



CLL SOCIETY

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CLL AND THE IMMUNE SYSTEM: PRACTICAL IMPLICATIONS

AUGUST 29, 2024

9 AM PT, 10 AM MT

11 AM CT, 12 PM ET

SPEAKERS



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(SPEAKER)**

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Medical Oncology
Mass General Cancer Center
Boston, Massachusetts



Andres Chang

**MD, PhD
(SPEAKER)**

Department of Hematology & Medical Oncology
Emory University School of Medicine
Winship Cancer Institute
Atlanta, Georgia



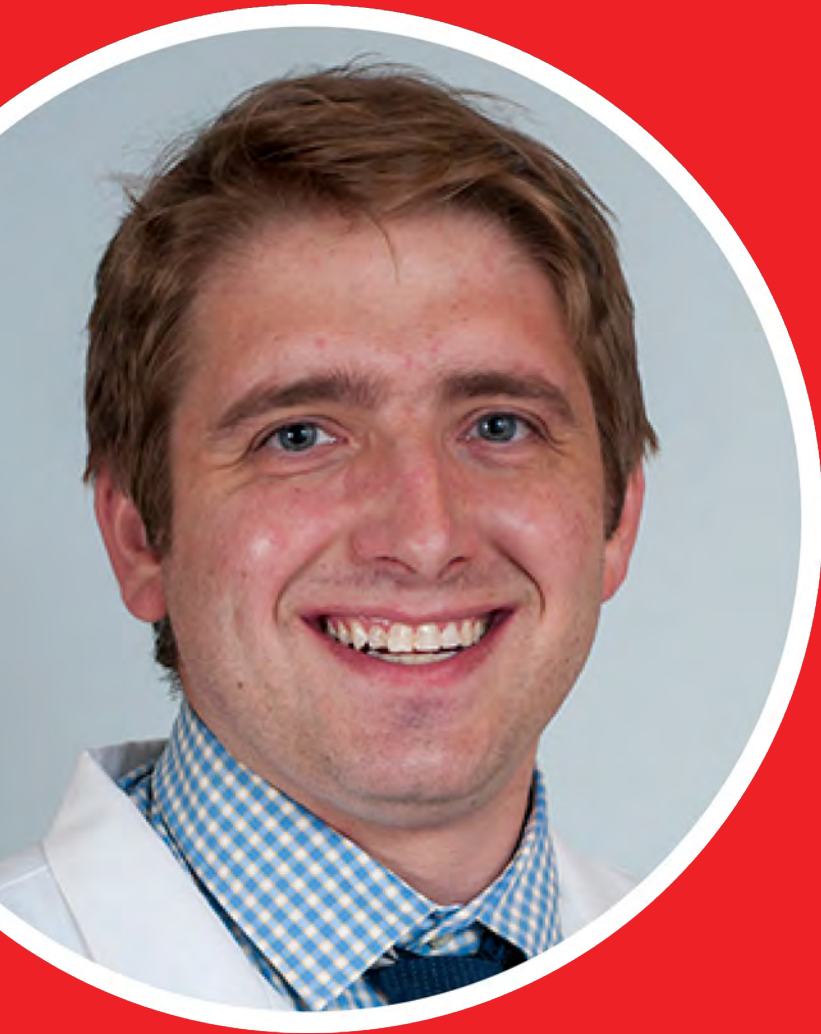
Brian Koffman

**MDCM (retired) MS Ed
(MODERATOR)**

Executive Vice President &
Chief Medical Officer
CLL Society



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SPEAKER

Jacob D. Soumerai, MD

Assistant Professor of Medicine
Harvard Medical School
Center for Lymphoma, Mass General Cancer Center



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CLL AND THE IMMUNE SYSTEM: PRACTICAL IMPLICATIONS

LEARNING OBJECTIVES

- **How is the immune system affected by CLL?**
- **How is the immune system affected by anti-CLL therapy?**
- **What does this mean for patients?**



EARLY HINTS OF ABNORMAL IMMUNITY IN CLL

- Recurrent infections a common way that patients with CLL presented in the past before blood counts were routine:



Bacterial infections



Viral infections



Fungal infections

- Infection risk appeared higher with higher disease burden.
- Opportunistic infections can occur from the CLL or its treatment. These are infections caused by bacteria, viruses and fungi that don't usually cause a problem in those with normal immunity.

Forconi, Blood 2015

THE IMMUNE SYSTEM

- **Many components**
 - “Innate” immune system = More primitive, first line of defense
 - “Adaptive” immune system = Very specialized and targeted, long acting
- **Evolved to be highly coordinated**
- **Protection against invaders (infections and cancers)**
- **Delicate balance – immune system can cause harm (“autoimmunity”)**
- **Many other functions (not the focus of today’s discussion)**

Chow et al, Nat Rev Microbiol 2022

INNATE IMMUNITY FIRST RESPONDERS NON-SPECIFIC

Key components
dysfunctional



Macrophage



Dendritic cells



Natural Killer Cell

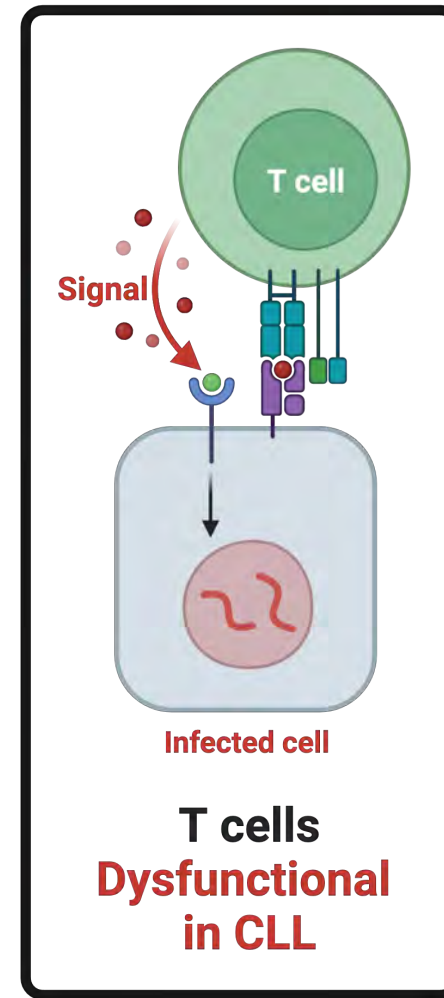
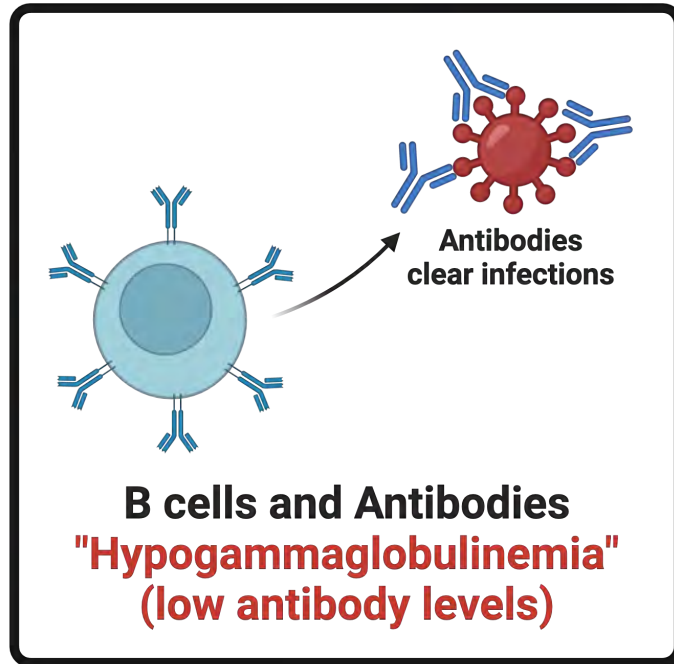


Neutrophil

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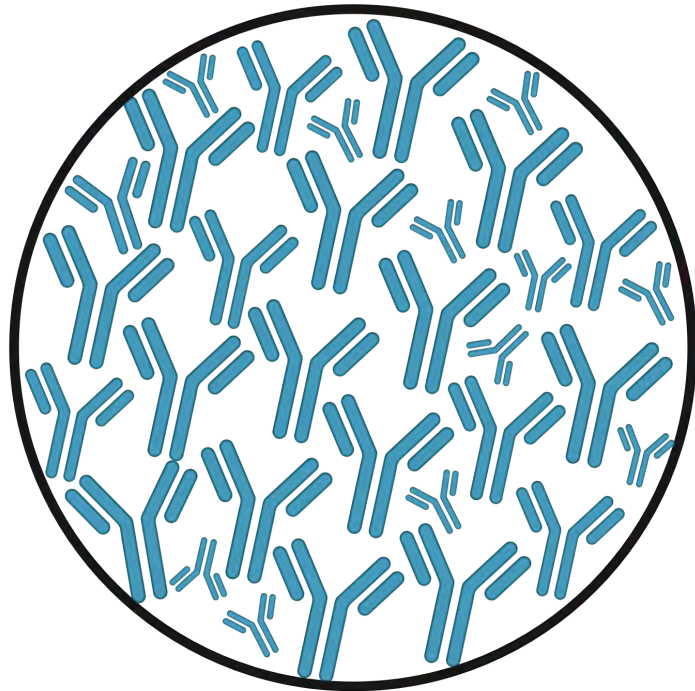


ADAPTIVE IMMUNITY HIGHLY SPECIFIC LONG LASTING

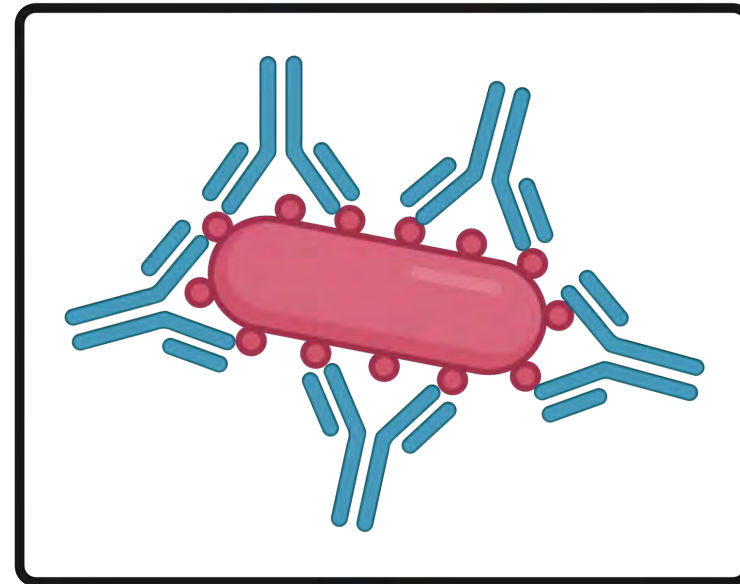


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IgG ANTIBODIES HELP CLEAR INFECTIONS



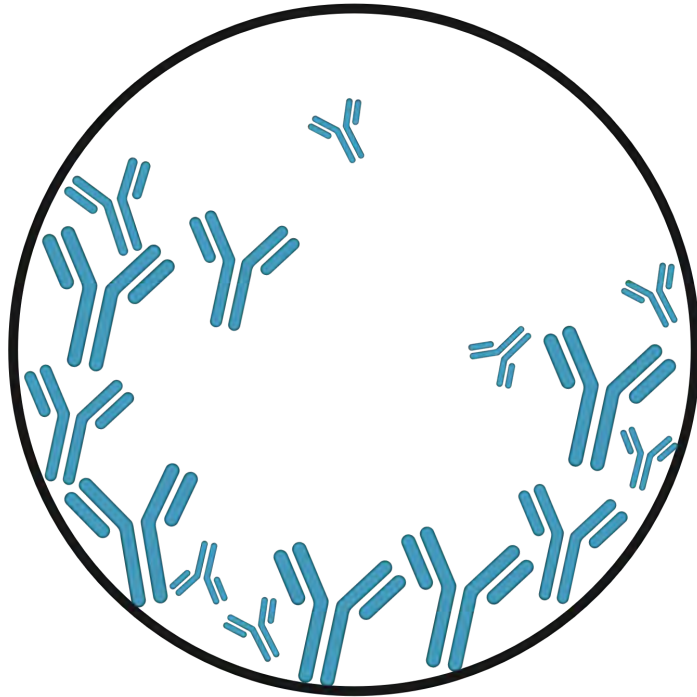
IgG Antibodies
Normal amount and function



Antibodies clearing bacteria
Effective immune response

Created by Jacob D. Soumerai with BioRender.com

IgG ANTIBODIES CAN BE REPLACED



Low IgG Antibody Level
"Hypogammaglobulinemia"

Two-thirds of patients with CLL

- Only some have recurrent infections
- Our approach is reactive. Give IgG antibody ("IVIG") if severe or recurrent infections

Why do some people have infections despite low-normal antibody levels, and others have no infections despite extremely low levels?

Can we do better?

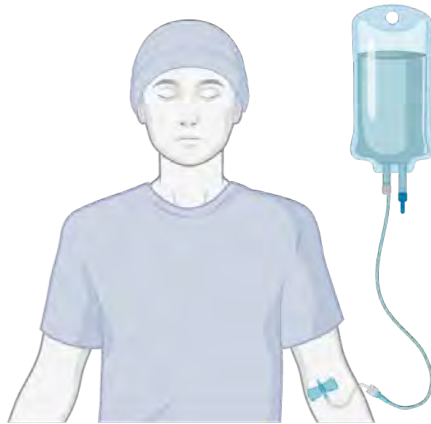
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CLL TREATMENTS IMPACT IMMUNITY

Chemotherapy

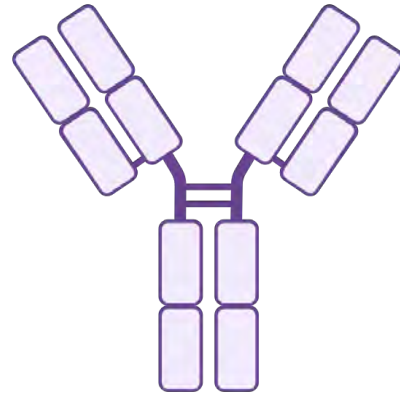
*Examples: Bendamustine
or Fludarabine*



Long-lasting impact
on immunity

Immunotherapy

*Examples: Obinutuzumab
or Rituximab*



Reduce B-cells and
antibody levels

Targeted therapies

Many examples:

*Ibrutinib
Acalabrutinib
Zanubrutinib*

Venetoclax

*Idelalisib
Duvelisib*

Complex interactions
with the immune system

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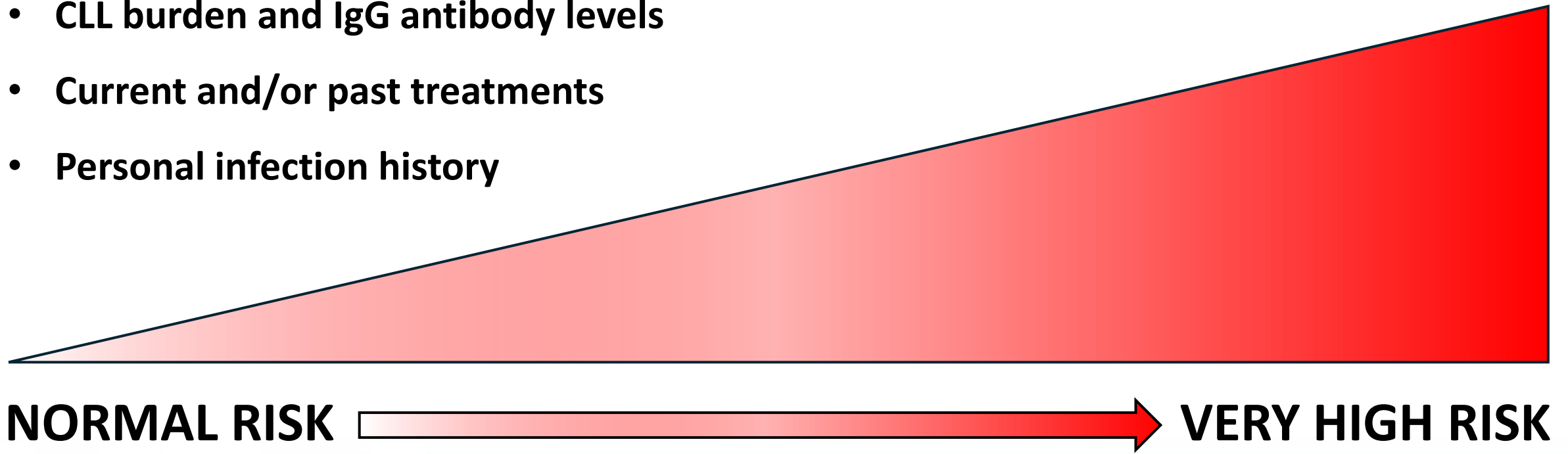
ESTIMATING INFECTION RISK IS DIFFICULT

- **Before 2020s: Chemotherapy era**
- **Early 2020s: Early phases of COVID19 pandemic**
- **What is the infection risk in patients with CLL who are diagnosed now and only receive modern therapies?**

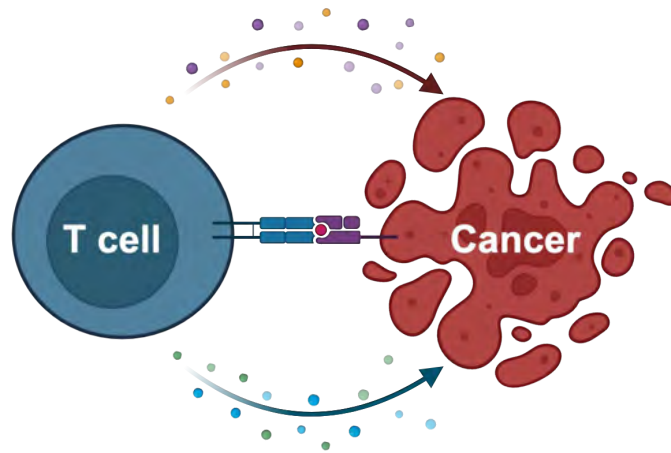


WHAT IS MY INDIVIDUAL INFECTION RISK?

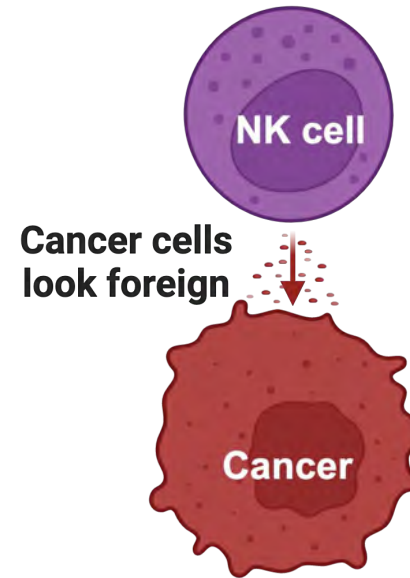
- Patient age and other conditions
- CLL burden and IgG antibody levels
- Current and/or past treatments
- Personal infection history



IMMUNE SYSTEM PREVENTS CANCERS



T cells kill cancer cells



NK cells detect anything "non-self" (e.g., cancer cells)

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CLL AND CANCER RISK

- **Increased risk of other cancers**
- **Skin cancers**
- **Most of our information comes from the chemotherapy era**
- **Routine age- and risk factor-guided cancer screening**
- **Dermatology for skin cancer screening**

Fedele, J Clin Oncol 2024; van der Straten, Blood Cancer J 2023; Kuma, Blood Cancer J 2023; Solomon, J Clin Oncol 2023



AUTOIMMUNE: IMMUNITY AGAINST “SELF”

- Immune system off-kilter (“dysregulation”)
- Autoimmune complications of CLL
 - Low red blood cells (blood cells that carry oxygen)
 - Low platelets (blood cells that form clots and prevent bleeding)
 - Low neutrophils (white blood cells that fight infections) (rare)
 - Other autoimmune conditions (rare)
- Often treated with steroids, but some require treatment of CLL

Barcellini, Haematologica 2006; Hamblin, Semin Oncol 2006

TAKEAWAYS

- Immune system can be off kilter (“dysregulated”)
- Infections, other cancers, and autoimmune complications
- Take all infections seriously and don’t wait to ask your healthcare team about management
- Talk to your doctor if you experience recurrent infections
- Cancer screening based on your age and risk factors
- Dermatologist regularly for full skin exams

Barcellini, Haematologica 2006; Hamblin, Semin Oncol 2006



SPEAKER

Andres Chang, MD, PhD

Instructor
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Department of Hematology and Medical Oncology



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**PREVENTING
INFECTIONS
AND IMMUNE
RECONSTITUTION**

LEARNING OBJECTIVES

- **To provide an overview of strategies to minimize frequency and severity of infections**
- **To discuss potential strategies to reconstitute the immune system**



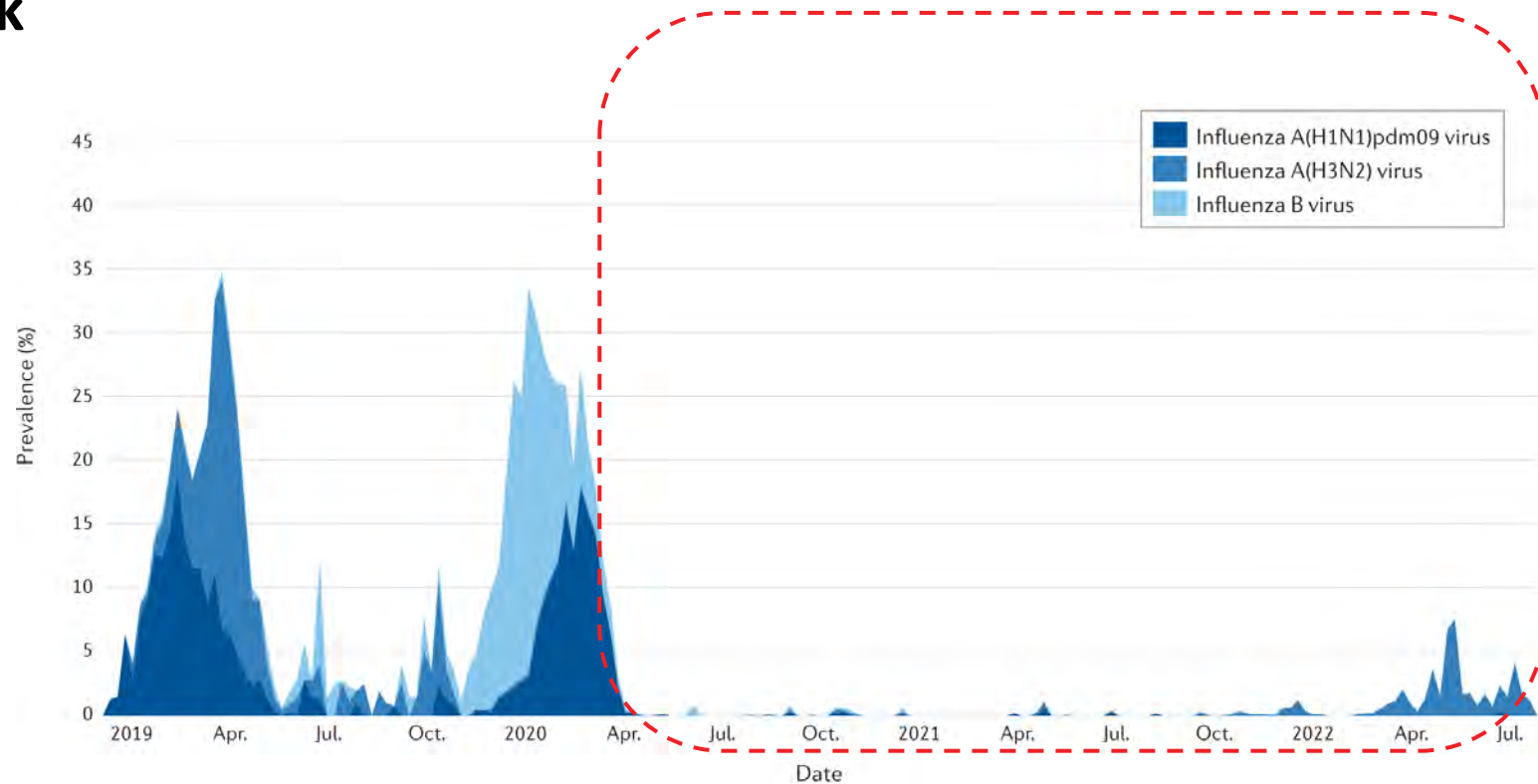
INFECTION PREVENTION

**“An ounce of prevention is worth a pound of cure”
-Benjamin Franklin**

“Common sense” measures work

- **Avoiding sick contacts**
- **Hand hygiene**
- **Masks**
- **Air quality improvement**
- **Community surveillance**
- **Public health measures**
- **Etc.**

Prevalence of Influenza in Seattle



Chow et al, Nat Rev Microbiol 2022



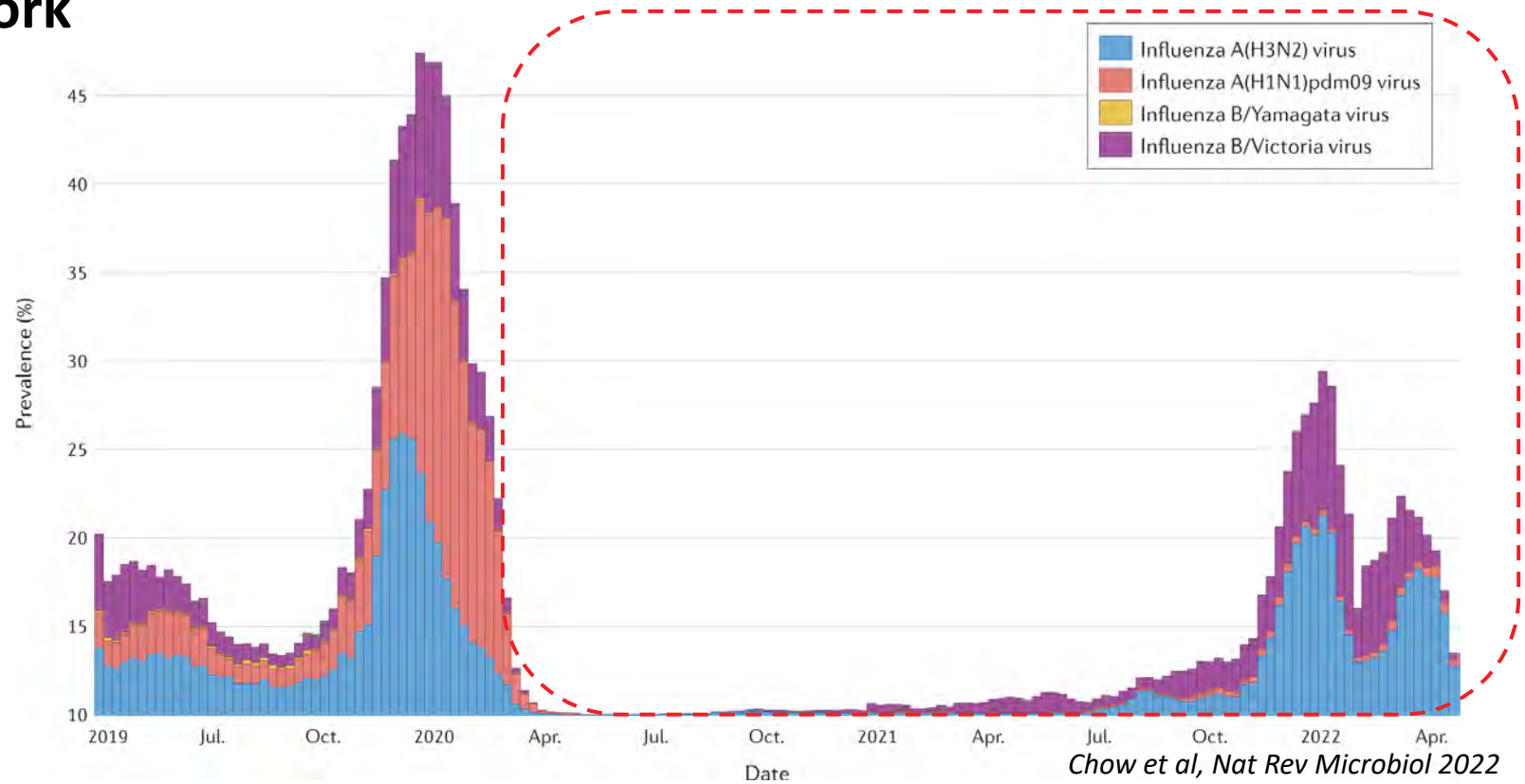
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- Etc.

Prevalence of Influenza Worldwide



Chow et al, Nat Rev Microbiol 2022

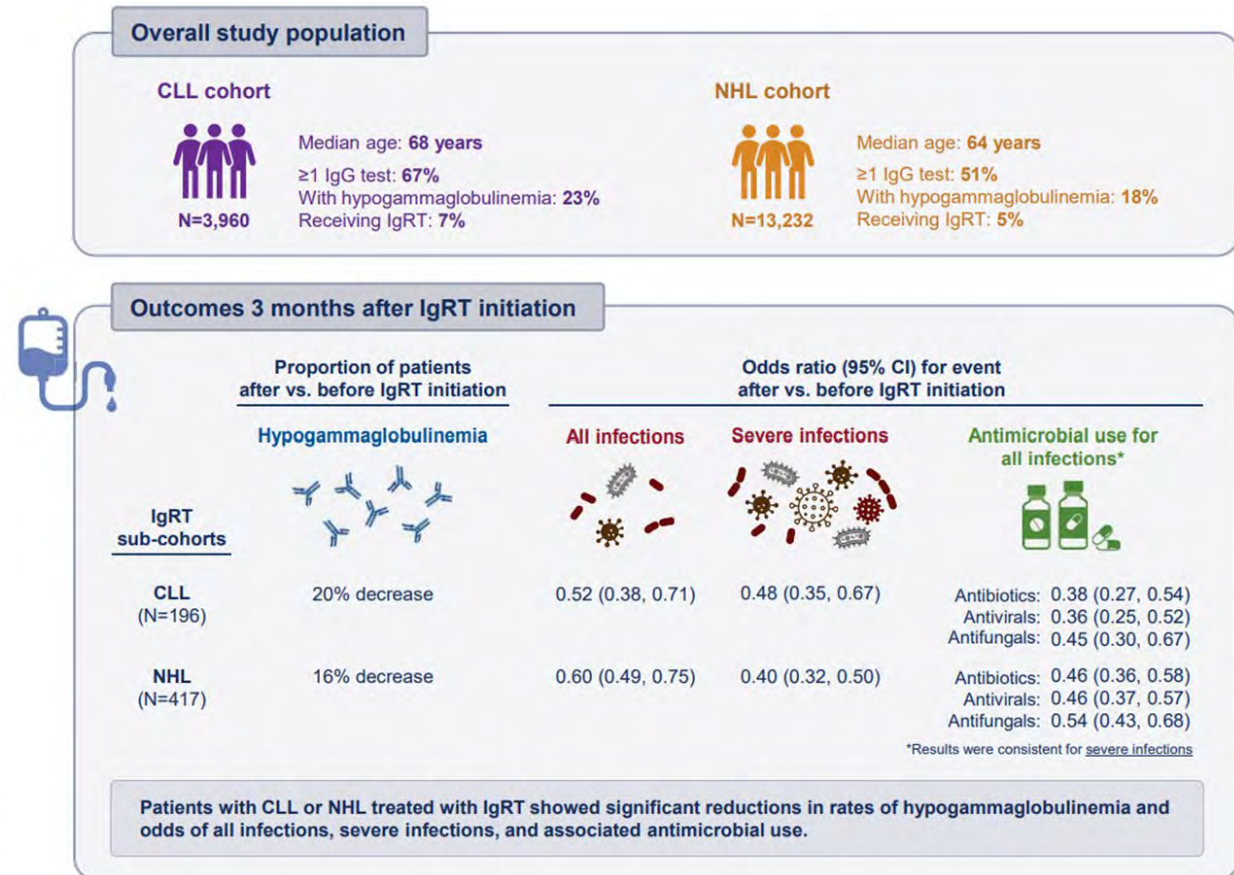
VACCINES

- **Suboptimal antibody responses to vaccines:**
 - Additional booster may help
 - T cell responses are less clear
 - Some response is better than none
- **Recommendations:**
 - Influenza, COVID, RSV, pneumococcus, VZV/shingles, Tdap
 - Vaccinate close contacts
 - Avoid live vaccines during periods of significant immunosuppression



PROPHYLAXIS

- AZD7442 no longer effective nor available
- Pemivibart – monoclonal antibody
 - EUA authorization
 - No publication out yet
- Sipavibart – monoclonal antibody
 - No EUA authorization
 - No publication out yet
- *IVIG – polyclonal antibodies
 - PRO-SID trial ongoing
- *Acyclovir, valacyclovir, entecavir, trim/sulfa, antifungals, etc.



MANAGEMENT OF INFECTIONS

- **Prompt initiation of therapy is key**
 - Seek care with early signs of infection
- **Influenza: oseltamivir**
- **COVID: remdesivir, nirmatrelvir/ritonavir, molnupiravir, others**
- **Bacterial infections: antibiotics**



REVERSING IMMUNODEFICIENCY

- **BTKi therapy may improve T cell function**
 - However, BTKi reduces antibody responses
- **PI3K inhibitors may also improve T cell function**
 - However, high risk of opportunistic infections
- **More studies are needed to clarify mechanisms of immunodeficiency in CLL**



CONCLUSIONS

- **Prevention is better than treatment**
 - “Common sense” measures
 - Vaccines (self and closed contacts)
 - Antimicrobial prophylaxis
 - **Preexposure prophylaxis*
 - **IVIg*
- **Early treatment of confirmed infections**
- **More studies are needed to understand mechanisms of immunosuppression and how to reverse this**



AUDIENCE Q&A



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Your Medicare Guide: Tackling Costs and Answering Your Questions
on September 9th

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