Inflammatory Markers: When and What to Order and What to Do With the Number

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Disclosures
• None to disclose

Learning Objectives:
• Discuss the physiology of acute phase reactants and their importance in defining illness and injury in children.
• List the three most common inflammatory markers utilized in pediatrics.
• Discuss how inflammatory markers can help in the initiation of or discontinuing of antibiotic therapy.

We Need More than a Marker for Inflammation
• Early Diagnosis
• Differentiating Infectious from Noninfectious causes
• Prognostic marker
• Antibiotic guidance strategies

Marker for Inflammation

Acute Phase Reactants
• erythrocyte sedimentation rate (ESR) - Indirect
• C Reactive Protein (CRP)
• procalcitonin (PCT)
• serum amyloid A (SAA) protein
• fibrinogen
• ferritin
• alpha-1 antitrypsin
• haptoglobin
• alpha-1 acid glycoprotein
• ceruloplasmin
• complement proteins C3 and C4

**Erythrocyte Sedimentation Rate - ESR**

- ESR was discovered by Polish physician, Edmund Faustyn Biernacki (1866–1911)
- Swedish physicians came behind him in 1920's and “discovered” ESR again.

*Normal values*
- Women: 0 – 30 mm/hr
- Men: 0 – 22 mm/hr
- Children
  - Newborn: 0-2 mm/hr
  - Newborn to puberty: 3-13 mm/hr

- May be helpful as adjunct finding in many inflammatory diseases.
- Low Sensitivity and High Specificity
  - High ESR does not identify someone with the disease (true positive)
  - Low ESR is good at detecting who DOES NOT have disease (true negative)

**How good is this test?**

- **Sensitivity** is the ability of a test to correctly identify those with the disease (true positive rate).
- **Specificity** is the ability of the test to correctly identify those without the disease (true negative rate).
**How good is this test?**

- **sensitivity** is the ability of a test to correctly identify those with the disease (true positive rate).
- **specificity** is the ability of the test to correctly identify those without the disease (true negative rate).
- **ESR** – low sensitivity, high specificity

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**The Problem with ESR**

- ESR inflammation, pregnancy, anemia, autoimmune disorders (such as rheumatoid arthritis and lupus), infections, some kidney diseases and some cancers (lymphoma and multiple myeloma).
- The ESR is decreased in polycythemia, hyperviscosity, sickle cell anemia, leukemia, low plasma protein (due to liver or kidney disease) and congestive heart failure.
- More useful in monitoring the response to therapy in certain inflammatory diseases such as temporal arteritis, polymyalgia rheumatica and rheumatoid arthritis.

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**CRP – C-Reactive Protein**

- William Smith Tillett
- Univ of NC and Graduate of Johns Hopkins Medical School
- Working on the Pneumonia Ward of Rockefeller Institute when he discovered an “antigen” that was in the serum of patients acutely ill with c-pneumococcal pneumonia. They called it Fraction-C.

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**CRP**

- Levels begin to rise within 4 to 6 hours of the onset of signs of infection or tissue injury and peak 24 to 48 hours later.
- They rapidly disappear as the infection or inflammatory process resolves
- 2-5 mg/L is most common with upper limit of normal 10mg/L
- Fetus can produce CRPs with no crossing at placenta

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**CRP**

- Binding sites allow CRP to recognize and bind to damaged cell walls and chromatin and nuclear antigens resulting in CRP-ligand complexes.
- CRP-ligand complexes activate the complement system, facilitating phagocytosis and the removal of materials released from damaged cells and toxic materials from invading microorganisms.
- CRP-ligand complexes also bind directly to neutrophils, macrophages, and other phagocytic cells, stimulating an inflammatory response and the release of cytokines.
CRP and Pre-albumin levels

- CRP is a positive acute phase reactant
- Pre-Alb is a negative acute phase reactant
- SO if the CRP is high the Pre-Alb will be low.

Case Studies

- 3 wk old – Monday AM labs included a CRP/Pre-Albumin
  - CRP = 78.10 (normal < 10)
  - Pre-Alb = 9.3 (normal 15 – 30)
- 3 month old - HLHS – heart failure
  - Pre-op - CRP 9.4 PreAlbumin 21.9
  - Post op - CRP 104 PreAlbumin 10.6

Procalcitonin - PCT

Claude Bohuon, PhD

Procalcitonin

- Discovered while working with calcitonin levels as a marker for thyroid cancer. Initially found in the lungs of patients with lung cancer. Work abandoned and then restarted in 1991 during Gulf War.
- Injected "safe" endotoxin and then measured PCT levels.

A brief history of procalcitonin

Bohuon, C.

What is Procalcitonin?

- Precursor peptide of hormone calcitonin (thyroid)
  - Conversion of PCT to calcitonin is inhibited in presence of cytokines or endotoxins.
- The reference value of procalcitonin in adults and children older than 72 hours is 0.15 ng/mL or less. May be lower and not detected in healthy adults
- Reference values have not been established in infants younger than 72 hours.
- Starts to rise 2-4 hrs and half-life of procalcitonin is 25-30 hours (not significantly altered in individuals with renal dysfunction).

PCT in Children and Infants

- Neonates PCT levels – Serious Bacterial Infections
  - > 1 ng/mL at birth,
  - ≥ 100 ng/mL at age 24 hours
  - ≥ 50 ng/mL or more at age 48 hours
- In children with urinary tract infection, a procalcitonin level of more than 0.5 ng/mL suggests renal involvement.
PCT Sensitivity and Specificity

- distinguishing between viral and bacterial infections cut off .53
  - Sensitivity - 65.5%
  - Specificity - 94.3%

- Invasive v. noninvasive infections cut off level .59
  - Sensitivity - 91.3%
  - Specificity - 93.5%

Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants. Results of a multicenter study and utility of a rapid qualitative test for this marker.


Case Study

- 18 year old admitted with fever, CP, lethargy
- Hx – mechanical aortic valve for aortic insufficiency secondary to truncus arteriosis.
- 22q11 deletion syndrome (DeGeorge)

Endocarditis

Mildly Elevated PCT levels

- Conditions associated with mildly elevated serum procalcitonin (PCT) levels (0.15-2 ng/mL) include the following:
  - Localized mild-to-moderate bacterial infection
  - Noninfectious systemic inflammatory response
  - Untreated end-stage renal failure

Elevated PCT levels

Conditions associated with elevated serum procalcitonin levels (>2 ng/mL) include the following:

- Bacterial Sepsis
- Severe localized bacterial infection (eg, severe pneumonia, meningitis and peritonitis)
- Severe noninfectious inflammatory stimuli (eg, major burns, severe trauma, acute multi-organ failure, major abdominal or cardiothoracic surgery)
- Medulillary thyroid cancer (may exceed 10,000 ng/mL)
Neonatal Sepsis and PCT

Increased levels of PCT in neonates with bacterial sepsis.

Osteoarticular Infections

- About equal sensitivity and specificity between ESR, CRP and PCT
- ESR was a better indicator of recovery after 7 days
- PCT is more suitable for rule-in diagnosis in meta analysis with cut-off value of 0.2 to 0.3 ng/ml
- In patients with inflammatory rheumatic disease with concern for bacterial joint infection – PCT may be useful.

Bacterial Infections in Pediatrics

- 158 children who had a PCT level drawn
- Serious Bacterial Infections (SBI) n =28. Mean PCT 6.48 ng/ml compared with 0.23 ng/ml for those without SBI n=47 (P < .0001)
- Other clinical markers like fever and WBC count were not significantly different.
- Discussion
  - Supported use of PCT to guide discontinuation of unnecessary antibiotics
  - Did NOT support use as a solitary marker for initiating or withholding antibiotics.


PCT after Cardiac Surgery

- PCT level will be high post op for about 3 days then starts to drop off towards normal by day 7.
- If the level does not drop or rises after the first three days – start looking for infection.

4 mos old with Fever

- POD #5 cardiac surgery – develops fever
- MOC sick with cough
- Central Line in place
- Foley for two days post op
- Antibiotics?

4 mos old with Fever

- POD #5 cardiac surgery
- MOC sick with cough
- Central Line in place
- Foley for two days post op
- Continue Antibiotics?
What’s Coming Next:

- [http://r.smarbrief.com/resp/JmCnflJYDabCrC1eiegCdC7XhPcQ?format=standard](http://r.smarbrief.com/resp/JmCnflJYDabCrC1eiegCdC7XhPcQ?format=standard)
- In a double-blind, investigator-driven validation study in febrile children, the ImmunoXpert assay (MeMed Diagnostics) was significantly more accurate than measurements of C-reactive protein (CRP), procalcitonin, and routine laboratory parameters, Dr. Isaac Srugo from Bnai-Zion Medical Center in Haifa, Israel and colleagues report in Pediatrics September 13
- The ImmunoXpert assay integrates measurements of blood-borne host proteins (TRAIL, IP-10 and CRP). TRAIL and IP-10 are more elevated in viral infections, whereas CRP is more elevated in bacterial infections.

Using Inflammatory Markers Today

- Early Diagnosis
- Differentiating Infectious from Noninfectious causes
- Prognostic marker
- Antibiotic guidance strategies