Using C-reactive protein levels to determine pathological grading of pediatric appendicitis in the pediatric population

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Appendicitis

- Appendicitis is the inflammation of the appendix
- Acute appendicitis is one of the most common causes of abdominal pain and is the most frequent condition leading to emergent abdominal surgery in children
- There are an estimated 70,000 pediatric cases per year of acute appendicitis in the United States

Diagnosis

- History: periumbilical pain, right lower quadrant abdominal pain, fever, vomiting, and anorexia
- Exam: tenderness to RLQ, Rovsing’s sign, psoas sign, obturator sign, pain with cough or jumping
- Bloodwork: CBC, chemistry, CRP
- Imaging: ultrasound, CT scan
Treatment

- Acute appendicitis is usually treated with antibiotics and emergent surgery.
- Hospitals in Europe and Asia are beginning to treat some appendicitis cases with antibiotics without surgery.
- In the United States, the treatment in the pediatric population is surgery plus antibiotics.

Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients

- Prospective control trial, adult patients.
- Randomized based on birth date (even vs odd days).
- Study patients received intravenous antibiotics for 24 hours and continued at home with oral antibiotics for 10 days (n = 106).
- Control patients had a standard appendicectomy (n = 154).
- Follow-up at 1 and 12 months.

Results

- Those that were treated with antibiotics:
  - 15 (13.9 per cent) had recurrent appendicitis at a median of 1 year.
  - One-third of recurrences appeared within 10 days of hospital discharge and two-thirds between 3 and 16 months from discharge.
  - Twelve of these 15 patients had surgery, and three had a second round of antibiotic therapy with success during the later follow-up.
  - Four relapsing patients had gangrenous or perforated appendicitis, and others had less severe inflammation.
  - One patient had ileocecal resection because of pronounced inflammatory changes.
Antibiotics-first strategy for uncomplicated acute appendicitis in adults is associated with increased rates of peritonitis at surgery. A systematic review with meta-analysis of randomized controlled trials comparing appendectomy and non-operative management with antibiotics.

- The surgeon. March 2017. Podda et al. Italy
- Systematic literature search for randomized controlled trials comparing antibiotic therapy and surgical therapy-appendectomy for uncomplicated acute appendicitis (5 studies)
- Trials were reviewed for primary outcome measures:
  - treatment efficacy based on 1 year follow-up
  - recurrence at 1 year follow-up
  - complicated appendicitis with peritonitis identified at the time of surgical operation and post-intervention complications
  - Secondary outcomes were length of hospital stay and period of sick leave

Results

- 632 in AT (antibiotic therapy) group and 719 in ST (surgical therapy) group
- Higher rate of treatment efficacy based on 1 year follow-up was found in ST group (98.3% vs 75.9%, P < 0.0001)
- Recurrence at 1 year was reported in 22.5% of patients treated with antibiotics
- Rate of complicated appendicitis with peritonitis identified at time of surgical operation was higher in AT group (19.9% vs 8.5%, P = 0.02)
- No statistically significant differences were found when comparing AT and ST groups for the outcomes of overall post-intervention complications (4.3% vs 10.9%, P = 0.32), post-intervention complications based on the number of patients who underwent appendectomy (16.8% vs 10.9%, P = 0.33), length of hospital stay (3.24 ± 0.40 vs 2.88 ± 0.39, P = 0.13) and period of sick leave (8.91 ± 1.28 vs 10.27 ± 0.24, P = 0.06)

Current logistical issues with surgical treatment for appendicitis

- Appendectomies usually occur during the day when the operating room (OR) is fully staffed
- At night, the OR is reserved only for emergency surgeries, and patients with appendicitis diagnosed late at night often wait until the morning
- What can we do to help determine which cases need to go to the OR soon vs those who can wait (or even avoid the OR)?
Extent of Inflammation

- When the appendix is removed, a pathologist is able to determine the extent of inflammation by examining the tissue.

- If inflammation is limited to the mucosa only, it can be argued that these cases may be conservatively treated with antibiotics alone, or the surgery can be delayed until daytime when a full OR staff is available.

- If inflammation is more extensive, those patients may need to go to the OR sooner rather than later.

- However, the extent of inflammation will not be determined until the appendix is surgically removed.

CRP

- CRP is a protein made by the liver and released into the bloodstream shortly after the onset of an infection, tissue injury, or other types of inflammation.

- CRP is usually elevated in the bloodstream of patients with appendicitis.

- However, it is a non-specific test, since other reasons may cause its elevation as mentioned.

- Has the potential to predict the severity of the inflammation of the appendix.

Diagnostic power of inflammatory markers in predicting severity of appendicitis


- 632 patients who underwent appendectomy were retrospectively reviewed.

- Clinical parameters are compared among the three pathological grades: simple (G1), gangrenous (G2), and perforated appendicitis (G3).

- WBC count and CRP concentration were evaluated whether they can be used in discriminating the severity of appendicitis.
Results

- CRP concentration was well correlated with the severity of appendicitis (p<0.0001).
- In receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) was remarkably higher in CRP (AUC 0.809) compared with that in WBC count (AUC 0.617).
- Multivariate analysis confirmed that CRP concentration >6.2mg/dL (OR: 5.12; 95% CI: 2.17-12.7) and diameter >12mm (OR: 4.33; 95% CI: 1.98-9.95) were strong predictive factors for advanced appendicitis.

Diagnostic value of blood inflammatory markers for detection of acute appendicitis in children

- 211 patients with suspected appendicitis were enrolled.
- 1992 and 1996, ages 4 - 14 years of age.
- 22 patients were diagnosed with nonsurgical abdominal pain.
- 189 patients underwent appendectomy.
- Lab markers: CBC, ESR, CRP, IL-6, TNF-α, endotoxin, acid alpha 1 glycoprotein.
- Results: The higher the CRP value, the more likely the patient had advanced or perforated appendicitis.

Diagnostic Value of D-Dimer Combined with WBC Count, Neutrophil Percentage and CRP in Differentiating Between Simple and Severe Acute Appendicitis in Children

- Clinical Laboratory, 2016. Bu, et al. China
- A retrospective study
- 327 patients who underwent appendectomy for acute appendicitis (aged 13 days to 14 years) in Qingdao Women & Children’s Hospital from Jan 2013 to Dec 2014.
- WBC count, neutrophil percentage, CRP, and D-dimer levels were measured.
- Descriptive analyses, Student’s t-test, and receiver operating characteristic (ROC) analyses were used to quantify the correlation between D-dimer level and the severity of appendicitis and to evaluate the differential diagnostic value of D-dimer combined with WBC count, neutrophil percentage and CRP between simple and other severe appendicitis.
Results

- WBC count, neutrophil percentage, CRP, and D-dimer levels were all significantly higher in severe appendicitis ($p < 0.01$) vs simple appendicitis.
- Both CRP and D-dimer levels were positively correlated with the severity of disease.
- In differentiating between simple and severe appendicitis, CRP (area under the ROC curve (AUC): 0.841) showed the highest sensitivity (80.7%) and the highest negative predictive value (NPV) (80.0%).
- D-dimer (AUC: 0.793) showed the highest specificity (90.0%) and the highest positive predictive value (PPV) (94.9%).
- Combined CRP and D-dimer had a sensitivity, specificity, PPV, NPV, and accuracy of 87.5%, 94.6%, 97.8%, 72.9%, and 89.4%, respectively.

Current study in our ED

- Patients in our ED ages 4-17 years with suspected appendicitis
- Look at CRP levels in patients diagnosed with appendicitis
- Exclusion criteria:
  - (1) Patients with known inflammatory bowel disease, sickle cell disease,
  - (2) Patient is on chronic steroids or on chronic immunosuppressant treatment
  - (3) any chronic medical condition that could affect the patient’s CRP level
  - (4) Patient has been given more than one dose of antibiotic for appendicitis or other infection
- Pathologist will grade severity of appendicitis based on histology
  - Simple (mucosal inflammation), supplicative, gangrenous
- We will compare CRP levels with severity of appendicitis

What can you do to help?

- Please don’t forget to order CRP on your next patient with suspected appendicitis!
- See research assistant for enrollment/consent forms
- Thank you!
References

- Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis
  of antibiotics versus appendectomy as primary treatment of acute appendicitis
  uncomplicated acute appendicitis is associated with increased rates of peritoneal
  contamination in comparison with non-operative appendicitis management: a meta-analysis.
- Bu X, Chen J, Wen Y, Fu L. Diagnostic Value of D-Dimer Combined with WBC Count,
  Neutrophil Percentage and CRP in Differentiating Between Simple and Severe
- Shindoh J, Higa K, Kozai K, Ohara K. Diagnostic power of inflammatory markers in

Thank you