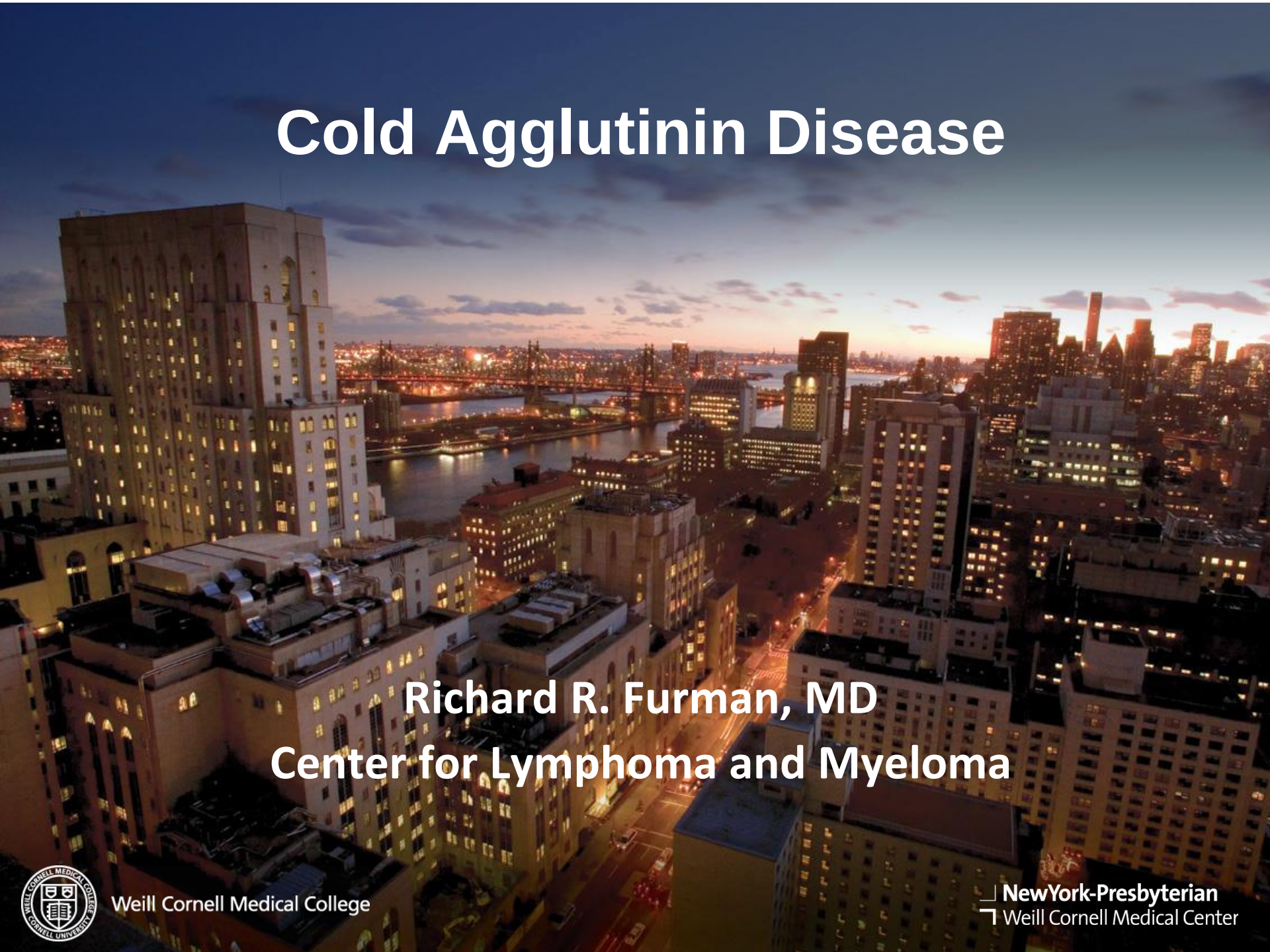
Cold Agglutinin Disease



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Topics for Discussion

1. Cold Agglutinins
2. Primary vs Secondary CAD
3. Symptoms
4. Therapy

Cold Agglutinin Disease: Definitions

- **Primary Cold Agglutinin Disease (aka Cold Agglutinin Disease):**
  - **distinct B-cell lymphoproliferative disease with clonal cells producing a cold agglutinin causing complement mediated hemolysis.**

- **Secondary Cold Agglutinin Disease: (aka Cold Agglutinin Syndrome-CAS)**
  - **cold agglutinin induced hemolytic anemia with an associated condition, such as infection (EBV, mycoplasma), autoimmune disorder, overt evidence of lymphoma**

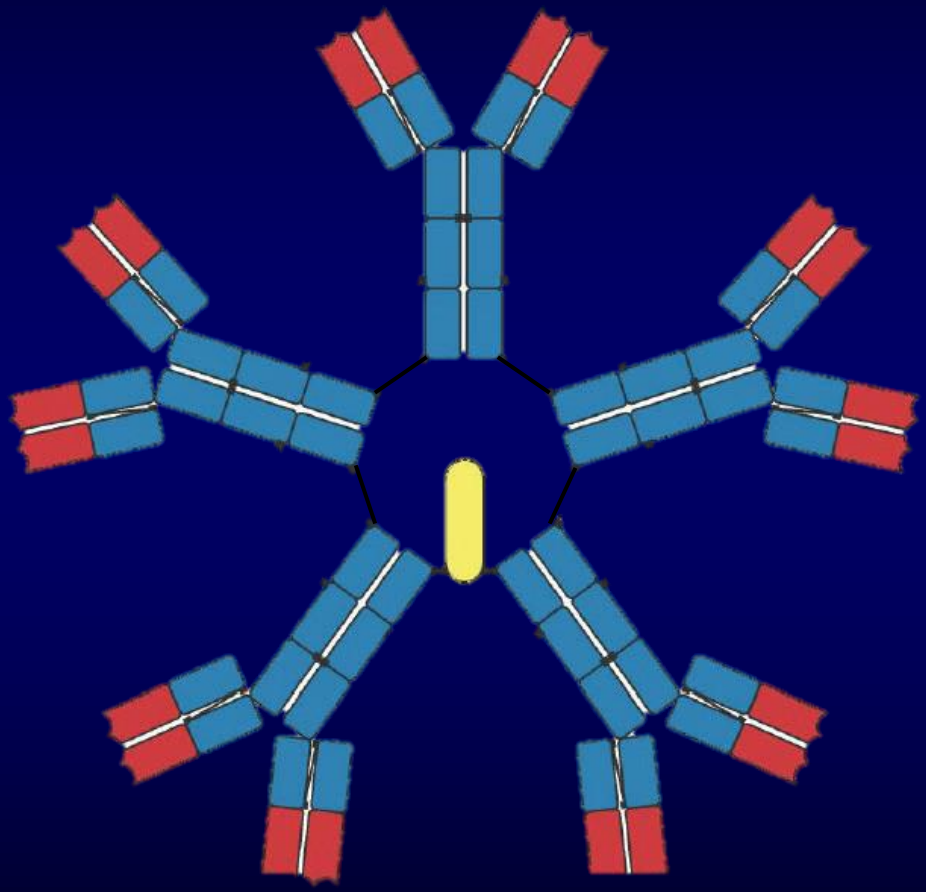
- **both can be clonal LPDs with monoclonal IgM**

Cold Agglutinin Disease: Definitions (more)

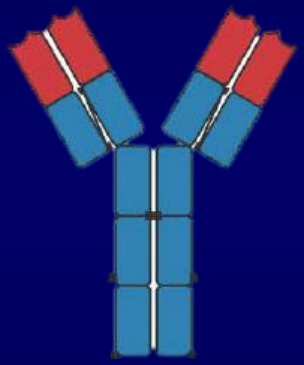
- **Cold agglutinin Disease:**
  - **autoimmune hemolytic anemia (AIHA) with**
    1. **a direct antiglobulin test (DAT, Coombs) positive for C3d and negative of weakly positive for IgG**
    2. **cold agglutinin titer of 64 or greater at 4ºC**

- **Cold Agglutinin:**
  - **IgM kappa antibody directed again "I" antigen**
  - **Naturally occurring: polyclonal, active at 4ºC**
  - **Acquired: monoclonal, active at >30ºC**
    - **encoded by VH4-34 immunoglobulin gene segment**

IgM versus IgG

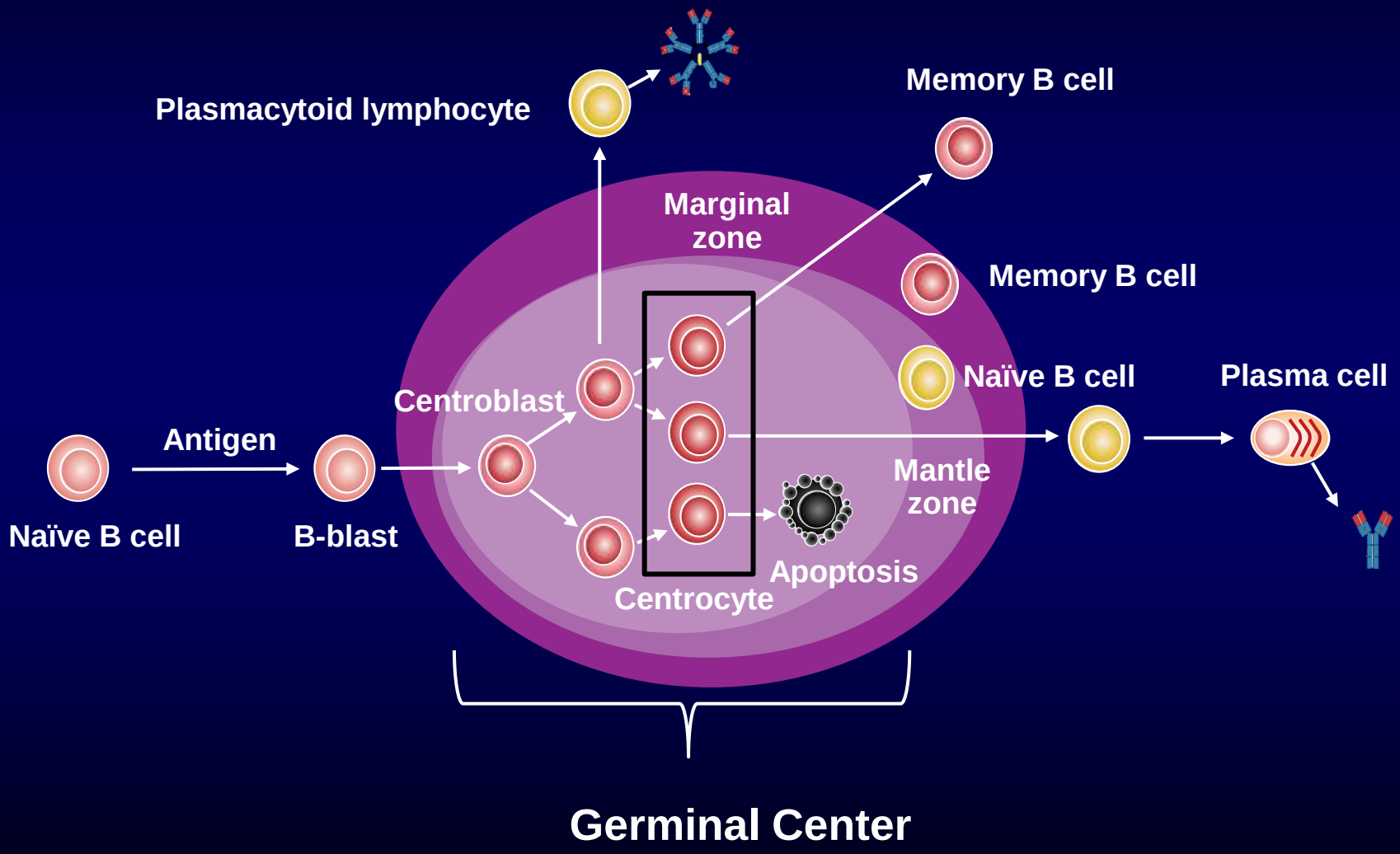


IgM



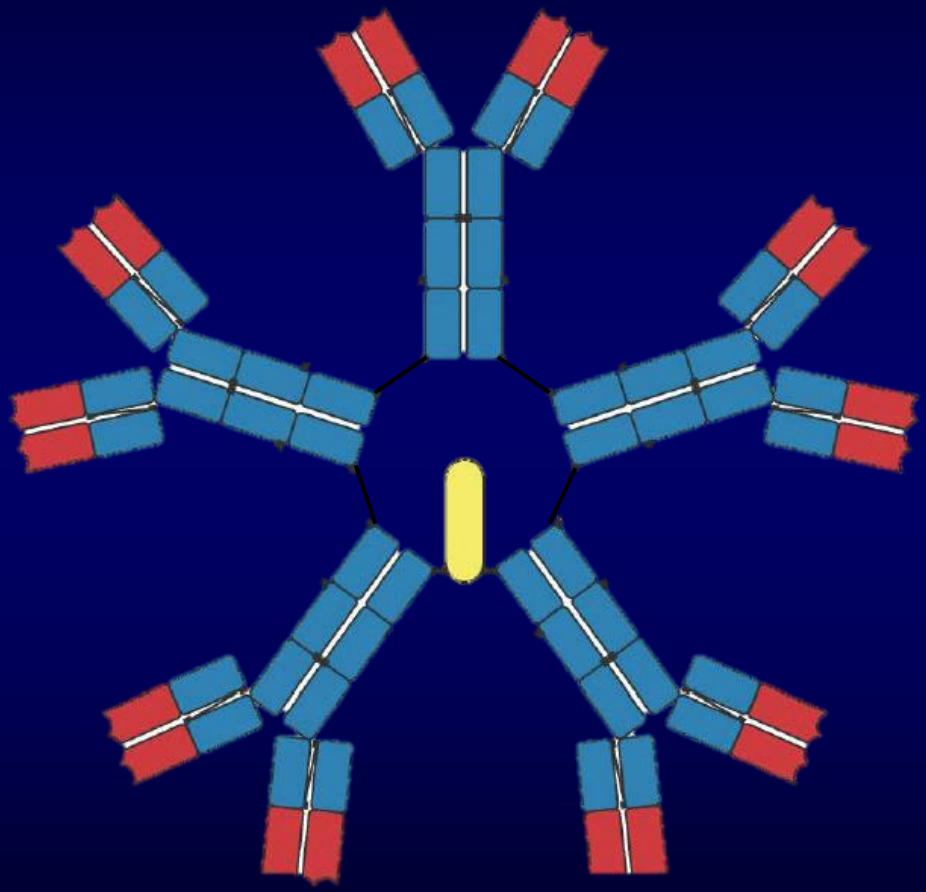
IgG

Normal B Cell Ontogeny

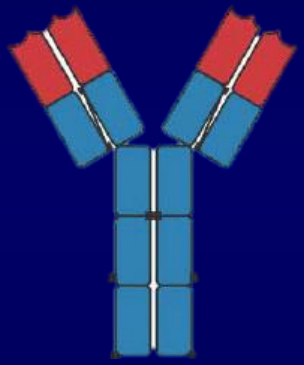


Kuppers R. Nat Rev Cancer 2005; 5:251

IgM versus IgG

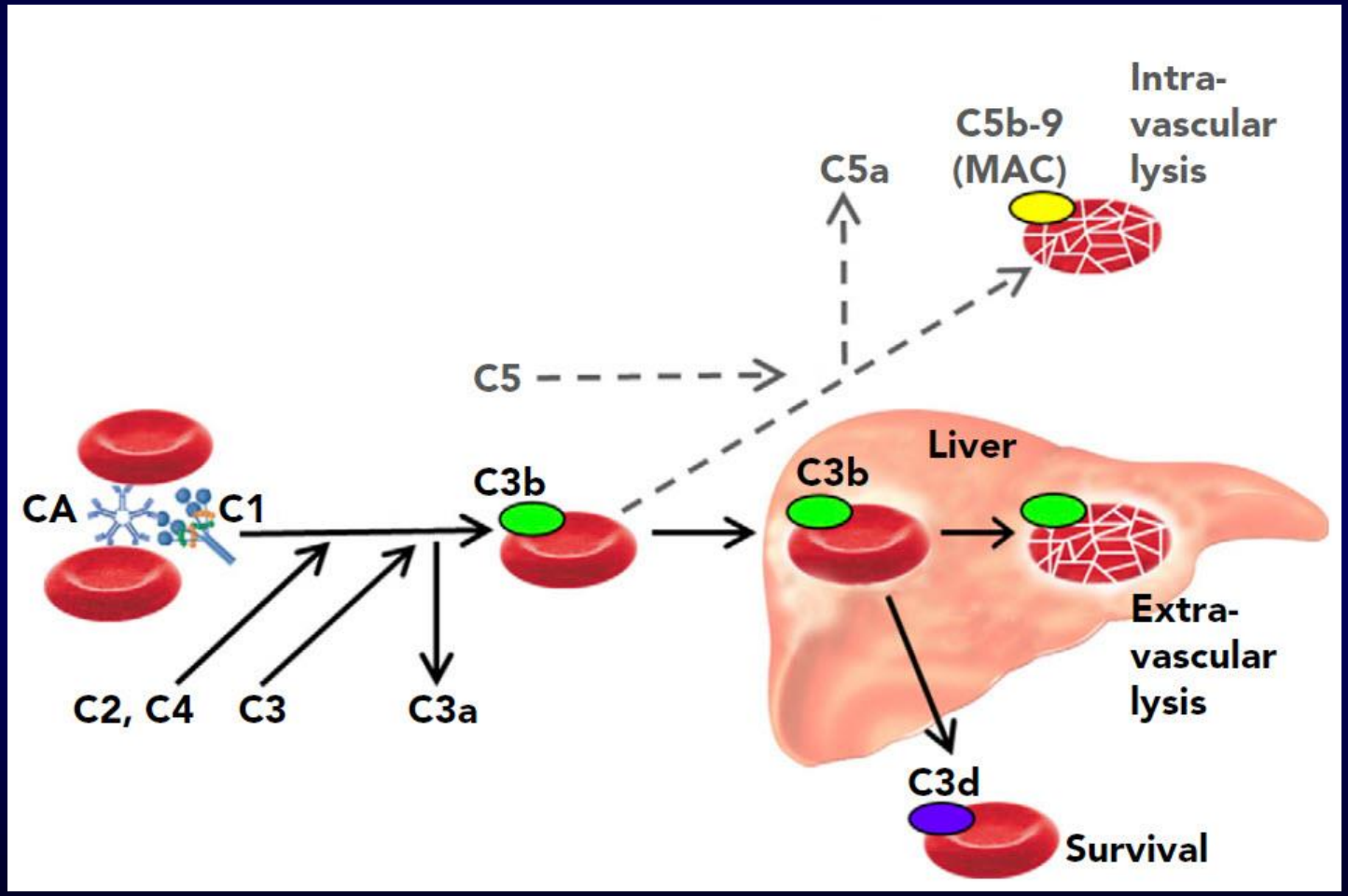


IgM

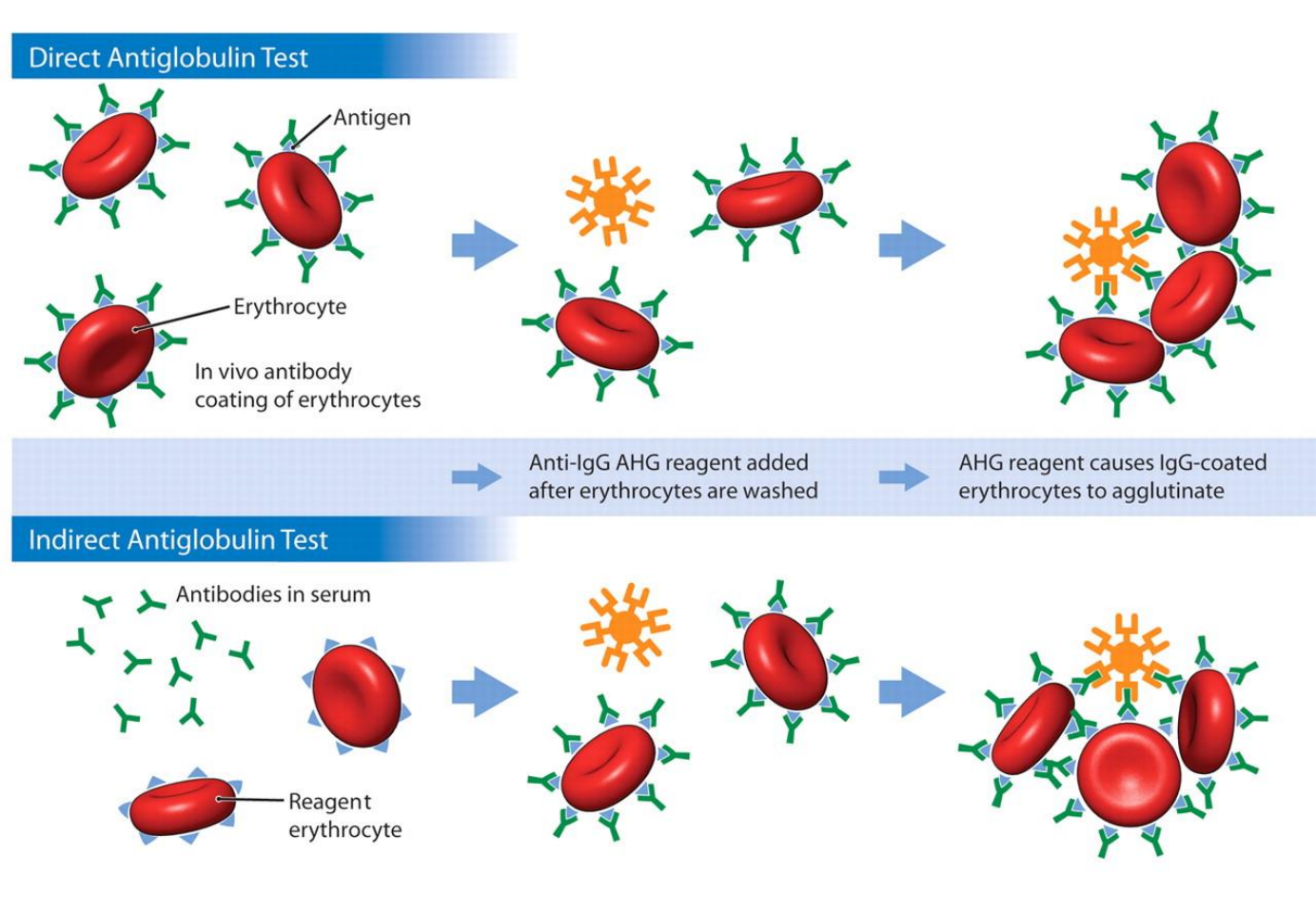


IgG

CAD: Mechanism of Hemolysis



Direct Antiglobulin Test (DAT) "Coombs Test"



Cold Agglutinin Disease

- incidence: 1 in 1,000,000
- median age of diagnosis: 67 years
- Presentation (non-clinical):
  - agglutination on routine laboratory assessment
  - large mcv
  - calculated hematocrits unreliable
- Presentation (clinical):
  - cold-induced circulatory symptoms seen in 90%
  - acrocyanosis
  - Raynaud-like symptoms
  - hemolytic anemia
  - livedo reticularis
  - severity of agglutination symptoms do not correlate with severity of hemolysis

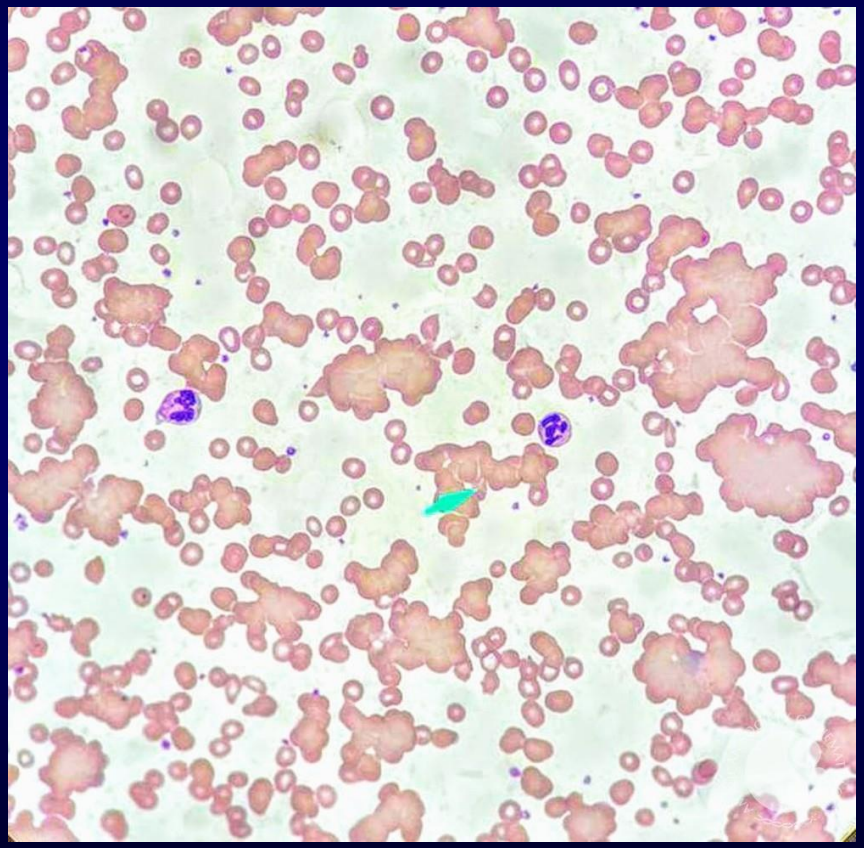
Cold Agglutinin Disease

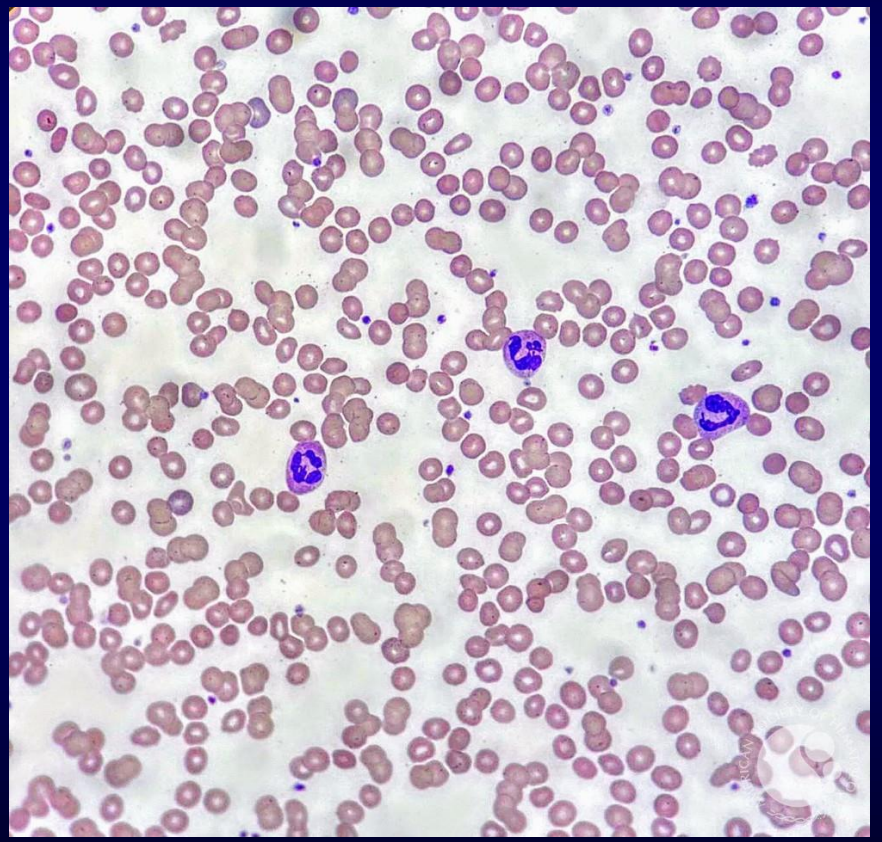
- **Anemia:**
  - **often mild to moderate (Hg 8.0 – 10.4 g/dL)**
  - **often compensated hemolysis**
  - **unclear if increased risk of venous or arterial thrombotic disease exists**
  - **see exacerbation of anemia during febrile illnesses and transfusion of plasma products**

Evaluation

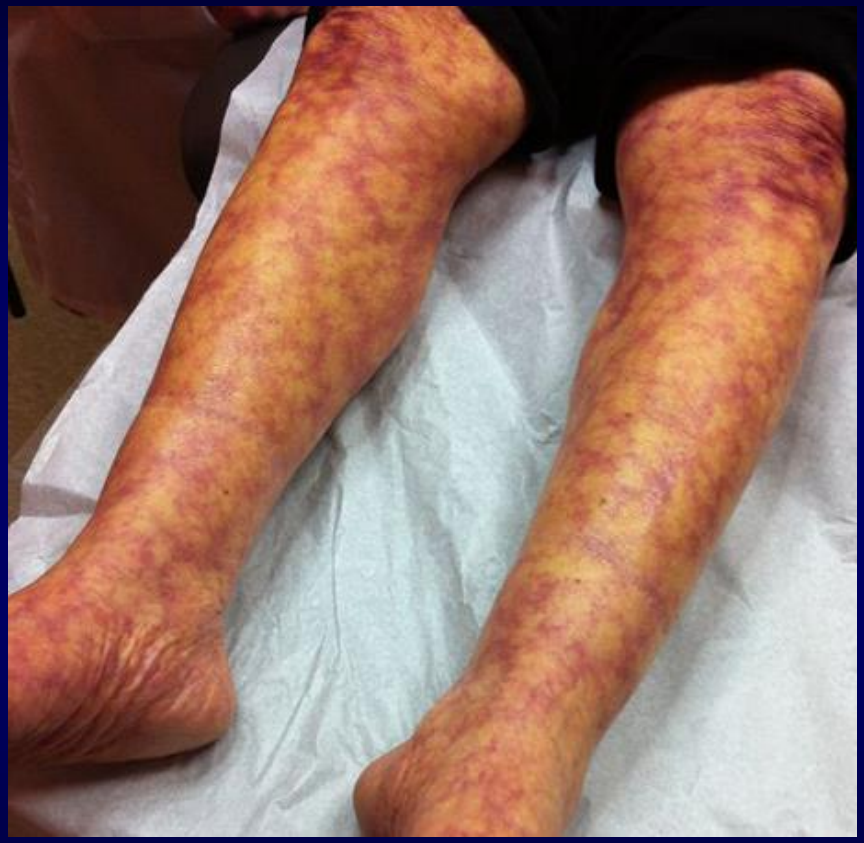
- CA titer (thermal amplitude not performed)
- DAT
- reticulocyte count
- haptoglobin
- PBS review
- serum immunofixation electrophoresis (IFE)
- Bone marrow biopsy and aspirate

Agglutination on Blood Smear





Livedo Reticularis



Raynaud Phenomena

Indications for Treatment

- **Symptom based**
- **Attitude toward treatment probably to conservative**

Treatment:
B cell vs Complement Directed Therapy

B cell directed

Advantages:

1. attack production of cold agglutinin
2. remitting
3. treat agglutination symptoms

Disadvantages:

1. toxicity to normal B cells and / or bone marrow cells
2. lower response rates

Complement Directed

Advantages:

1. quick onset
2. very tolerable
3. high response rates

Disadvantages:

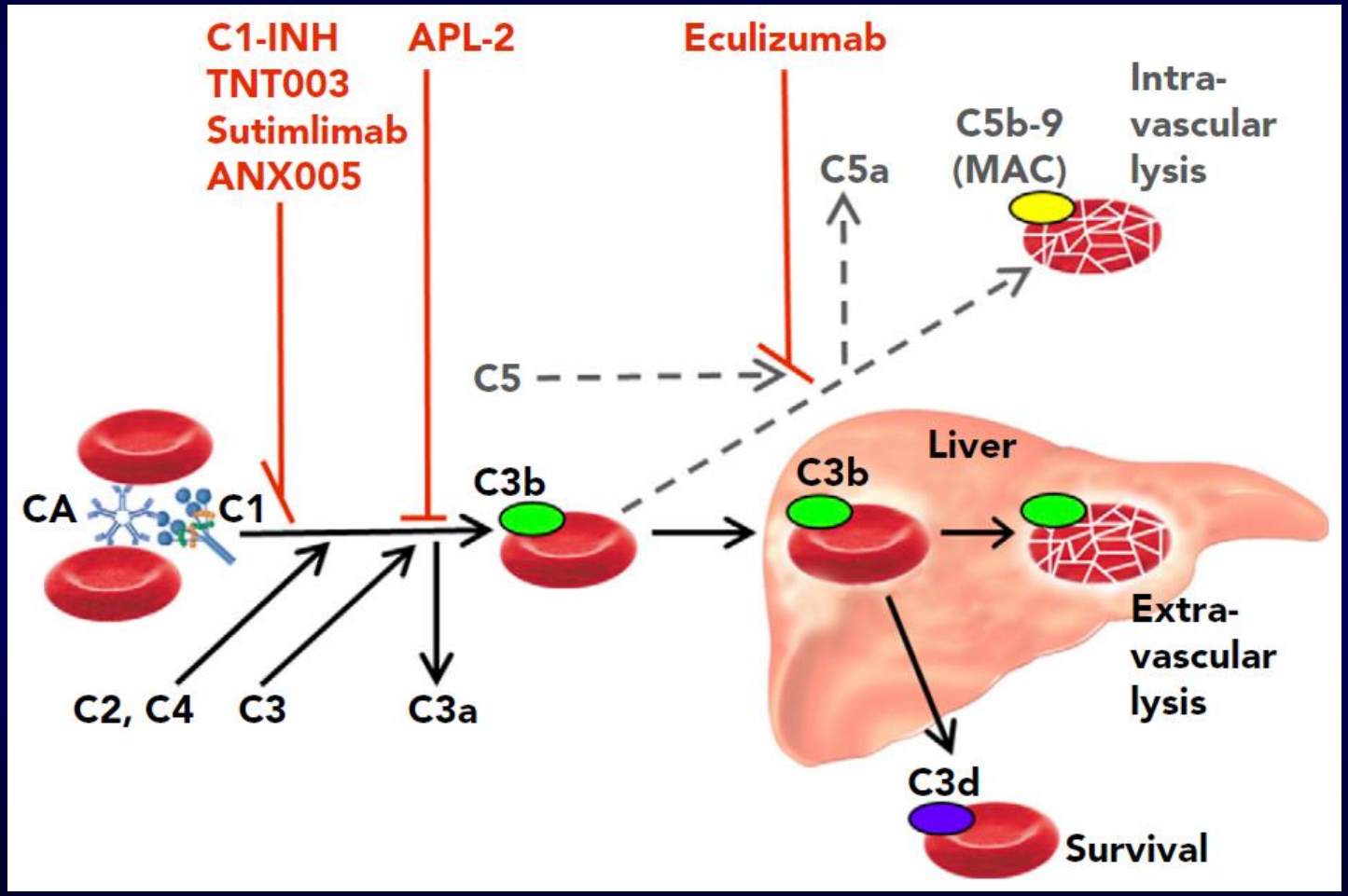
1. continued treatment required
2. do not address agglutination symptoms

Treatment

- **B cell directed:**
  - **rituximab: ORR: 45-54%**
  - **fludarabine + rituximab (FR): ORR=76%; CR=21%, PR=55%**
  - **bendamustine + rituximab (BR): ORR=71%; CR=40%, PR=31%**
  - **bortezomib: ORR=31%; CR=15.5%, PR=15.5% (refractory patients)**

- **Complement directed:**
  - **eculizumab (anti-C5): 9/13 transfusion independence**
  - **sutimlimab (anti-C1s): 70% response rate**
  - **APL-2 (pegcetacoplan): in study**
  - **ANX005 (anti-C1q): in study**
  - **“plasmapheresis”**

Complement Directed Therapies

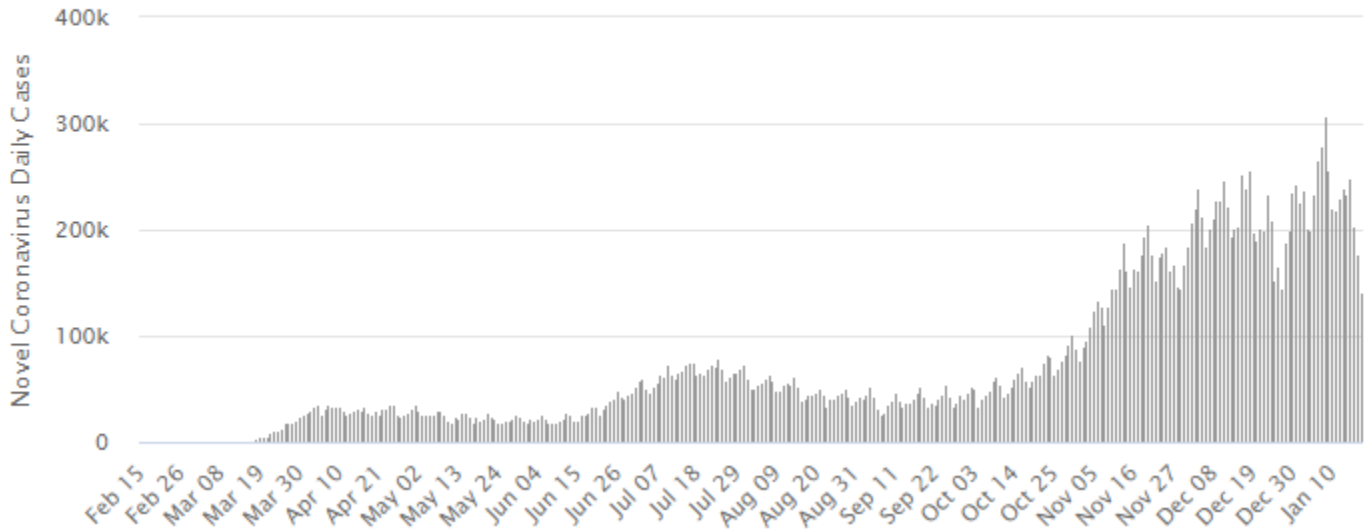


COVID-19: Statistics

(worldometers.com/coronavirus accessed 01/19/21)

	Cases	Deaths
US	**24,626,376**	**408,620**
Worldwide	**96,009,891**	**2,049,348**

United States: Daily New Cases



COVID-19 in Cancer Patients

- Preliminary reports indicate patients with malignancy have inferior outcomes
  - In China:
    - case fatality rate: cancer vs entire population: 5.6% vs 2.3%
    - cancer patients excess OR = 2.17 for death

- UK Coronavirus Cancer Monitoring Project (UKCCMP)
  - Largest prospective database of COVID-19 in patients with cancer
  - 800 patients with cancer and documented, symptomatic COVID-19
    - 22% lymphoma or other hematologic
  - Presenting symptoms: 61%: fever, cough, SOB
  - Mortality rate=28%, but ICU admission rate=6%
  - No significant difference in mortality for those receiving active treatment

Wu Z. JAMA 2020; 323:1239. Dai M. Cancer Dis 2020; 10:783. Lee LYW. Lancet 2020; 395:1919

COVID-19 in Patients with LPDs

- Data indicates immune system important in causing complications
  - cytokine storm, complement activation
- Factors impacting COVID-19 in LPD patients:
  1. Immune dysfunction
     - Immune dysfunction: protective vs harmful?
     - T vs B cell dysfunction?
     - no COVID-19 immunity in IV IG
  2. Advance age
  3. Morbidity due to interruption of therapy

COVID-19 Summary

- published data only examined symptomatic patients
- bias in those tested
- no age match comparator

COVID-19 Therapeutics

Severe COVID-19 pathophysiology characterized by:

1. **viral replication**
2. **complement activation**
3. **coagulopathy**
4. **cytokine storm: IL-1, IL-6, GM-CSF**

COVID-19 Therapeutics

Possible interventions:

1. **remdesivir: viral replication**
2. **dexamethasone: cytokine production**
3. **anticoagulation**
4. **bamlanivimab (Eli Lilly)**
5. **casirivimab + imdevimab (Regeneron)**
6. **convalescent plasma**

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7. **eculizumab / ravulizumab: complement**
8. **anti-cytokine therapy**
   - **anakinra (IL-1), sarilumab/tocilizumab (IL-6), mavrilimumab (GM-CSF)**
     - **sarilumab trial halted; anakinra and mavrilimumab on-going**
   - **BTKi: ibrutinib, acalabrutinib, zanubrutinib**