

Rheumatology for the Allergist/Immunologist

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Competing Interests

- ▶ Principal Investigator for Clinical Trials (all contracts through University and paid to Division)
 - Astra Zeneca, Genentech
- ▶ Consultant
 - Astra Zeneca, Boehringer Ingelheim, Genentech
- ▶ Promotional speaker
 - Astra Zeneca, Circassia, Genentech, Merck, Meda, Novartis, TEVA
- ▶ Legal reviews
 - Drug allergy and anaphylaxis, asthma death, immunodeficiency, metal allergy, latex allergy



Learning Objectives: Rheumatology for the Allergist

- ▶ Upon completion of this session, participants will be able to:
 - Better interpret the results of common tests for autoimmune disease;
 - More accurately assess the value of screening tests for autoimmunity in urticaria;
 - More readily identify serious vasculitic conditions that may present with sinus or skin manifestations.

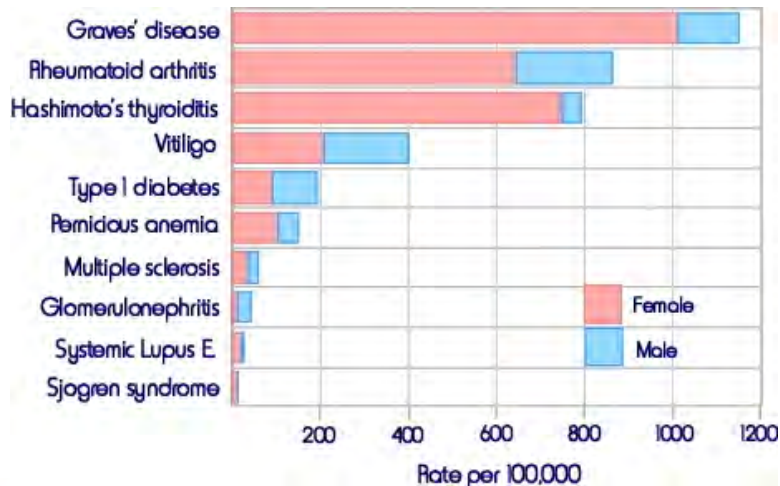
Outline of Presentation

- ▶ Autoimmune diseases likely to present to an allergist/immunologist
- ▶ Clinical diagnostic features of autoimmune disease
- ▶ Practical aspects of lab testing for auto-antibodies: ANA, specific ANA's, rheumatoid factors, anti-CCP, ANCA, anti-IgE receptor antibodies.

Autoimmune Disease or Impostor?

- ▶ Auto-antibodies and self-reactive T cell clones are seen in numerous patients and a variety of diseases.
- ▶ But causative role needed to have a true autoimmune disease.
- ▶ Other considerations are chronic infection, malignancy or autoinflammatory disorder.

Prevalence of most common autoimmune diseases in the United States



Clin Immunol Immunopathol 84: 223–243, 1997.

Autoimmune diseases may be organ-specific or systemic

▶ Organ or tissue-specific autoimmune diseases

- Type 1 diabetes
- Goodpasture's syndrome
- Multiple sclerosis
- Grave's disease
- Myasthenia gravis
- IgG4 related disease

▶ Systemic autoimmune diseases

- Rheumatoid arthritis
- Primary Sjögren's syndrome or disease
- Systemic lupus erythematosus
- "Amyloidosis"

Clinical Features of Autoimmune Disease

- ▶ Anything is “possible autoimmune disease”
 - Fatigue is the most common initial symptom of SLE
- ▶ Document fever, weight loss
- ▶ Joint examination looking for OBJECTIVE measures of inflammation
 - Early morning pain and stiffness
 - Tenderness of MCC of thumb < MCP of fingers
- ▶ Skin: acral erythema or scleroderma, Raynaud's, mouth ulcerations, facial rash, lower extremity rash, telangiectasia in areas not exposed to sun, rash below the knees

Clinical Features of Autoimmune Disease

- ▶ More skin: palpable purpura (beware of post pruritic purpura), urticaria lasting more than 24hours, urticaria with fever, urticaria with burning > itching, urticaria below the knees
- ▶ Peripheral neuropathy: decreased sensation to light touch, assymetrical vibratory sensation, absence of DTRs in distal extremities
- ▶ Iritis or uveitis (look for synechiae)

Autoimmune, Malignant or Inflammatory Diseases Likely to Present to Allergist/Immunologist

- ▶ Facial rash with multiple symptoms
- ▶ HIV disease with lymphadenopathy, oral candidiasis or immunoglobulin abnormality
- ▶ Autoimmunity associated with hypocomplementemia (C2 or partial C4 deficiency)
- ▶ Red eye with scleritis, episcleritis, uveitis
- ▶ Cough or dyspnea with restrictive spirometry findings or symptoms >> FEV1 /FVC ratio

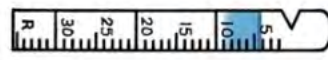
Rash



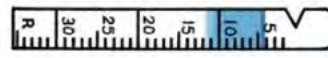
Autoimmune, Malignant or Inflammatory Diseases Likely to Present to Allergist/Immunologist

- ▶ Urticarial vasculitis, autoinflammatory disorders
- ▶ Pruritus with lymphoma, primary biliary cirrhosis, celiac disease, autoimmune thyroid disease
- ▶ Rash with SLE (subacute cutaneous lupus)
 - Acts like eczema, upper back or mantle distribution
- ▶ Palpable purpura with RA, cryoglobulinemia, drug allergy with hypersensitivity vasculitis, Granulomatosis with polyangiitis (WG), Eosinophilic granulomatosis with polyangiitis (CS)
- ▶ Rhinitis with conjunctivitis with Sjögrens or pterygoiditis

Schirmer's Test



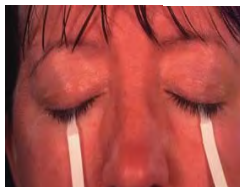
< 10 mm/min => Pathologischer STT



10 - 15 mm/min => Verdächtiger STT



15 mm/min => Physiologischer STT

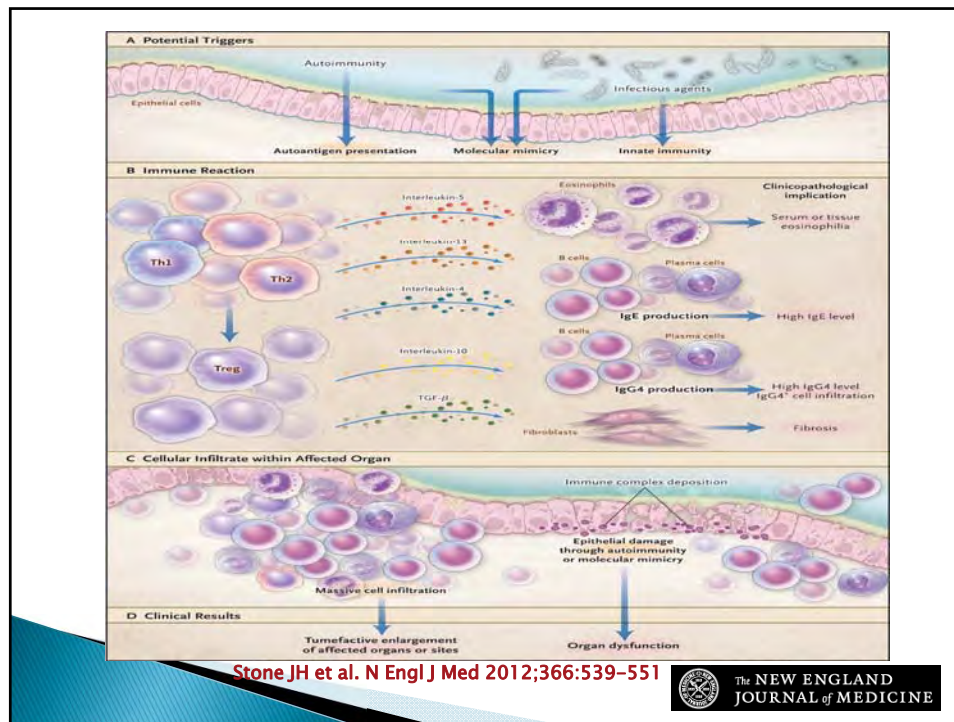


Autoimmune, Malignant or Inflammatory Diseases Likely to Present to Allergist/Immunologist

- ▶ Headache due to isolated CNS vasculitis, TMJ, herpes zoster, iritis/uveitis, GPA, GCA
- ▶ Hearing loss due to GPA, Cogan's syndrome, autoimmune hearing loss, EGPA
- ▶ Foot drop with EGPA in subject with known asthma and sinus disease
- ▶ Angioedema due to SLE or mixed cryoglobulinemia with C1q decrease or antibody specific for C1 esterase inhibitor

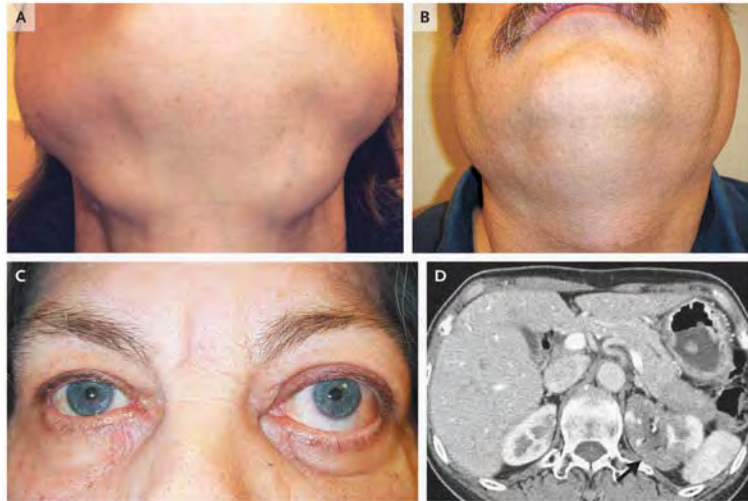
IgG4-Related Disease

- ▶ Increase in peripheral blood IgG4 (but not always)
- ▶ More common in males
- ▶ Inflammatory fibrosis of pancreas, biliary tree, salivary glands, lacrimal glands and other
- ▶ May be referred to allergist/immunologist due to increase in blood IgG4 or persistent swelling



Organ Involvement with IgG4-Related Disease

- ▶ Parotid and lacrimal glands
- ▶ Nose with or without polyps
- ▶ Pancreas
- ▶ Kidney with tubulointerstitial nephritis
- ▶ Thyroid with fibrosis
- ▶ Lung with pleural or interstitial disease
- ▶ Liver and biliary tree



Stone JH et al. N Engl J Med 2012;366:539-551.

NEW ENGLAND
JOURNAL OF MEDICINE

Statistics

- ▶ “Lies, damn lies and statistics”
- ▶ Sensitive assays are useful screening tests
 - Increased false positive
 - Enhanced negative predictability
- ▶ Specific assays are useful confirming tests
 - Increased false negative
 - Enhanced positive predictability
- ▶ Generally, sensitivity and specificity are inversely related

Tests to be Discussed

- ▶ Acute phase reactants
- ▶ Immunofixation
- ▶ Autoantibodies
- ▶ Complement measurements
- ▶ Immune complex assays

Acute Phase Reactants

- ▶ Most useful
 - Erythrocyte sedimentation rate
 - C reactive protein
 - Platelet count
 - Ferritin
- ▶ Regulated by
 - IL-1
 - IL-6
 - Tumor necrosis factor (TNF)

Erythrocyte sedimentation rate

- ▶ Useful inexpensive test
- ▶ Depends upon production of fibrinogen
- ▶ Affected by RBC number and morphology
- ▶ Tends to be slow to rise and fall, 3–7 days
- ▶ Normal value increases with age, approximately half of age in years, if female add 10

Quantitative C–Reactive Protein

- ▶ Precisely quantitated
- ▶ Not dependent on RBCs
- ▶ Changes within hours of a change in stimulus

Typical Case Presentations

- ▶ Urticaria versus urticarial vasculitis
- ▶ Atypical pruritus
- ▶ Unusually ill appearing patient with upper airway complaints or findings
- ▶ Cough or asthma with systemic complaints
- ▶ Multi-organ or multi-system findings or complaints

Immunofixation

- ▶ Useful in patient with pruritus, immunodeficiency like presentation with normal or borderline low IgG, urticaria with atypical features or fatigue
- ▶ Detects monoclonal gammopathy
 - Benign monoclonal gammopathy
 - MUGA, monoclonal gammopathy of unknown significance
 - Multiple myeloma, lymphoma

Autoantibodies

- ▶ Antinuclear antibody (ANA)
 - Smith antibody
 - Anti-Ro and anti-La (ENA antibody)
 - dsDNA antibody
- ▶ Rheumatoid factor
 - Vectra D (12 cytokines, enzymes or receptors)
 - Anti-CCP
- ▶ Antineutrophil cytoplasmic antibody
- ▶ Antithyroid antibodies
- ▶ Antimitochondrial antibodies

Other Autoantibodies

- ▶ Glutamic acid decarboxylase
- ▶ Acetylcholine receptor, GQ1b, GM1, GD1a
- ▶ Smooth muscle
- ▶ Parietal cell
- ▶ *Saccharomyces cerevisiae*
- ▶ I, i, CD47, Duffy, Pr
- ▶ Liver/kidney microsomes or cytosol proteins

Practical use of ANA test

- ▶ The ANA test should not be used to screen patients with joint pain due to lack of specificity.
- ▶ Usual ANA now is ELISA or Hep-2 cell and is very sensitive, producing many false positives.
- ▶ Cutoff for positive ANA is now agreed to be $> 1:80$.

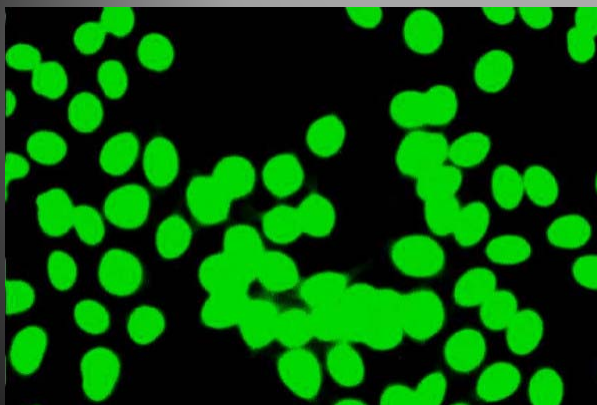
Antinuclear antibody testing overview

- ▶ Some problems – labs vary in methods, cut-off points for pos or neg, results reporting.
- ▶ Widely seen in the healthy and non-rheumatic diseases.
- ▶ High negative predictive value for SLE.
- ▶ The disappearance of the ANA negative lupus patient.
- ▶ Pattern of IF test (FANA) has limited value.

ANA pitfalls to avoid

- ▶ ANA a good screening test, but low specificity for any one disorder. It has high negative predictive value for SLE patients.
- ▶ Consequences of prematurely speculating about lupus with the parents.

Practical aspects of ANA's and specific antinuclear antibodies

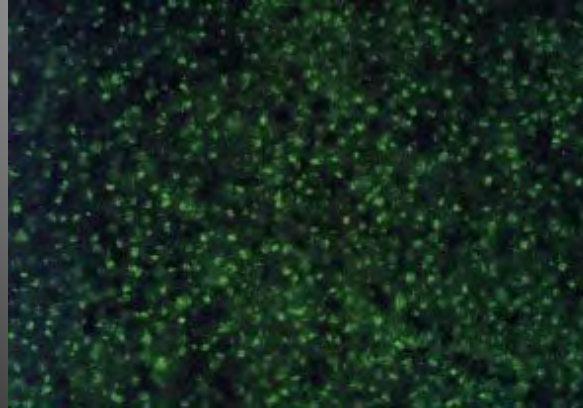


High titer
homogeneous
staining on
HEp-2
substrate

Zachou et al. J.
Autoimm Dis. 2004

In early years, ANA assay on rodent tissue was less sensitive and more specific

Rat liver section as substrate for ANA



Diseases with positive ANA

► Specific organ autoimmune diseases

- Hashimoto's thyroiditis -46%
- Graves' disease -50%
- Autoimmune hepatitis -63-91%
- Primary biliary cirrhosis -10-40%
- Primary autoimmune cholangitis -100%
- Primary pulmonary hypertension -40%

ANA Positive test result is very non-specific

▶ Auto-immune diseases (sensitivity)

- SLE -93% to 99%
- Scleroderma -85%
- MCTD -93%
- PM/DM -61%
- RA -40%
- Rheumatoid vasculitis -33%
- Sjögren's Syndrome-48%
- Drug induced lupus -100%
- Discoid lupus -15%
- Pauci type IJA - 70%

Reichlin, 2004

Diseases associated with positive ANA

▶ Miscellaneous

- EBV disease
- Hepatitis C infection
- SBE
- Tuberculosis
- HIV
- Other lymphoproliferative disorders

Clinically significant specific ANA's

- ▶ Significance of several specific ANA's well established
- ▶ Anti-dsDNA (specific for SLE, renal disease)
- ▶ Anti-Smith (specific for SLE)
- ▶ Anti-RNP (mixed connective tissue disease)
- ▶ Anti-centromere (CREST syndrome, Pul HBP)
- ▶ Anti-topoisomerase (SCL-70, systemic sclerosis, pulmonary fibrosis)

Measurement of Anti-dsDNA Antibodies

- ▶ Farr assay: precipitation of radio-labeled DNA/anti-DNA complexes in 50% ammonium sulfate
- ▶ Crithidia luciliae: unicellular trypanosome with circle of dsDNA at base of flagellum; test by indirect immunofluorescence; primarily recognizes high affinity antibodies.
- ▶ ELISA: detects high and low affinity antibody; positive in 70-80% of lupus patients; good correlation to disease activity.

Indirect IF staining of Crithidia luciliae

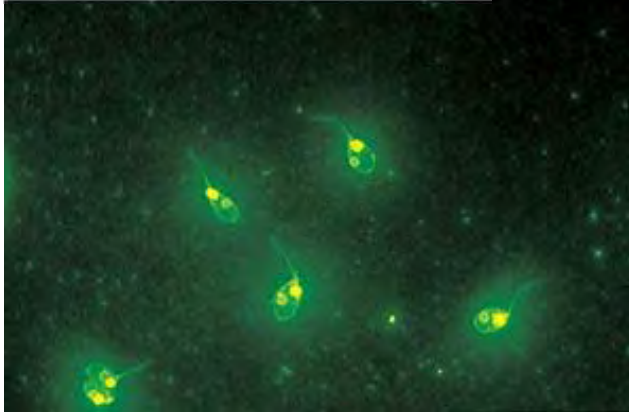


Photo from
Casesblog.blogspot.com/2007/11/what-is-crithidia

Measurement of Anti-dsDNA Antibodies

- ▶ Farr assay: precipitation of radiolabeled DNA/anti-DNA complexes in 50% ammonium sulfate
- ▶ Crithidia luciliae: unicellular trypanosome with circle of DSDNA at base of flagellum; test by indirect immunofluorescence; primarily recognizes high affinity Ab's
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- ▶ Haugbro et al., 2004 : 158 ANA positive sera tested for dsDNA antibodies showed

ELISA sensitivity=79 and specificity = 73

Crithidia sensitivity=41 and specificity = 99

Rheumatoid factors

- ▶ Auto-antibodies that react with Fc portion of IgG
- ▶ Classic test was Rose-Waaler agglutination of sheep RBC's
- ▶ Usual test detects IgM RF. Importance of IgA, IgG isotypes of RF's unclear.
- ▶ Older technique: human or rabbit IgG coated particle used as target (latex bead or tanned RBC)
- ▶ Newer techniques are nephelometry, RIA, or ELISA with IgG coated plastic wells.

Utility of obtaining a test of RF

- ▶ Almost no value as a screening test: Schmerling and Delbanco reported pos. predictive value of 24% for RA and 34% for any rheumatic disease in unselected pts. (Arch Intern Med, 2002)
- ▶ Better positive predictive value if ordered selectively in pts having modest or high chance of RA or Sjögren's syndrome
- ▶ Prognostic value limited in RA pts, but higher titers have higher positive predictive value for RA
- ▶ RF production associated with HLA DRB1*0401

Conditions associated with presence of rheumatoid factor

Immune system disorders: RA, Sjögren's synd, SLE, Sarcoidosis, Waldenstrom macroglobulinemia, MIXED CRYOGLOBULINEMIA

Infectious diseases: SBE, Tuberculosis, leprosy, Syphilis, Lyme disease, Viral infections, Leishmaniasis, HIV

Malignancies: Leukemias, Lymphomas

Miscellaneous conditions: Seniors, Interstitial pulmonary fibrosis, Chronic liver disease, Chronic renal disease

Anti-CCP antibodies

- ▶ Various autoAb's described since 1960's: antiperinuclear factor, anti-filaggrin, anti-keratin, anti-Sa.
- ▶ 1998 recognized that all of above target citrullinated peptides
- ▶ Citrulline: a non-standard amino acid created by deamination of arginine
- ▶ Assay widely available by ELISA

Anti-CCP antibodies: clinical associations

- ▶ Similar sensitivity to RF, but higher specificity
- ▶ 90–95% specificity
- ▶ Anti-CCP can precede clinical expression of RA symptoms by years.
- ▶ Higher titers of anti-CCP Ab's more likely to have aggressive disease.
- ▶ Anti-CCP found in 1 / 3 of RF neg RA adults
- ▶ High negative predictive value in early RA cases

Anti-CCP clinical utility (Lee and Schur study 2003)

- ▶ Anti-CCP in RA had sensitivity 66% and specificity 90%
- ▶ Rheumatoid factor had sensitivity 71% and specificity 80%
- ▶ Positive RF or anti-CCP raised sensitivity to 81%
- ▶ For RA with neg RF, 10/29 pos anti-CCP

Lee DM and Schur PH. Annals of Rheu Dis 2003;62:870.

Antineutrophil cytoplasmic antibody (ANCA)

- ▶ Three patterns
 - Cytoplasmic
 - Perinuclear
 - Mixed
- ▶ Not related to ANA
- ▶ Cytoplasmic
 - Granulomatosis with polyangiitis/GPA (Wegener's granulomatosis)
- ▶ Perinuclear
 - EGPA
 - Microscopic polyangiitis

Sensitivity of ANCA

Disease	c-ANCA/pr-3	p-ANCA/MPO
Wegener's granulomatosis	80-90%	5-10%
Microscopic polyangiitis	40-50%	40-50%
Polyarteritis nodosa	5-10%	5-10%
Churg-Strauss	10%	70-80%
Idiopathic pauci-immune GN	5-10%	65-75%
Goodpasture synd.		20-30%

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Other autoantibodies

- ▶ Anti-SCL 70/Jo-1
 - Scleroderma with lung involvement
 - Dyspnea with restrictive pulmonary disease
- ▶ Antimitochondrial antibody
 - Primary biliary cirrhosis, which may present as pruritus
- ▶ Antibody to alpha chain of high-affinity IgE receptor
 - CD63 or CD203c
 - Histamine basophil release

Other autoantibodies

- ▶ Anti-thyroglobulin/Anti-thyroid peroxidase
 - Associated with Hashimoto's disease and Grave's disease
 - Identifies the individual as being "autoimmune prone"
 - 20% of normal women are positive
- ▶ Anti-mitochondrial antibody
 - Associated with primary biliary cirrhosis
 - Early symptom of generalized pruritus
- ▶ Histone antibodies
 - Associated with drug induced lupus, usually ANA positive

Other autoantibodies

- ▶ Other antibodies
 - Glomerular basement membrane antibody
 - Anti-U3-RNP (fibrillarin)
 - Cardiolipin antibody, anti-beta2-glycoprotein
 - Histone antibodies

Other autoantibodies

- ▶ Glomerular basement membrane antibody
 - Associated with Goodpasture's syndrome with hemoptysis and cough and hematuria
- ▶ Cardiolipin antibody, anti-beta2-glycoprotein antibody
 - Cold sensitivity, livedo reticularis but not usually urticaria, miscarriage and arterial or venous thrombosis
- ▶ Liver/kidney microsomal antibodies
 - Associated with autoimmune hepatitis which may present with itching

Immune complex assays

- ▶ No generally reliable test
- ▶ Most useful for allergists is cryoglobulins
 - urticarial vasculitis
- ▶ Interpretation of other studies difficult
 - C1q binding
 - RAJI cell assay
 - Polyethylene glycol precipitation (PEG)

Complement assays

- ▶ CH 50 best screening assay for deficiency
 - C4 has 2 alleles on each chromosome so may be deficient with mild decrease or normal CH50
- ▶ C4 generally more useful than C3 in monitoring inflammatory disease (and C1EInh)
- ▶ C2 most common deficiency associated with autoimmune disease but any “early” deficiency a consideration
- ▶ AH50 useful for screening alternative pathway but not always easy to find

