Approach to inflammation

Dr . Parisa Noorabadi

Assistant professor of Rheumatology

UMSU

- APPs are non-specific markers of inflammation, and the tests used should be interpreted in conjunction with history, physical examination, and other laboratory tests and imaging.
- Their levels will be elevated during both acute and chronic inflammation.

- The best accepted clinical measures of acute inflammation are CRP and ESR.
- CRP is more sensitive and easily measured in the majority of clinical laboratories.
- ESR is an indirect measure of APR proteins, mainly fibrinogen.

- The normal ESR value for **men is 0 to 15** mm/hour and for **women 0 to 20 mm/hour.**
- **Factors that increase ESR include**:
- infection, inflammation, malignancy, pregnancy, autoimmune diseases (SLE, RA, GCA, polymyalgia rheumatic, thyroiditis), multiple myeloma,
- Waldenstrom macroglobulinemia, anemia, macrocytosis, and old age.
- **Factors that decrease ESR** include hypogammaglobulinemia, hypofibrinogenemia, microcytosis, spherocytosis, sickle cell disease, polycythemia, and extreme leukocytosis (e.g., chronic lymphocytic leukemia).

- After an acute inflammatory stimulus, **CRP** concentration **increases rapidly** and **peaks at 2 to 3 days** at levels that reflect the extent of tissue injury.
- If the stimulus has been removed, serum CRP levels **drop rapidly**, with a half-life of roughly **19 hours**.

Persistent elevations in CRP are seen in **chronic inflammatory** or i**nfectious** states such as **active RA** or **pulmonary tuberculosis**, and may be observed also in **extensive malignant disease**.

TABLE 60.4 Conditions Associated With Elevated C-Reactive Protein Levels

Normal or Minor Elevation (<1 mg/dL)

Vigorous exercise
Common cold
Pregnancy
Gingivitis
Seizures
Depression
Insulin resistance and diabetes
Several genetic polymorphisms
Obesity

Moderate Elevation (1 to 10 mg/dL)

Myocardial infarction
Malignancies
Pancreatitis
Mucosal infection (bronchitis, cystitis)
Most systemic autoimmune diseases
Rheumatoid arthritis

Marked Elevation (>10 mg/dL)

Acute bacterial infection (80% to 85%)
Major trauma
Systemic vasculitis

- Haptoglobin levels increase during inflammation and decrease during hemolysis.
- In patients with hemolysis and inflammation, levels can appear normal.
- **Procalcitonin** is a sensitive marker for **sepsis** and can be used to guide treatment.
- **PCT has higher sensitivity** than CRP in sepsis. CRP is useful in the follow-up.
- in some vasculitis syndromes such as **Kawasaki's disease, Goodpasture's syndrome, adult-onset Still's** disease ,**granulomatosis with polyangiitis**, **elevated levels of PCT** in patients **without evidence** of bacterial infection.

Calprotectin

- Systemic lupus erythematosus (SLE) has also been associated with higher levels of calprotectin and with **disease activity and flares.**
- adult-onset Still's disease, gout, Sjögren's syndrome, scleroderma, Behçet's disease, and ANCA-associate vasculitishave all been associated with **higher** levels of **calprotectin.**

Anemia

- Ferritin levels are **increased** in inflammatory conditions, and levels of transferrin, **decrease**.
- Prolonged inflammation or malignancy can lead to anemia of chronic disease.
- Iron deficiency anemia and anemia of chronic disease can both present as microcytic anemia. They can be distinguished by assessing ferritin and transferrin levels.
- Anemia of chronic disease patients will have elevated ferritin and low transferrin.
- Iron deficiency anemia patients will have lower ferritin and elevated transferrin.

- The prolonged elevation of serum amyloid A (SAA) can eventually lead to **secondary amyloidosis**.
- Some of the diseased states with a prolonged elevation of SAA include chronic infection, rheumatoid arthritis, familial Mediterranean fever (FMF), inflammatory bowel disease, and malignancy.

Infections

- the highest levels are attained in acute inflammation during an acute infection or after trauma resulting in CRP of **50 to 100** mg/L and ESR **exceeding 50** mm/hour.

- The best recent evidence relates to **procalcitonin** (PCT).
- PCT levels can be used to guide treatment in patients with pneumonia.
- PCT levels **greater than 0.25 mcg/L** correlate with bacterial infections of the lower respiratory tract.

- After 2 or 3 days of treatment, lower PCT levels can facilitate the decision to discontinue pneumonia antibiotic treatment.
- PCT levels greater than 0.5 ng/mL can confirm sepsis.
- PCT should not be used for the diagnosis of pneumonia or for deciding if the antibiotics are necessary to treat pneumonia.
- It should only be as a guide antibiotic treatment.

Cardiovascular

- Some of the APRs, like CRP, are unique because they can be used in cardiovascular risk assessment for patients.
- It has also been shown in patients with acute coronary syndromes that elevated CRP levels assayed by the high sensitivity (hsCRP) assay are indicative of **poor cardiovascular prognosis.**
- Poor prognosis includes increased mortality, post-myocardial infarction, and unstable angina, among others.

Cardiovascular

- In patients without ASCVD, a hsCRP between 3 to 20 mg/L, on two occasions at least six weeks apart, confers an increased risk for ASCVD provided a nidus for inflammation has been excluded.
- Cardiovascular disease is also accompanied by the reduction of negative acute phase reactants such as albumin, transferrin, transthyretin, retinol-binding protein, antithrombin, and transcortin.

Cardiovascular

- among apparently healthy individuals, the baseline level of CRP predicts the long-term risk of a first myocardial infarction (MI), ischemic stroke, hypertension, peripheral vascular disease, sudden cardiac death, and all-cause mortality.
- While serum CRP does appear to act as an independent predictor of ASCVD in the general population, the predictive value added to that determined by screening for other coronary risk factors is small.

SLE

- In patients with systemic lupus erythematosus (SLE), CRP is often within normal limits, **and ESR is generally elevated**.
- In SLE patients with elevated high-sensitivity CRP (hsCRP), an infection should be ruled out because elevated **hsCRP** is a predictor for **active infection with high specificity in patients with SLE.**

SLE

- In lupus patient Serum levels of **SAA** are also **relatively low** in comparison with those of patients with RA, which may explain why rates of secondary amyloidosis are decreased in these patients.
- In contrast, **ESR** correlates with **disease activity** and accrued tissue damage in SLE.
- **Fibrinogen** levels increased over time in patients, **regardless** of disease activity.

SLE

- **low CRP levels** may be related to the pathogenesis of SLE:
- (1) an association has been noted between SLE and a genetic polymorphism associated with low CRP levels;
- (2) it has been observed that low CRP levels may contribute to defective clearance of autoantigens during apoptosis;
- (3) therapeutic efficacy of CRP has been reported in mouse models of SLE.

SLE

- Substantial CRP elevation in SLE patients is more likely to result from superimposed infection than from activation of lupus.
- **CRP elevation** related to **active SLE** can be seen in the **absence of infection.**
- **Carotid plaque** and intima-media wall thickness, correlates of atherosclerotic vascular disease, have been found in association with minor CRP elevation in women with SLE.
- many SLE patients with normal CRP levels show **elevated IL-6** concentrations.

Giant cell arteritis

- It involves monocytes differentiating into giant cells and macrophages within the vessel walls producing **IL-6**.
- IL-6 is an AP protein that mediates the systemic response to inflammation like fever, weight loss and causes the liver to produce other acute-phase proteins.
- IL-6 is also responsible for elevated ESR in patients with GCA.
- Tocilizumab is an IL-6 receptor inhibitor used in patients with GCA, and it can reduce relapses and lower glucocorticoid requirements to maintain disease remission.

- The diagnosis of PMR or GCA is supported by an elevated ESR, often **greater than 50 mm/hr.**
- **10% to 20% of patients** with PMR can have a **"normal" ESR**.
- The report that IL-6 is more sensitive than ESR for indicating disease activity in GCA is of particular interest.

- Subsets of patients with PMR who have persistently elevated levels of CRP and IL-6 despite corticosteroid treatment have a higher risk of relapse.
- Clinical manifestations of disease, even in the presence of a PCT levels in patients with PMR or GCA are usually normal.
- Elevated PCT levels in these patients with a normal temporal artery biopsy would be suggestive of an **alternate diagnosis**.

Rheumatoid arthritis

- (RA) is a chronically inflammatory disease of the articular synovial, with severe, progressive and irreversible articular destruction.
- ESR and CRP cannot be used definitively in the diagnosis of RA, because **45% of patients** may have **normal serum levels** at **presentation**, and these parameters represent part of the diagnostic syndrome or classification criteria sets.
- **for monitoring disease activity** and evaluating **response to therapy** in the context of other clinical modalities.
- ESR traditionally has been more widely used for these purposes, many studies have suggested that CRP levels correlate better with disease activity.

Rheumatoid arthritis

- The serum levels of **IL-2** have been found **low** in patients with RA in the **active stage** of the disease.
- the **lowest values** having been determined at the patients in the **3rd stage** of the disease, who also have the highest values of pro-inflammatory cytokines.

chronic renal disease

- Recurrent or chronic inflammatory processes are common in individuals with (CKD) and especially end-stage renal disease (ESRD).
- This is due to many underlying factors, including the:
- **uremic milieu, elevated levels of circulating proinflammatory cytokines, oxidative stress, carbonyl stress, protein-energy wasting (PEW), enhanced incidence of infections (especially dialysis access related)**, and others
- CKD-associated chronic inflammation, as assessed by increased (CRP) levels above 5 mg/L over at least three months.

- Among patients with CKD, the presence of an inflammatory state may also be closely related to **accelerated atherogenesis, protein-energy malnutrition** , and **anemia**
- **Decreased clearance of proinflammatory cytokines** .
- Oxidative and carbonyl stress
- Increased production of cytokines due to oxidative stress

End-stage renal disease

- among (ESRD) patients with residual renal function,
- **higher serum CRP** concentrations are observed among those with relatively less native kidney function.
- Increased production of cytokines may also be observed.

Dialysis

- ●Exposure to dialysis tubing and dialysis membranes, particularly less biocompatible membranes
- ●Poor quality of dialysis water.
- ●The presence of foreign bodies (such as polytetrafluoroethylene [PTFE] chronic access grafts) or an intravenous catheter, which may harbor chronic or recurrent latent infection via the formation of a biofilm
- ●Peritoneal dialysis :Episodes of overt or latent peritonitis or peritoneal dialysis catheter-related infections .

- Among the proinflammatory cytokines, IL-6 may have a central role in the pathophysiology of inflammation in patients with renal disease

- The measurement of serum **CRP and IL-6**, may help distinguish the relative contributions of inflammation and malnutrition to the development of **hypoalbuminemia .**

- **hyperferritinemia** in dialysis patients is due to iron overload or inflammation.
- when the serum ferritin level **is >800** ng/mL but the serum transferrin saturation is within the normal range (<50 percent)
- The association between **increased mortality** and serum ferritin levels >800 ng/mL appears to be primarily due to the confounding effect of inflammation.

- increased serum C-reactive protein (**CRP)** levels in ESRD patients are as strong a predictor **of cardiovascular mortality** as serum albumin concentration .
- ●Increased serum levels of interleukin **(IL)-6** are associated with increased **dialysis mortality** , and progression of **carotid atherosclerosis** during dialysis may be related to increased IL-6 levels.

Adult still disease

- (ASD) is an inflammatory disorder characterized by (daily) fevers, arthritis, and an evanescent rash.
- Markedly elevated concentrations of **ferritin**, It has been suggested that **IFN-α** may be responsible for the hyperferritinemia .
- **higher levels** of **TNF, IL-6, and IL-8, in addition to IL-18**.
- The role of **IL-1** has been inferred from significant improvement in disease activity by the IL-1 receptor antagonist, anakinra.
- **CRP** levels are usually markedly elevated in this disease, and **PCT levels** have also been found to be disproportionately elevated without evidence of acute bacterial infection in these patients.

IBD

- **Elevated (ESR) or (CRP)** –
- Approximately 65 to 75 percent of patients have an elevated ESR at diagnosis of IBD, and about 85 percent have **elevated CRP** .
- These markers are somewhat more sensitive for detecting CD than UC, and CRP is more sensitive than ESR.
- **Depressed albumin level** – Approximately 40 percent of patients with IBD have depressed albumin levels at diagnosis .
- **Calprotectin** can also be used to monitor disease activity in IBD. Calprotectin is now well established in distinguishing between IBD and nonorganic disease (such as irritable bowel syndrome)

IBD

- calprotectin is not specific to IBD.
- Increased calprotectin levels are seen in other causes of gut inflammation such as with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin, colorectal cancer,gastrointestinal infections,and diverticulitis.
- dietary fiber intake and physical activity may also affect measured levels of calprotectin.

OA

- **Minor CRP elevations** of 0.3 to 1.0 mg/dL have been reported in patients with osteoarthritis, particularly those **with progressive joint damage**.

- **CRP levels** are **higher** in patients with **erosive osteoarthritis** of the hand than in those with nonerosive osteoarthritis.

Spondyloarthropathy

- ankylosing spondylitis, ordinarily **does not** lead to a substantial increase in ESR or CRP.
- **Median ESR and CRP levels** are 13 mm/hr and **1.6** mg/ dL, respectively, in patients with **only spinal** involvement, and 21 mm/hr and **2.5** mg/dL in patients with **peripheral** involvement or associated **IBD**.
- patients with **higher CRP** values show **better responses** to anti-TNF treatment than patients with lower CRP levels.

Spondyloarthropathy

- **High-sensitivity CRP** may better correlate with clinical **disease activity** compared with standard CRP testing.
- It has been reported that levels **of IL-8, IL-17, and IL-23** are elevated in the serum of patients with active ankylosing spondylitis, and polymorphisms in the **IL-23** receptor gene are associated with the disease.

Spondyloarthropathy

- **Calprotectin** levels are also **elevated** in the serum and **synovial fluid** of patients with axial spondyloarthritis and correlate with effective therapy.
- Patients with psoriasis alone produce elevated levels of calprotectin from keratinocytes, but have **lower levels** than comparable patients with psoriatic arthritis, underlying the importance of the synovium in calprotectin production.

Thank you