Utility of CRP for diagnosis in the ED

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Likelihood ratios

Positive LR = sensitivity / (1 – specificity)

Negative LR = (1 – sensitivity) / specificity

Post-test odds = pre-test odds x LR

In general terms, a ‘useful’ value is:

LR+ 10
LR- 0.10
CRP in the diagnosis of

- Appendicitis
- Diverticulitis
- Cholecystitis
- Giant cell arteritis
- Septic arthritis
- Infection in febrile neutropaenia
- Pharyngitis
- Pneumonia
- A couple of miscellaneous conditions
Paediatrics

Prospective study (n=185) of children (2-14 yrs) with abdominal pain suspicious for appendicitis after EP review. 

- Measured WBC / ANC / CRP
  - Disclosed to clinician &
- Measured PCT, CP & Appy1 panel (a mathematical combination of WCC, CRP & CP)
  - Not disclosed to clinician
- Primary outcome = appendicitis on pathology (n=89, 48%)
- CRP <2mg/dL, LR- 0.41
- Appy1 panel neg, LR- 0.06

CRP and appendicitis

- Paediatrics
  - Prospective study of Alvarado score vs Alvarado score + CRP did not show any improvement in diagnosis
  - Retrospective study (n=344) clinically suspected acute appendicitis underwent appendicectomy (89% positive)
    - CRP LR+ 2.2, LR- 0.4
  - Multiple inflammatory markers (WCC, CRP, ANC) normal in children
    - no cases of appendicitis in 2 studies

- Study of D-dimer → not a useful diagnostic marker

CRP and appendicitis

- Retrospective study all adult appendicectomies (n=320):
  - CRP cut off 46, did not distinguish positive from negative appendicectomy

- Four year retrospective analysis of all appendicectomies (n=663):
  - CRP cut-off 55, LR+ 3, LR- 0.4

- One year retrospective analysis of all appendicectomies (n=275):
  - CRP LR+ 1.2, LR- 0.5

- Secondary retrospective analysis of a prospective cohort of ED adult patients with suspected appendicitis (n=1024)
  - 580 (57%) appendicitis on pathology
  - Looked at positive and negative predictive combinations of WCC and CRP, duration of symptoms (up to 5 days)
  - No value of CRP, WCC, or combination achieved NPV 90%
  - WCC >20 and duration of symptoms >48 hrs gave 100% PPV, but only occurred in 8 patients
  - No other CRP, WCC or combination achieved PPV 80%

CRP and appendicitis

Adults

Do blood results improved surgical decisionmaking in acute appendicitis?

“CRP and WCC are used as a diagnostic supplement despite relatively low Sn and Sp”

Prospective observational study (n=226) of pts >15 years admitted for appendicitis.

Surgeons estimated pre-test probability as greater or less than 50% after examination, then given blood results and re-estimated probability. Changed probability in nine cases.

91 (40%) appendicitis on pathology. Blood results had no impact on clinical decisionmaking.
Non diagnostic uses (appendicitis)

- Once patients have already been diagnosed as having appendicitis:
  - CRP is associated with increased risk of prolonged operation (as are overweight, symptoms >3 days, appendix diameter >10mm, and abscess)
  - CRP is associated with higher risk of complicated appendicitis (perforation, abscess, etc)
CRP and diverticulitis

- Consensus practice guideline (Netherlands working group of surgeons, internal medicine, gastroenterologists, and radiologists) 2013

- “The clinical diagnosis of ACD, based on reported complaints, physical examination and laboratory results, is correct in 43–68% of patients”

- “The (ED) triad of pain in the lower left abdomen on physical examination, the absence of vomiting and a C-reactive protein >50 mg/l has a high predictive value to diagnose ACD (97% accuracy).

- If this triad is present and there are no signs of complicated disease, patients may be withheld from further imaging.

- If imaging is indicated, conditional computed tomography, only after a negative or inconclusive ultrasound, gives the best results.

- Reference for ”ED triad”: Prospective study of consecutive adults patients with suspected acute diverticulitis (n=126)

- Diagnosis confirmed on CT or operative findings (n=80)

- Of 30 patients with the triad of LLQ tenderness only, no vomiting, and CRP >50, 29 pts (97%) had acute diverticulitis.

- “ED triad”, LR+ 18, LR- 0.65

- The authors suggested that patients with this triad did not require further imaging.

- However 2 patients in this group had complicated diverticulitis requiring acute operative intervention on CT

- CRP cut off 50 mg/L, LR+ 2.2 (NB: Only LLQ tenderness had a LR+ of 10.4)

CRP and diverticulitis

- Retrospective study of consecutive adult patients admitted with suspected left-sided diverticulitis (n=287)
  - Diagnosis confirmed on CT or operative findings (n=124)
  - Logistic model used to derive decision rule using symptoms, signs and laboratory results → derived a point-based nomogram
    - CRP cut off 50 mg/L, LR+ 1.5, LR- 0.6
    - Example of LLQ tenderness, no vomiting, CRP>50 → 190 points → 20% probability of disease !!
- Validation cohort study: each of the scoring tools (above) validated in the other cohort, and an independent cohort
  - “ED triad” still performed the best but less well in either validation cohort
    - CS cohort: LR+ 5 in 20 pts, LR- 0.7
    - Independent cohort: LR+ xxx in 14 pts (14%), LR- 0.8

Non diagnostic uses (diverticulitis)

- Predictors of acute diverticulitis severity: systematic review
  - 21 articles: pt characteristics, medications, biomarkers, imaging
  - Severe disease defined as either:
    - Haemorrhage, abscess, phlegmon, perforation, purulent / faecal peritonitis, stricture, fistula, small bowel obstruction, or
    - Prolonged hospital admission, surgery or death
  - CRP had an association with severe disease in 5 of 6 studies, cut-off values in the range of 150-200 mg/dL, with CRP >200 giving PPV of 59-90%
  - CRP lower in repeat presentations than in initial presentations
  - CT remains the gold standard for diagnosing complicated disease
- Retrospective review of patients with first episode acute diverticulitis and initial CRP <150
  - No significant difference in CRP values between complicated and uncomplicated cases (mean 101 vs 89)
- Pattern of CRP in the first 24 hours of admission as a predictor of severity of diverticulitis
  - A rapid rise in CRP was NOT associated with ultimate need for intervention (percutaneous or surgical) during the admission.
  - In fact CRP rise was more dramatic in uncomplicated cases and, if used to predict severity, would have led to many unnecessary procedures

Chirurgia (Bucuresti) 2016. Kechagias A, Rautio T, Makela J
CRP and cholecystitis

CRP in the diagnosis of cholecystitis

- Retrospective audit of cholecystectomies over 5 yrs (n=1843)
- About half of the admissions were elective, only 398 had CRP measured
- CRP cutoff value in diagnosing AC was 30.5 mg/L, LR+ 10.6, LR- 0.16
- Conclusion: CRP is a useful diagnostic marker of cholecystitis

CRP effect on management of cholecystitis

- Retrospective audit of cholecystectomies over 5 yrs (n=414) comparing whether CRP was measured or not
- Those who had CRP measured had a longer time to operation and higher rate of acute gangrenous gallbladder
- Conclusion: CRP measurement does not influence management

In 2007 and 2013, the Japanese Society of Hepato-Biliary-Pancreatic Surgery developed the Tokyo Guidelines (TG07, TG13) for acute cholecystitis and proposed to use CRP as its additional diagnostic criterion.

What is the most important blood test for making a diagnosis of acute cholecystitis?

- There are no specific blood tests for making a diagnosis of acute cholecystitis.
- When ultrasonography shows findings suggest acute cholecystitis and a CRP > 3 mg/dl, a diagnosis of acute cholecystitis can be made with 97% sensitivity, 76% specificity, and 95% positive predictive value, ie. LR+ 4.0, LR- 0.04 (original study, n=129, done in 1992!)

CRP and Giant Cell Arteritis

- Retrospective review of all temporal artery biopsy cases (n=204) → clinical and biochemical parameters
  - Lab marker with strongest association was Plt >400 (RR 3.3)
  - CRP >0.5mg/dL (RR 1.8), but only measured in 77 pts (38%)
  - Jaw claudication was only individually predictive clinical factor (RR 3.3)

- Case report
  - 3 ESR ‘negative’ cases, CRP elevated in all
  - Subsequent review of all biopsy-proven GCA at one hospital (n=25) showed only 52% had ESR>50 mm/hr but 96% had elevated CRP

- About one third of GCA patients have a relapse within 2-3 years and in 20% of these relapses both CRP & ESR normal

Nederlands Tijdschrift voor Geneeskunde 2015. Bernelot Moens HJ
CRP and septic arthritis

✧ Prospective study of adult suspected septic arthritis
   ✧ ED and rheumatology clinic (n=105)
     ✧ Mean CRP level 135 for septic arthritis (vs 95 for other)
     ✧ CRP >15 mg/L, LR+ 1.1, LR- 0.44
     ✧ CRP >100 mg/L, LR+ 1.7, LR- 0.64
     ✧ Multivariate analysis: CRP did not retain significance
   ✧ Prospective study of adult suspected septic arthritis (n=78)
     ✧ Mean CRP 171 for septic arthritis (vs 119 for other)
     ✧ AUC for CRP was 0.672, LR could not be calculated from data
   ✧ Systematic review of diagnostic tests for septic arthritis (32 trials)
     ✧ Six studies provided data on CRP with cut-off values ranging from 10-200 mg/L
     ✧ LR+ 1.1 to 4.5, LR- 0.7 to 0.3
     ✧ Serum inflammatory markers such as WCC, ESR and CRP are not useful acutely

CRP and neutropaenia

- Systematic review of diagnosing severe infection in febrile neutropaenia
  - CRP LR+ 1.8, LR- 0.4
  - Prospective study of 20 adult pts with febrile neutropaenia without proven infection vs 28 with proven infection (17 with bacteraemia)
    - No significant difference of any conventional biomarker (CRP, PCT, IL-6) could be found at fever onset. Median CRP at onset 40 mg/L vs 47 mg/L
- Prospective study of FN pts with lung cancer (n=14)
  - Mean CRP on day 1 of fever only 8 mg/dL
- Prospective study of neutropaenic SIRS pts to identify infection
  - None of the evaluated biomarkers was able to adequately identify infection
- Mean CRP over first 5 days when added to Multinational Association of Supportive Care in Cancer (MASCC) risk score improves the correlation with 30 day survival after FN

CRP and neutropaenia

- Paediatric FN episodes (381 in 169 pts) to identify severe infection defined as:
  - Bacteraemia, positive culture of normal sterile body fluid, invasive fungal infection, localised infection at high risk of extension
  - Mean CRP 29 vs 47 mg/L (p=0.02)
  - CRP >50, LR+ 1.3, LR- 0.93
  - CRP >90, LR+ 4.2, LR- 0.90 (only positive in 8 patients)

- Paediatric FN episodes (50 in 37 pts) to compare clinically identified infection, microbiologically documented infection, and fever of unknown origin
  - CRP levels did not differ significantly among groups

CRP and pharyngitis

- Prospective observational study of adults with acute pharyngitis and the presence of all 4 Centor criteria (tonsillar exudates, tender cervical glands, history of fever, and absence of cough)
  - All patients (n=149) had throat swab and CRP
  - Group A streptococcus present in 83 pts (56%)
  - CRP concentrations were not associated with Grp A strep

- Prospective observational study of adults with acute pharyngitis (n=100) and 1 or more Centor criteria
  - All patients had rapid antigen detection test (RADT) & CRP
  - Prevalence of Group A strep was 26%
  - CRP LR+ 1.6, LR- 0.2
  - RADT LR+ 30, LR- 0.10

Random article find !!

- RCT of 22 pts with epiglottic abscess (Seoul, Korea) were randomised to management with:
  - Antibiotics only, or
  - Needle aspiration and antibiotics
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- Antibiotics only, or
- Needle aspiration and antibiotics
- Needle aspiration was done:
  - In awake patients,
  - Using indirect laryngoscopy,
  - Under local anaesthesia, and
  - Using an 18-gauge spinal needle !!
RCT of 22 pts with epiglottic abscess (Seoul, Korea) were randomised to management with:

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Needle aspiration was done:

- In awake patients,
- Using indirect laryngoscopy,
- Under local anaesthesia, and
- Using an 18-gauge spinal needle!!

Findings: no benefit of needle aspiration, other than reduced hospital LOS.

“Further proof with a large-scale study is needed”
CRP and pneumonia

- Cochrane review of point of care CRP to reduce antibiotic prescribing for respiratory infections by GPs
  - Six trials (n=3284) showed overall reduction (37% vs 49%)
    - Large heterogeneity and significant subgroup differences suggest results should be interpreted with caution
    - No difference in clinical recovery (substantial improvement day 7)
    - One study showed increased hospital admissions in CRP group
    - Conclusion: Point of care CRP can reduce antibiotic use by GPs, but the degree of reduction remains uncertain and does not affect patient-reported outcomes
    - A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point of care biomarker to other antibiotic saving strategies

- Prospective observational study of adults with suspected pneumonia (n=100)
  - All patients had FBC and CRP measured, and available to GP
  - Infiltrate on CXR as gold standard (45%)
  - CRP >50, LR+ 2.2, LR- 0.3

CRP and pneumonia

European Respiratory Society Guidelines on Pneumonia (2011)

- The decision to admit to hospital remains a clinical decision. This decision should be validated against an objective tool of risk assessment (CURB or PSI, etc)
- Biomarkers have not been sufficiently evaluated for the decision to hospitalise
- Biomarkers for assessment of pneumonia severity (not diagnosis) have recently gained much attention.
- Currently CRP and PCT are best available and may be implemented as an additional severity tool (over clinical assessment and scoring systems), however the evidence is still limited.

Differentiating pneumonia and pulmonary embolus

- Prospective observational study of adult patients admitted via ED or chest clinic with suspected PE (n=34) or CAP (n=38)
- All had FBC, ESR, CRP and D-dimer measured
- All 38 with suspected CAP had CXR infiltrates (24 lobar, 3 bronchopneum, 11 interstitial)
- Mean body temperature higher (37.7 vs 36.9) in CAP group
- CRP >40, LR+ 3.9, LR- 0.12
- Neutrophil to lymphocyte ratio / D-dimer LR+ 32, LR- 0.15

CRP - miscellaneous

- Diagnosis of pyelonephritis in children (Cochrane)
  - 13 studies on CRP with cut-off value of 20 mg/L
  - Low CRP somewhat useful in ruling out pyelonephritis (reducing probability to <20%)
  - Unexplained heterogeneity in studies ⇒ cannot recommend

- Biomarkers for diagnosis of endometriosis (Cochrane)
  - 141 studies of 122 blood biomarkers, all poor quality
  - No biomarker showed enough accuracy to be used clinically outside a research setting

ACEM / RCPA guideline

- ACEM Guideline number G125
- Suggested tests for common conditions (Appendix 2)
  - CRP is not ‘suggested’ for any common condition
  - CRP is listed as ‘consider’ for:
    - Atraumatic back pain that requires admission
    - Fever for investigation
    - Fever for investigation with significant travel history
    - Suspected septic joint
Conclusions

✧ There are few, if any, situations in which CRP has evidence that it assists diagnosis.

✧ There is a possible role for CRP in diagnosis of diverticulitis in the following conditions:
  ✧ There is no history of vomiting & the patient has LLQ tenderness only, and
  ✧ When, if CRP >50, the surgical team would not proceed to imaging (CT abdomen)
  ✧ In these circumstances, the diagnostic yield is about 20%.

✧ Use of CRP in the diagnosis of first episodes of giant cell arteritis may be considered.
  ✧ Although the evidence base is small,
    ✧ Clinical signs are non-specific and unreliable
    ✧ CRP (& platelet count >400) are more diagnostic than ESR
    ✧ Sequelae of non-diagnosis or delayed diagnosis are severe

✧ There is evidence (of variable quality) for the use of CRP to risk stratify patients AFTER the diagnosis has been made and the patient requires admission to hospital for some conditions.