Starting at 400-600 mg/kg every 4 weeks is accepted
- Targeting trough levels that keep the patient infection free is the recommendation and they suggest 800 mg/dL as a goal

Periodic reassessment of need is also recommended

- Once a patient has been starting on IgRT, we should be periodically assessing their continued need
- If they have finished treatment for their underlying disease, you may choose to pause the patients IgRT and follow levels and infection frequency. The authors suggest a period of 3-4 months as the half life of IVIG is 21 days and it takes 4-5 half lives to clear the exogenous IgG from the system.

Causes of secondary hypogammaglobulinemia

Medications that cause hypogammaglobulinemia

Medication class	Medication names	Laboratory abnormalities
Anti CD20 therapy	Rituximab Ocrelizumab Obinutuzumab Veltuzumab ofatumumab	B-cell depletion HG Rituximab: late-onset neutropenia
Anti CD38 therapy		Decreased plasma cells Lymphopenia HG
CD19 CAR-T cell therapy		Immune-related adverse effects: cytokine release syndrome, neurotoxicity B-cell aplasia, HG
BTK inhibitors	Bortezumib	Decreased IgG levels starting at 12 mo Some patients experience increase in IgA, with increase in IgA >_50% from baseline associated with significantly less infections

Medications that cause hypogammaglobulinemia

BTK inhibitors	Bortezumib	HG (IgG < 500 mg/dL) in 42% (5 of 12) with lupus nephritis; no opportunistic infections observed
Corticosteroids		HG in 12%-56% on prolonged or high-dose corticosteroids IgG more affected than IgA or IgM Specific antibody responses typically preserved CD4 lymphopenia
Other immunosuppressive therapies	Methotrexate	HG inhibition of dihydrofolate reductase Decreased IgG, IgA, IgM Decreased antibody responses to nonlive vaccines (influenza, pneumococcal)

Medications that cause hypogammaglobulinemia

Antipsychotic	Clozapine	Antipsychotic most often associated with immunosuppression and need for IgG-RT in 1 cohort Low IgG, IgA, and IgM Low class-switched memory B cells and plasmablasts Longer duration associated with low IgG and low class-switched memory B cells
Anti-epileptic	Phenytoin	HG, B-cell and T-cell lymphopenia
	Carbamazapine	Carbamazepine: HG, B-cell lymphopenia, transient monoclonal gammopathy, recurrent HSV encephalitis, interstitial pneumonitis
	Valproate	HG
	Lamotrigine	IgA deficiency

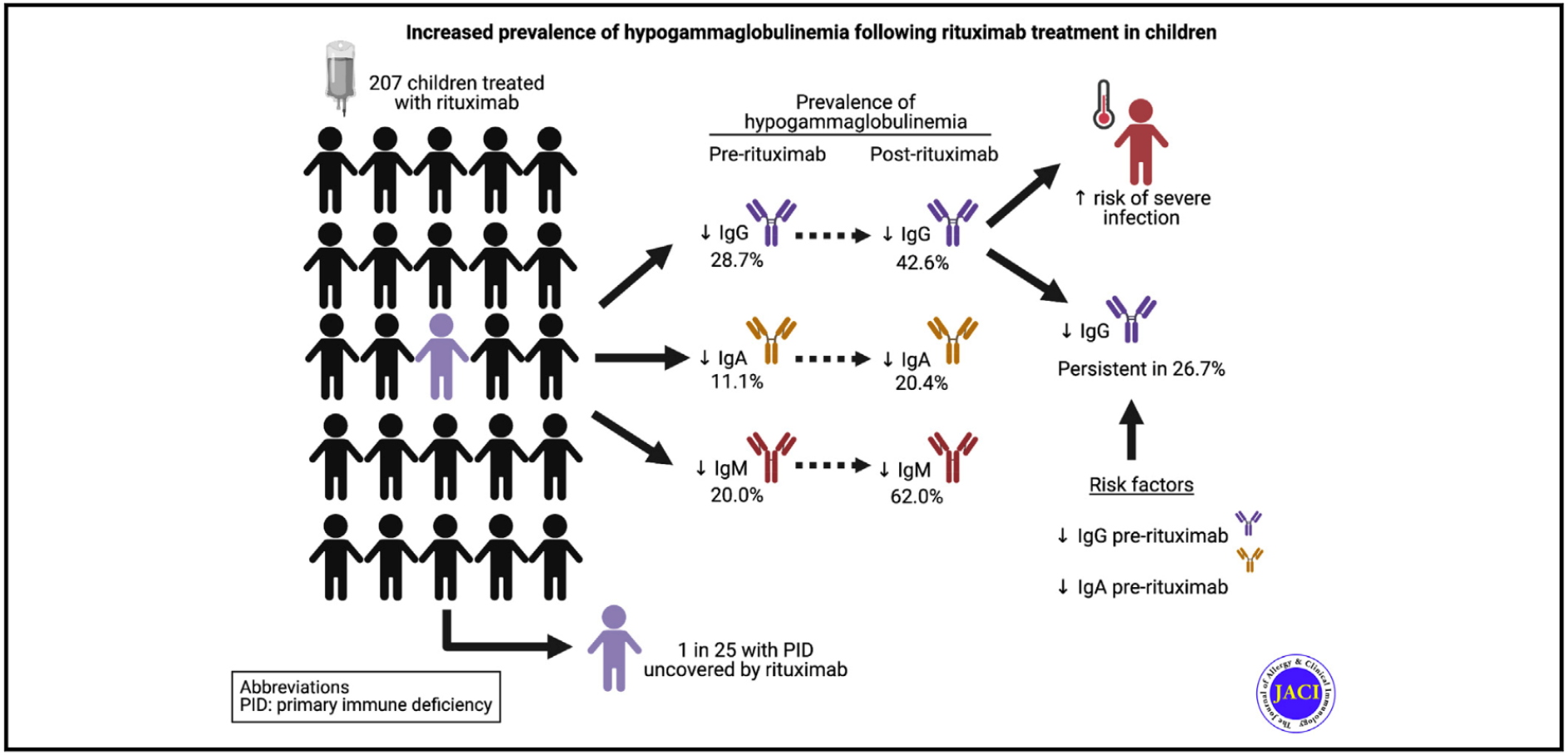
B cell targeted therapy

- Most literature exists for Rituximab
- RTX targets CD20-expressing B cells in the pro- to pre-plasma cell stages and does not target plasma cells, which produce most antigen-specific IgG
  - That would suggest that patients would not develop HG on therapy, but some do
- Patients at risk to develop HG include patients being treated for malignant disease
  - 14-50% of those being treated for lymphoma, versus 3.5% in RA and 4.2% in ANCA associated vasculitis
- Also patients with lower pre-treatment IgG levels are at higher risk
- Concomitant treatment with mycophenolate and cyclophosphamide increase risk but not methotrexate
- Patients who develop post RTX HG do have higher likelihood to develop infections

After treatment with BCTT

- B cell recovery occurs about 6-9 months after treatment with RTX alone, and 18-24 months if patients receive a combination of RTX and other chemotherapy
  - Kinetics are similar in pediatric patients
- The recovery time is likely influenced by several factors including underlying disease, age related immune maturation and concomitant treatments

RTX also causes hypogammaglobulinemia in the pediatric population



Labrosse, R. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol. 2021 Aug;148(2):523-532.e8.

Corticosteroid effects on antibody production

- The most common finding with corticosteroid therapy is CD4 T cell lymphopenia
- In adult patients, 12-58% of those on chronic or high dose corticosteroid therapy can develop HG
  - IgA and IgM are less affected than IgG
- Short courses of OCS have been associated with a transient drop in serum IgG which can last for several weeks after stopping
- Long term OCS therapy has been associated with significantly decreased levels of IgG
- No effect on IgG has been seen with high dose inhaled corticosteroids

Patients on chronic corticosteroids do not seem to have an increased risk of infection

- Unlike BCTT, hypogammaglobulinemia from corticosteroid use has not been associated with increased frequency or severity of infection
- These patients also have normal specific antibody production
- High dose corticosteroid use is associated with increased risk of opportunistic infection, moreso due to lymphopenia
  - PJP prophylaxis is recommended for patients with underlying immunocompromising conditions (post-transplant, malignancy, and other forms of immunosuppression) who are also on high dose corticosteroids and for 1 month after discontinuation
    - Prednisone >20 mg daily or equivalent dosing for 1 month

Protein losing conditions: Nephrotic syndrome

- Patients with nephrotic syndrome develop HG due to urinary losses, but can also have decreased synthesis of IgG
- Patients are sometimes treated with RTX which further complicates their hypogammaglobulinemia
- Patients with hypogammaglobulinemia due to nephrotic syndrome, especially when on RTX, have a high risk of infections
  - In both adult and pediatric patients
- There is insufficient evidence to guide who/when to treat, especially as the administered IgG is quickly lost in the urine
  - Also we have to be thoughtful about IgRT formulations in patients with renal disease
  - Sucrose free formulations are preferred

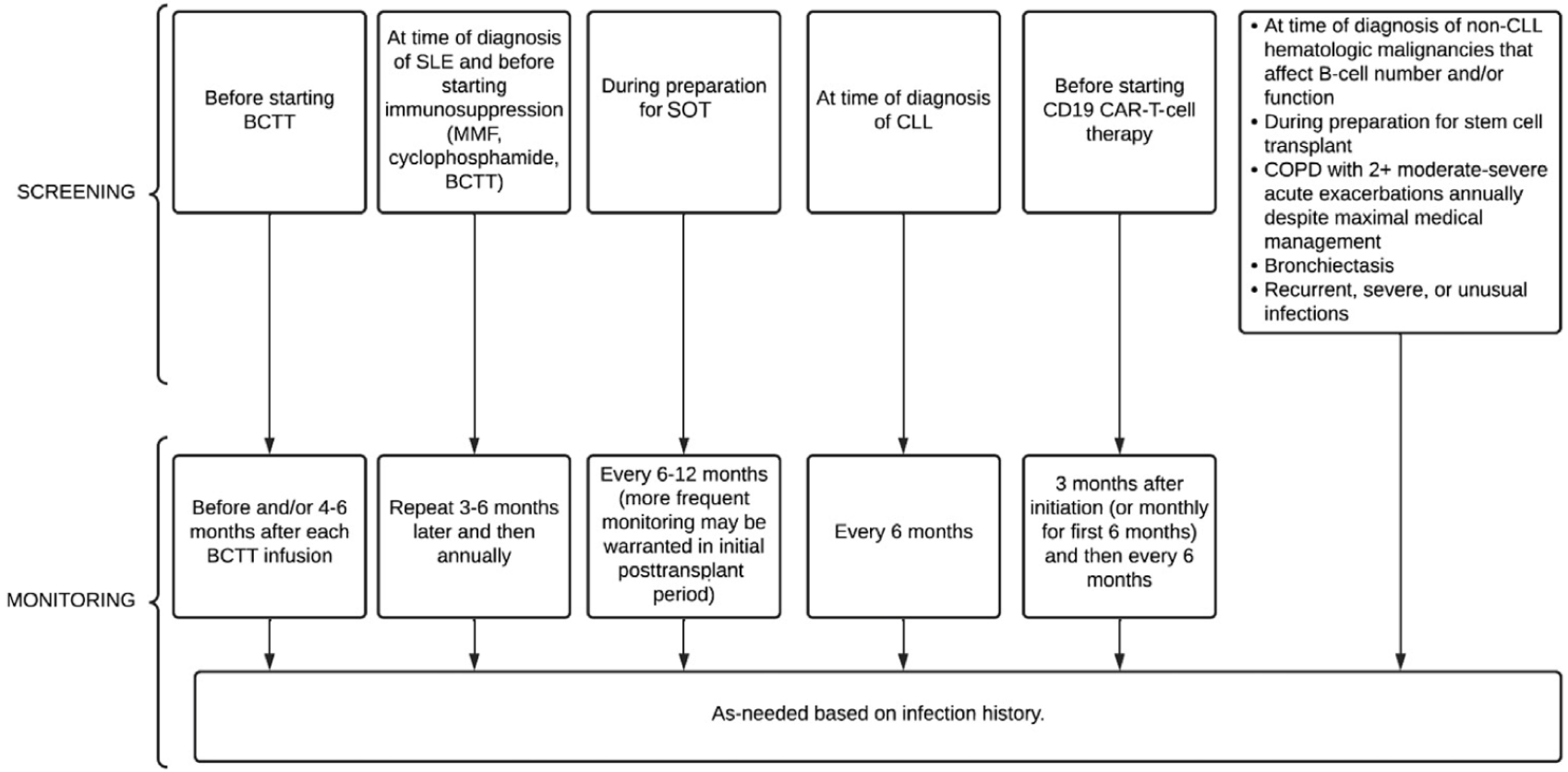
Protein losing conditions: protein losing enteropathy

- PLEs occur when intestinal leakage of plasma proteins occurs through 1 of 3 pathologic mechanisms:
  - presence of mucosal injury due to erosive or ulcerative gastrointestinal disorders, allowing inflammatory exudates to cross the epithelium
  - increased mucosal permeability due to compromised mucosal integrity, which allows protein to leak into the lumen
  - intestinal loss of lymphatic fluid secondary to lymphatic obstruction
- Patients with PLE are at risk for HG, lymphopenia and infections

Protein losing conditions: protein losing enteropathy

- Again, there is limited evidence for the use of IgRT in the treatment of HG due to PLE.
- It has been suggested that IgRT be considered if prophylactic antibiotics are inadequate at preventing infections
- When considering starting IgRT for patients with PLE, it is felt that subcutaneous IgG may be preferable due possibly to more favorable pharmacokinetics
  - It is not FDA approved for this indication and thus would be considered off label

Recommendations for screening/monitoring



Switching away from secondary hypogammaglobulinemia

Let’s think about a patient

- 2 year old male, s/p liver transplant 1 year ago for biliary atresia, coming in for routine follow up
- His tacrolimus levels have been in range and he has had no episodes concerning for rejection
- He has not had great weight gain in general, but in the 6 months, he has lost 2 kg
- He has frequent vomiting, but it doesn’t seem to correlate with any specific foods
- Minimal lower GI symptoms; has occasional diarrhea
- No history of food impaction or choking
- He also has atopic dermatitis which has worsened quite a bit in the last year, currently needing topical steroid most days with continued disease

Post transplant eosinophilic gastrointestinal disorders (PTEGID)

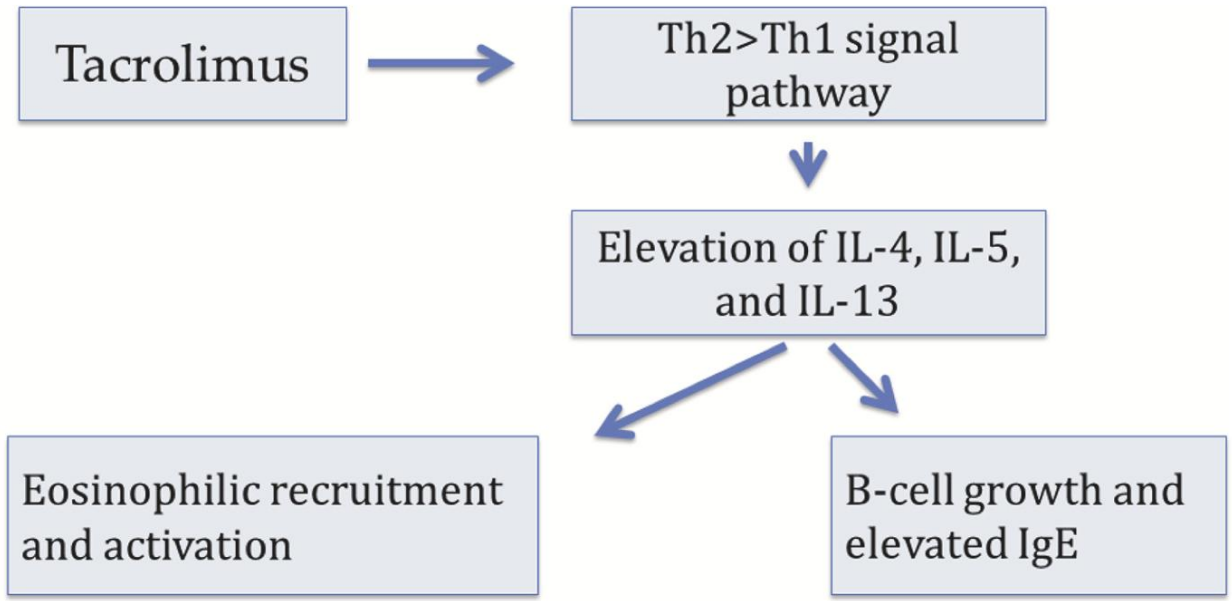
- Eosinophilic esophagitis, gastritis, enteritis, gastroenteritis and colitis
  - EoE has a prevalence of roughly 25.9 per 100,000 people (0.02%)
- In the pediatric liver transplant population, tacrolimus is often the preferred choice for immunosuppression as it has been shown to promote graft survival
- It can also lead to an increase in allergic disease in these patients
- In a cohort of 98 patients at Johns Hopkins, 14% had PTEGID and of those, 12% had EoE
- The mean time to diagnosis was 1.9 years post transplant
- Transplant age less than 1 year old was associated with a significantly increased risk

Wasuwanich P, Batsis I, Thawillarp S, Alford MK, Mogul D, Wood RA, Karnsakul W. Post-transplant eosinophilic gastrointestinal disorders and lymphoproliferative disorder in pediatric liver transplant recipients on tacrolimus. Transpl Immunol. 2021 Oct;68:101438. PMID: 34320385

Post transplant eosinophilic gastrointestinal disorders (PTEGID)

- Also interestingly in their cohort, they found that eosinophilia was associated with the development of post transplant lymphoproliferative disease (PTLD)
- And that an AEC greater than or equal to 500/microliter was associated with at least 1 episode of acute rejection
- They also found increased rates of food associated anaphylaxis and that that is associated with the development of asthma
- Compared to other pediatric solid organ transplant, liver transplantation seems to increase risk for development of allergic conditions

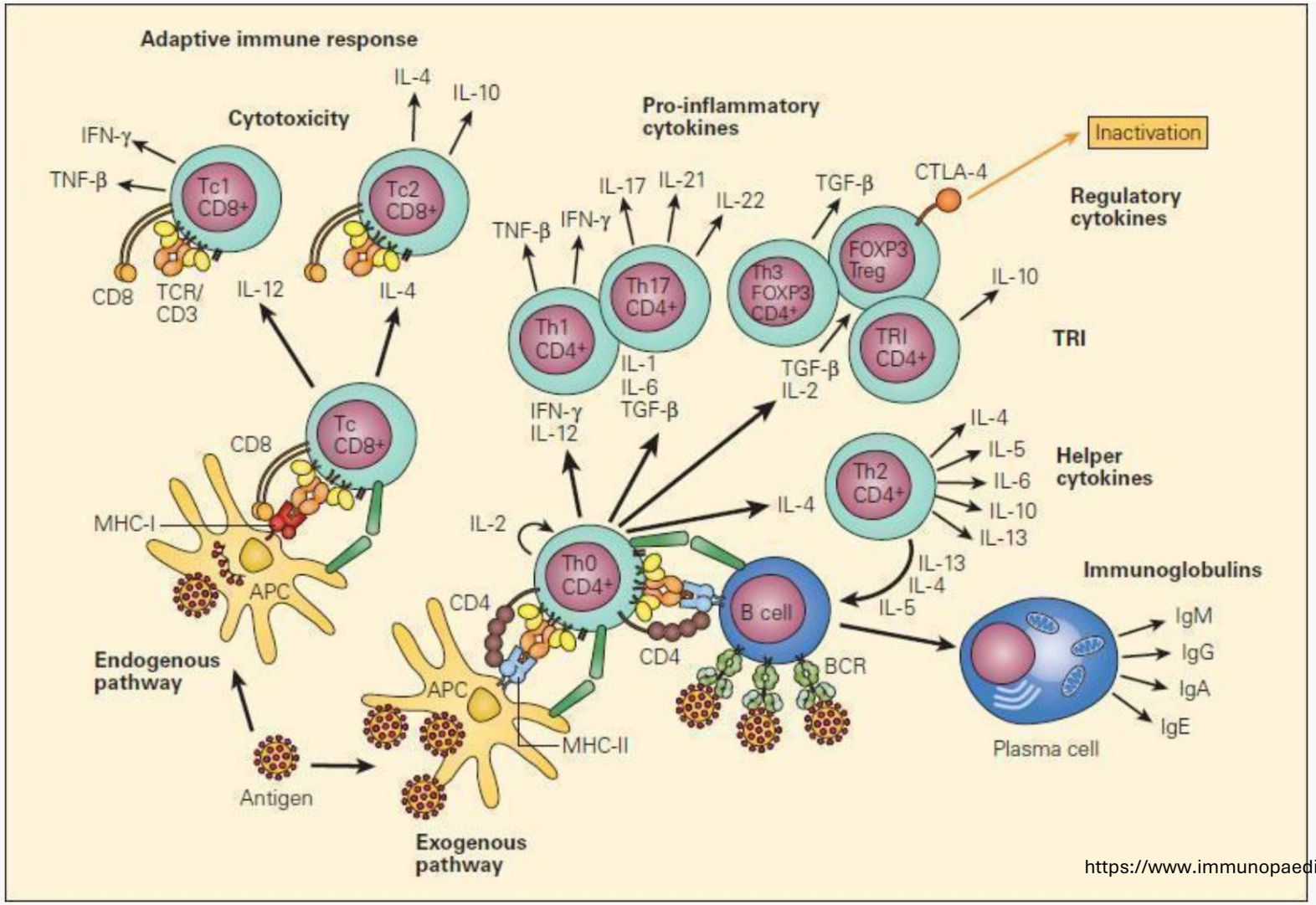
Proposed mechanism for tacrolimus and PTEGID



Back to our patient

- He undergoes EGD which shows >100 eosinophils per HPF distally and in the mid esophagus and some linear furrowing
- He is started on swallowed budesonide and dairy is removed from his diet
- Appetite improves and he starts to gain weight slowly
- In the meantime, his skin continues to worsen
- On his first ingestion of scrambled egg, he develops rapid onset of hives and facial swelling so they go to the ED and he is treated with Benadryl, steroids and pepcid

Differentiation into T helper 2 cells depends on IL-4

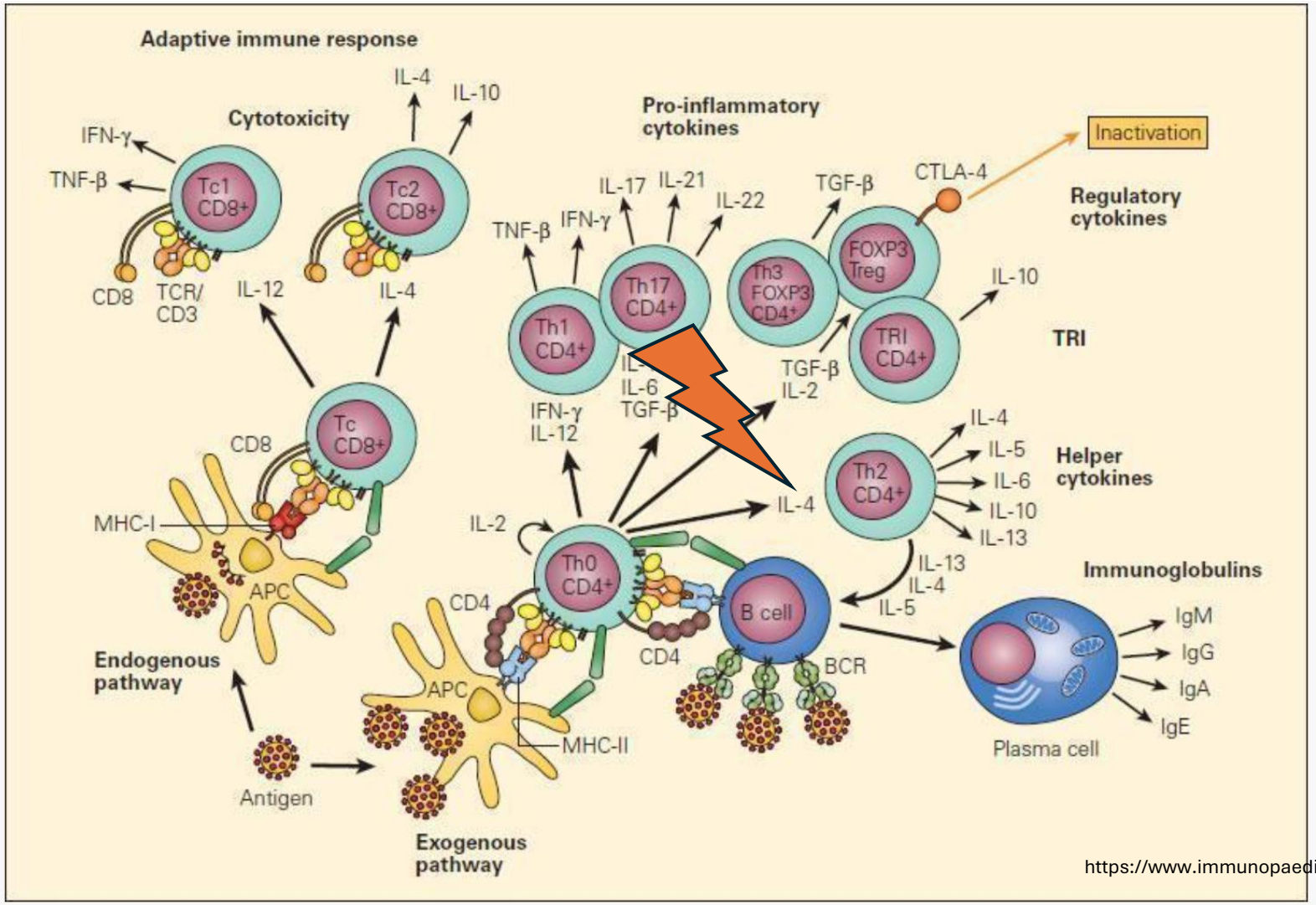


https://www.immunopaedia.org.za/immunology/basics/5-overview-of-t-cell-subsets/

Post transplant eosinophilic gastrointestinal disorders (PTEGID): treatment

- Dupilumab is a monoclonal antibody that targets a subunit of the IL-4 and IL-13 receptors, blocking Th2 activation
- It is currently FDA approved for treatment of atopic dermatitis, asthma, and eosinophilic esophagitis in children, in addition to CRS with nasal polyps, COPD and chronic urticaria in adults
- We often use this therapy for our patients with PTEGID or who have moderate to severe atopic dermatitis because it has very few side effects, is very well tolerated and is does not cause further immunosuppression

Differentiation into T helper 2 cells depends on IL-4



https://www.immunopaedia.org.za/immunology/basics/5-overview-of-t-cell-subsets/

Characteristics of IgE mediated food reaction

- Rapid onset after ingestion (eg, within minutes to 2 hours)
  - Skin: most common (80%)
  - Respiratory
  - GI
  - Circulatory
- Small amount allergen ingested can give serious reaction
- Reproducible

IgE mediated food allergy

- Over 170 foods have been described as triggers of food related reactions
- 9 foods account for 90% of food allergies
  - Aka the Top Nine
  - peanut, tree nuts, fish, shellfish, milk, egg, wheat, soy, and sesame

Transplant acquired food allergy (TAFA)

- Separate to EGID, patients can also develop transplant acquired food allergy
- Transplantation-associated food allergy (TAFA) refers to the *de novo* development of food-specific serum IgE (sIgE) after solid organ transplantation
  - In many patients, they also have reactivity to these foods, but not always
- It seems to be most common in pediatric patients who have received a liver transplant and are on tacrolimus for immunosuppression
- This has been described in liver and bone marrow/stem transplant receipents, both in the adult and pediatric literature
- One center in Montreal looked retrospectively at renal and cardiac transplant receipents and found no TAFA in the renal group and 1 new egg allergy 1 year after cardiac transplantation at age 1mo
  - Their immunosuppression regimen is either tacrolimus or cyclosporine

Cardet JC, Boyce JA. Addition of mycophenolate mofetil to tacrolimus is associated with decreases in food-specific IgE levels in a pediatric patient with liver transplantation-associated food allergy. J Allergy Clin Immunol Pract. 2013 Jan;1(1):104-6. PMID: 24229832

Graham F, Racicot F, Jamali L, Cong VP, Raboisson MJ, Paradis J, Paradis L, Des Roches A. Tacrolimus use in renal and cardiac pediatric transplantation: no increased risk of food allergies. Ann Allergy Asthma Immunol. 2015 Aug;115(2):155-7. PMID: 26094803.

Transplant acquired food allergy (TAFA)

- Tacrolimus may be implicated in TAFA possibly through effects on gut permeability, which could change the way the gut immune system perceives the food antigen
- It may also preferentially suppress T-regulatory cells, which leads to T_H2-type inflammation
- There are also several case reports of food allergy being transferred from donor to recipient
  - First described in 1988 in bone marrow transplant
  - Well described in a small Swiss case series of solid organ transplant from a donor that died of fatal food anaphylaxis
  - This seems to be organ specific and has been described in liver, lung and combined cardiac-pancreas

Agosti JM, Sprenger JD, Lum LG, Witherspoon RP, Fisher LD, Storb R, Henderson WR Jr. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. N Engl J Med. 1988 Dec 22;319(25):1623-8. PMID: 3059190.

Muller YD, Vionnet J, Beyeler F, Eigenmann P, Caubet JC, Villard J, Berney T, Scherer K, Spertini F, Fricker MP, Lang C, Schmid-Grendelmeier P, Benden C, Roux Lombard P, Aubert V, Immer F, Pascual M, Harr T; Swiss Transplant Cohort Study. Management of allergy transfer upon solid organ transplantation. Am J Transplant. 2020 Mar;20(3):834-843. PMID: 31535461

Back to our friend

- He is diagnosed with egg allergy and has testing for peanut since he has never eaten it, which is also positive
- Milk IgE is also high but it is unclear if this is a true allergy or just sensitization, but he is recommended to continue to avoid it
- He has developed chronic cough that has been treated with oral steroids a few times by his PCP
- He is not tolerating swallowed budesonide well, so he is started on dupilumab for the primary indication of atopic dermatitis and secondary indication of EoE

Back to our friend

- His skin improves quickly, though family isn’t always consistent with dosing so we have some ups and downs
- He is also started on inhaled corticosteroid and cough resolves
- He has an episode of anaphylaxis after an accidental ingestion of milk, which confirms it as a true allergy
- He is growing, attending school and overall doing great

Drug allergy in pediatric solid organ transplant

- In recent years, we have learned that much of what is labelled as a life threatening drug allergy is not actually a reason to avoid the drug
- Compared to adults, pediatric transplant recipients are higher risk of developing primary infections for 3 major reasons
  - Due to their age, they may lack natural immunity if not previously exposed to certain microbes
  - They may not be completely vaccinated
  - Use of immunosuppression
- Infections remain a major source of hospitalization, morbidity and mortality
- Having a listed antibiotic allergy makes it harder to treat infections and often leads to use of non-first line agents
- It also limits options for prophylactic antibiotic therapy
  - This is especially important for trimethoprim-sulfamethoxazole given its use in *Pneumocystis jirovecii* pneumonia prophylaxis

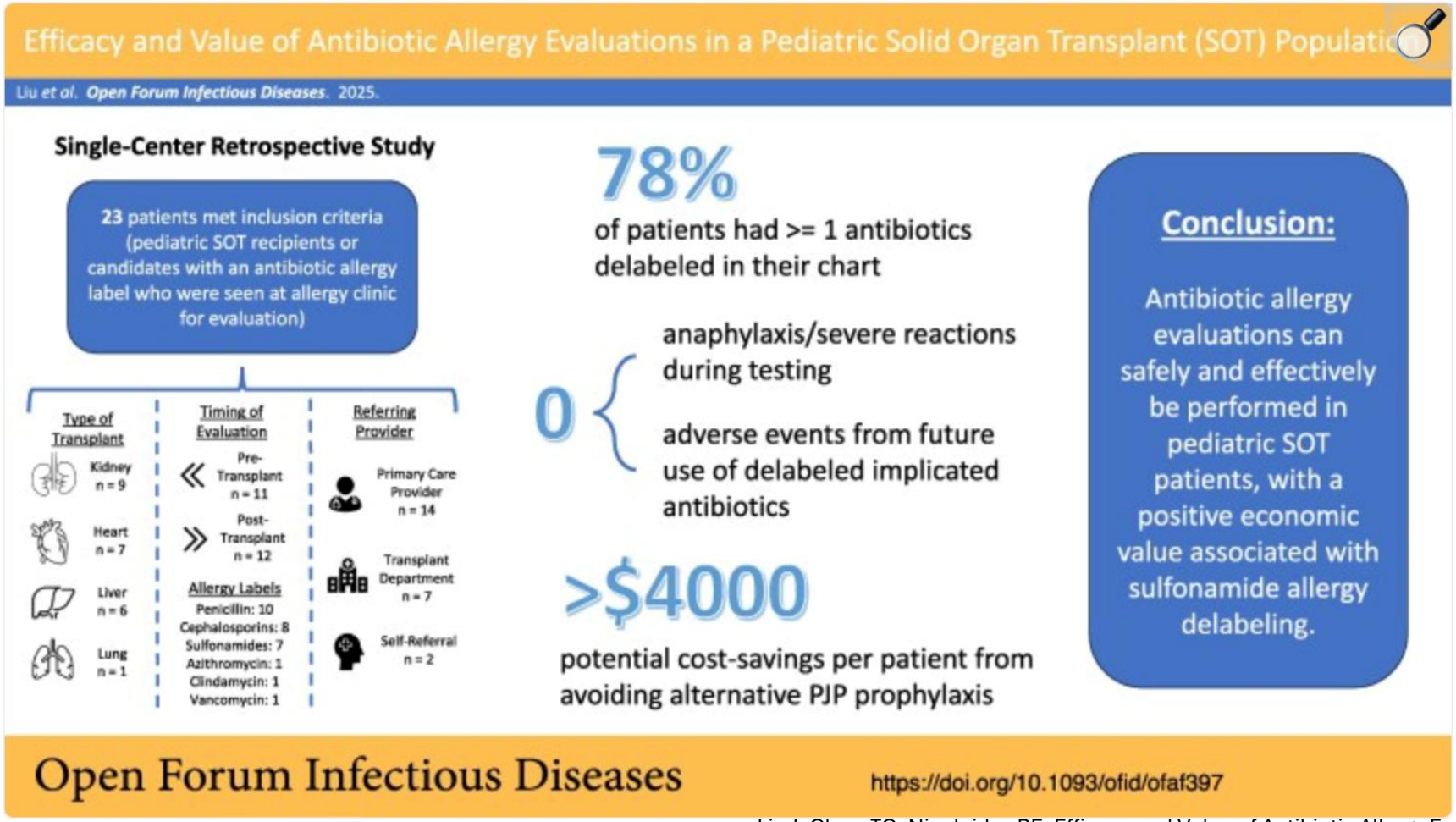
Liu J, Chow TG, Nicolaides RE. Efficacy and Value of Antibiotic Allergy Evaluations in a Pediatric Solid Organ Transplant Population. Open Forum Infect Dis. 2025 Jul 1;12(7):ofaf397. PMID: 40689248

Drug allergy in adult solid organ transplant

- Around 30% of transplant patients report antibiotic allergies
- Among adult hematopoietic stem cell transplant patients with β-lactam allergies, it was found that delabeling resulted in shorter durations of therapy and associated cost savings
- Our own Vanderbilt adult allergy group found that 96.3% of pretransplant recipients with antibiotic allergies were safely able to receive implicated antibiotics following a delabeling intervention

Gorsline CA, Afghan AK, Stone CA Jr, Phillips EJ, Satyanarayana G. Safety and value of pretransplant antibiotic allergy delabeling in a quaternary transplant center. Transpl Infect Dis. 2022 Oct;24(5):e13885. PMID: 35765165

Delabelling patients is safe and cost effective

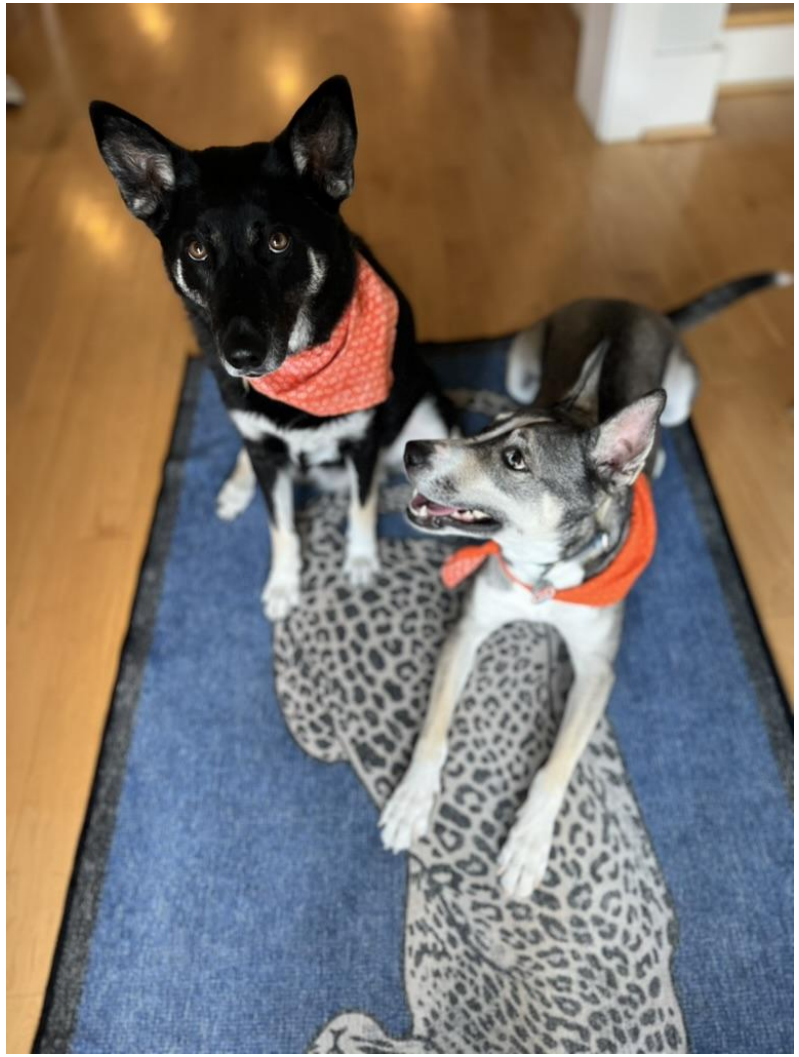


Liu J, Chow TG, Nicolaides RE. Efficacy and Value of Antibiotic Allergy Evaluations in a Pediatric Solid Organ Transplant Population. Open Forum Infect Dis. 2025 Jul 1;12(7):ofaf397. PMID: 40689248

In summary

- Our post transplant patients have so much going on already, but can additionally develop atopic diseases
- Pretreatment labs are so helpful in patients that are being treated with immunosuppressive therapy, especially B cell targeted therapy
  - Encourage your friends to do it regularly! Maybe even develop a CPG ☺
- Food allergy can develop after SOT, in addition to other atopic conditions like atopic dermatitis, asthma and allergic rhinitis
- Think about drug allergy delabeling ideally pre transplant (especially if you are going to need TMP-SMX), but post transplant is great too
- Make friends with your allergy colleagues! We are happy to help

Thank you for your attention!



Monroe Carell Jr. Children's Hospital at Vanderbilt

VANDERBILT UNIVERSITY MEDICAL CENTER