1

Disclosures:

- Maculogix: advisory board
- Sun Pharmaceuticals: speakers bureau,
- Avellino: advisory board,
- Dompe: advisory board,
- RVL Pharmaceuticals: advisory board

2

Autoimmune Diseases

- Group of acquired diseases in which genetic factors appear to play a role
- They have in common widespread immunologic and inflammatory alterations of connective tissue
- The illnesses share certain clinical features and differentiation between them is often difficult because of this.
- Although thought to be acquired diseases, often their causes cannot be determined .

3

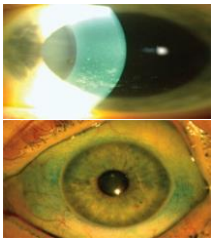
Case

- 55 yr white female complains of fluctuating vision
  - Worse at near
  - Spends 8-10 hours/day on the computer
- Medical Hx:
  - Hypertension for 10 years
  - Joint pain
- Medications:
  - HCTZ for HTN
  - Celebrex for her joint pain

4

Exam Data

- VA (corrected):
  - OD/OS: 6/7.5 (20/25)
- PERRL
- EOM's: FROM
- CVF: FTFC
- SLE:
  - TBUT 5 sec OD, OS
  - Positive NaFl staining and Lissamine green staining of conj and cornea
  - Decreased tear prism



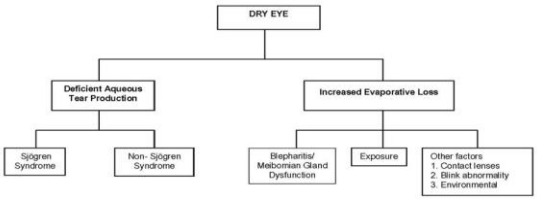
5

Additional Testing/Questions

- Schirmer: < 5 mm of wetting in 5 minutes OD, OS
- RF (rheumatoid factor) and ANA (anti-nuclear antibodies): normal for patients age
- SS-A: 2.0 (normal < 1.0), SS-B: 1.9 (normal <1.0)
- Additional symptoms reported:
  - Patient experiences dry mouth and taking Salagen
- **Diagnosis: Sjogren Syndrome**

6

Differential Diagnosis of Dry Eye

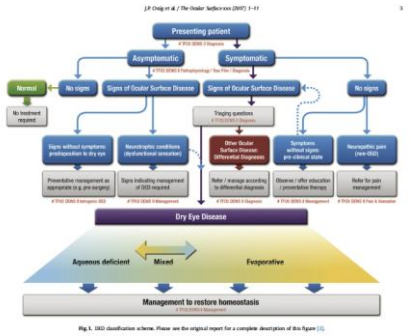


7

DEWS 2: DED Definition

"Dry eye is a multifactorial disease of the ocular surface characterized by a **loss of homeostasis** of the tear film, and accompanied by ocular symptoms, in which tear film instability and **hyperosmolarity**, ocular surface **inflammation** and damage, and **neurosensory abnormalities** play etiological roles."

8



9

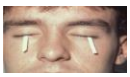
Signs and Symptoms of Dry Eye

Signs:

- Ocular Surface Damage
  - Corneal Staining (Fluorescein and/or Rose Bengal)
  - Conjunctival Staining (Lissamine Green)
- Decreased Tear Quantity
  - Schirmer Score
  - Phenol Red Thread Test
  - Tear Meniscus Height
- Decreased Tear Quality
  - Tear Break Up Time (TBUT)
  - Tear Osmolarity

Symptoms:

- Grittiness
- Burning
- Irritation
- Stringy discharge
- Blurring of vision
- Ocular Surface Disease Index (OSDI)


10

Treatment

- We initiated:
  - Omega-3 supplements (2 grams per day)
  - Recommended warm compresses and lid washes qhs
  - Testosterone cream 3% applied to upper lid bid
- Patient had significant improvement in symptoms with the use of the topical testosterone cream.
  - However, she was still symptomatic at the end of the day and she still had significant staining on her cornea and conjunctiva
  - Initiated FML tid for 1 month, Restasis bid after 2 weeks
    - 2 months later patient reported further improvement in her symptoms
    - No conjunctival staining was noted and only slight SPK
    - Schirmer values improved to OD: 9 mm, OS: 10 mm

11

Role of Androgens?

- Recent studies have suggested that androgen deficiency may be the main cause of the meibomian gland dysfunction, tear-film instability and evaporative dry eye seen in Sjogren patients
- Transdermal testosterone 3% promotes increased tear production and meibomian gland secretion, thereby reducing dry eye symptoms (Dr. Charles Connor).
- Progesterone 0.05%/Testosterone 0.05% Ophthalmic Solution BID (local compounding pharmacy?)
- **Topical Testosterone 0.5% drops BID (compounding pharmacy)**

12

Sjogren Syndrome

- Chronic AI disease that involves diffuse exocrine gland dysfunction and lymphocytic infiltration throughout the body
- Decreased lacrimal gland secretion results in K sicca
- Decreased salivary gland secretion results in sicca complex
- Emotional tearing is not affected

13

SJOGREN SYNDROME: OLD/NEW CLASSIFICATION

- Old:
  - 1º Sjogren: occurs when sicca complex manifests by itself
    - no systemic disease present
  - 2º Sjogren: occurs in association with collagen vascular disease such as
    - RA and SLE
    - significant ocular/systemic manifestations
- New:
  - The diagnosis of SS should be given to all who fulfill the new criteria while also diagnosing any concurrent organ-specific or multiorgan autoimmune diseases, without distinguishing as primary or secondary.

14

Antibodies to SS-A and SS-B

- Sjogren Syndrome Antibodies A and B
- Typically tested by ELISA and immunoblot
- Associated Conditions:
  - Uncommon in the normal population and in patients with rheumatic diseases other than Sjogren syndrome and SLE
  - Present in 75% of patients with "primary" Sjogren but only 10-15% of patients with RA and secondary Sjogren Syndrome

15

Antibodies to SS-A and SS-B

- Indications:
  - Should be measured in patients with a clinical suspicion of Sjogren or SLE
- Interpretation:
  - Presence of AB's is a strong argument for the diagnosis of Sjogren Syndrome in a patient with sicca syndrome

16

Sjogren Syndrome Ocular and Systemic

- Recently published article comments:
  - all patients had dry eye symptoms for approximately 10.4 years before presentation
  - 42% of the patients had systemic manifestations resulting from primary SS
  - **SS has been shown to be an independent risk factor for the development of non-Hodgkin's lymphoma.**

17

Sjogren Syndrome Ocular and Systemic

- Authors recommendation:
  - primary SS is associated with vision- and life-threatening complications
  - presence of SS needs to be explored in patients with clinically significant dry eye because dry eye precedes the occurrence of the systemic manifestations

18

Dry Eye Summit

- Held in December 2014
  - Combination of optometrists, an ophthalmologist and industry
- Goal:
  - to find a way to encourage optometrists to look for, diagnose and manage dry eye in their patients
  - Come to a consensus on the minimum:
    - 3 questions that should be asked to identify dry eye patients
    - 3 diagnostic tests
    - 3 initial treatments

19

REV. as of March 13, 2015

Consensus on Screening Questions

1. Do your eyes ever feel dry or uncomfortable?
2. Are you bothered by changes in your vision throughout the day?
3. Are you ever bothered by red eyes?
4. Do you ever use or feel the need to use drops?

Recommendations from the ***Dry Eye Summit 2014***

20

Consensus on Baseline Diagnostic Options for Entry Level Dry Eye Disease

1. The lid
2. Staining
3. Tear stability

REV. as of March 13, 2015

Recommendations from the ***Dry Eye Summit 2014***

21

REV. as of March 13, 2015

Consensus on Baseline Management

1. For all patients:
   A. Ocular lubrication
   B. Lid hygiene
   C. Nutrition
2. Topical anti-inflammatories

Recommendations from the ***Dry Eye Summit 2014***

22

DREAM Study

- In a multicenter, double-blind clinical trial, we randomly assigned patients with moderate-to-severe dry eye disease to receive a daily oral dose of 3000 mg of fish-derived n−3 eicosapentaenoic and docosahexaenoic acids (active supplement group) or an olive oil placebo (placebo group).
- "The results of the DREAM study do not support use of omega-3 supplements for patients with moderate to severe dry eye disease"

23

DREAM Study

- In DREAM, most dry eye symptoms and signs appear to improve in both arms.
- In each trial group, there was a meaningful statistical change between baseline and 12 months (with time as a continuous variable) in the conjunctival staining score, the corneal staining score and the tear break-up time

24

Cequa (cyclosporine 0.09%)

- From Sun Pharmaceuticals
- Offers a novel nanomicelle formulation that helps improve the delivery of cyclosporine
- Enhanced solubility and increased ocular penetration of cyclosporine

25

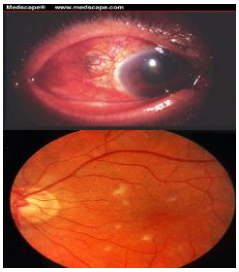
Case: Gonzalez

- 33 HF presents with a painful, red right eye
  - Started a couple of days ago, deep boring pain
  - Has tried Visine but hasn't helped the redness
- PMHx: patient reports she has been diagnosed with rheumatoid arthritis 3 years ago
  - Takes Celebrex for the joint pain
  - Patient reports she occasionally gets a skin rash when she is outdoors in the sun
- POHx: unremarkable
- PMHx: mother has rheumatoid arthritis

26

Case: Gonzalez

- VA:
  - 6/7.5 (20/30) OD,
  - 6/6 (20/20) OS
- Pupils: PERRL –APD
- VF: FTFC OH
- EOM's: FROM OU
- BP: 130/85 mm Hg RAS
- SLE: see picture
  - 2+ cells, mild flare
- IOP's: 16, 16 mm HG
- DFE: see fundus photo



27

Etiologies of Cotton Wool Spots

Vascular Occlusive Disease	Hypertension	Ocular Ischemic Syndrome
Autoimmune Disease e.g. SLE	Hyperviscosity syndromes	Trauma
Pre-eclampsia	Radiation Retinopathy	Toxic e.g. interferon
Neoplastic e.g. leukemia	Anterior Ischemic Syndrome	Infectious e.g. HIV

28

Patient Update

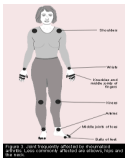
- Patient was worked up for lupus and diagnosed with lupus.
- Patient was already taking Celebrex which was not effective in treating the scleritis she presented with
  - upon referral to rheumatology it was discovered that she had several organs already being affected by the lupus
  - she was put on immunosuppressive agents to treat the systemic and ocular manifestations
- Patient was taken off of Celebrex and put on plaquenil (hydroxychloroquine) 400 mg po qd

29

RHEUMATOID ARTHRITIS

30

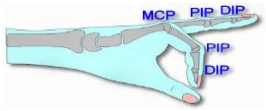
RA Epidemiology

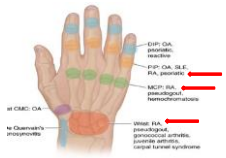


- Affects ~1% of the US population
- **Female** 3:1
- Most common age of onset: 50-75 years
  - though patients 35-50 may have early symptoms
- Lower prevalence in African Americans & Chinese (more common in Native Americans)
- **Smoking and obesity are risk factors***
- Genetic association (familial predisposition)
  - HLA-DR4 and HLA-DRB present in 50-75% of cases

31

RA presentation





- Slow, **symmetric** polyarthritis
- Pain, stiffness, swelling, limited movement in the **small peripheral joints** (**hands**, **wrist**, ankle, feet). Can progress to larger joints and organs
- Other symptoms: Weight loss, fatigue, fever, malaise

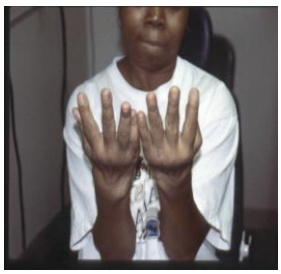
32

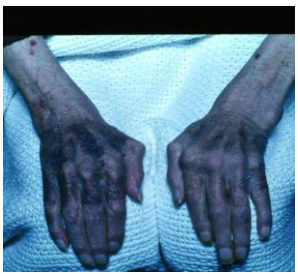
Rheumatoid Arthritis

- Rheumatoid Arthritis (RA) is not a benign disease.
- RA is associated with decreased life expectancy.
  - The risk of cardiovascular mortality is twice that of the general population.
- Affecting approximately 1% of the adult population, RA is associated with considerable disability.
- It is now well recognized that there is a "window of opportunity" early in the disease process to initiate treatment which will fundamentally change the course of the disease.

33

Rheumatoid Arthritis

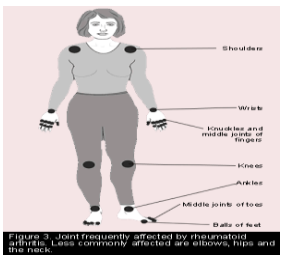




34

Epidemiology-Systemic

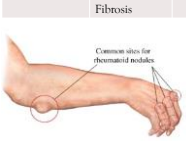
- Primary sites of infl' n are centered around musculoskeletal tissues
  - small joints with synovial linings are most commonly affected ie hands/feet early in disease
- RA joint characterized by hypertrophic, inflamed synovial tissue with fluid accumulation and adjacent soft tissue swelling
  - this is responsible for hot, swollen, tender joints that are hallmark of RA

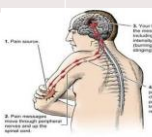


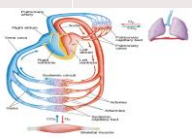
35

Other Diagnostic Criteria for RA

Cutaneous	Ocular	Pulmonary	Cardiac	Neurological	Hematological
Nodules	Sicca	Pleuritis	Pericarditis	Peripheral neuropathy	Leukopenia
Vasculitis	Episcleritis	Nodules	Atherosclerosis	Cervical myelopathy	Anemia of chronic disease
	Scleritis	Interstitial lung disease	Myocardial infarction		Lymphadenopathy
	Fibrosis				







36

Osteoarthritis (OA) vs. RA

- Etiology of RA is inflammatory which improves with activity while osteo is mechanical and worsens with activity
- Infl' n secondary to mechanical insults in osteo while no previous insult required in RA
- Joint cartilage is primary site of articular involvement in osteo while its the bony surfaces of the joints in RA

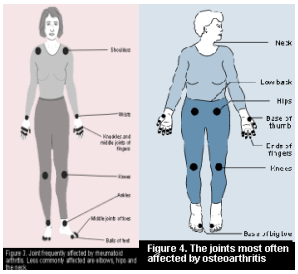
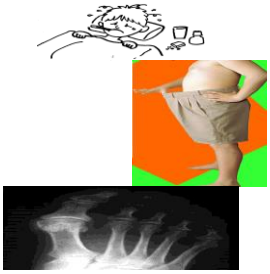


Figure 4. The joints most often affected by osteoarthritis

37

Diagnosis

- Many patients have symptoms that are not exclusive to RA making diagnosis difficult
  - prodromal systemic symptoms of malaise, fever, weight loss, and morning stiffness
- Lab tests and radiographic studies are necessary for initial diagnosis and are helpful in monitoring progression
  - no one single test is confirmatory of disease



38

Criteria for Diagnosis of RA

RA likely if:

- Morning stiffness > 30 minutes
- Painful swelling of 3 or more joints
- Involvement of hands and feet (especially MCP and MTP joints)
- Duration of 4 or more weeks
- Differential diagnoses include: crystal arthropathy, psoriatic arthritis, lupus, reactive arthritis, spondyloarthropathies.

39

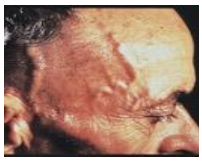
Lab Testing for RA

Tests	Diagnostic Value	Disease Activity Monitoring
ESR or CRP	Indicate only inflammatory process - Very low specificity	ESR elevated in many but not all active inflammation. Maybe useful in monitoring disease activity and response to treatment
RF	RF has a low sensitivity and specificity for RA. Seropositive RA has worse prognosis.	No value
ANA	Positive in severe RA, SLE, or other connective tissue disorders (CTD)	No value-do not repeat
X-rays	Diagnostic erosions rarely seen in disease of <3 mo's duration	Serial x-rays over many years may show disease progression and indicate med change
Joint aspiration	Indicated if infection suspected	

40

Giant Cell Arteritis

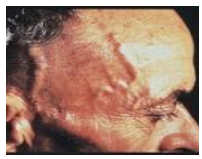
- vessels most often involved are the arteries over the temples,
  - GCA = "temporal arteritis."
- symptoms, such as fatigue, loss of appetite, weight loss or a flu-like feeling
  - pain in the jaw with chewing (jaw claudication).
  - Sometimes the only sign of GCA is unexplained fever.
  - Less common symptoms include pains in the face, tongue or throat.



42

Giant Cell Arteritis

- GCA is a clinical diagnosis!
- If patient meets criteria of clinical symptoms then treatment will be started regardless of whether lab test or biopsy are positive
- Treatment should be started before lab results are back.



43

GCA Treatment Update!!

- May 22, 2017:
  - FDA expanded and approved the use of subcutaneous Acetemra (tocilizumab) to treat adults with giant cell arteritis.
    - Approved in Canada
  - First FDA approved therapy, specific to this type of vasculitis
  - Compared to placebo and standardized prednisone treatment

44

Rheumatoid Factor (RF)

- RF is an autoantibody directed against IgG
- Most common lab testing are latex fixation and nephelometry
- RF present in 70-90% of patients with RA
  - However RF is not specific for RA
  - Occurs in a wide range of autoimmune disorders
  - Prevalence of positive RF increases with age
    - As many as 25% of persons over age of 65 may test positive
  - High titer for RF almost always reflects an underlying disease

45

Antibodies to Cyclic Citrullinated Peptides (ACPA)

- Proteins that contain citrulline are the target of an AB response that is highly specific for RA
- Associated conditions:
  - Appears to be quite specific for RA
    - Specificity as high as 97%
  - Sensitivity in the range of 70-80% for established RA and 50% for early-onset
  - Has superior specificity and comparable sensitivity for diagnosis of RA as compared to RF
    - **80-97% of patients have RA if they are RF+ and ACPA+**

47

Diagnosis

- Joint x-ray and radionucleotide evaluation of suspected inflamed joints are indicated

49

Rheumatoid Arthritis: Treatment

- Treatment must be started early to maximize the benefits of medications and prevent joint damage.
- The use of traditional medications in combination and the new biologic therapies has revolutionized the paradigm of RA treatment in recent years.
- There is no curative treatment for RA
  - treatment is to minimize inflammation
  - minimize damage and
  - maximize patient functioning

50

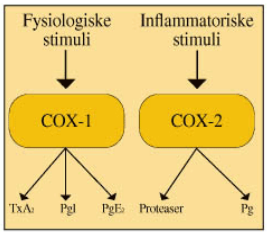
Treatment and Management-Systemic

- Current Tx regimens utilize a step-down approach with initiation of one or more DMARD's at time of diagnosis.
- RA most destructive early in disease
- "Easier" and more effective if Tx initiated early.
- DMARD-disease modifying antirheumatic drug
  - these drugs not only reduce inflammation but also change the immune response in a long-term and more dramatically than NSAID's
  - give chance of permanent remission

51

Treatment and Management: Aspirin and NSAID's

- block infl'n by inhibition of prostaglandin release in response to cell trauma
- arachadonic acid converted by COX (1&2) enzymes into inflammatory mediators including:
  - Thromboxanes
  - Prostaglandins
  - Leukotrienes



52

Cox-2 Inhibitors

- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.
- Major agent available on the market is Celecoxib (Celebrex).
  - Other agents Valdecoxib (Bextra) and Rofecoxib (Vioxx) were removed from the market due to increased risk of heart attacks and strokes.
- It is approved for the treatment of osteoarthritis and rheumatoid arthritis.
  - Dosage: 100 mg BID or 200 mg daily

53

Side Effects of Oral NSAID's

- NSAID's are excreted from the body via urine. Must monitor kidney function.
- NSAID's block prostaglandins to the kidney which causes renal blood flow to decrease and increases the retention of sodium and fluid.
  - Risk factors for kidney damage include:
    - Dehydration
    - Hypertension
    - Congestive Heart Failure
    - Use of ACE Inhibitors
    - Advanced Age
  - This will affect Cardiovascular homeostasis – can exacerbate heart failure.
    - NSAID's can cause hyperkalemia and have been linked to cardiac arrest in patients at risk.

54

NSAIDS Black Box Warning

- BLACK BOX WARNING:
  - May increase the risk of serious thrombotic events, MI, and stroke.
  - Increase risk of serious GI adverse effects such as bleeding, ulcer, and perforation.

55

Treatment and Management: Antimalarials

- Hydroxychloroquine (HCQ) more common and less toxic than more effective chorloquine
- usual dose is 200-400 mg/d @night with onset of action after a period of 2-4 months
- has mild DMARD effect, does not slow radiographic progression and has relatively slow onset of action, useful with other DMARD's

56

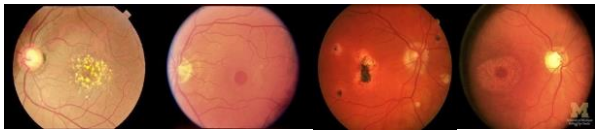
Treatment and Management: Antimalarial Ocular Complications

- Have affinity for pigmented structures such as iris, choroid and RPE
- Toxic affect on the RPE and photoreceptors leading to rod and cone loss.
- Have slow excretion rate out of body with toxicity and functional loss continuing to occur despite drug discontinuation.

57

Question

Which of the following depicts a retina undergoing hydroxychloroquine toxicity?

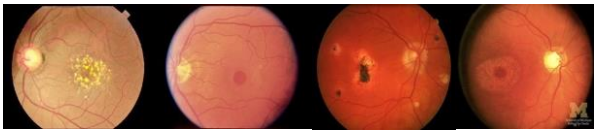


1 2 3 4

58

Question

Which of the following depicts a retina undergoing hydroxychloroquine toxicity?



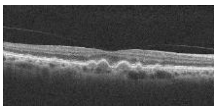
ARMD Macular Hole OHS Bull's Eye Maculopathy

59

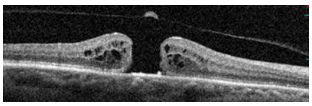
Question

Which OCT goes with a patient undergoing hydroxychloroquine toxicity?

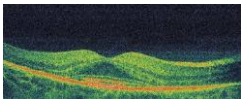
1



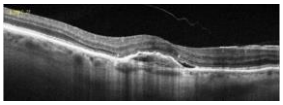
2



3



4



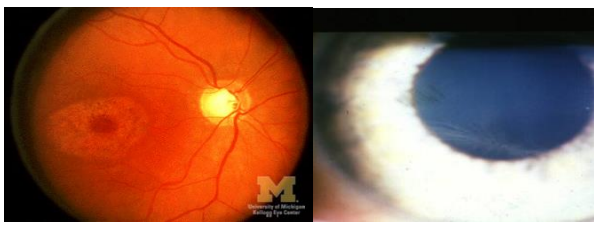
60

Treatment and Management: Antimalarial Ocular Complications

- Toxicity can lead to whorl keratopathy, "bulls eye" maculopathy, retinal vessel attenuation, and optic disc pallor.
- Early stages of maculopathy are seen as mild stippling or mottling and reversible loss of foveal light reflex
- "Classic" maculopathy is in form of a "bulls eye" and is seen in later stages of toxicity
  - this is an irreversible damage to the retina despite discontinuation of medication

61

Treatment and Management: Antimalarials



Bulls Eye Maculopathy Whorl Keratopathy

62

Revised Recommendations on Screening for Retinopathy

- 2002 recommendations for screening were published by Ophthalmology
- Revised recommendations on screening published in Ophthalmology 2011;118:415-42
  - Significant changes in light of new data on the prevalence of retinal toxicity and sensitivity of new diagnostic techniques
  - Risk of toxicity after years of use is higher than previously believed
    - Risk of toxicity approaches 1% for patients who exceed 5 years of exposure

63

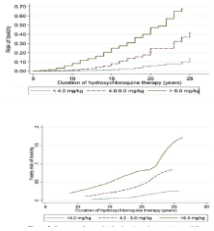
"New" New Recommendations

- **Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy** – Ophthalmology 2016; 123:1386-1394
  - Released March 2016 from American Academy of Ophthalmology
  - revised in light of new information about the prevalence of toxicity, risk factors, fundus distribution, and effectiveness of screening tools.

64

2016 Recommendations

- maximum daily HCQ use of 5.0 mg/kg real weight, which correlates better with risk than ideal weight.
- risk of toxicity is dependent on daily dose and duration of use.
  - at recommended doses:
    - risk of toxicity up to 5 years is under 1%
    - up to 10 years is under 2%
    - rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.



65

2016 Recommendations

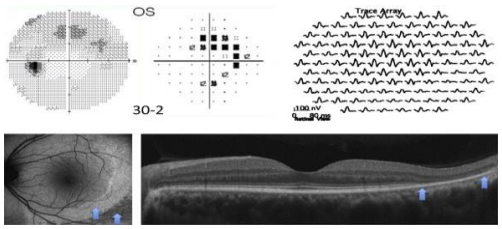
- High dose and long duration of use are the most significant risks.
  - Other major factors are concomitant renal disease, or use of tamoxifen
- A baseline fundus examination should be performed to rule out preexisting maculopathy.
- Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.

66

2016 Recommendations

- primary screening tests are automated visual fields plus spectral-domain optical coherence tomography (SD OCT)
- wider test patterns (24-2 or 30-2) are needed for Asian patients in whom toxicity often manifests beyond the macula. These larger patterns have only 4 central test spots, and even a single central spot of reduced sensitivity should be taken seriously.

67



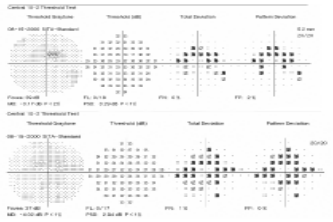
68

Revised Recommendations on Screening for Retinopathy

- Parafoveal loss of visual sensitivity may appear before changes are seen on fundus evaluation
  - Many instances where retinopathy was unrecognized for years as field changes were dismissed as "non-specific" until the damage was severe
  - 10-2 VF should always be repeated promptly when central or parafoveal changes are observed to determine if they are repeatable
  - Advanced toxicity shows well-developed paracentral scotoma

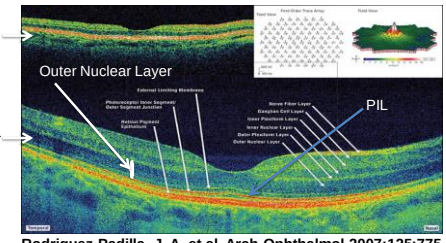
70

Paracentral Scotomas



71

Normal Retina: VF/OCT/ERG

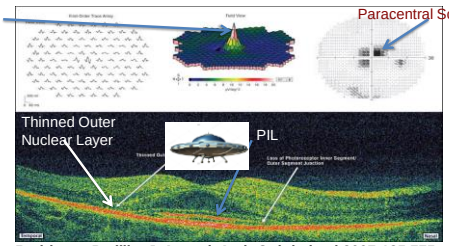


Rodriguez-Padilla, J. A. et al. Arch Ophthalmol 2007;125:775-780.

PIL=PR Integrity Line

72

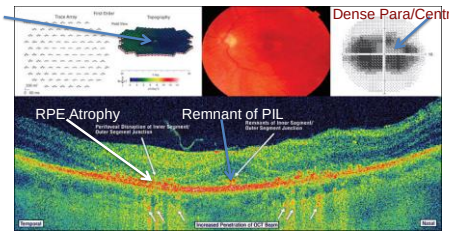
Mild Maculopathy



Rodriguez-Padilla, J. A. et al. Arch Ophthalmol 2007;125:775-780.

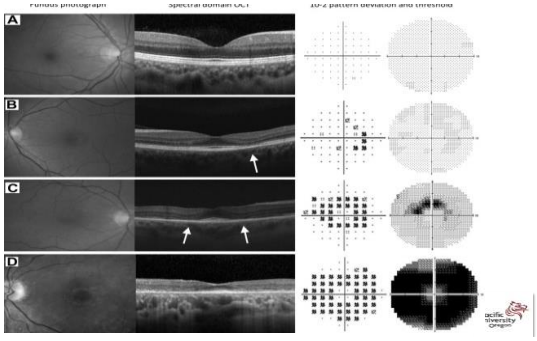
73

Bull's Eye Maculopathy



Rodriguez-Padilla, J. A. et al. Arch Ophthalmol 2007;125:775-780.

74



75

Major Risk Factors

Table 1. Major Risk Factors for Toxic Retinopathy

Daily dosage	
HCQ	>5.0 mg/kg real weight
CQ	>2.3 mg/kg real weight
Duration of use	>5 Yrs, assuming no other risk factors
Renal disease	Subnormal glomerular filtration rate
Concomitant drugs	Tamoxifen use
Macular disease	May affect screening and susceptibility to HCQ/CQ

CQ = chloroquine; HCQ = hydroxychloroquine.

76

Screening Recommendations

Table 2. Screening Frequency

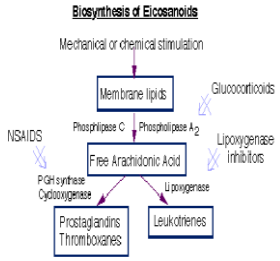
Baseline Screening
Fundus examination within first year of use
Add visual fields and SD OCT if maculopathy is present
Annual Screening
Begin after 5 yrs of use
Sooner in the presence of major risk factors

SD OCT = spectral-domain optical coherence tomography.

77

Treatment and Management: Steroids

- steroids interfere with all facets of the inflammatory process and effectively shut it down
- rapidly bring down joint infl' n and increase physical function and reduce progression of joint damage



78

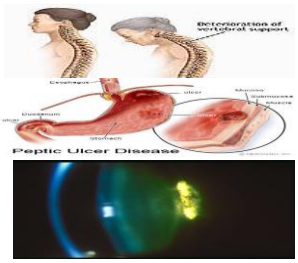
Systemic Corticosteroids

- Often grouped based on duration of action:
  - **Short acting**: Hydrocortisone and Cortisone
  - **Intermediate acting:** Prednisone, Prednisolone, Methylprednisolone, and Triamcinolone
  - **Long acting**: Dexamethasone
- Most commonly used oral steroid by Optometrists: **Prednisone**
- Most commonly used IV steroid by Optometrists: **Methylprednisolone**

80

Treatment and Management: Steroids

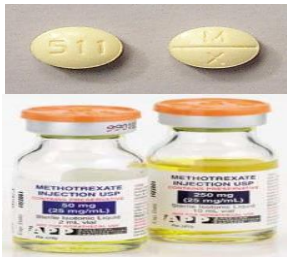
- usually used in short-term pulse dosages (e.g. 7.5 mg/day in combination with DMARD to reduce joint damage in early disease Tx).



83

Treatment and Management: Methotrexate

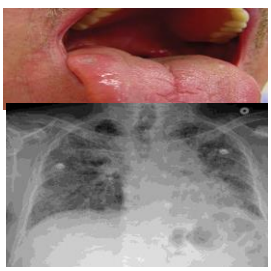
- now considered as part of mainstay treatment
- antimetabolite used in cancer therapy that inhibits DNA synthesis (thought to cause suppression of lymphocyte proliferation)
- low dose in RA (7.5-25mg) once weekly orally or injection with onset of action 6-8 weeks



84

Treatment and Management: Methotrexate

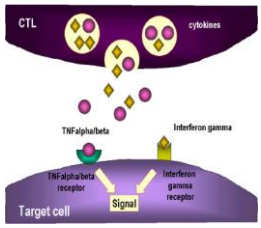
- toxicity not uncommon but adverse events tend to be minor and can be managed by cessation of drug.
- supplement of folic acid prevents common SE of oral ulceration and nausea.
- serious complications of lung disease and fibrosis with incidence of 3-15% and fatality of 17%.



85

Treatment and Management: Biological Therapies-TNF Inhibitor

- High concentration of TNF-alpha in synovial fluid in RA and increased in areas of bone erosions
- TNF-alpha released in cell damage and binds to receptors that increase the inflammatory process and cell death



86

Treatment and Management: Biological Therapies-TNF Inhibitor

- inhibitors bind TNF before it can be bound to the receptor (infliximab [Remicade], etanercept [Enbrel], adalimumab [Humira]) and newest golimumab (Simponi)
- quicker onset of action (several weeks)
- new studies indicate use as first line therapy, potentially combined with methotrexate

87

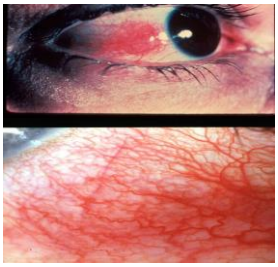
Treatment and Management: Biological Therapies-TNF Inhibitor

- Remicade: 3 mg/k as IV infusion followed by similar doses at 2 and 6 weeks and then every 8 weeks after
- Enbrel and Humira are SC injections every 2weeks
- Newest is Simponi which is once a month injection
- Adverse affects include increased risk of opportunistic infections (TB most common), malignancies (lymphoma) and neurological disease.
- common SE's include nausea and vomiting

88

Episcleritis

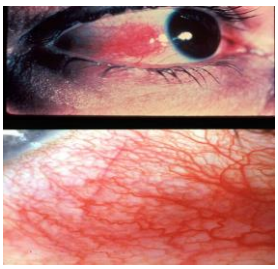
- self-limiting, recurring, idiopathic inflammation of the episcleral tissue that does not threaten vision
- Symptoms are a localized area of hyperemia of the globe, irritation, and lacrimation. Diagnosis is clinical. Treatment is symptomatic
- Unilateral (bilateral possible but rarely simultaneously)



89

Episcleritis

- occurs in young adults, more commonly among women. It is usually idiopathic; it can be associated with connective tissue diseases and rarely with serious systemic diseases.
- Recurrent episodes of episcleritis usually manifest prior to active periods of arthritis and a better indicator than dry eye
- Episcleritis will recur despite systemic treatment



90

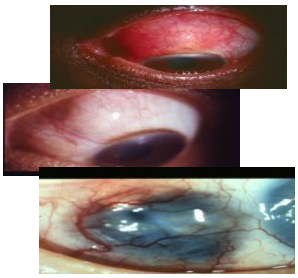
Treatment and Management: Episcleritis

- Treatment of episcleritis is dependent upon severity and chronicity.
- Palliative care maybe considered for mild cases (ocular lubrication).
- Utilization of vasoconstrictors, NSAIDs and steroid (Pred mild, Lotemax) use for more severe or chronic cases.

91

Scleritis

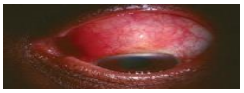
- chronic, painful, and potentially blinding inflammatory disease that is characterized by edema and cellular infiltration of the scleral and episcleral tissues
- Symptoms of scleritis can include pain, tearing or photophobia, tenderness, and decreased visual acuity. The primary sign is redness.

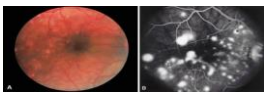


92

Ocular Manifestations-Scleritis

- classified into anterior and posterior.
- Anterior:
  - Diffuse and nodular forms
  - Necrotizing (with/without inflammation) less frequent
    - Have the most serious systemic implications
    - Scleromalacia perforans
- Posterior:
  - characterized by flattening of the posterior aspect of the globe, thickening of the posterior coats of the eye (choroid and sclera), and retrobulbar edema.





93

Treatment and Management: Scleritis

- Scleritis treatment depends on both the type and severity.
- Aggressive treatment is necessary in order to prevent structural damage.
- Topical steroids (e.g. Pred Forte) have ease of use and relatively minimal side effect profile when compared to systemic therapy are advantageous, scleritis does not usually respond to topical corticosteroids alone
- Subconjunctival/subtenon's triamcinalone:
  - A multicenter retrospective case series of 68 eyes with either diffuse or nodular scleritis showed that 89.7% of eyes had complete resolution after a single injection
  - Only indicated in non-necrotizing forms

94

Treatment and Management: Scleritis

- Oral NSAIDs:
  - considered first-line therapy for scleritis for their ease of use, cost, and relatively mild side effect profile for both anterior and posterior scleritis
  - E.g. Ibuprofen 400-600 mg QID, Naproxen 250-500 mg BID, or Indomethacin 25-50 mg TID
  - short term use of an NSAID is often well tolerated, NSAIDs can cause adverse effects which include peptic ulcer disease, hypertension, increased heart disease, bleeding, fluid retention, renal disease, and mood change

95

Treatment and Management: Scleritis

- Oral Prednisone:
  - considered to be the first line therapy for the treatment of non necrotizing scleritis in the setting of poor control on oral NSAIDs, or as a first line agent for necrotizing scleritis.
  - Typically start at between 40-60 mg until resolution with a slow taper

96

Treatment and Management: Scleritis

- If necrotizing present patient needs to receive aggressive medical therapy by rheumatologist
  - patients have better prognosis when immunosuppressive therapy is instituted

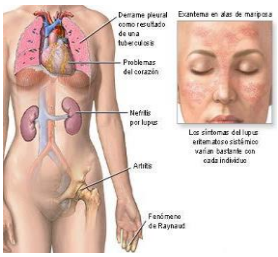
97

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

98

Systemic Lupus Erythematosus (SLE)

- Idiopathic, multisystemic inflammation disorder characterized by hyperactivity of immune system and prominent auto-antibody production
  - against components of cell membranes and nuclear material
- Acute periods followed by periods of remission are common
  - gives disease an unpredictable course



99

Systemic Lupus Erythematosus (SLE)

- Definite genetic predisposition has been demonstrated
  - environmental factors also play a role especially as triggers
- Clinical course varies from mild episodic disorder to rapidly developing fatal disease

100

Epidemiology

- SLE is not uncommon with prevalence exceeding 1:2000 persons with 85% being female
- Disease may occur at any age though most patients are b/w ages 20-40
  - AA being affected 3x more than any other race (and more severely)

101

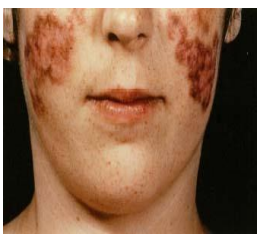
Epidemiology

- Have to ensure that condition is not secondary to a drug response (several drugs produce lupus-like syndrome)
  - Agents strongly associated include:
    - Procainamide (cardiac arrhythmias), hydralazine (high blood pressure) and isoniazid (anti-tuberculosis)
    - Others include: phenytoin, quinidine, tetracyclines and TNF inhibitors.

102

Diagnosis

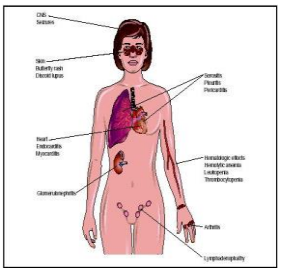
- Based on clinical presentation and lab results
- Systemic features include
  - fever
  - anorexia
  - malaise and
  - weight loss.
- Most patients have skin lesions at some time with the characteristic "butterfly" rash (occurs apprx 50%) and often precedes disease manifestations



103

Diagnosis

- Joint symptoms (with/without active synovitis) occur in >90% of patients and are often the earliest manifestation.
- Other organs affected include heart, kidney, lungs, CNS.
- American Rheumatolgy Association established 11 criteria for diagnosis (8 clinical manifestations and 3 lab).
  - Minimum of 4 needed serially or simultaneously.



104

Lab Tests: Antinuclear Antibodies (ANA)

- AB's directed against nuclear material:
- Detection is via indirect immunofluorescence
  - ANA with titers ≥ 1:40 considered positive
- Associated conditions:
  - Positive tests occur in a wide variety of conditions
    - Low-titer ANA are relatively common among healthy adults

105

Conditions Associated with Positive ANA

Rheumatic Diseases	Organ-Specific AI Diseases	Other
SLE	AI thyroid disease	Drug-induced lupus
Mixed connective tissue disease	AI hepatitis	Asymptomatic drug-induced ANA
Scleroderma	Primary biliary cirrhosis	Chronic infections
Sjogren syndrome	AI cholangitis	Idiopathic pulmonary fibrosis
RA		Primary pulmonary hypertension
Polymysositis		Lymphoproliferative disorders
Dermatomyositis		Type 1 diabetes (ketoacidosis)
Discoid Lupus		

106

Lab Tests: Antinuclear Antibodies (ANA)

- Indications:
  - Very useful initial test when there is clinical suspicion of:
    - SLE,
    - drug induced lupus
    - Mixed connective tissue disease
    - Scleroderma
- Interpretation:
  - Sensitivity of ANA for SLE is very high (>95%)
    - Negative result is very strong evidence against the diagnosis and usually precludes the need to pursue further testing

107

Lab Tests: Antinuclear Antibodies (ANA)

- Interpretation:
  - Probability of an underlying AI disease increases with the titer of the ANA
  - In an unselected population:
    - Positive test has a predictive value for SLE of 30-40%
    - Negative predictive value for SLE is >99%
  - In proper clinical context a positive ANA provides support for further testing for SLE

108

Lab Tests: Antibodies to Double-Stranded DNA

- ELISA is most commonly used
- Associated conditions:
  - Occurs in SLE and is rare in other diseases and in healthy persons
- Indications:
  - Should be measured when there is clinical suspicion of SLE and the ANA is positive
- Interpretation:
  - Specificity for SLE is 97% and approaches 100% when titer is high
  - AB's occur in 60-80% of patients with SLE

110

Lab Tests

- Decreased serum complement C1 level is 90% predictive for SLE and C4 is 75%
  - simultaneous presence of both a decreased C1 level and native DNA Ab's has been been reported to be virtually 100% predictive
- Decreased serum complement levels result from activation and consumption of complement components

111

"New" Lab Tests

- Anti Sm is found almost exclusively in people with lupus.
  - It is present in 20% of people with the disease
  - rarely found in people with other rheumatic diseases and its incidence in healthy individuals is less than 1%
- Anti-RNP antibodies are commonly found along with anti-Sm antibodies in people with SLE.
  - The incidence in lupus is approximately 25%, while less than 1% of healthy individuals possess this antibody.
- Anti-Ro/SSA and Anti-La/SSB are antibodies found mostly in people with systemic lupus (30-40%) and primary Sjogren's syndrome.
  - They are also commonly found in people with lupus who have tested negative for anti-nuclear antibodies.

112

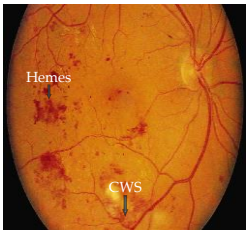
Treatment and Management

- No cure for SLE (rest, reduce stress and avoid UV exposure)
- Medical management includes:
  - Salicylates and NSAIDs employed to treat arthralgias, arthritis, myalgias and fever in 20-30% of Px with mild disease
  - Antimalarials (Plaquenil) used to treat discoid lesions and joint disease
  - High dose, short-acting steroids are used in life-threatening and severely disabling cases. Prolonged maintenance at low dosages needed after.
  - Cytotoxic controversial-used when steroids ineffective
  - Exp therapy: high dose immunoglobulin injections

113

Ocular Manifestations

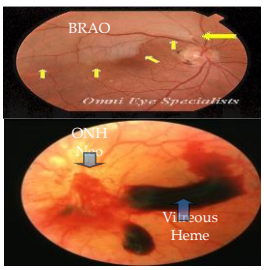
- SLE produces various ocular complications which tend to manifest in more acutely ill patients.
- Retinal vasculopathy is believed to be due to autoimmune reactions to Ab/Ag complexes deposited in the retinal/choroidal vessel walls.
- Common retinal finding include:
  - Cotton wool spots (CWS)
  - Retinal hemes



114

Ocular Manifestations

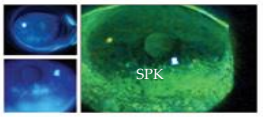
- Occlusions are uncommon but occur more frequently in arteries and can result in nonperfusion and hypoxia.
- Optic nerve and retinal neo may arise.
- Vitreous heme and RD may also occur.
- Optic atrophy and blindness may result in severe occlusions.

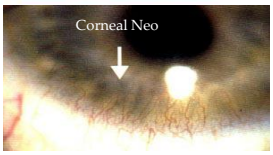


115

Ocular Manifestations

- SPK most common corneal change
- In patients with uncontrolled systemic disease sicca syndrome is common
- Occasional corneal manifestations may include infiltrates, ulcers and neo.

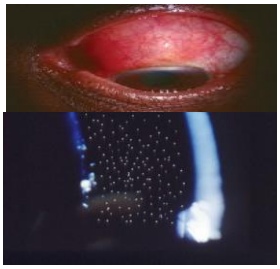




116

Ocular Manifestations

- Scleritis is usually diffuse and nodular and is fairly common. It may be the presenting feature of SLE.
- Non-granulomatous uveitis is sometimes found
- Diplopia and pupillary abnormalities secondary to cranial nerve palsies also arise



117