

Cold Agglutinin Disease

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Topics for Discussion

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

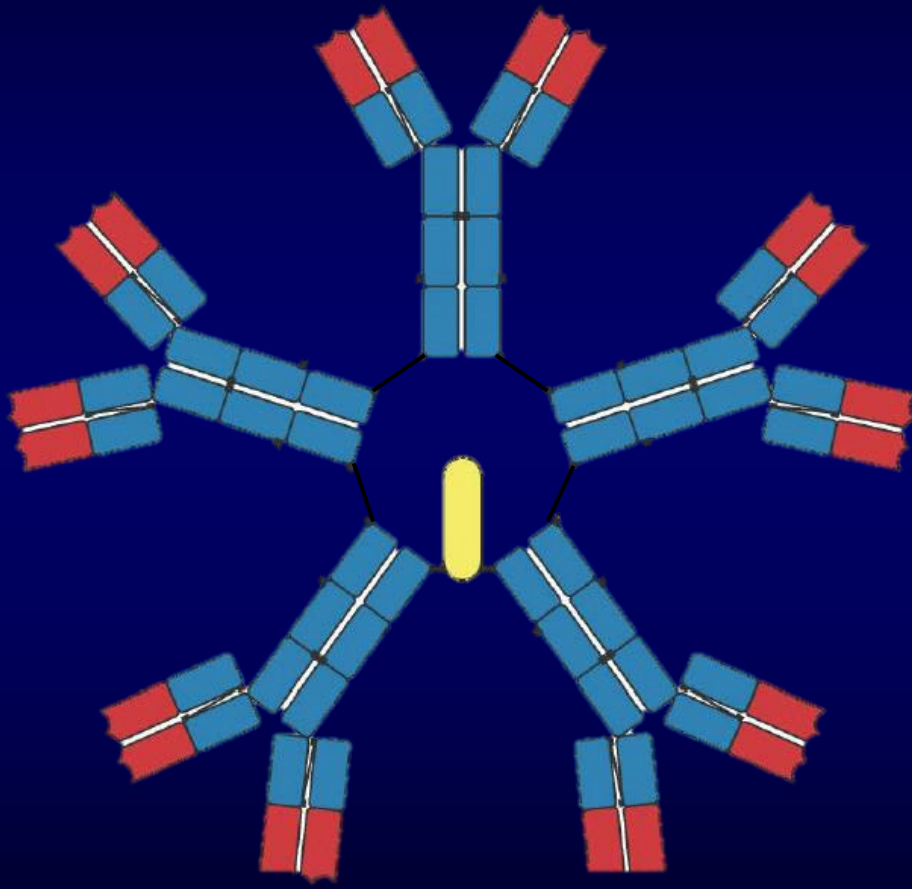
Cold Agglutinin Disease: Definitions

- **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**

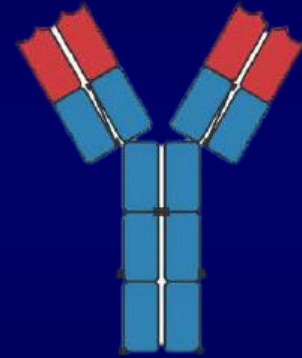
Cold Agglutinin Disease: Definitions (more)

- **Cold agglutinin Disease:**
 - autoimmune hemolytic anemia (AIHA) with
 1. a direct antiglobulin test (DAT, Coombs) positive for C3d and negative or weakly positive for IgG
 2. cold agglutinin titer of 64 or greater at 4°C
- **Cold Agglutinin:**
 - IgM kappa antibody directed against “I” antigen
 - Naturally occurring: polyclonal, active at 4°C
 - Acquired: monoclonal, active at >30°C
 - encoded by VH4-34 immunoglobulin gene segment

IgM versus IgG

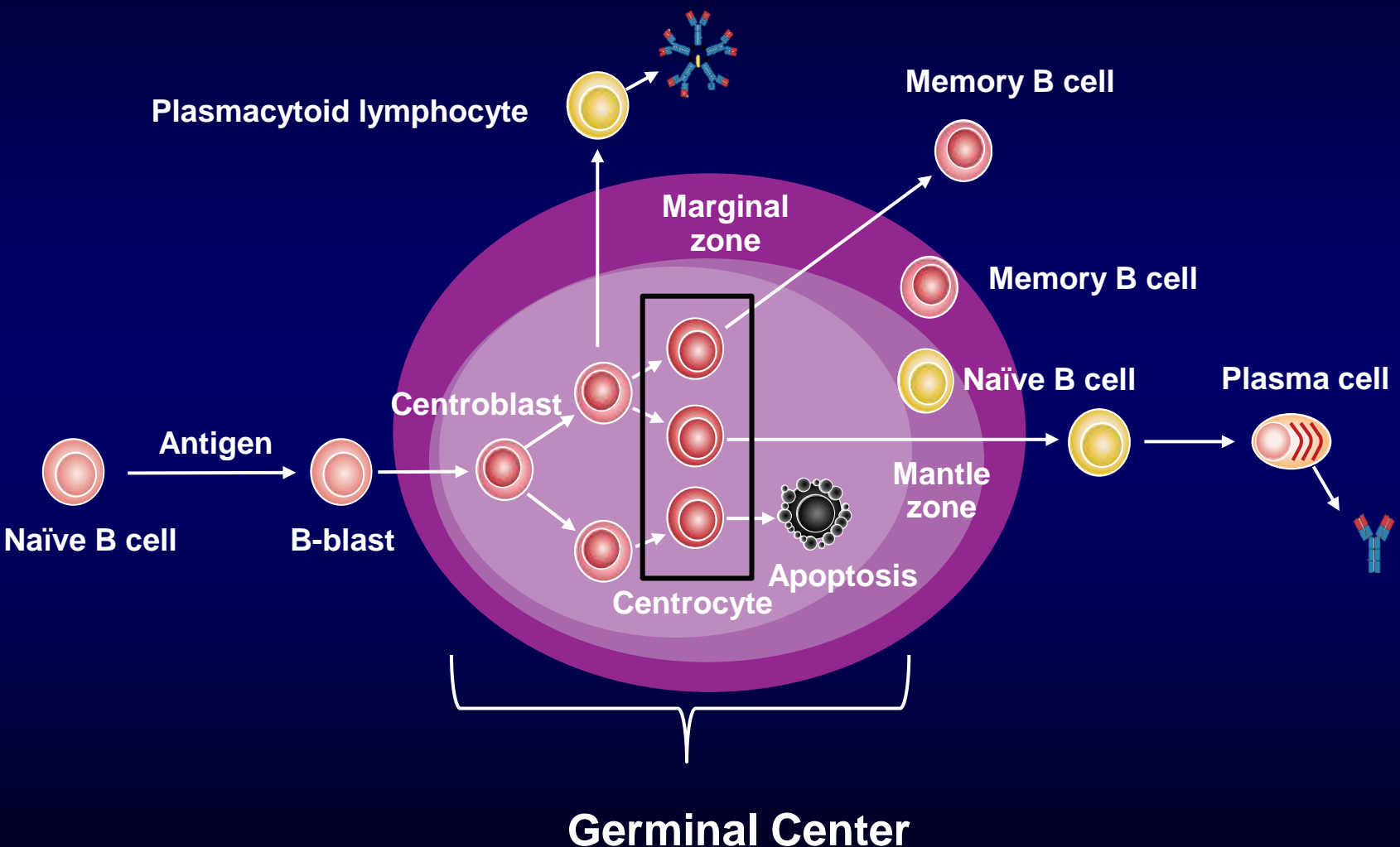


IgM

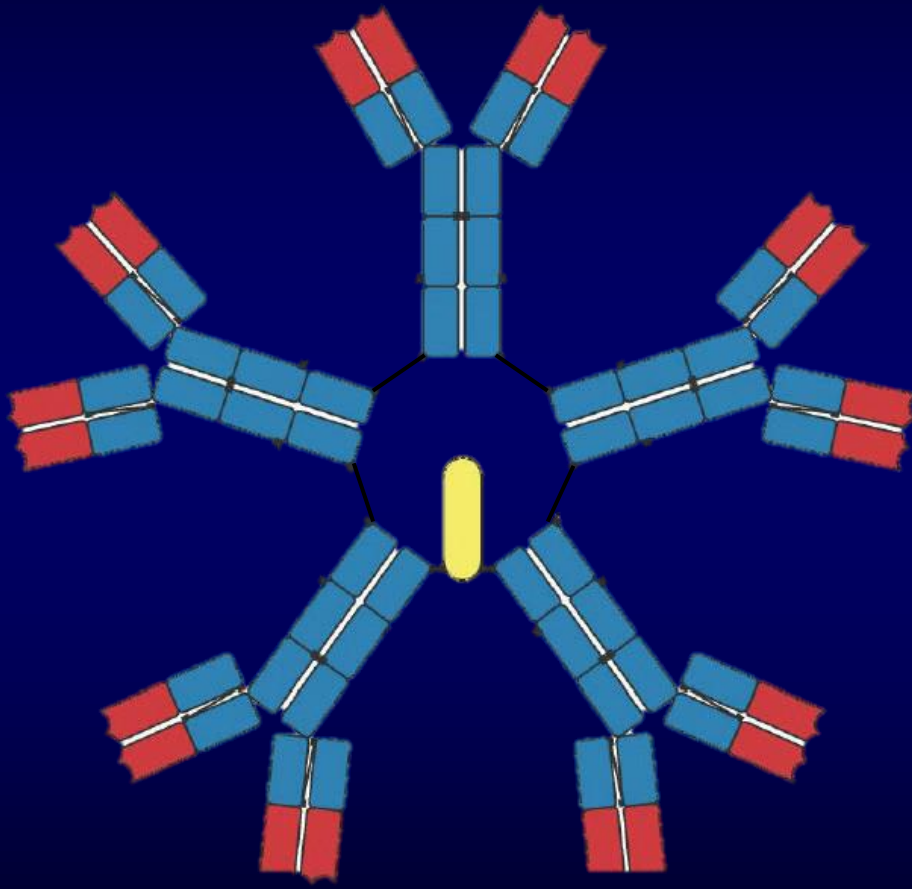


IgG

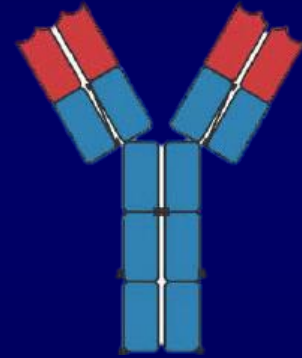
Normal B Cell Ontogeny



IgM versus IgG

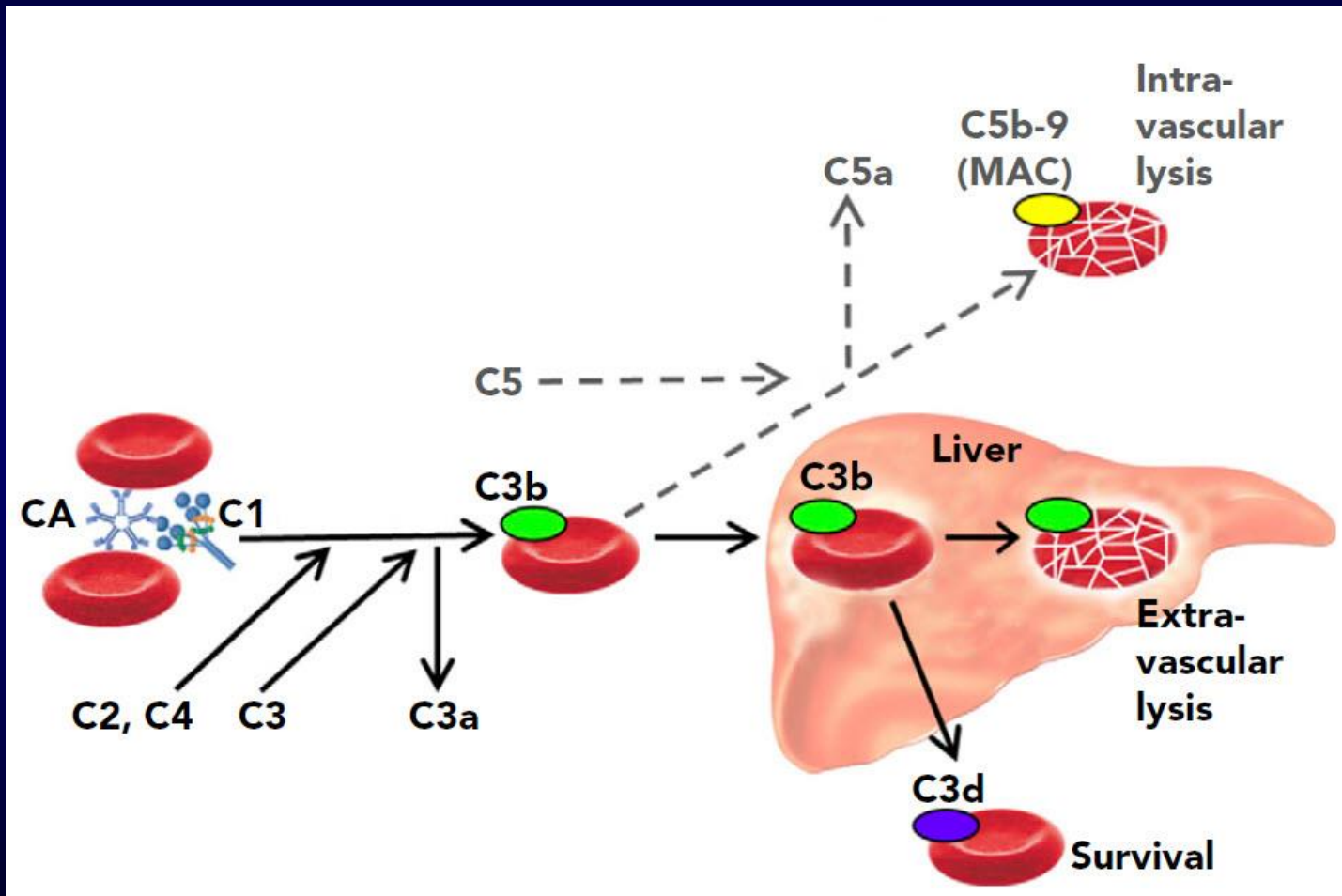


IgM

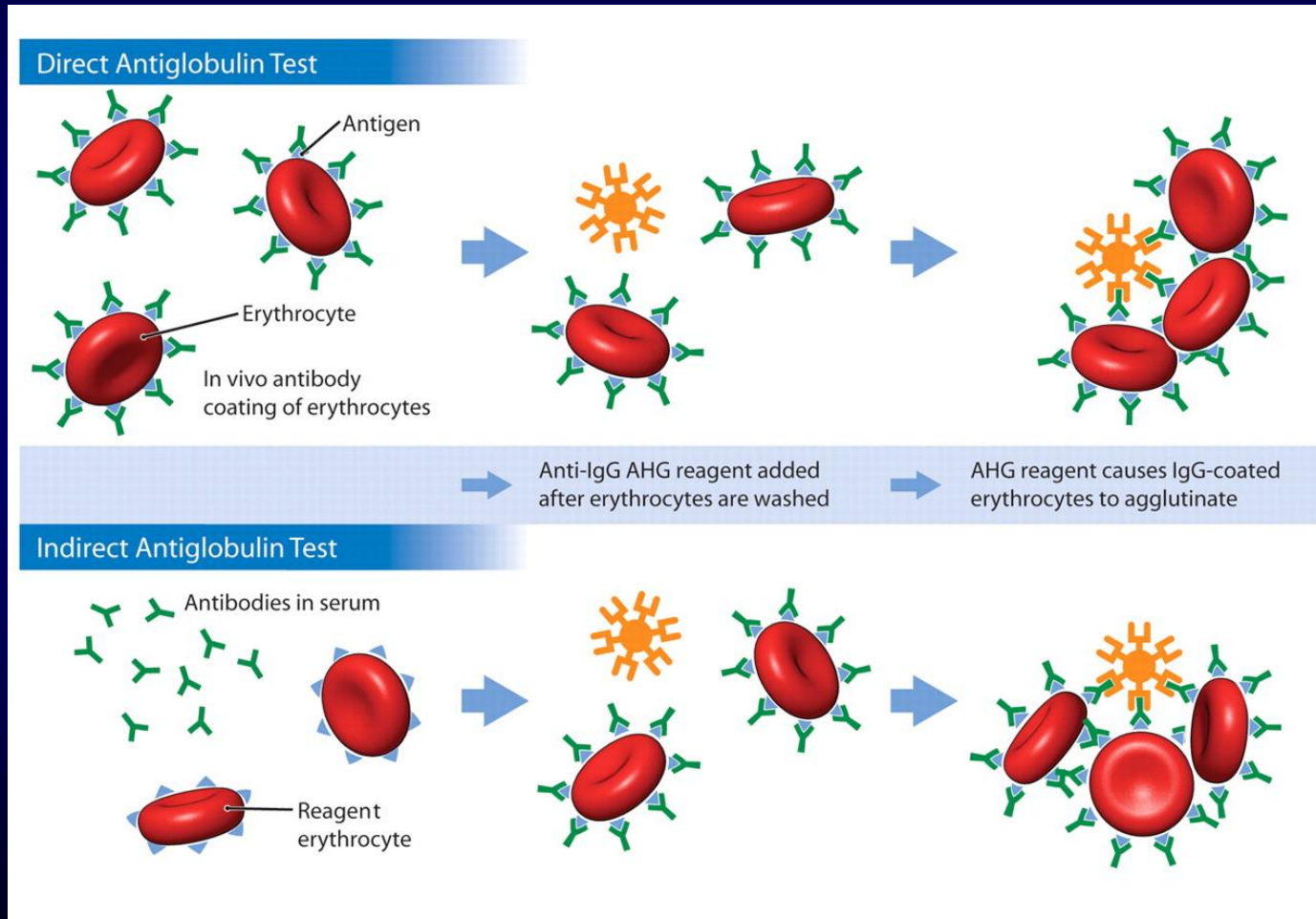


IgG

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**

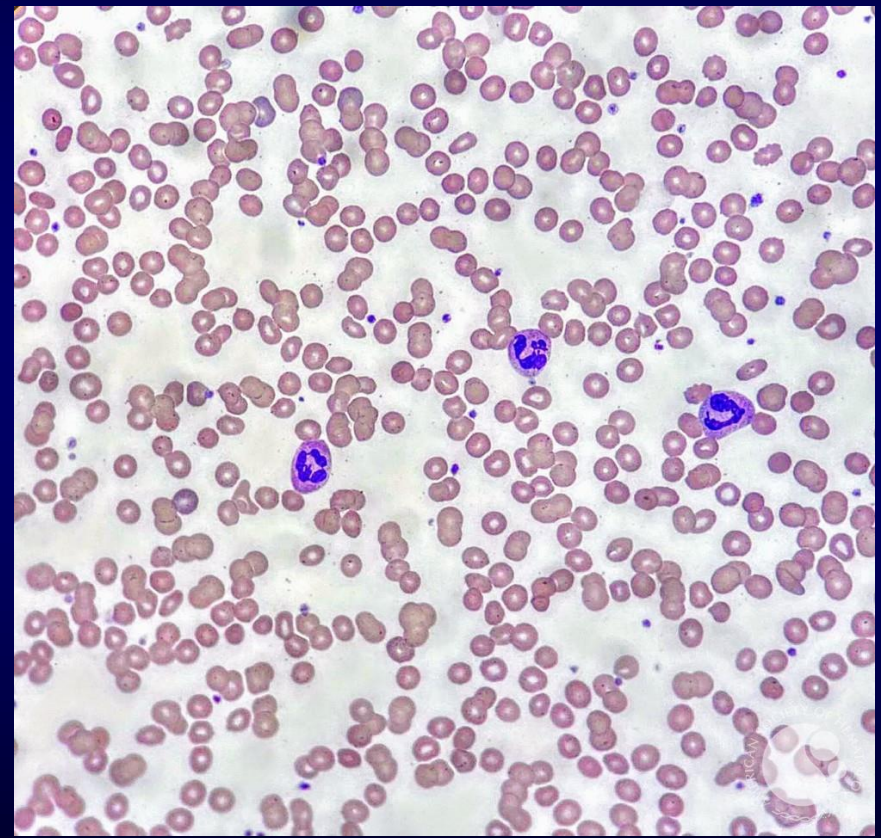
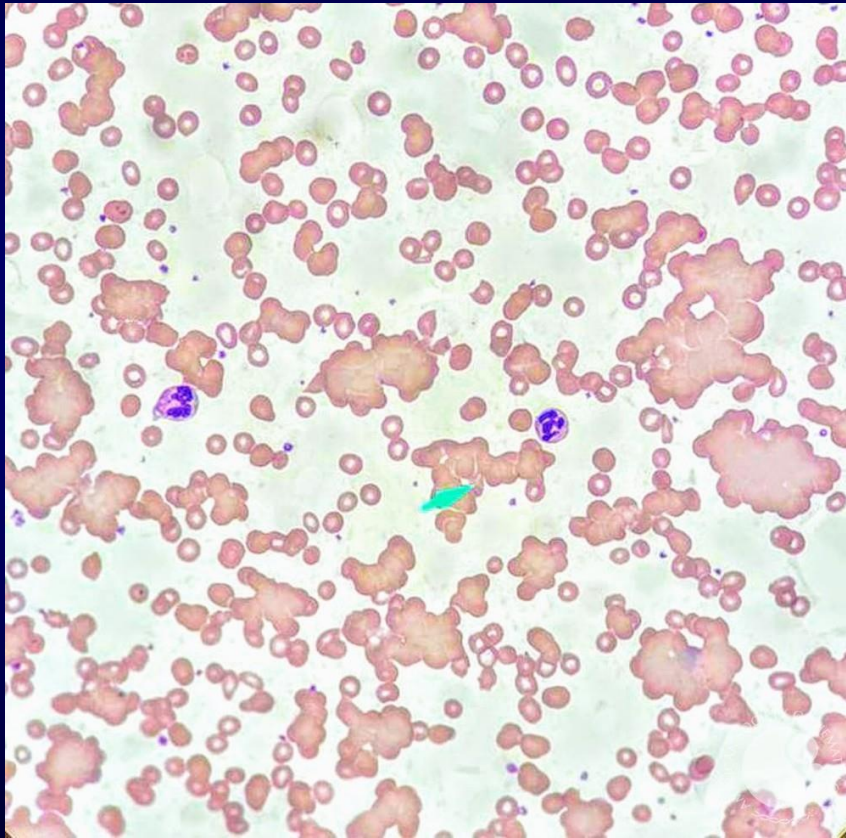
Cold Agglutinin Disease

- **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

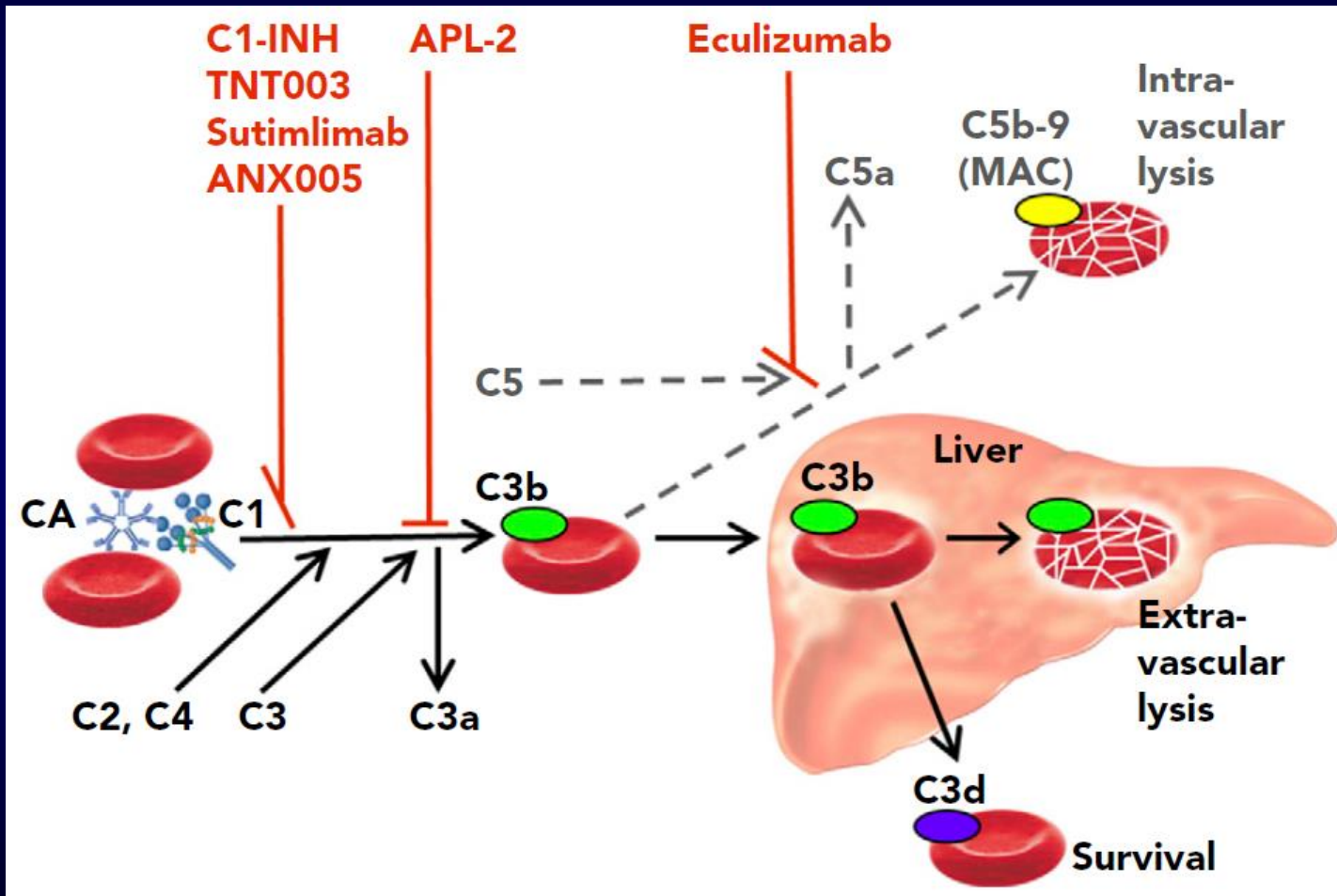
Disadvantages:

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

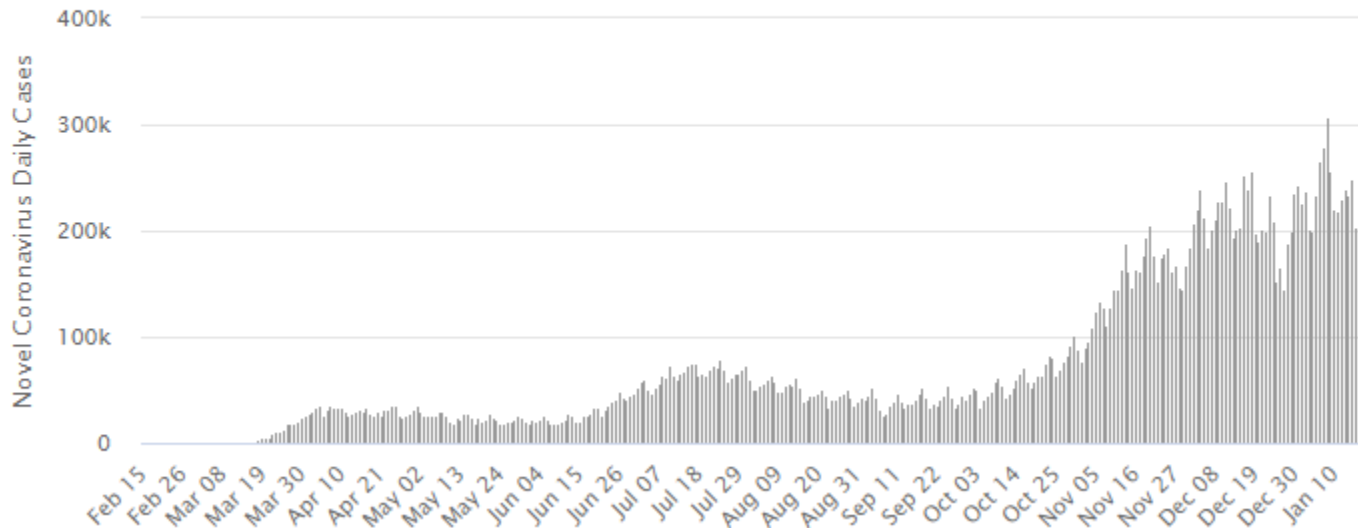


COVID-19: Statistics

(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**

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
-
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