Diagnostic Utility of CRP in the ED

Joanna Middleton
Objectives

• Review the utility of a CRP in diagnosing various ED conditions
C Reactive Protein

A Blood Test For Inflammation In The Body
Discovery

• 1930 – Tillett and Francis
  – Substance in serum that reacted with C-polysaccharide of pneumococcus

• 1941

THE OCCURRENCE DURING ACUTE INFECTIONS OF A PROTEIN NOT NORMALLY PRESENT IN THE BLOOD

II. ISOLATION AND PROPERTIES OF THE REACTIVE PROTEIN

By COLIN M. MACLEOD, M.D., AND OSWALD T. AVERY, M.D.
• Schieffelin and Company
  – Commercial manufacturing of CRP test
In Myocardial Infarction

**C•R•P•A**

*C-Reactive-Protein Antiserum — Schieffelin*

**A highly sensitive test for presence of inflammation**

- Investigators have found this test to be consistently negative in cases of cardiac insufficiency uncomplicated by myocardial infarction and inflammation.

- Based upon presence of specific C-reactive protein in serum of patients with certain inflammatory diseases — characteristic precipitin reaction develops upon addition of C•R•P•A to serum of such patients... C-reactive protein is never found in normal serum.

- Simple, economical, routine laboratory procedure that has been demonstrated to be the most consistently positive test in the presence of rheumatic activity... often reveals presence of subclinical inflammatory reactions... detects relapse or recurrence of inflammatory disease... and aids in gauging adequacy of therapeutic regimens.

- "False positive tests do not occur since CRP is not present, even in trace amounts, in normal sera..." accurate qualitative reading may be made within 30 minutes... preliminary quantitative estimate obtained within 2 hours.

For detailed instructions on the materials and techniques required for the use of C•R•P•A — Schieffelin, just send us a request and we will mail you a descriptive brochure.
• 1960’s-1990’s
  – Clinical use/measurement of CRP became largely ignored in NA
• 1990’s
  – New immunoassay’s with greater sensitivity
What is a CRP?
IL-6

6-12 hours
CRP Production

• CRP production starts ~4-6 hours after stimulus occurs
  – After that exponential rise – doubling every 8 hours
  – Peaks at 48-72 hours, remains as long as stimulus is present

• Short half-life (19 hours)
  – Levels drop quickly after stimulus resolves
Point #1 for EM
CRP levels are not reliable in the first 12 hours after a stimulus...
Point #2:
Serial measurements are much more useful than an isolated result

ie: this test is perfect for SJRH, where patients spend 3 days in the ER.
What is normal?

Healthy Adults

Median - 0.8 mg/L

90\textsuperscript{th} Percentile 3 mg/L

99\textsuperscript{th} Percentile 10 mg/L

Lab “normal” = usually <10 mg/L

Horizon Health “normal”: <4.9 mg/L
Point # 3
Healthy patients should have a CRP <2-3
Point #4:
Much of the published literature used a CRP cut-off of 10...

But we know that the “normal” for 90% of people is <3
hsCRP

• hsCRP - <1, 1-3, >3mg/L – low/med/high vascular groups
What stimulates CRP production?

TISSUE INJURY
What determines magnitude of CRP response?

• EXTENT OF TISSUE DAMAGE
  – CRP levels correlate to magnitude of damage
  – Lots of interpatient variability in response to a given stimulus
    • Tissue damage is often caused by our own immune response, not by pathogen itself
    • This is not a new concept in medicine

• TIME FROM INSULT
POINT #5:
LOTS OF THINGS ELEVATE CRP

Anything that causes tissue/cell damage can elevate CRP.
What causes elevation of CRP?
ELEVATED CRP...WHAT IS YOUR DDX?

- Infection – bacterial, viral, parasitic, fungal, mycobacterial
- Trauma
- Surgery
- Tissue necrosis
- Ageing
- Inflammatory disease
- Malignancy
- OBESITY
- Smoking
- Allergies
- Hypersensitivity – rheumatic fever
- Fractures
- Diabetes
- Thromboembolic events
- Ischemic injury to tissue
- Elevated triglycerides
- Pain
- CKD
- Serotonin syndrome
- Race – african americans
- Exercise
- IUD
- Pregnancy
- Scoiizophrenia
- Pain
- Child maltreatment
- OSA
- ETC
Elevated CRP

• Infection
  – In general – rising CRP is a early and sensitive indicator of most forms of microbial infection
  – In general – bacterial infections result in higher levels of peak CRP’s than viruses
  – Viral infection: 10-40
  – Bacterial infection: 40-200
Point #6: CRP cannot differentiate between viral and bacterial unless...
Point # 7:
CRP >100 is probably a bacterial infection

But a CRP of >100 is RARE
Elevated CRP

- **Trauma/Surgery/#’s**
  - Extent of tissue damage correlates to CRP
    - Crush injury > ankle #
    - Hartmann’s resection > hernia repair

- **Tissue Necrosis/Ischemia**
  - Pancreatitis, acute MI

- **Malignancy**

- **Inflammatory Diseases**

- **Burns**
  - Huge elevations in CRP
Other Causes...

- Smoking
- Obesity/Metabolic Syndrome/Elevated trig/Diabetes
- Intense Exercise
- PAIN
- Race
- IUD
- Pregnancy
- Poor oral/dental hygiene
Obesity

Chi Square $P_{\text{trend}} < 0.0001$

- Normal: 3.4%
- Overweight: 7.0%
- Class I: 11.1%
- Class II: 30.4%
- Class III: 35.0%
More causes....

- Allergies
- Hypersensitivity reactions
- Thromboembolic events – DVT, PE, CVA
- Chronic kidney disease
- OSA
- Serotonin syndrome
- Child maltreatment
- Schizophrenia
Point # 8:
JUST ABOUT ANYTHING CAN ELEVATE CRP
EXCEPT...
Exceptions to Point #8

• Diseases that cause tissue damage, but do not give usual CRP response:
  – Scleroderma, dermatomyositis, Sjogren’s
  – Ulcerative colitis
  – Leukemia
  – Some viral infections
  – Lupus...without serositis/vasculitis

• Conditions that suppress CRP production
  – Steroids/drugs that lower IL-6 levels
  – Liver failure (severe)
Dr. Oz's 5 Ways to Lower Your CRP Levels

Our favorite doctor has some easy ways to keep your CRP where it should be.

Dr. Oz
Point #9: 
STEROIDS SCREW UP CRP LEVELS.

And so do some auto-immune diseases.
Point #10 – Joanna’s Rule: If your patient in the ED has a CRP <0.3*....

They should not be in the ED.
THERE IS NOTHING WRONG WITH THEM.
THEY ARE NOT IN PAIN.
THEY AREN’T EVEN CRAZY.

*sx >24 hrs, excluding factors in point #9
COST

• ~$25/CRP

"In our medical culture, doctors often talk about what more could have been done, but rarely talk about what less could have been done"
RESPONSIBILITY

• What is the legal responsibility of an ED physician for following up on an elevated CRP?
Is an elevated CRP level akin to a positive D-dimer?

A positive D-dimer is never really helpful....
CRP in the DIAGNOSIS of ED Conditions
I'm sorry to hear about your abdominal pain. If you could put down the Mtn Dew and wipe the Cheeto dust off your fingers, I'll jump right on your emergency.
Acute Abdomen in the ED

• Does a normal CRP predict a normal CT scan?
ABDOMINAL PAIN?
Bottom Line

• Normal CRP does not rule out bad things in the abdomen on CT.
Acute Abdomen – can CRP differentiate urgent vs non-urgent?

• Meta-analysis
  – 3000 patients with acute abdo pain in ED
  – 45% had an urgent final diagnosis

• CRP cut-off <10 missed the urgent diagnosis in 23% of cases.
  – Pain <24 hrs – 36%
  – Pain 24-48 hrs – 36%
  – Pain >48 hrs (but still defined as “acute”) – 9%
Bottom Line

• CRP levels are significantly higher in patients with urgent conditions

• Not cutoff that can adequately distinguish enough patients with an urgent condition.
  – Ie – normal CRP does not rule out bad things, but a high CRP makes bad things more likely
  – Longer duration of pain improves accuracy
What did I learn?

• This study mirrors what I see in my own practice...
  – I don’t tend to order a lot of CRP’s in generalized abdo pain. I am not going to change that.
DIVERTICULITIS?

• If unsure of diagnosis:
  – CRP <10 – does not rule out diverticulitis

• If diagnosis made:
  – If CRP is really high (>150) – likely complicated diverticulitis that will need an intervention (admit)
  – If CRP is lowish (25) – can probably be treated as an outpatient
    • (although ~10-15% still have complicated disease)
BOTTOM LINE

• CRP doesn’t really help in diagnosing or ruling out diverticulitis in the ED

• Low CRP does not rule-out perf/abscess
What did I learn?

- CRP <10 DOES NOT rule out diverticulitis...a low CRP doesn’t even rule out an abscess! (I was surprised by this)

Change my practice?
- I think I will order the test less...
ADULT APPENDICITIS

• Evidence not great...frustrating
  – LOTS of heterogeneity
  – Cut-off values varied wildly
  – Early studies did not discriminate based on time of presentation
APPENDICITIS

• In general:
  – CRP correlates with severity of inflammation
    • Very high levels predict perforation/gangrenous changes (>35-50)
  – Complete lack of specificity
    • Could be a TOA causing the elevation.
  – Median CRP for non-perforated appy’s - **20**
Normal inflammatory markers in appendicitis: evidence from two independent cohort studies

Table 5
Comparison of demonstrated sensitivity and specificity of CRP with previous papers\textsuperscript{12,15,20–28}

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample</th>
<th>Patient Selection</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies et al.\textsuperscript{20}</td>
<td>37</td>
<td>Appendectomy</td>
<td>93.5</td>
<td>83.3</td>
<td>–</td>
</tr>
<tr>
<td>Birchley\textsuperscript{15}</td>
<td>75</td>
<td>Appendectomy</td>
<td>77</td>
<td>43</td>
<td>&gt;12 mg/dl</td>
</tr>
<tr>
<td>Asfar et al.\textsuperscript{21}</td>
<td>78</td>
<td>Appendectomy</td>
<td>93.6</td>
<td>86.6</td>
<td>&gt;2 mg/dl</td>
</tr>
<tr>
<td>Gurleyik\textsuperscript{22}</td>
<td>108</td>
<td>Appendectomy</td>
<td>93.5</td>
<td>80</td>
<td>–</td>
</tr>
<tr>
<td>Agrawal et al.\textsuperscript{23}</td>
<td>145</td>
<td>Appendectomy</td>
<td>74.8</td>
<td>66.7</td>
<td>&gt;6 mg/dl</td>
</tr>
<tr>
<td>Al-Saigh\textsuperscript{24}</td>
<td>189</td>
<td>Appendectomy</td>
<td>39.7</td>
<td>76.3</td>
<td>–</td>
</tr>
<tr>
<td>Vaughan-Shaw et al.\textsuperscript{25}</td>
<td>286</td>
<td>Appendectomy</td>
<td>67.4</td>
<td>63.3</td>
<td>&gt;10 mg/dl</td>
</tr>
<tr>
<td>Nordback and Harju\textsuperscript{26}</td>
<td>354</td>
<td>Appendectomy</td>
<td>52.7</td>
<td>75.3</td>
<td>–</td>
</tr>
</tbody>
</table>
APPENDICITIS

• Meta-analysis 2013
  – 87% and 57% for CRP
  – 75% and 62% for WBC
  – *did not separate <24/>24 hours
ADULT APPENDICITIS

• Pain <24 hours
  – CRP levels start to rise 8-12 hrs after onset of inflammation, peak >48 hrs (later than WBC)
  – Therefore CRP has little diagnostic utility early in the case of an appendicitis
APPENDICITIS

• Pain >24 hours:
  – Acute appendicitis is very unlikely when WBC, CRP and PMN ratio are all within normal limits.*
BOTTOM LINE – CRP and RLQ pain

• If normal CRP/WBC/neuts
  – Very reassuring, but doesn’t rule-out

• If CRP elevated *(which it probably will be)*:
  – NOT DIAGNOSTICALLY HELPFUL....
    • Does not help differentiate from any of the other causes of RLQ pain...
What Did I Learn?

• Don’t order a CRP if patient has had pain < 24 hours
• Elevated CRP – not helpful to me
• How will I change MY practice?
  – I will order a CRP more often in a select patient population...
    • Pain > 24 hrs and CRP < 5/normal WBC/neuts, I will probably rule-out appendicitis
PEDIATRIC APPENDICITIS

• Evidence is worse.
  – Many more variables
  – Lots of different data
    • ?10-20% of cases with “normal” CRP, different cut-offs
Pediatric Appendicitis

• WBC trumps CRP in first 24 hours
• CRP is not sensitive enough to rule-out appendicitis in children
  – Particularly if age <12 yrs old
  – >12 yr old – start to treat more like an adult
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Definitive appendicitis (n = 115)</th>
<th>No definitive appendicitis (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/mL)</td>
<td>0.8 ± 1.9</td>
<td>0.4 ± 1.5</td>
<td>.001</td>
</tr>
<tr>
<td>WBC (cells × 1000/mm³)</td>
<td>15.3 ± 5.0</td>
<td>11.2 ± 6.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRP level (mg/dL)</td>
<td>5.9 ± 6.8</td>
<td>3.2 ± 7.7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
PEDIATRIC APPENDICITIS

• *British Journal of Surgery* 2013; **100**: 322–329
  – Combination increased WBC and CRP is strongly predictive of appendicitis
    • Positive likelihood ratio is 23.32 (95% CI, 6.87-84.79)
    • Negative likelihood ratio is 0.03 (95% CI, 0.0-0.14)
Bottom Line

• If CRP <3 and WBC normal – unlikely to be appendicitis, but doesn’t rule-out
• If CRP>10 and WBC elevated – it’s probably appendicitis
  – Not a lot of other things cause RLQ pain in kids
What did I learn?

• >12 yrs – same as adults
• < 12 yrs:
  – Use CRP to support diagnosis, but not rule out*
    • <24 hours pain – WBC more sensitive
    • >24 hours pain – CRP more accurate, <3 reassuring
TEMPORAL ARTERITIS

• Traditionally, ESR part of diagnostic evaluation
  – ESR – also an acute phase reactant
    • Slower to rise, slower to fall, degree of change smaller than CRP
    • Less reliable – many factors alter result

• In Horizon, cannot order CRP and ESR together...
TEMPORAL ARTERITIS

• BAD NEWS:
  – Prospective head-to-head studies on the use of the ESR and CRP for the diagnosis of GCA are lacking.
  – There is no “rule-in” value for CRP

• GOOD NEWS:
  – CRP VS ESR
    • CRP is more sensitive
    • If CRP is negative, highly unlikely the ESR will be positive, unless patient has patient any of point #9.
TEMPORAL ARTERITIS

• BAD NEWS:
  – Up to 4% of biopsy proven temporal arteritis had a negative CRP AND ESR
    • I.e - negative APR do not r/o TA

• OLD NEWS:
  – Temporal arteritis is STILL a clinical diagnosis
    • If you think about it, you should treat and biopsy
Assess GCA probability

1. Evidence of anterior extracranial circulation ischemia (AION, PION, ophthalmic artery occlusion, CRAO, cilioretinal artery occlusion, amaurosis fugax)
2. New onset headache or neck pain
3. Abnormal laboratory results (ESR, platelets or CRP)
4. Jaw claudication
5. Abnormal superficial temporal artery (beading, nodularity, absence of pulse, local tenderness)
6. Constitutional symptoms (fatigue, malaise, fever, weight loss)
7. Polymyalgia rheumatica
Temporal Arteritis

Utility of Erythrocyte Sedimentation Rate and C-Reactive Protein for the Diagnosis of Giant Cell Arteritis

Tanaz A. Kermani, MD¹, Jean Schmidt, MD², Cynthia S. Crowson, MS¹,³, Steven R. Ytterberg, MD¹, Gene G. Hunder, MD¹, Eric L. Matteson, MD, MPH¹, and Kenneth J. Warrington, MD¹

Results

• Elevated ESR
  – Sensitivity 86%, specificity of 27%
• Elevated CRP
  – Sensitivity 87%, specificity of 31%
• Normal ESR and normal CRP
  – 4%
    • Other studies quote lower numbers – <1%
Bottom Line

• CRP <10 makes diagnosis of temporal arteritis unlikely, but does not rule-out, and going blind sucks.
What did I learn?

• I will still order a CRP, but won’t r/o TA if negative.
  • A CRP level BEFORE starting steroids is extremely useful for rheumatology to follow the disease

• My practice will change in that I will order an ESR instead of a CRP if the patient has Lupus/scleroderma/Sjogren’s/dermatomyositis
CRP in Neonates

• Expect CRP to rise in first 3 days of life
  – PROM
  – Maternal fever
  – PIH
  – Steroids
  – Stress of labor

• Preterm baby values are different
Neonatal Sepsis

- CRP - Sensitivity 74-98%, specificity 94%
  - Lower sensitivity <24 hours

- Serial levels q24 hrs improves diagnostic accuracy
  - 2 consecutive CRP <10 have NPV of 99%
Bottom Line

• An isolated level has no role in the early diagnosis of neonatal sepsis
  – Normal level does not support the withholding of antibiotics
  – Serial levels are extremely useful.

• I will continue to order a CRP in this patient population
CRP in PID

• CRP >10mg/L
  – 74-93% sensitive, 50-83% specific

• CRP levels *generally* much higher in severe PID/TOA but lots of interindividual variation
  – PID – 30’s
  – TOA – 100’s
Bottom Line

• PID is still a clinical diagnosis and CRP does not change that.
  – CRP does risk stratify, along with gestalt
  – I will continue to order a CRP if I think the patient if going to be admitted
CRP in Septic Arthritis

- CRP >10 (systematic review)
  - Sensitivity 80-90%
  - Specificity 20-40%
- CRP >2 (single study)
  - Sensitivity 92%
Bottom Line

• Still need to stick a needle in it.
Post-Op Infection

• CRP always goes up after surgery
  – Peaks day 3 post-op
  – Severity of increase corresponds to amount of surgical trauma - tissue damage/cautery/stress etc
Bottom Line

• No role for CRP in first 3 days
  – A rising CRP *after* POD#3 *may* indicate infection – *not* diagnostic.
Lupus Patients

- CRP does not increase with the activity of SLE, except in the presence of serositis/polyarthritis/vasculitis.
- In the absence of these characteristics, an increase suggests infection, and ESR should be chosen to detect the activity of the disease.
REVIEW

- CRP levels <12-24 hrs are unreliable
- A “normal” CRP is <2-3, median is 0.8
- Most of the published literature looks at CRP cut-offs of <10
- Anything that causes tissue damage will elevate CRP
  - Except – point #9
- Most CRP values you see will be <100
  - In this range – does not differentiate between viral and bacterial (or any other disease)
REVIEW

• CRP is not specific to any disease or condition
• My ‘rule’
  – CRP <0.3 – get out of my ED
Question

• How many people have you seen in the ED with a CRP <3?
  – Should we be ordering the test?
COMMENTS?
Thanks.