Complement Deficiencies

Kate Sullivan
Children's Hospital of Philadelphia

Colorado Springs circa 1960

Colorado Springs yesterday

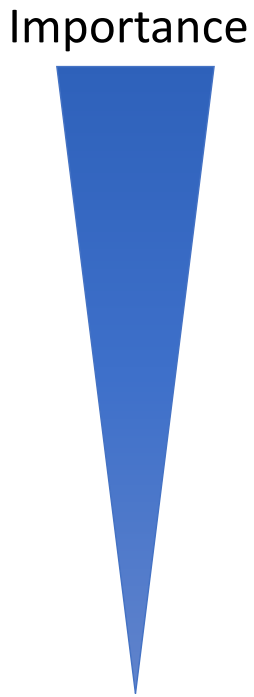
Outline

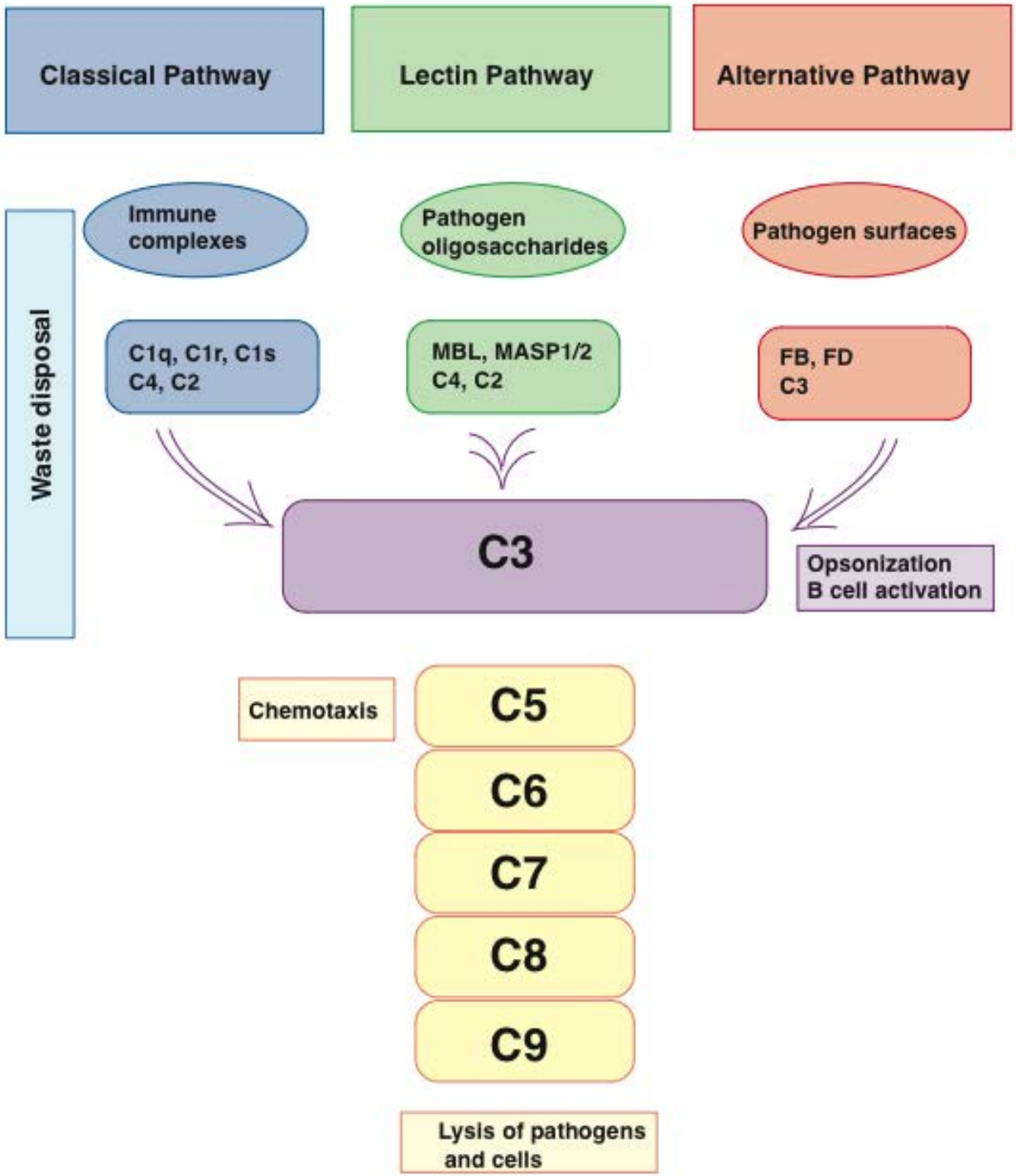
- Complement rocks!
- Complement deficiencies
  - Early complement component deficiencies
  - Terminal complement component deficiencies
  - Regulatory component deficiencies
- Hereditary angioedema
- Secondary deficiencies

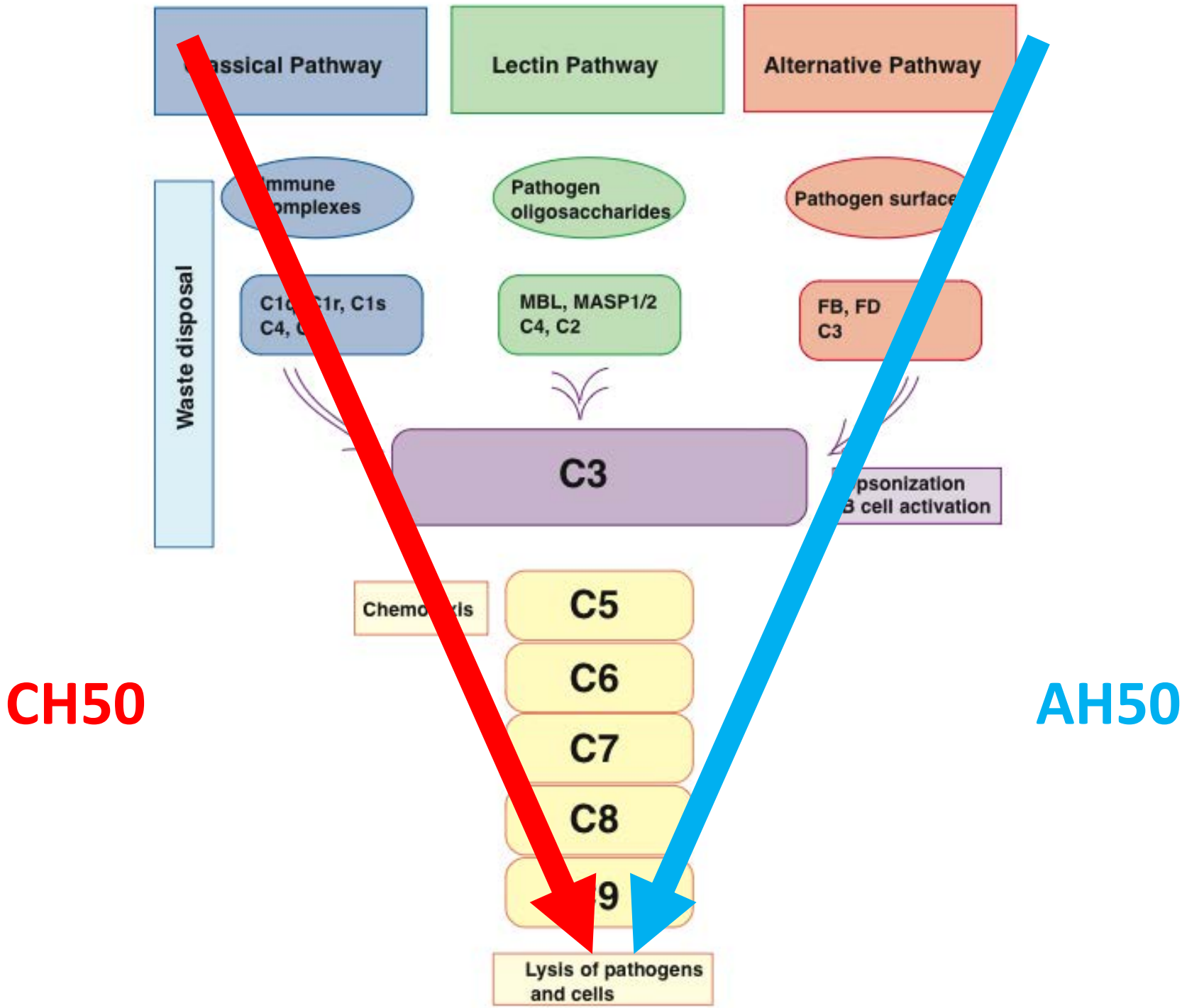
Mechanisms

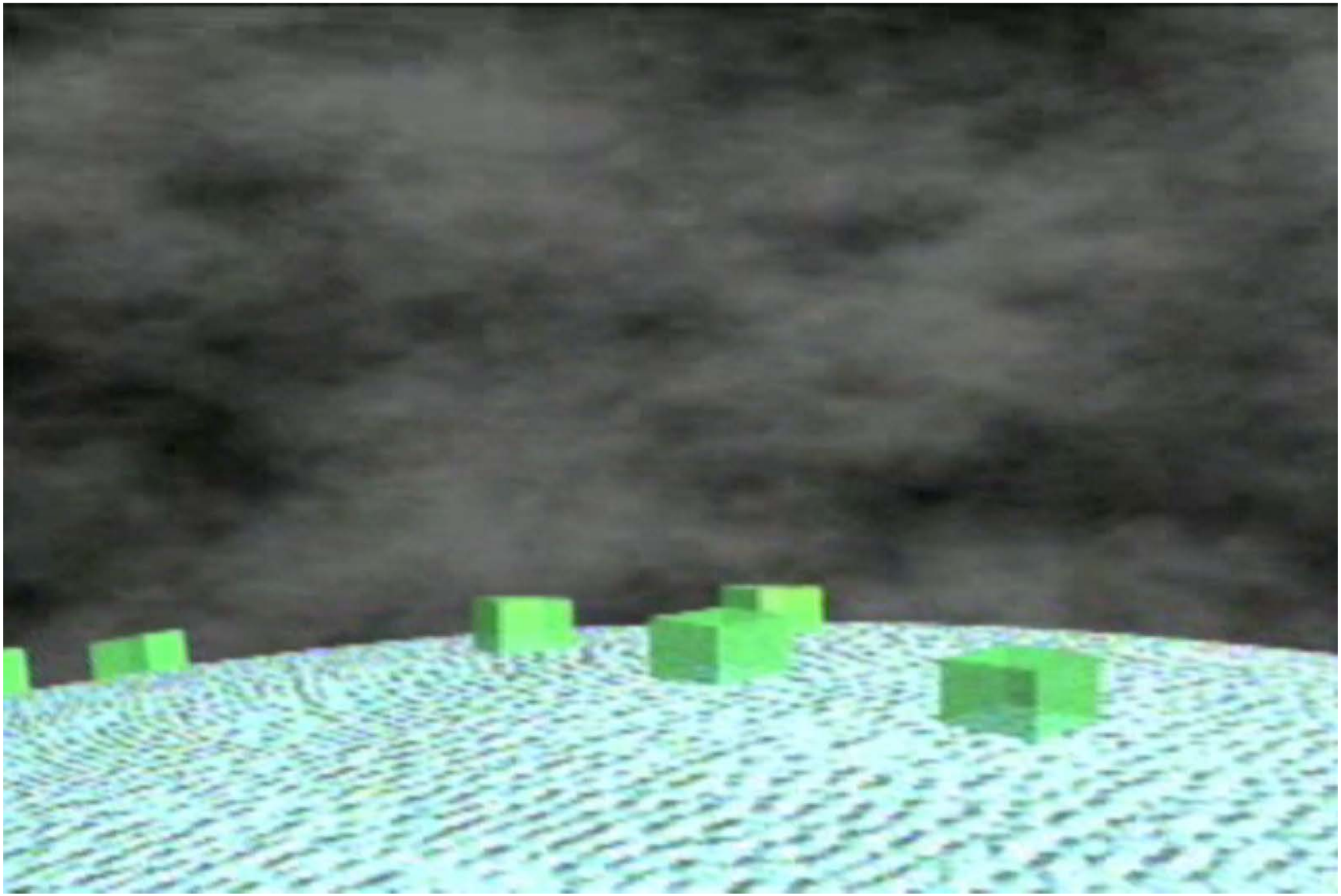
Function

- Opsonization (C3)
- Removal of apoptotic cells (C1)
- B cell costimulation/Antigen (C3)
- Cytolysis (Gram negative bacteria) (C5-9)
- Tolerance (C4)
- Cholesterol clearance (early)
- Chemotaxis (C5)
- T cell metabolism (C3, MCP)



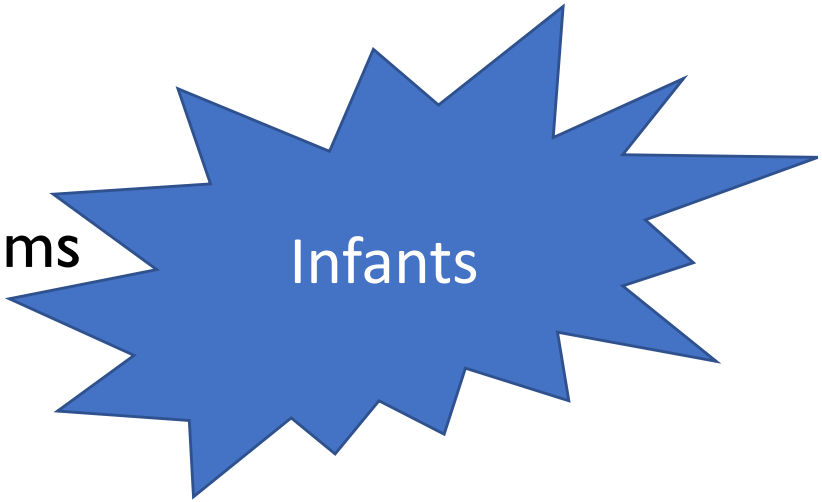

Classical Pathway
Lectin Pathway
Alternative Pathway
Immune complexes
Pathogen oligosaccharides
Pathogen surfaces
Waste disposal
C1q, C1r, C1s C4, C2
MBL, MASP1/2 C4, C2
FB, FD C3
C3
Opsonization B cell activation
Chemotaxis
C5
C6
C7
C8
C9
Lysis of pathogens and cells


Classical Pathway
Lectin Pathway
Alternative Pathway
Waste disposal
Pathogen oligosaccharides
MBL, MASP1/2
C4, C2
FB, FD
C3
C3
C5
C6
C7
C8
9
Lysis of pathogens and cells
CH50
AH50



Opsonization

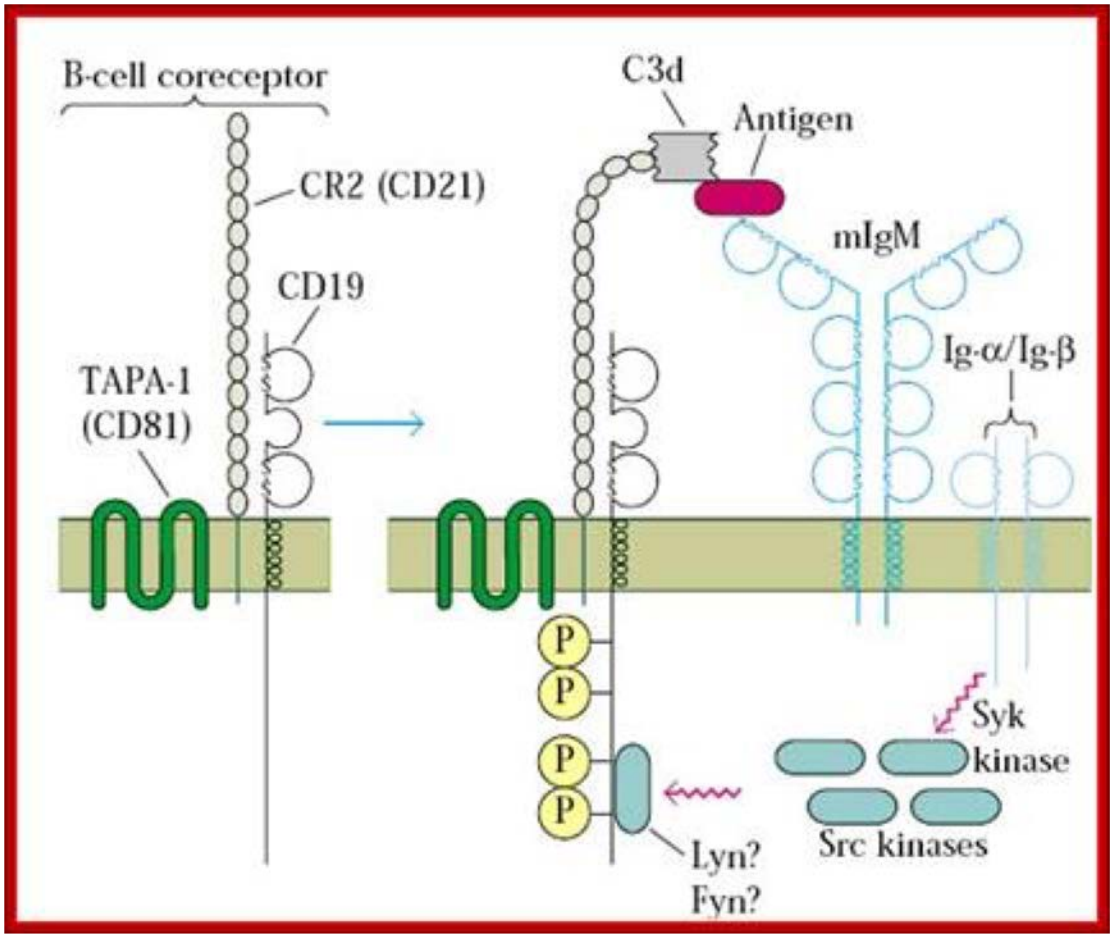
- Opsonin: Greek for tasty treat
- C3 and antibody are opsonins
- Important for encapsulated organisms
  - Haemophilus influenzae
  - Streptococcus pneumoniae
  - Neisseria meningitidis
  - Group B Streptococcus
  - Salmonella typhi
  - Klebsiella pneumoniae
  - Pseudomonas aeruginosa
  - Kingella kingae-bone and joint infections



BACTERIAL CAPSULE

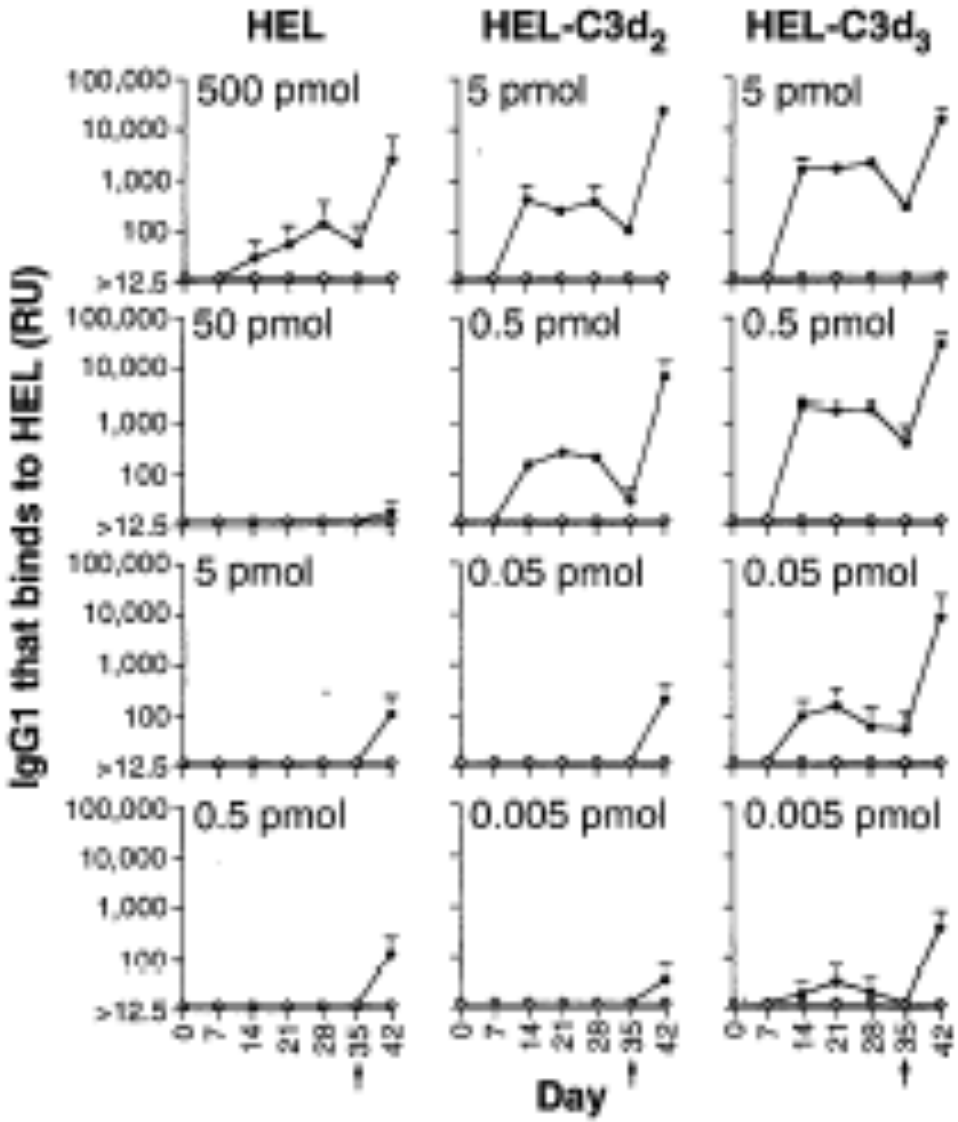
The slippery capsule of *Streptococcus pneumoniae* helps these bacteria avoid being eaten by neutrophils

C3 is also important for antibody production



Gonzalez Ann Rev Imm 2011

It takes 1/100 the amount of protein to induce and antibody response, if the protein is tagged with complement



Dempsey Science 1996

Complement Deficiencies

Categories

- Early complement component deficiencies
  - C1, C4, C2, C3
  - SLE (glomerulonephritis)
  - Encapsulated bacteria
  - Accelerated atherosclerosis
- Terminal components
  - C5-C9
  - Neisseria
- Regulatory components
  - FD, Properdin, FH, FI
  - Neisseria
  - aHUS
- C1 esterase inhibitor (HAE)

Founder effects

Deficiency	Frequency	Population
C7	1:400	Israeli Moroccan Jews
C9	1:1000	Japanese
C6	1:1400	African Americans
C2	1:10,000	Caucasians

Early Classical Pathway

Early Classical Defects

- Systemic infections (sepsis, pneumonia, meningitis)
  - Encapsulated organisms
  - Not usually OM, sinus infections
- SLE
  - Early onset severe: C1, C4
  - Mild-moderate, cutaneous C2
  - Membranoproliferative glomerulonephritis (C3)

- Most common cause of death is infection
- Second most common cause of death is MI

Who?

- Rate of complement deficiency in adult lupus cohorts is about 1-2%
- Higher in pediatric onset SLE

- Unselected children with pneumonia have a very low rate of complement deficiency
- Recurrent systemic infections with encapsulated organisms
  - 11% of kids with recurrent invasive pneumococcal infection have C2 deficiency
    - Sepsis, meningitis
    - Ingels Ped Inf Dis J 2015

What to order?

- CH50 is a great screening test
- C3 and C4 not very useful at the first stage

Interpret

- Infants have low complement levels
- Complement is consumed in sepsis and autoimmunity
  - Optimal to wait until recovered

- Look for CH50=0

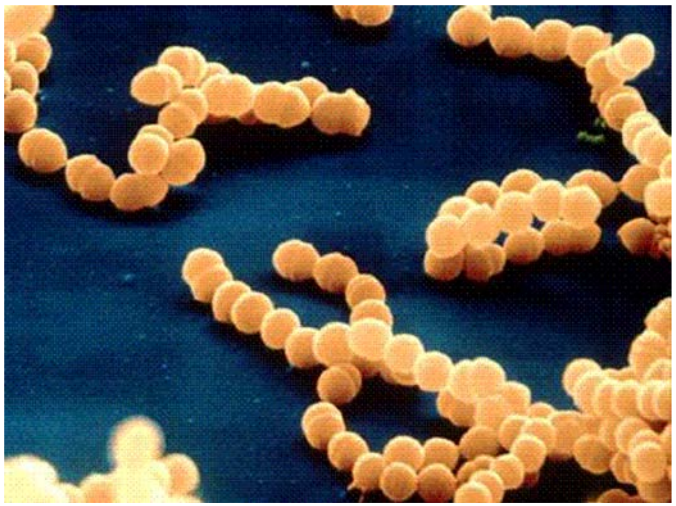
Therapy

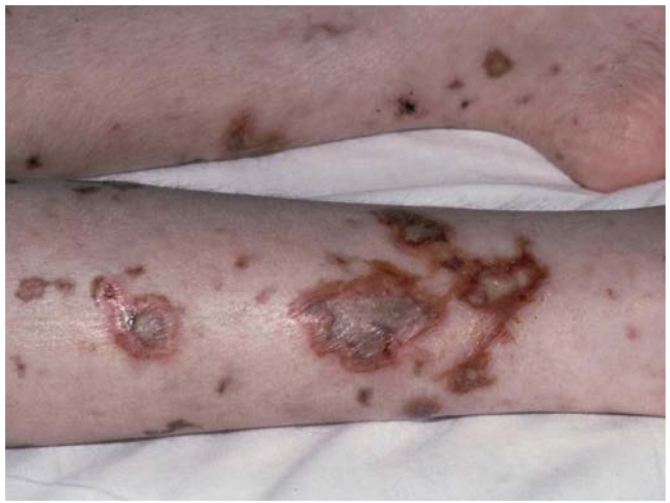
- Hypervaccination?
  - Extrapolate from data in MAC defects
- Antibiotic prophylaxis?
  - Tried and true but resistance common
- FFP?
  - Tough logistically
  - Effective in SLE
- Statins?
  - Sensible for cardiac risk mitigation
- BMT?
  - C1q deficiency
- Liver Tx?
  - C2, C3, C4 deficiencies

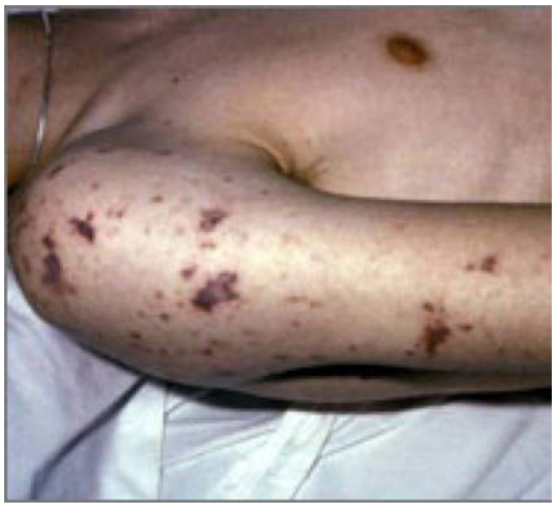
Terminal components (MAC)

Terminal C' Deficiencies

- Meningococcal infection
- Disseminated gonococcus
- Chronic meningococcemia

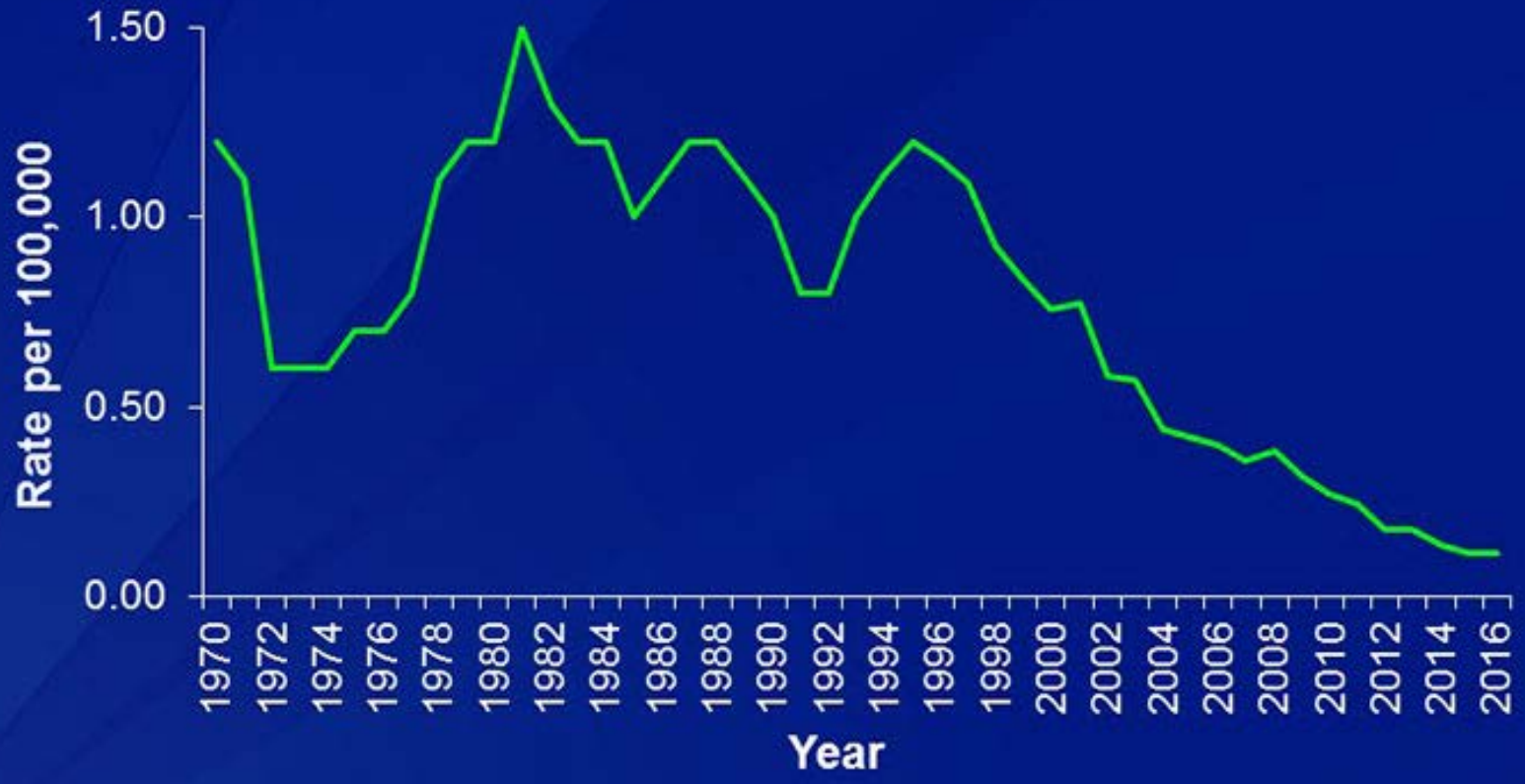






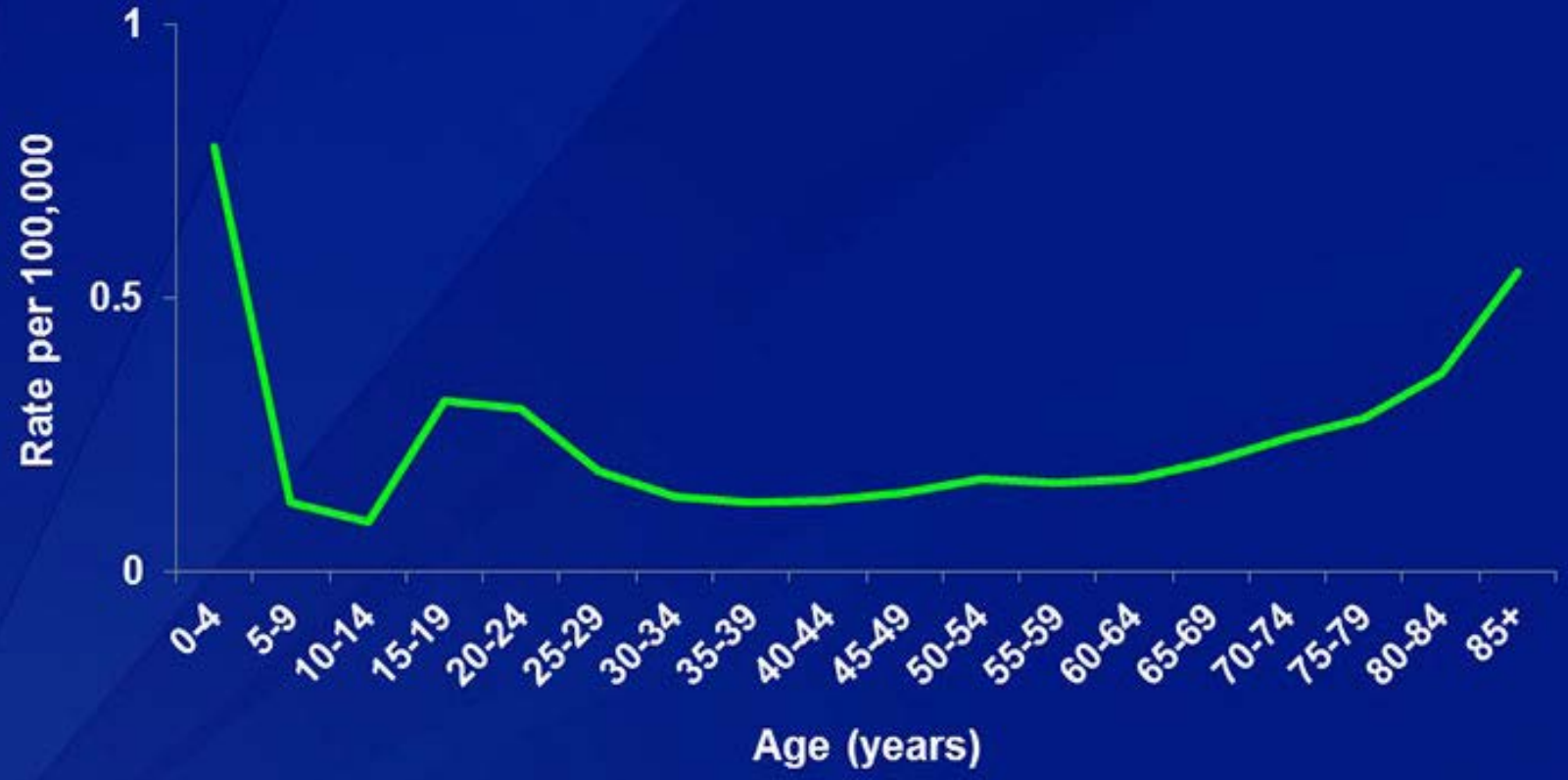
Brown.edu Srs.dl.ac.uk Meningococcal.com

Meningococcal Disease Incidence, United States, 1970-2016



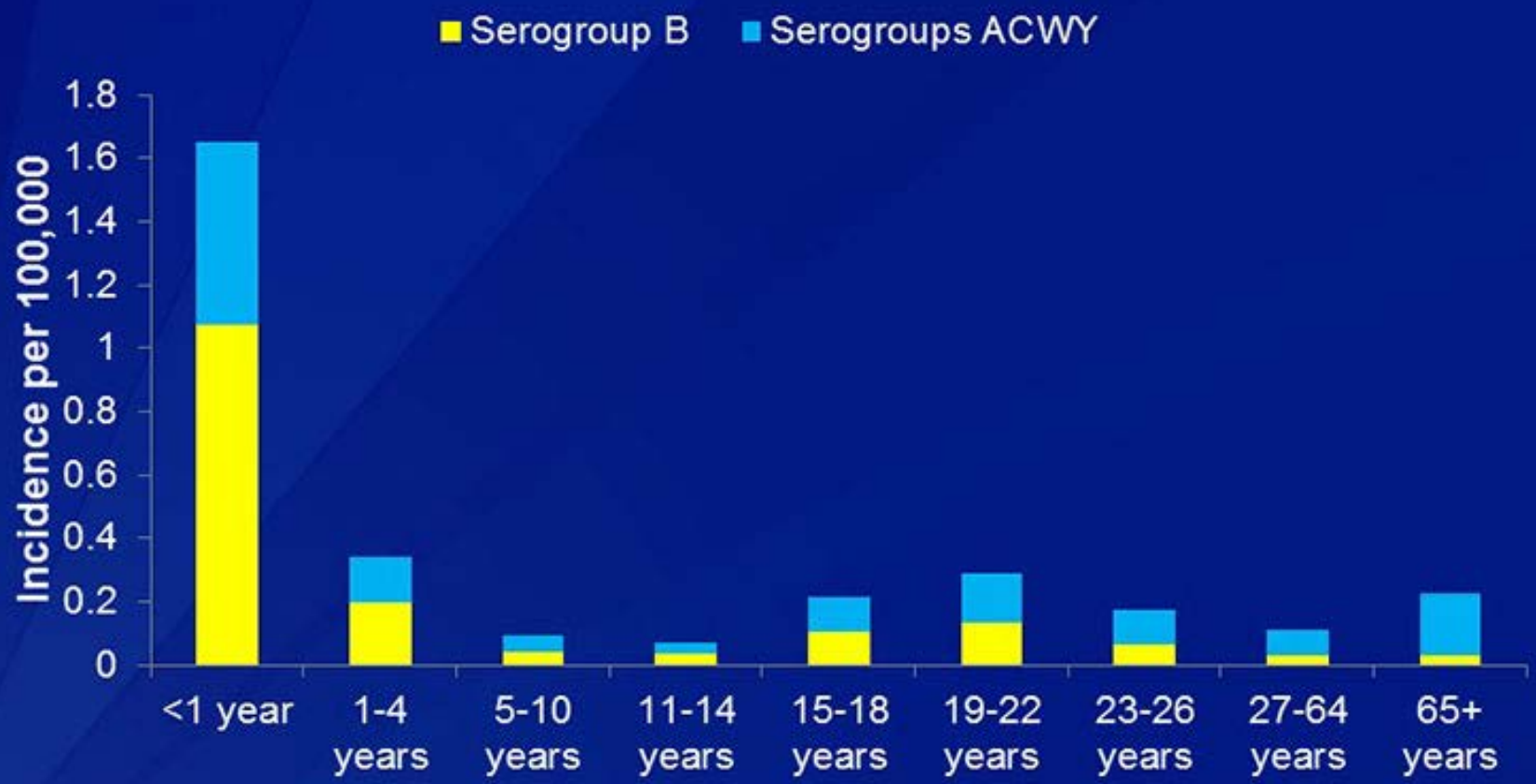
SOURCE: CDC; National Notifiable Diseases Surveillance System

Meningococcal Disease Incidence by Age 2007–2016



SOURCE: CDC; National Notifiable Diseases Surveillance System

Meningococcal Incidence by Serogroup* and Age-Group, 2007–2016

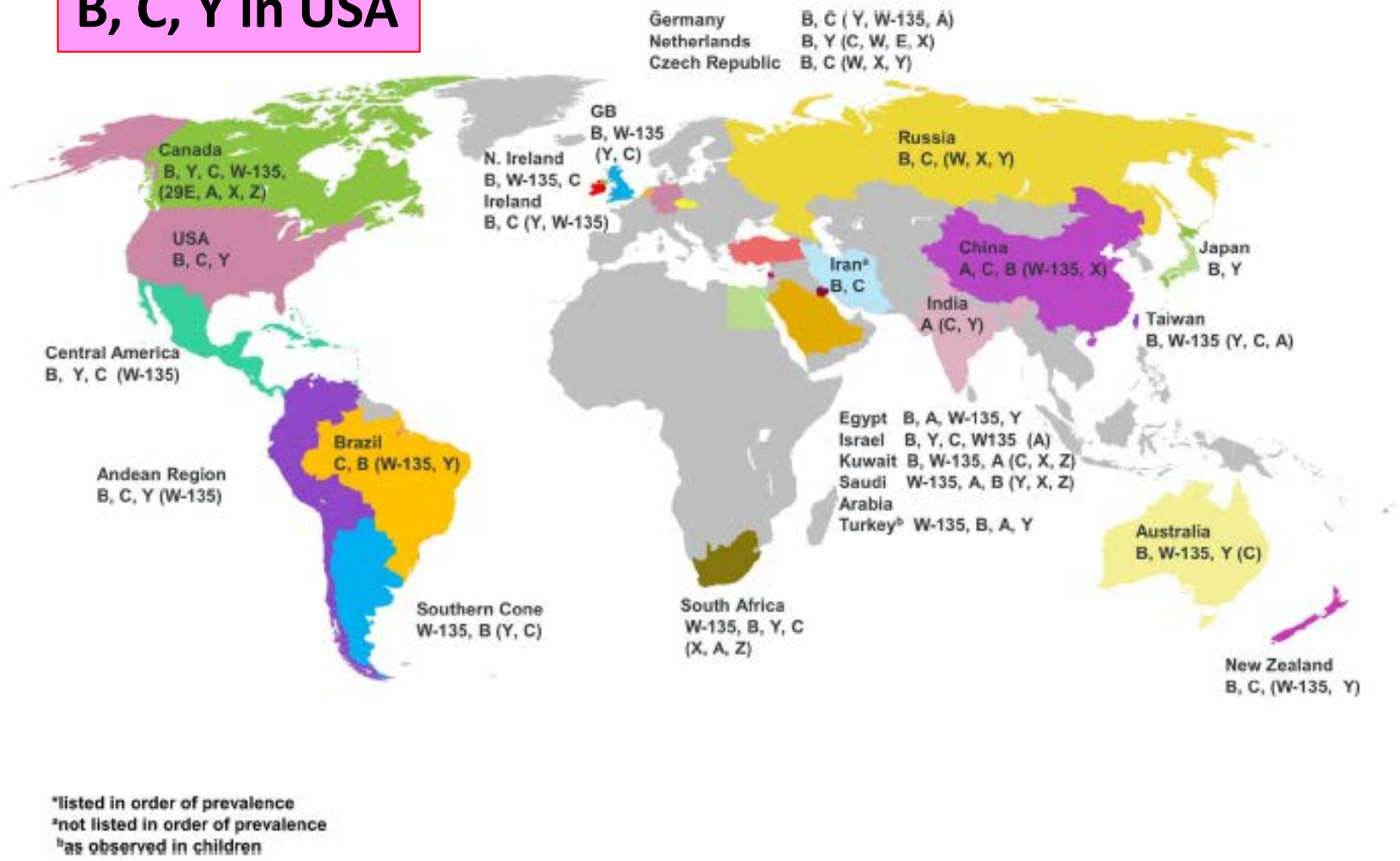


SOURCE: CDC; National Notifiable Diseases Surveillance System with additional serogroup data from Active Bacterial Core surveillance and state health departments.

Unknown serogroup (19%) and other serogroups (5%) excluded

Meningococcus

B, C, Y in USA



[a]listed in order of prevalence
[a]not listed in order of prevalence
[b]as observed in children

Polysaccharide vaccine is A,C, W-135, Y

Millar JR Army Med Corp 2017

Who?
First Episode

Rate of Complement Deficiencies	Country	Reference
3%	Netherlands	Fijen Lancet 1989
1-15%	USA	Merino J. Inf Dis 1983, Lee Inf Imm 1979, Eng J Clin Mic. 1980, Winkelstein Ped Inf Dis J 1987, Ellison NEJM 1983
1.5%	USSR	Platonov Medicine 1993
1%	Faroe islands during epidemic	Moller J. Clin Lab Imm 1988
23%	Tunisia	Kallel-Salami Arch Inst Past 2006
53%	New Caledonia	Daures J Clin Imm 2015

Who?
Special settings

Rate of Complement Deficiencies	Setting	Country	Reference
30-41%	Recurrent disease	USA, Denmark	Merino J Inf Dis 1983 Nielsen Scand J Inf Dis 1989
27-50%	Uncommon serotypes	Netherlands	Cees Clin Inf Dis 1999, Mayateek Ped Inf Dis J 1993
14%	Family History	Denmark	Nielsen Scand J Inf Dis 1989

Who?

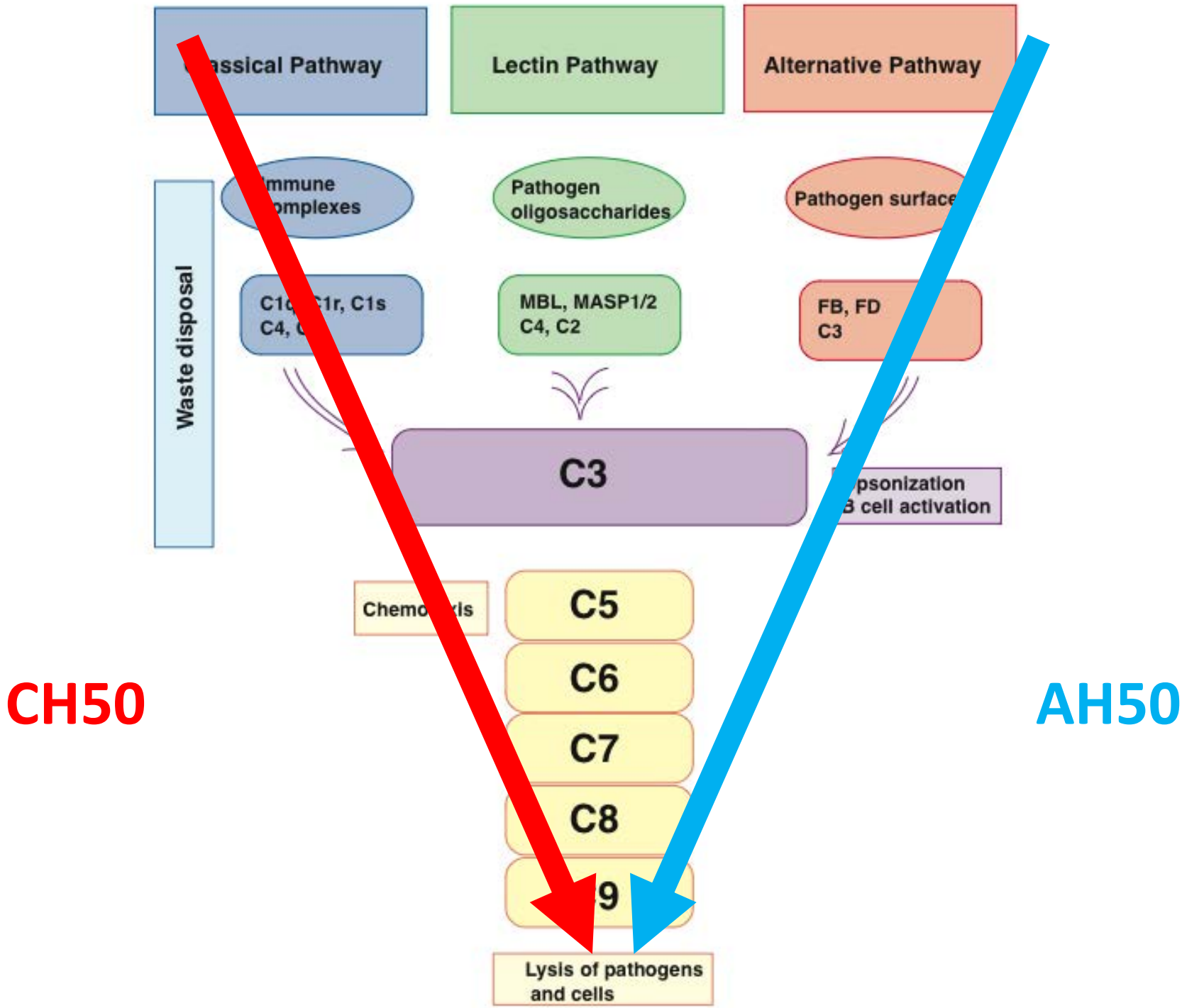
- Screen all patients >1y age with N. meningitidis outside of an epidemic

- Family members as appropriate
  - Only 27% of affected family members had disease

- Recurrence of meningococcal disease = 0.12/y
- Terminal components confer protection from deafness and severe disease
- Properdin and factor D deficiencies → severe disease

What to order?

- CH50
- AH50


Classical Pathway
Lectin Pathway
Alternative Pathway
Waste disposal
Pathogen oligosaccharides
MBL, MASP1/2
C4, C2
FB, FD
C3
C3
C5
C6
C7
C8
9
Lysis of pathogens and cells
CH50
AH50

Interpret

- Properdin and factor D deficiencies are associated with more severe disease
  - AH50=0

- Terminal component deficiencies
  - CH50=0, AH50=0
  - C9 is an exception

Caution

- Somewhat low CH50 and AH50
  - Check specimen handling
  - Consider underlying consumption-associated disease
  - Liver disease
  - Consider C9

Therapy

- Vaccinate every 3-5 years
  - Halves the risk of meningococcal disease (probably better now with better vaccines)

ACIP:

- Menveo (MenACWY-CRM): 2, 4, 6, 12m with boost at 4y

Or

- Menactra (MenACWY-D): 9, 12m with boost at 4y (special reccs for asplenia)

Or

- Menhibrix (Hib-MenCY-TT): 2, 4, 6, 12m. Boost with quadrivalent at 4y

And

- Trumenba (MenB-FHbp)
  - 3 doses age 10-25y

Or

- Bexsero (MenB-4C)
  - 2 doses age 10-25y

Regulatory defects

Regulatory defects

- Factor H, Factor I, Factor B (GOF), C3 (GOF), MCP
  - Atypical hemolytic uremic syndrome
    - FH, FI, FB, C3
      - FFP
      - Eculizumab ($10,000 per dose)
      - Liver-kidney transplant
  - FH, FI
    - Neisseria (distinct mutations from aHUS)
  - MCP
    - Kidney transplant
- Factor D, Properdin
  - Hypervaccination?
  - Antibiotic prophylaxis

Who?

- All aHUS (including pregnancy)
  - Sequencing typically required

- Neisserial infection with normal or slightly low CH50

Lab interpretation

- CH50=0 for most inherited deficiencies
  - Except regulatory defects

- AH50=0 for FD, Properdin, FH, FI
  - For the FH and FI mutations associated with Neisseria
  - AH50 often normal for aHUS mutations

What? No MBL?

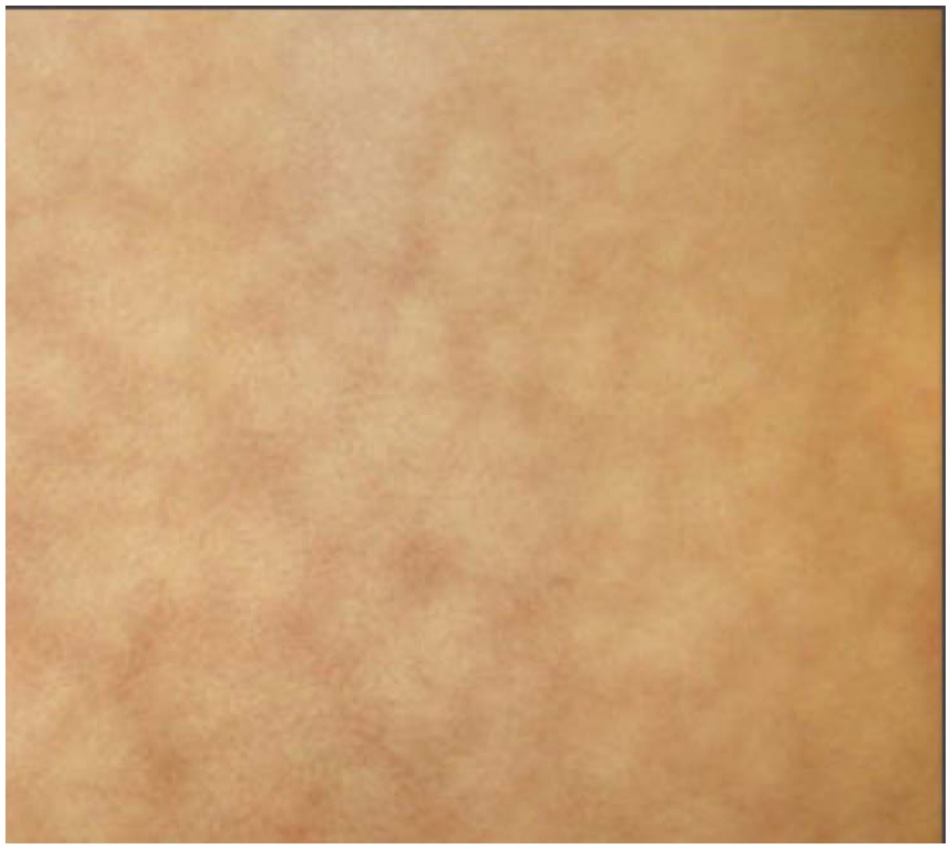
- May increase Neisseria risk 2-3X
  - But probably not at all
- May increase S. pneumoniae risk 2-4X
  - But probably not at all

- The fact that all alleles are in Hardy Weinberg equilibrium in all populations argues against a major effect
- MBL not found in any infection GWAS to date

C1 esterase inhibitor

Hereditary Angioedema

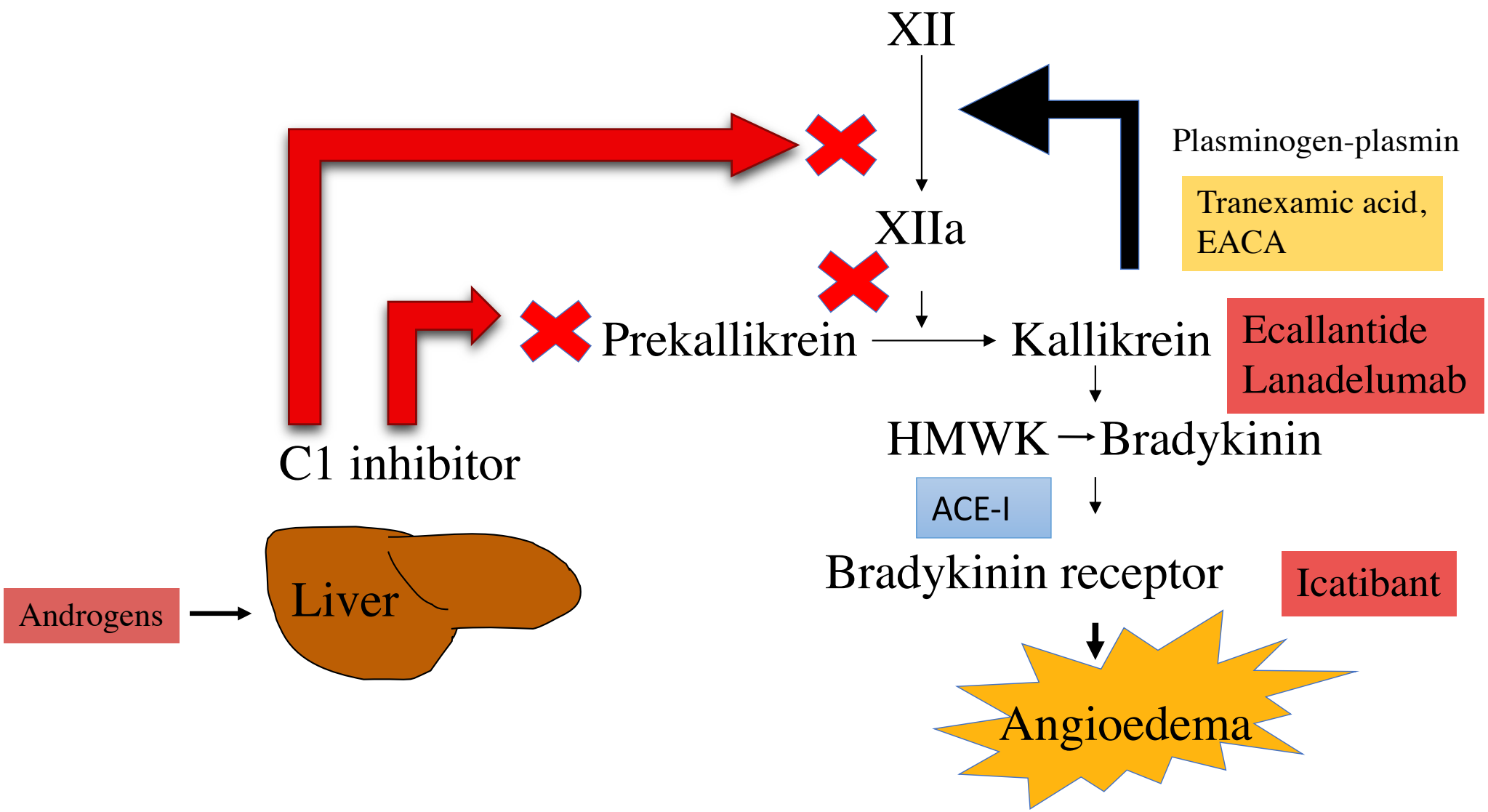
- Periodic episodes of angioedema beginning in childhood or adolescence
- Autosomal dominant inheritance
- Angioedema often precipitated by mild trauma
- Each episode lasts 2-4 days
- Some patients have a reticular rash but not urticaria



Evaluation/management

- C4 is a reasonable screen for low risk cases
- Highly suggestive history:
  - C1 inhibitor function (30-50% of normal)
- In older people or those with malignancy/autoimmunity
  - C1 inhibitor antigen level
  - C1 inhibitor function
  - C1q level
- In all cases: avoid estrogen, ACE inhibitors
- EDUCATION, EDUCATION, EDUCATION

Tissue damage drives activation of Hageman factor (XII)



Prophylaxis

- Pre-procedure
  - C1 Inhibitor 1000U
    - Cinryze, Berinert, Haegarda (subQ), Ruconest
  - FFP 2U
  - Danazol 200mg po TID 5-7 days before procedure
  - Oxandrin 2.5-20mg QD 5-7 days before procedure
- Long term
  - C1 Inhibitor 1000U twice a week
  - Lanadelumab 300mg every 2 weeks
    - Takhyzro (kallikrein inhibitor)
  - Danazol 200mg PO QD (titrate to effect not labs)
  - Oxandrin 2.5-20mg PO QD (titrate to effect not labs)

On demand

- Firazyr (Icantibant) Home use
  - 2.5 hours
- Kalbitor (Ecallantide)
  - 3-4 hours for effect
  - 3% Anaphylaxis risk
- Berinert can be self administered IV (for some)
  - Response time 15-60 minutes
- Ruconest
  - Response time is 15-60 minutes

Evolving!

- Adverum
  - Gene therapy
  - Cure
- Biocryst
  - BCX7353
  - Phase 2 effective
  - FDA fast track
  - Oral daily pill
  - Preventive

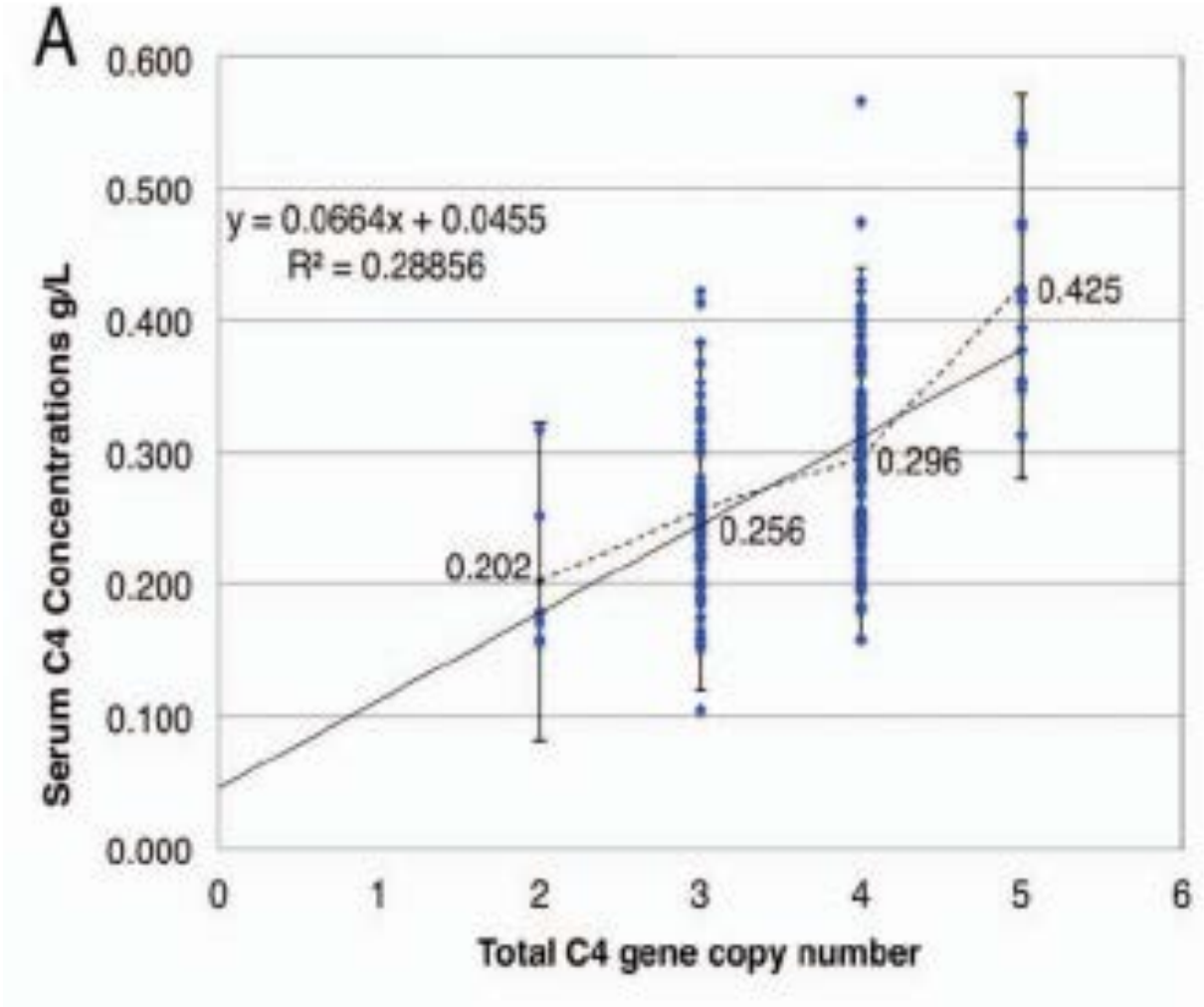
Secondary deficiencies

Secondary deficiencies

- Low C4 + C3
  - Classical pathway activation
    - 65% SLE
    - 8% viral
    - 7% vasculitis
    - 5% Hemolytic anemia
    - 5% Liver failure
    - 5% IgG4 disease
    - 4% Renal disease
    - 3% Cryoglobulinemia
- Low C3, Nl C4
  - Alternative pathway activation
    - C3 Nephritic factor
      - 80% of pediatric patients with lipodystrophy
      - 80% of patients with MPGN Type II

Saeki Rheum Int 2009

Caution: C4 is highly variable



Margery-Muir A&R 2014

Secondary deficiencies

- 50% of SLE patients have low complement
  - 250X risk of meningococcal disease
  - 5X risk of invasive pneumococcal disease

- Cirrhosis
  - 3X increased risk of invasive pneumococcal disease

- Nephritic factor
  - Risk for Neisseria increased

- Eculizumab
  - 4/1000 patients meningococcal disease

Summary

- Early classical pathway deficiencies
  - Cardiac risk
  - Infection prevention
- Terminal component deficiencies
  - Infection prevention
- Regulatory components
- Secondary deficiencies common
  - Patients need our help

Thank you!!!

Dawn Westerfer
Kelly Maurer
Daniella Levy Erez
Lihua Shi
Melanie Ruffner
Li Song