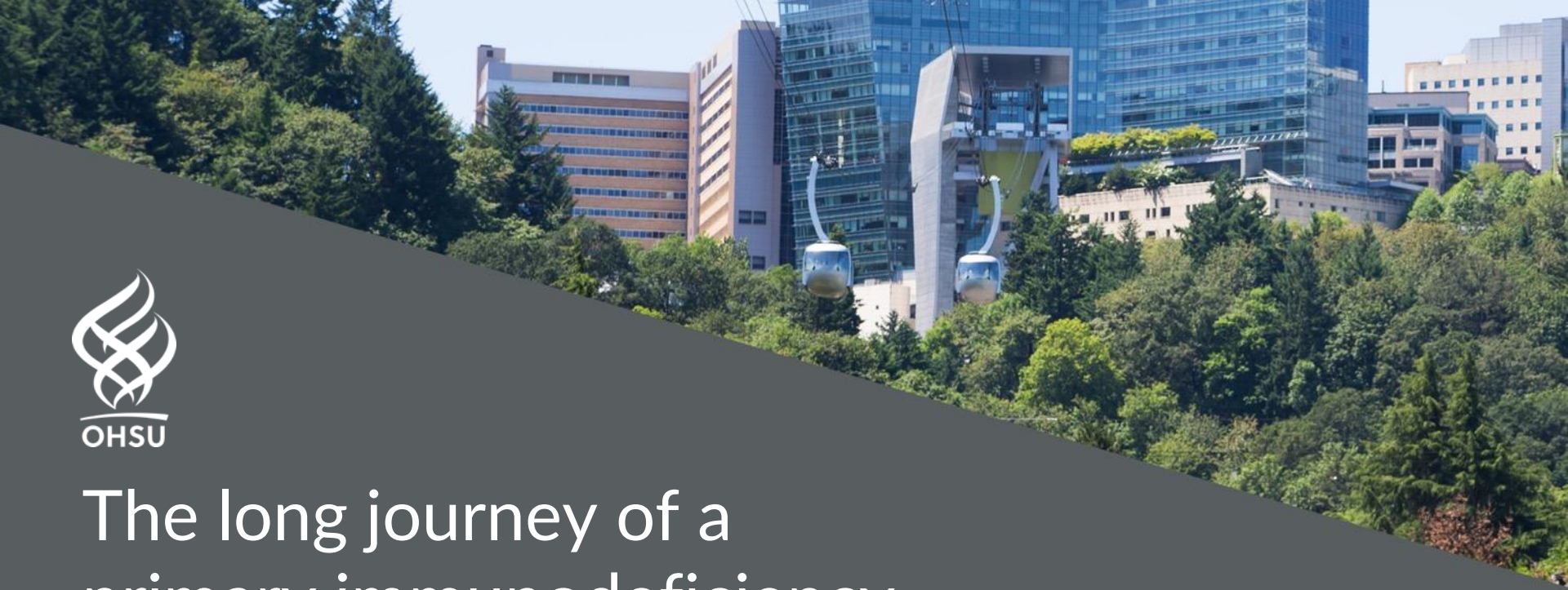

The long journey of a primary immunodeficiency

West Coast TID Meeting

Feb 5, 2025 - Lorne Walker, MD PhD

Learning Objectives

- Recognize patterns of inborn errors of immunity (IEI) in children
- Describe variations in the genetics of IEI in unusual situation
- Consider the importance of immune reconstitution in difficult to clear infections

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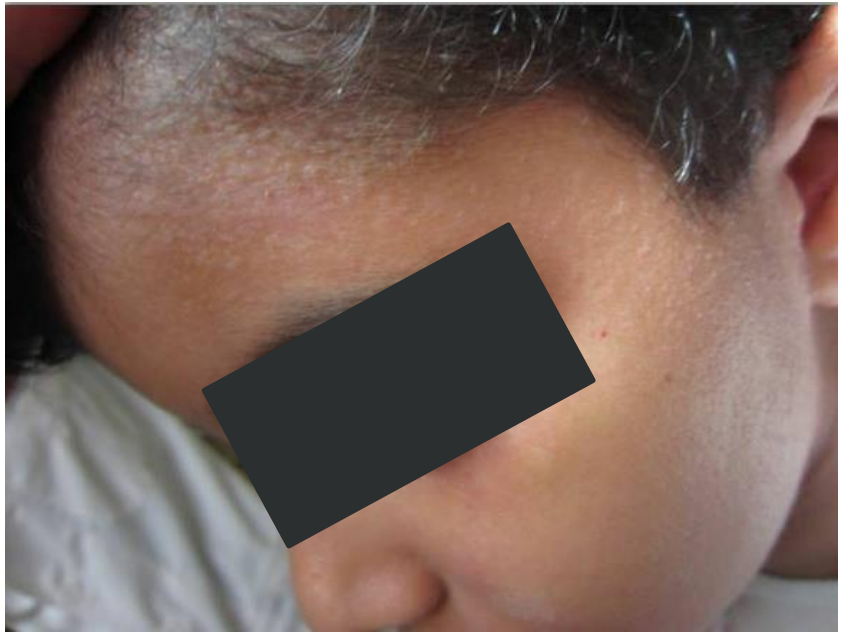
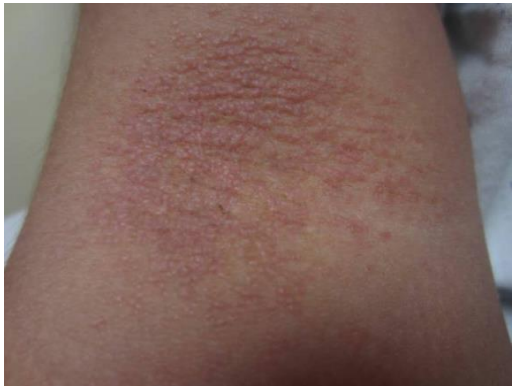
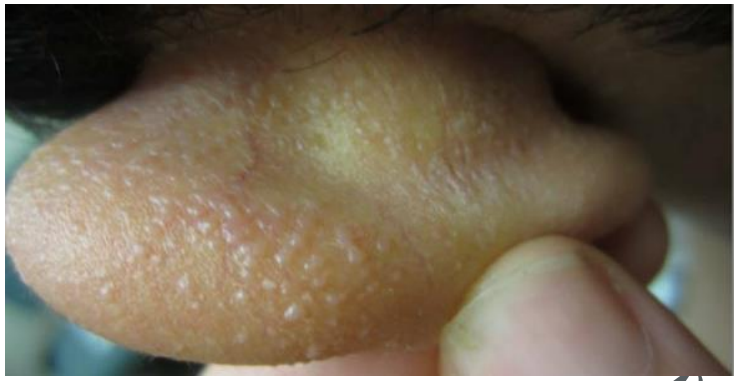
Background - 2011

- [redacted]-year-old [redacted] presenting with a diffuse rash







Biopsy: Verruca plana
(papillomavirus)

Past Medical History

- Term uncomplicated delivery in [redacted]
- Family emigrated to US in 2010 via refugee camp in [redacted]
- 1-month hospitalization due to rotavirus ([redacted])
- Celiac disease, primary sclerosing cholangitis, recurrent pancreatitis
- Unexplained anaphylaxis
- s/p splenectomy due to splenic hemangioma
- Numerous clinic/ED/UC visits for acute infections

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Histories

- FH
  - Parents healthy
  - Younger brother also seems to have difficulty with infections
  - No consanguinity
- Vaccinations
  - Up to date per family recollection
- SH
  - Lives with parents and brother in [redacted] suburbs
  - No pets, other unusual exposures
  - Family extremely avoidant of infections: no preschool, homeschool kindergarten, minimal contact outside the home

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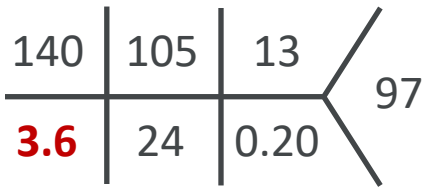
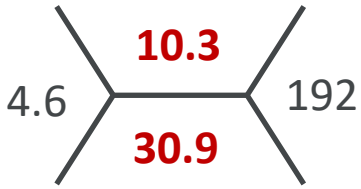
Labs (2011)



Ca: 9.1
TP: 6.7
Alb: 4.3
Bili: 0.3
ALT: 34
AST: **36**



N59 L31 M8 E2
ANC: 2720
ALC: 1450

IgG: **291**
IgA: **391**
IgM: **37**
T-cells: 1275
- CD4+: **398**
- CD8+: 667

B-cells: 488
- Naïve: **99%**
- Class-switched: **0.3%**
- Memory: **0.8%**

NK-cells: **3.9**
Lymphocyte mitogens: Normal

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Clinical Course

- Verruca plana rash is chronic but stable
- Started IgG replacement due to low serum level
- No hospitalizations or life-threatening infections
- Continued frequent and prolonged community-acquired infections
- “Immune screening” at OSH negative

This child's immune deficit is most likely due to a defect in:

A. Lymphocyte number
B. T-cell function
C. B-cell function
D. NK-cell function
E. Complement function

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This child's immune deficit is most likely due to a defect in:

A. Lymphocyte number

B. <u>T-cell function</u>

C. B-cell function

D. NK-cell function

E. Complement function

Combined immunodeficiency

- poor control of papilloma viruses (T-cell, NK)
- Autoimmunity
- poor tumor surveillance (CD8+ T-cell)
- prolonged rotavirus diarrhea (antibody deficiency)

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Re-presentation - 2021

- [redacted] y/o adolescent preparing for HSCT
- Continued IgG supplementation
- Bronchiectasis, chronic verruciform rash
- Genome sequencing: IL2RG mutation (common gamma chain)
  - Known mutation causing **X-linked Severe Combined Immunodeficiency**

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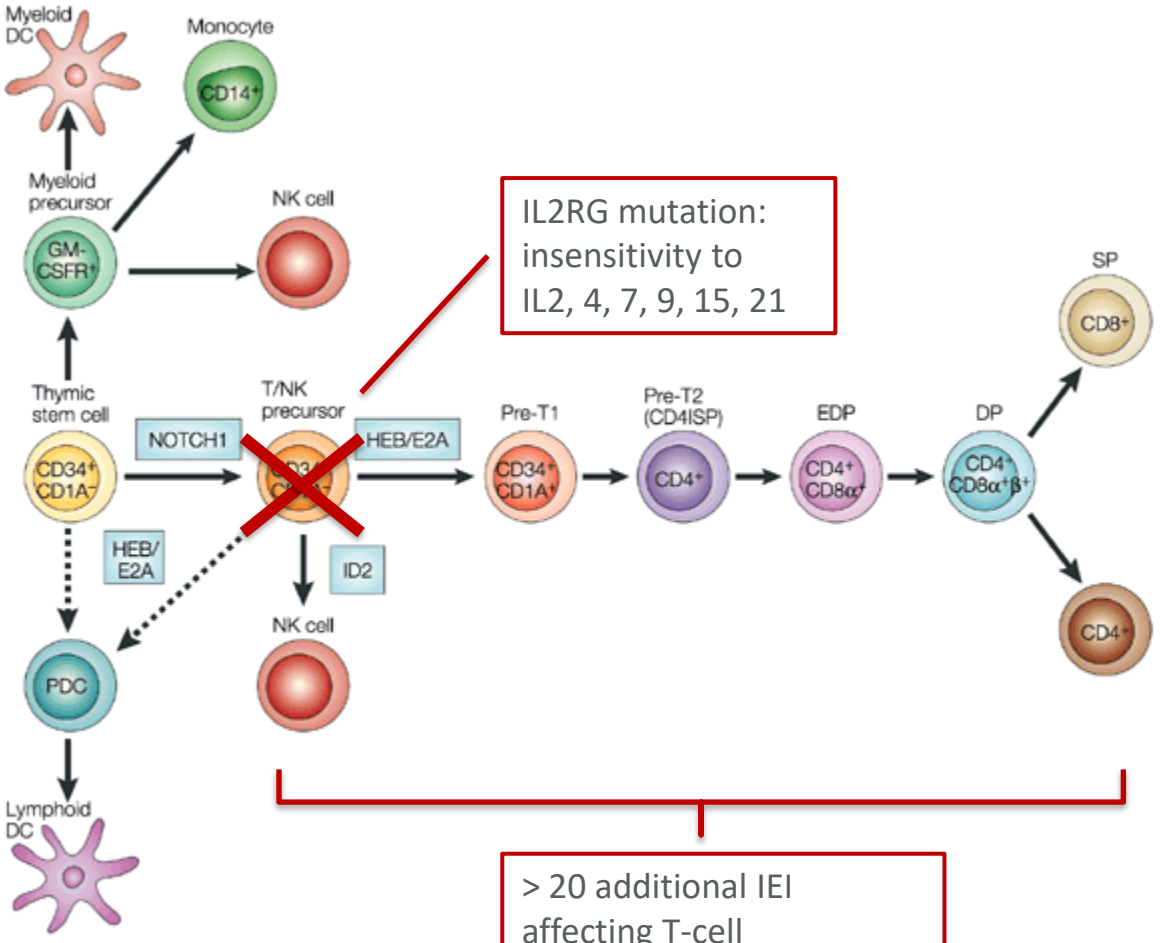
SCID

- IEI affecting T-cell function
- Unable to stimulate B-cells
- May also affect NK cells



Spits H, PMID: 12360214 **Nature Reviews | Immunology**

SCID - Presentation

https://www.npr.org/2018/10/13/657080482/opinion-the-doctor-and-the-boy-in-the-bubble

- Presents with failure to thrive and severe recurrent infections
- Untreated infants typically die in the first year due to infection

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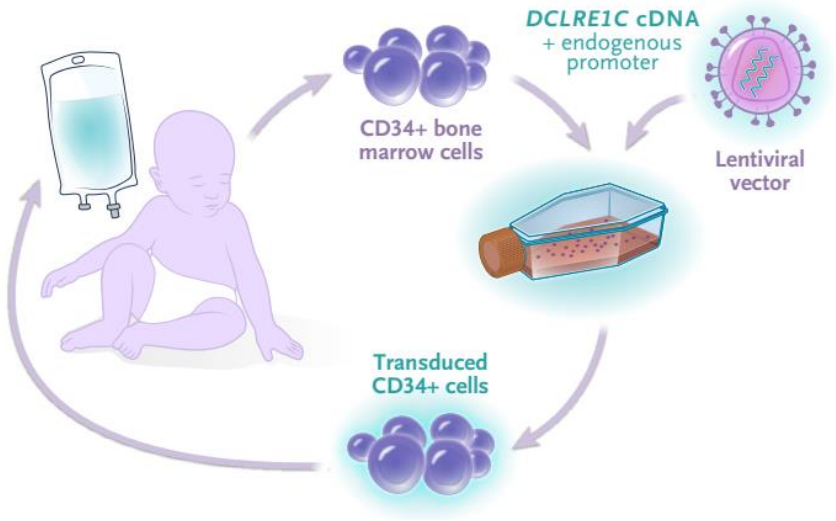
SCID - Treatment

- Traditional treatment: HSCT
- Enzyme replacement: PEG-ADA
- Gene therapy
  - Artemis: 2022
  - ADA: 2016
  - IL2RG: **1999**



Cowan MJ et al. PMID: 36546626

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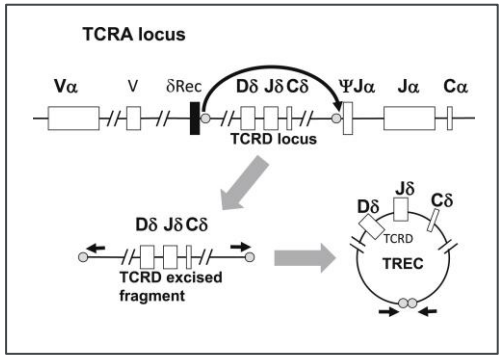
SCID - Screening

2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Wisconsin	Massachusetts	California	Delaware	Colorado	Minnesota	Guam	Arkansas	Alaska	Arizona	Nevada
		New York	Michigan	Connecticut	Ohio	Illinois	Hawaii	Georgia	Kansas	Alabama
				Florida	Pennsylvania	Iowa	Montana	Idaho	Missouri	Indiana
				Mississippi	Utah	Maine	New Hampshire	Kentucky	North Carolina	Louisiana
				Navajo Nation		Nebraska	Oklahoma	Maryland		
				Texas		New Jersey	Puerto Rico	North Dakota		
				Wyoming		New Mexico	South Carolina	Tennessee		
						Oregon	South Dakota	Vermont		
						Rhode Island	Virginia			
						Washington				
						Washington, D.C.				
						West Virginia				



Currier R, et al. PMID: 33551023

https://primaryimmune.org/resources/news-articles/history-scid-newborn-screening

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Why has this adolescent survived to age [redacted]?:

A. Infection avoidance (social isolation)
B. Immunoglobulin supplementation
C. Incomplete penetrance
D. Incorrect diagnosis (not SCID)
E. Probabilistic effect (very good luck)

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Why has this adolescent survived to age [redacted]?:

A. Infection avoidance (social isolation)
B. Immunoglobulin supplementation
C. **Incomplete penetrance**
D. Incorrect diagnosis (not SCID)
E. Probabilistic effect (very good luck)

Mosaicism
- Somatic cells harbor differing genotypes, causing a mixed phenotype

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Mosaic SCID

- Somatic mosaicism: somatic cells with more than one genetic line
  - Somatic mutation
  - Meiosis errors
  - Mobile genetic elements
- Sequencing revealed WT **and** mutant sequences

https://www.wisdompanel.com/en-us/blog/the-genetics-of-chimerism-and-mosaicism-in-dogs-and

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Mosaic X-SCID

- Patients with mosaic X-SCID can have intermediate phenotypes

Germline mutation	Type of reversion	Revertant cell	Clinical impact	Reference
c.343T>C	Back mutation	$CD4^+T$, $CD8^+T$	Patient presented with a mild phenotype, but subsequentially underwent HSCT because of recurrent infections	(7)
IVS1+5G>A	Second-site mutation	T (only skin infiltrated)	Omenn syndrome	(9)
c.466T>C	Back mutation	αβT, γδT	Mild phenotype	(10)
c.284-15A>G	Multiple reversions	$CD4^+T$, $CD8^+T$	Mild phenotype	(11)
c.655T>A	Back mutation	$CD4^+T$, $CD8^+T$, γδT	Mild phenotype	(5)
c.260T>C	Back mutation	$CD4^+T$, $CD8^+T$, B	Mild phenotype	(12)
c.172C>A	Back mutation	$CD8^+T$, NK	Patient died of graft failure and fungal infection after HSCT	(13)

X-SCID, X-linked severe combined immunodeficiency; HSCT, hematopoietic stem cell transplantation; NK, natural killer.

Miyazawa H, et al. PMID: 34868061

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Re-re-presentation - 2024

- Discussed gene therapy with NIH
  - Ultimately deemed unlikely to succeed
- Now ready to proceed with HSCT
- Clinically similar to 2021 evaluation
- Pre-HSCT BAL done
  - Fungal culture: *Aspergillus brasiliensis*
  - Pre-induction initiation of voriconazole

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HSCT

- Conditioning and infusion well-tolerated
  - MUD PBSC 8/8 match
- Post-HSCT infections
  - Prolonged cryptosporidium diarrhea
  - EBV viremia
  - BKV viremia
  - Stenotrophomonas bacteremia
- Recalcitrant GVHD treated with: steroids, tacrolimus, cyclosporine, rituximab, eculizumab, infliximab, anakinra, ruxolitinib

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Enterococcus meningitis

- Episode of enterococcal bacteremia ~45 days post HSCT associated with altered mental status
- MRI and LP done -> bacterial meningitis growing E faecalis
  - Meningitic doses of ceftriaxone + ampicillin
- Repeat LP in 1 month still positive
- Meningitic symptoms relatively mild
  - Worse when immune suppression weaned

What antibiotic combination ultimately cleared his CSF?

A. Continuous ampicillin + q12h ceftriaxone
B. Continuous ampicillin + q6h vancomycn + q12h ceftriaxone
C. Continuous vancomycin + continuous ampicillin + q12h ceftriaxone
D. Ampicillin q4h + Daptomycin q24h + Linezolid q12h
E. Ampicillin q4h + Ceftaroline q8h + Meropenem q8h
F. None of the above

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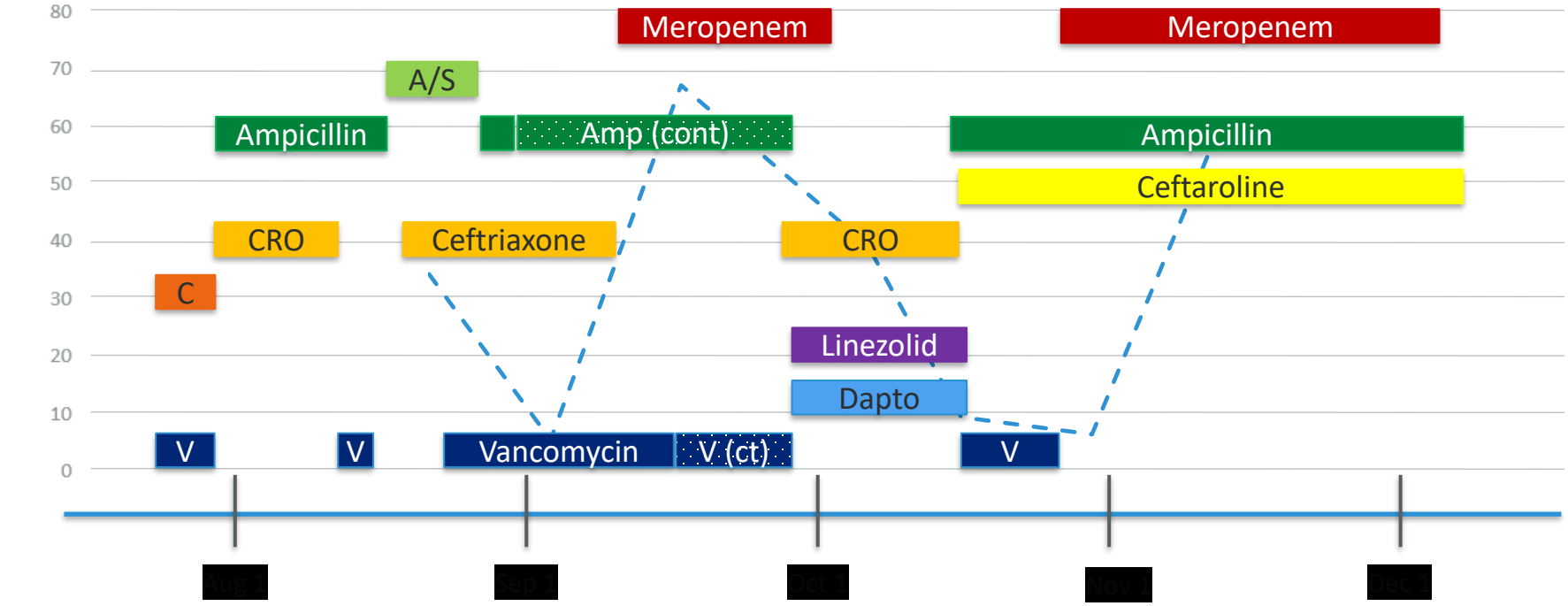
80
70
60
50
40
30
20
10
0
Meropenem
Meropenem
A/S
Ampicillin
Amp (cont)
Ampicillin
Ceftaroline
CRO
Ceftriaxone
CRO
C
Linezolid
Dapto
V
V
Vancomycin
V (ct)
V
CSF
Blood

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Clinical course

- Symptoms and CSF parameters varied over time
  - Primarily varied depending on degree of immune suppression
- Therapeutic approach discussed with ID listservs and enterococcal experts across country
  - Combination β-lactam therapy

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Clinical course

- Due to multiple infections on up to 12 anti-infectives
  (Ampicillin, Ceftaroline, Meropenem, Levofloxacin, Azithromycin, Nitazoxanide, TMP/SMX, Voriconazole, Cidofovir, Acyclovir, Letermovir, Acyclovir)
- Unfortunately, the patient died at day +177 from graft failure, GI hemorrhage and gut necrosis

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Follow-up

- 1 month later: [redacted] y/o younger brother seen in TID clinic
  - **Same mosaic mutation and phenotype**
  - He has elected to start in-person high school
  - Prophylaxis (valacyclovir, TMP/SMX) and infection avoidance
  - In [redacted] 2025 he attended his first day of in-person school (ever!)

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Thank You