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### Disclosures:

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



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### Case

- 30 BF presents with eye pain in both eyes for the past several days
  - Severe pain (8/10)
  - Never had eye exam before
- PMHx:
  - Has chronic bronchitis
  - Rash on legs
  - Has recently lost weight and has a fever
  - Taking aspirin for pain



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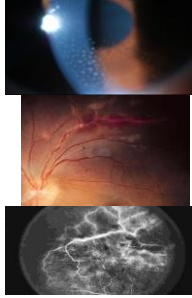
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# Ocular Health Assessment

- VA: 6/9 (20/30) OD, OS
- PERRL
- FTFC
- EOM's: FROM with eye pain in all quadrants
- SLE:
  - 3+ injection,
  - 3+ cells and trace flare,
  - deposits on endo (see photo)
- IOP: 18, 18 mmHg
- DFE:
  - see attached fundus image and fluorescein angiography.




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## Sarcoid Diagnosis

Lab Test	Findings
CBC with differential	Anemia/thrombocytopenia/leukopenia
Serum calcium/24 hour calcium	Hypercalcemia
Liver/Kidney function tests	AST/ALT/BUN/Creatinine elevated in hepatic disease
ACE (angiotensin converting enzyme)	Elevated in 60% of patients
Pulmonary x-rays	Hilar adenopathy



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## Blood Chemistry

- **Angiotensin-Converting Enzyme (ACE)**
  - Found mainly in lung and liver
  - Serum elevations are found in patients with sarcoidosis, and significant levels are achieved in pulmonary sarcoid
  - Cirrhosis of the liver may produce elevated ACE levels
  - **Active tuberculosis infection of the lung does NOT produce elevated ACE levels**



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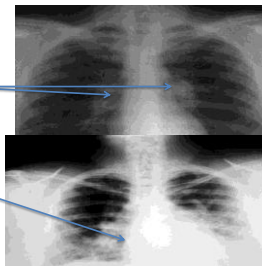
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## Diagnosis: Radiographic

- Radiographic involvement is seen in almost 90% of patients.
- Chest radiography is used in staging the disease:
  - Stage I disease shows bilateral **hilar lymphadenopathy** (BHL).
  - Stage II disease shows BHL plus pulmonary infiltrates.
  - Stage III disease shows pulmonary infiltrates without BHL
  - Stage IV disease shows pulmonary fibrosis.



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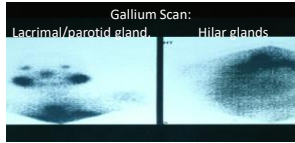
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## Diagnosis: Radiographic

- CT and MRI scans may be useful in finding granulomas in other organ systems
- Gallium scan-gallium 67 has been found to accumulate in active sarcoidal tissue



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**Table 1**

**5 Stages of syphilis**

Stage	Symptoms
Primary syphilis	Chancere in genitalia (often unnoticed)
Secondary syphilis	Maculopapular, non-tender rash; fever; lymphadenopathy; condyloma latum (genital)
Latent syphilis	Asymptomatic; serum nontreponemal and treponemal antibody tests are positive
Tertiary syphilis	Multiple organ-system involvement: Nerve involvement (deafness), aortic root dilation, aortitis, gummas (liver, bone, skin, spleen)
Neurosyphilis	Any stage can progress to neurologic involvement. Most common presentation is asymptomatic pupillary afferent defect (Argyll Robertson pupil). Focal symptoms include aphasia, paresis, blurry vision, hearing loss, seizures, ataxia, bowel or bladder incontinence, tabes dorsalis, loss of position and vibration senses, progressive ataxia, and sudden and severe pain, loss of balance, delirium, hydrocephalus, transverse myelitis, and stroke-like small vessel changes

<https://www.mdedge.com/psychiatry/article/110901/somatic-disorders/psychosis-treated-neurosyphilis-now-time-strn-his/hansa/01762e2f3a8>



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## Syphilis Diagnosis

- Typical diagnosis is with blood tests using nontreponemal and/or treponemal tests.
- Nontreponemal tests:
  - Although these screening tests are nonspecific, and therefore not definitive, they have traditionally been used for initial syphilis screening due to their relatively low cost, ease of performance, and ability to be quantified for the purpose of following response to therapy.
    - venereal disease research laboratory (VDRL)
    - rapid plasma reagin (RPR)
- False positives can occur with some viral infections such as (varicella and measles), as well as with lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, pregnancy



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## Syphilis Diagnosis

- confirmation is required with a treponemal test:
- Specific treponemal tests include:
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Microhemagglutination test for antibodies to *T. pallidum* (MHA-TP)
  - *T. pallidum* particle agglutination assay (TPPA)
  - *T. pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)



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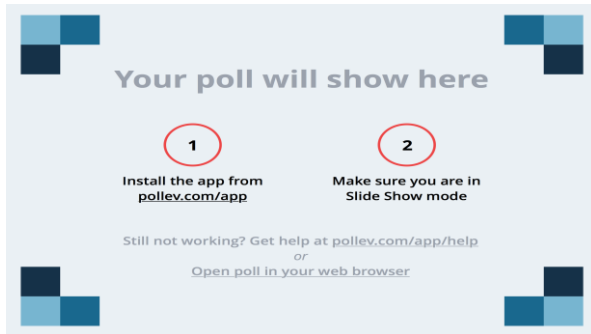
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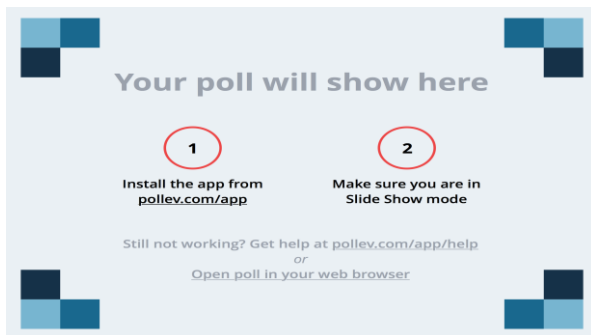
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## Tuberculosis

- Difficult to culture the slow-growing organism in the laboratory (it may take 4 to 12 weeks for blood or sputum culture).
- A complete medical evaluation for TB must include:
  - a medical history,
  - a physical examination,
  - a chest X-ray,
  - microbiological smears,
  - and cultures.
- It may also include a tuberculin skin test, a serological test.
  - The interpretation of the tuberculin skin test depends upon the person's risk factors for infection and progression to TB disease, such as exposure to other cases of TB or immunosuppression



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## Tuberculosis

- Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from *M. tuberculosis*.
- Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common



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## Tuberculosis

- The newer interferon release assays (IGRAs) overcome many of these problems.
  - IGRAs are in vitro blood tests that are more specific than the skin test.
  - IGRAs detect the release of interferon gamma in response to mycobacterial proteins
  - These are not affected by immunization or environmental mycobacteria, so generate fewer false positive results.



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## Rifampin

- **Treatment of tuberculosis**, there are three preferred regimens, chosen for effectiveness, safety and high treatment completion rates, **are rifamycin-based**. They are
  - three months of once-weekly isoniazid plus rifapentine for adults and children older than age 2, regardless of HIV status;
  - four months of daily rifampin; or
  - three months of daily isoniazid plus rifampin



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## Rifampin

- Rifampin:
  - **the most commonly used rifamycin for treatment of nontuberculous mycobacterial diseases, in combination with other agents.**
  - It is also used for treatment of tuberculosis (active disease and latent infection), for prophylaxis following exposure to *Neisseria meningitidis* or *Haemophilus influenzae*, and as an adjunctive agent for treatment of select deep-seated staphylococcal infections.



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## Rifampin

- Rifampin:
  - **The usual adult dose of rifampin for treatment of tuberculosis is 10 mg/kg (maximum 600 mg daily) given daily or three times weekly by directly observed therapy.**
  - Patients should be advised that rifampin typically causes an orange or **red-orange discoloration of body fluids** (including urine, sweat, saliva, and tears).
  - The potential for drug-drug interactions with rifamycins is high for individuals taking the following drugs: warfarin, oral or other hormonal contraceptives, some antihypertensives, some antiarrhythmics, some antidepressants, some anticonvulsants, methadone, and the protease inhibitor class of antiretroviral drugs.



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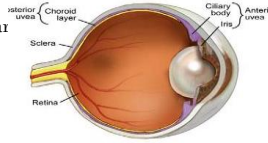
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## Uveitis

- Uveitis frequently is nonspecific but can be associated with:
  - systemic disease,
  - occur following trauma, or
  - be the result of a primary ocular disorder such as:
    - Fuchs's heterochromic iridocyclitis or
    - glaucomatocyclitic crisis (Posner-Schlossman syndrome)



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## Classification of Uveitis

- 4 main questions we need answered
  - Where is the inflammation located?
  - Is disease acute or chronic?
  - Granulomatous or non-granulomatous?
  - Unilateral or bilateral?




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## Classification of Uveitis

- Secondary Questions:
  - Demographics of the patient
  - Has this happened before? If so did it respond to treatment?
- Systemic questions:
  - Lung /breathing problems?
  - Rashes/skin problems?
  - Joint problems or low back pain?
  - Urination issues?
  - Digestive problems – diarrhea? Bloody stools? Cramps?
  - Have you been out of the country recently?
  - Have you been in a wooded area? Ticks?
  - Any other systemic/autoimmune diseases?




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## Classification

- Classification is the key to the proper diagnosis and management of the uveitic patient
- Most common classifications
  - Anterior vs. Intermediate vs. Posterior vs. Panuveitis
  - Acute vs. Chronic/Recurrent
  - Granulomatous vs. Non-granulomatous
  - Infectious vs. Autoimmune



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## Helpful Mnemonic

- Mnemonic for acute forms of non-granulomatous uveitis: **BLAIR G**
  - B:** Behcet's disease
  - L:** Lyme disease
  - A:** Ankylosing spondilitis
  - I:** Inflammatory bowel disease (Crohns/ulcerative colitis)
  - R:** Reactive arthritis
- G:** Glaucomatocyclitic crisis



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## Uveitis

- The clinical features of anterior uveitis are readily recognizable
  - complaints of:
    - photophobia,
    - pain,
    - blurred or variable vision
- A change in the blood-aqueous barrier results in the liberation of protein and cellular matter into the anterior chamber and the vitreous.



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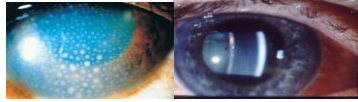
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# Uveitis

- Clinical findings of:
  - circumlimbal hyperemia,
  - cells and flare in the aqueous and anterior vitreous, and
  - keratic and trabecular precipitates




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## Uveitis: Treatment

- "Classical treatment":
  - Pred forte: prednisolone acetate 1% formulation which allows penetration through cornea to anterior chamber
  - dependent upon the severity of the uveitis
  - In severe uveitis an aggressive treatment may require a drop every 15-30 minutes (for 6-8 hours) then every hour (while awake) until the follow up exam
  - Mild to moderate: every 1-3 hours while awake until follow up exam
- "Newer" treatment option:
  - Durezol



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## Treatment Options

- Durezol:
  - Difluprednate
    - only difluorinated steroid
  - Steroid emulsion
  - BAK free
  - Increased "potency" so dosing needs to be less than "classical treatment" with Pred Forte
    - rough recommendation is 1/2 dosing of Pred Forte



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## Cycloplegics

- Common cycloplegic agents include:
  - cyclopentolate 1-2% tid for mild-to-moderate,
  - homatropine 5% BID
  - scopolamine 0.25%
  - atropine 1% bid-tid for moderate-to-severe inflammation
- most common is the use of Homatropine 5% bid (though challenging to find due to manufacturing)
- be careful using atropine as there is potential for severe systemic side effects
  - also makes the iris essentially immobile



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## Cycloplegics

- Cycloplegia:
  - used for reduction of pain,
  - break/prevent the formation of posterior synechiae
  - also functions in the reduction of inflammation
- Cycloplegics may not be enough to break existing synechiae
  - Consider adding a sympathomimetic drug such as phenylephrine which activates the iris dilator muscles and may break the synechiae
  - 2.5% is commonly used as part of "routine" dilation but 10% is also available and is primarily used for breaking synechiae
    - Word of caution: 10% is contraindicated in patients with hypertension or thyrotoxicosis and children under the age of 1.
    - Cardiovascular effects which have been seen primarily in hypertensive include marked increase in blood pressure, syncope, myocardial infarction, tachycardia, arrhythmia and subarachnoid hemorrhage



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## Treatment

- Topical administration is most common though periocular injections and systemic meds are useful for posterior uveitis and difficult cases
- Dosing is dependent upon severity of the inflammation
  - typically you want to hit the uveitis hard and fast!
    - E.g. In severe uveitis an aggressive treatment may require a drop every 15-30 minutes (for 6-8 hours) then every hour (while awake) until the follow up exam
    - Mild to moderate: every 1-2 hours while awake until follow up exam
    - Dosing should continue until the inflammation is gone (i.e. no cells or flare noted in the anterior chamber) before steroid tapering
    - If you have a minimal anterior chamber reaction then steroid may not be necessary at all (e.g. traumatic iritis)



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## Treatment

- **NOTE: it is crucial to taper your steroid treatment!**
  - You will have a rebound inflammation if you simply remove your patient from their steroids...especially if the anterior chamber is not completely resolved.
    - Consider beginning taper a day or two after you have seen resolution of the anterior chamber reaction to ensure no residual inflammation



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### Treatment

- The taper will be dependent upon how long you have had them on the steroid to get rid of the inflammation!
- Typically, a slow taper is better in order to prevent rebound inflammation
- If the patient has been on the steroid for less than a week a faster taper can be considered.
- Important to inform patient that they may be receiving steroid treatment for a significant time period (weeks to months) and important to not stop treatment even if feeling better.



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### Treatment

- NSAIDs:
  - do not play an important role in the treatment of an acute uveitis
    - Topical NSAID's may have a possible role as adjunctive therapy in reducing inflammation and potentially treat CME associated with the uveitis
    - Oral NSAIDs may reduce the chance of recurrence and reduce the total cumulative dose of steroids
      - Note: this has to be balanced with the side effects of chronic oral NSAID use



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### Follow-up

- Every 1-7 days in acute phase depending upon severity and every 1-6 months when stable.
- On each f/u visit the AC reaction and IOP should be evaluated
  - DFE should be performed for flare-ups, when VA affected, or every 3-6 months.



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## Follow Up

- If AC reaction improving, then steroid drops can be slowly tapered.
  - cycloplegia can also be tapered as the AC reaction improves.
  - slow taper recommended for chronic granulomatous uveitis.



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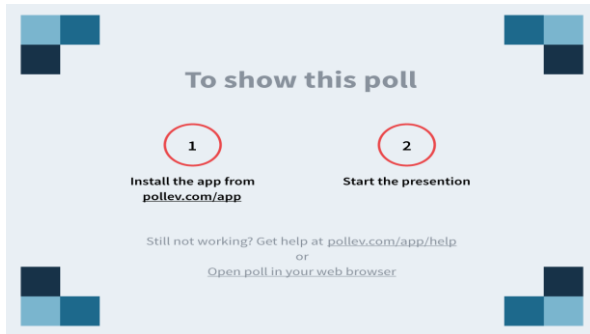
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## Systemic Corticosteroids

- Prednisone
  - Available as Oral: 1, 2.5, 5, 10, 20, 50 mg tablets and 1 and 5 mg/mL solution and syrup
- Ocular Treatment Guidelines:
  - Mild to Moderate: Initial dose of 20-40 mg
  - Moderate to Severe: 40 – 60 mg
  - Severe: Begin with 60 mg and increase if necessary
  - Specific Conditions: Giant Cell Arteritis
    - 80-100 mg Prednisone
    - Consider IV Methylprednisolone 250 mg IV q6hours for 12 doses



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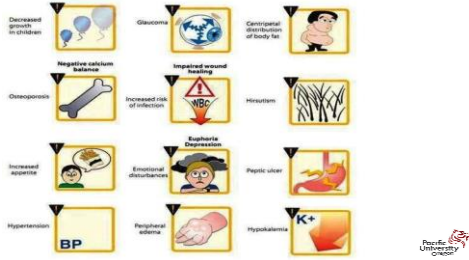
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### CORTICOSTEROIDS Side Effects



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### HLA-B27 Conditions

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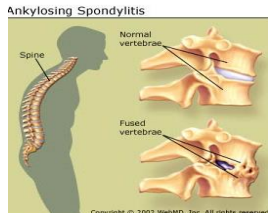
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### Ankylosing Spondylitis

- Ankylosing spondylitis is a type of arthritis that affects the spine:
  - symptoms include pain and stiffness from the neck down to the lower back.
- The vertebrae may grow or fuse together, resulting in a rigid spine.
  - these changes may be mild or severe, and may lead to a stooped-over posture.



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## Ankylosing Spondylitis

- Ankylosing spondylitis affects about 0.1% to 0.5% of the adult population.
- Although it can occur at any age, spondylitis most often affects men in their 20s and 30s.
  - It is less common and generally milder in women and most common in Native Americans.
- Early diagnosis and treatment helps control pain and stiffness and may reduce or prevent significant deformity.



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## Ankylosing Spondylitis

- Physical Exam:
  - The overall points taken into account when making an AS diagnosis are:
    - Onset is usually under 35 years of age.
    - Pain persists for more than 3 months (i.e. it is chronic).
    - The back pain and stiffness worsen with immobility, especially at night and early morning.
    - The back pain and stiffness tend to ease with physical activity and exercise.
    - Positive response to NSAIDs (nonsteroidal anti-inflammatory drugs).



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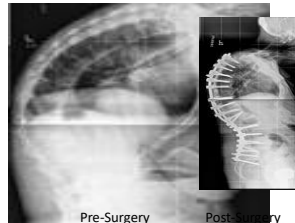
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## Ankylosing Spondylitis

- X-rays:
  - The hallmark of AS is involvement of the sacroiliac (SI) joint
  - show erosion typical of sacroiliitis (inflammation of the sacroiliac joints).
  - can take 7 to 10 years of disease progression for the changes in the SI joints to be serious enough to show up in conventional x-rays.



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### Psoriatic Arthritis

- Psoriasis is a scaly rash that occurs most frequently on the elbows, knees and scalp, but can cover much of the body.
- It is a chronic, inflammatory disease of the skin, scalp, nails and joints.



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### Psoriatic Arthritis

- In 5-10% of those with psoriasis, arthritis also appears.
  - In most cases the psoriasis will precede the arthritis, sometimes by many years.
- When arthritis symptoms occur with psoriasis, it is called psoriatic arthritis (PSA).
  - the joints at the end of the fingers are most commonly affected causing inflammation and pain, but other joints like the wrists, knees and ankles can also become involved.
  - usually accompanied by symptoms of the fingernails and toes, ranging from small pits in the nails to nearly complete destruction and crumbling as seen in reactive arthritis or fungal infections.



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## Psoriatic Arthritis

- About 20% of people who develop PsA will eventually have spinal involvement, which is called psoriatic spondylitis.
- The inflammation in the spine can lead to complete fusion - as in ankylosing spondylitis - or skip areas where, for example, only the lower back and neck are involved.
- Those with spinal involvement are most likely to test positive for the HLA-B27 genetic marker.
- Up to 40% of people with PsA have a close relative with the disease, and if an identical twin has it, there is a 75% chance that the other twin will have PsA as well.



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## Reactive Arthritis

- Reactive Arthritis (formerly known as Reiter's Syndrome) is a form of arthritis that can cause inflammation and pain in the:
  - joints, the skin, the eyes, the bladder, the genitals and the mucus membranes.
- Reactive arthritis is thought to occur as a "reaction" to an infection that started elsewhere in the body, generally in the genitourinary or gastrointestinal tract.



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## Reactive Arthritis

- Reactive arthritis occurs after exposure / infection caused by certain types of bacteria. These include:
  - Chlamydia
  - Bacteria such as Salmonella, Shigella, Yersinia or Campylobacter, which occurs after eating spoiled or contaminated food.
- Not everyone exposed to these bacteria will contract ReA.
  - Those who go on to develop ReA tend to test positive for the HLA-B27 genetic marker, although other genetic factors may be involved.
  - Thus, it is an interaction between an individual's genetic make-up and the initial infection that causes Reactive Arthritis.



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## Reactive Arthritis

- ReA usually develops 2-4 weeks after the infection.
- A tendency exists for more severe and long-term disease in patients who do test positive for HLA-B27 as well as those who have a family history of the disease.
- Reactive Arthritis typically follows a limited course, where symptoms subsiding in 3-12 months.
  - However, the condition has a tendency to recur.
- About 15-20% of people with ReA develop a chronic, and sometimes severe, arthritis or spondylitis.



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## ReA Conjunctivitis

- Eye involvement occurs in about 50% of men with urogenital reactive arthritis and about 75% of men with enteric reactive arthritis.
- Conjunctivitis and uveitis can include redness of the eyes, eye pain and irritation, or blurred vision.
- Eye involvement typically occurs early in the course of reactive arthritis, and symptoms may come and go
- Treatment includes NSAIDs and/or steroids



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## Enteropathic Arthritis

- Enteropathic arthritis is a form of chronic, inflammatory arthritis associated with the occurrence of an inflammatory bowel disease (IBD):
  - the two best-known types of which are ulcerative colitis and Crohn's disease.
- About one in five people with Crohn's or ulcerative colitis will develop enteropathic arthritis.
- The most common areas affected by enteropathic arthritis are inflammation of the peripheral (limb) joints, as well as the abdominal pain and possibly bloody diarrhea associated with the IBD component of the disease.
- In some cases, the entire spine can become involved as well.



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## Enteropathic Arthritis

- The course and severity of enteropathic arthritis varies from person to person.
- The disease "flares" - the times when the disease is most active and inflammation is occurring - tend to be self-limiting, often subsiding after 6 weeks, but reoccurrences are common.
- In some cases the arthritis may become chronic and destructive.



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## Juvenile Rheumatoid Idiopathic Arthritis (JRA/JIA)

- "Rheumatoid like" disease with onset before age 17
- Group of arthritides responsible for significant functional loss in children
- Most common chronic disease with genetic predisposition in children.
- 2:1 female:male, with peak incidence b/w 2-4 and then 10-12



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## Natural History



- Pathogenesis unknown
- Immune-mediated activity directed towards Type II collagen
- RF mediated responses rarely found
- 1° involves weight bearing joints of lower extremities (knees/ankles) as well as joints of elbows/hands
- Little associated pain/tenderness observed



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## Diagnosis



- Synovitis that persists for at least 6 weeks is the essential criterion for diagnosis.
- Hematologic and radiographic studies are beneficial in diagnosis and classification.
- Fewer than 20% of patients have positive RF
- Radiographic evaluation of inflamed joints reveal soft tissue swelling and peri-articular osteoporosis with possible new bone formation.
- Loss of the cartilaginous space with erosions occur after long duration.



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## Ocular Manifestations

- Classic triad of iridocyclitis, cataract and band keratopathy
- Overall incidence of iridocyclitis is approx 20%.
- Cataract, glaucoma, and band keratopathy are seen in 50% of patients who develop persistent iridocyclitis.



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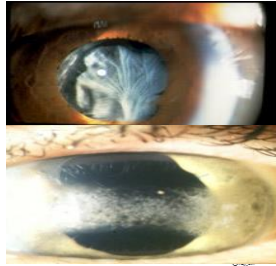
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## Ocular Manifestations

- Severe vision loss results primarily from cataract formation and less frequently from band keratopathy.
- Insidious onset of ocular involvement, with the iridocyclitis commonly following the arthritis symptoms (though occasionally preceding)
- Patients are often asymptomatic and therefore require ocular evaluation for detection



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## Ocular Manifestations

- Evidence of chronic iridocyclitis may be presenting sign leading to Dx of JIA
- Posterior segment involvement is not commonly seen
- Band keratopathy in children <16 is pathognomonic for JIA
  - results from aggressive/chronic ocular inflammation (not abnormal calcium metabolism).
- JIA patients do not present with the dry eye and K sicca manifestations that are so prevalent in RA.



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## Treatment and Management-Ocular

- Systemic medical therapy has minimal effect on ocular inflammation
- Topical steroids and short acting cycloplegics remain primary treatment
- Decreased VA 2° to cataract requiring extraction
- Band keratopathy develops in eyes with chronic iridocyclitis and require treatment with chelating agents
- Patients who develop glaucoma need to be treated aggressively



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