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Gastroenterology elsewhere

Louie TJ, Miller MA, Mullane KM, et al. **OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for *Clostridium difficile* infection.** N Engl J Med. 2011;364:422–31.

The incidence, severity and mortality associated with *C. difficile* infection have been increasing. Oral vancomycin or metronidazole is commonly used to treat *C. difficile* infection. Fidaxomicin is a macrocyclic antibiotic, which has more in vitro activity than vancomycin against clinical isolates of *C. difficile.* A phase II trial showed good clinical response and a low rate of recurrence after fidaxomicin treatment.

This was an industry-sponsored, prospective, multicenter, double-blind, randomized, parallel-group, phase III, non-inferiority study comparing the efficacy and safety of fidaxomicin with vancomycin in 629 patients with *C. difficile* infection (596 patients in intention-to-treat [ITT] analysis and 548 in per-protocol analysis). Patients with acute *C. difficile* infection were randomized to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. Patients with life-threatening or fulminant *C. difficile* infection, toxic mega-colon, previous exposure to fidaxomicin, inflammatory bowel disease, or >1 occurrence of *C. difficile* infection in the previous 3 months were excluded. The patients were followed for recurrence weekly, for 28 days after the last dose of medication. The primary end point was clinical cure. The secondary end points were recurrence of *C. difficile* infection (within 4 weeks after treatment) and global cure (cure without recurrence).

The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin in both the modified ITT analysis (88.2% vs. 85.8%) and the per-protocol analysis (92.1% vs. 89.8%, respectively). Subgroup analyses showed no difference between treatments. Fewer patients in the fidaxomicin group had recurrent infection, in both modified ITT (15.4% vs. 25.3%) and per-protocol analysis (13.3% vs. 24.0%). The lower rate of recurrence was seen with non–North American Pulsed Field type 1 strains. Treatment with fidaxomicin resulted in higher rates of resolution of diarrhea without recurrence and shorter median time to resolution of diarrhea.

The authors conclude that fidaxomicin is not inferior to vancomycin for clinical resolution of acute diarrhea disease due to *C. difficile* infection, but is associated with a lower rate of recurrence of *C. difficile* infection.

Poordad F, McCone J Jr, Bacon BR, et al. **SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection.** N Engl J Med. 2011;364:1195–206.

Rates of sustained virologic response (SVR) associated with peginterferon–ribavirin therapy for chronic hepatitis C virus (HCV) infection remain below 50% and are often <30% among patients with genotype 1 infection. Boceprevir is an oral serine protease inhibitor that binds reversibly to the HCV nonstructural-3 (NS3) active site and has been evaluated as an additional treatment in phase I/II studies. The SPRINT-2 (Serine Protease Inhibitor Therapy 2) trial compared the safety and efficacy of standard therapy with peginterferon alfa-2b and ribavirin (PEGIFN-R) with the safety and efficacy of two treatment regimens containing boceprevir in previously untreated patients with HCV genotype 1.

Subjects were randomly assigned to one of three treatment groups. In all groups, PEGIFN-R was administered for 4 weeks (the lead-in period). Subsequently, group 1 (control) received PEGIFN-R for 44 weeks. Group 2 received boceprevir plus PEGIFN-R for 24 weeks; those having a detectable HCV RNA level between weeks 8–24 received additional 20 weeks of PEGIFN-R. Group 3 received boceprevir plus PEGIFN-R for 44 weeks. Treatment was discontinued if the HCV RNA level was detectable at week 24. Non-black (n=1,246 screened, 940 randomized) and black (224 screened, 159 randomized) patients were analyzed separately.

Response rates were higher among patients receiving a boceprevir-containing regimen. In the non-black cohort, SVR was achieved in 40% in group 1, 67% in group 2 ($p<0.001$), and 68% in group 3 ($p<0.001$). In the black cohort, SVR was achieved in 23% in group 1, 42% in group 2 ($p=0.04$), and 53% in group 3 ($p=0.004$). A decrease in HCV RNA level by ≥1 $\log_{10}$IU/mL at the end of the lead-in period was strongly predictive of SVR. Anemia was reported in 29% of controls and 49% of boceprevir recipients, and led to dose reductions in 13% and 21%, and discontinuation in 1% and 2%, respectively.
Thus, in previously untreated adults with chronic HCV genotype 1 infection, the addition of boceprevir to standard therapy increased SVR rates.

Milano A, Balatsinou C, Filippone A, et al. **A prospective evaluation of iron deficiency anemia in the GI endoscopy setting: role of standard endoscopy, video-capsule endoscopy, and CT-enteroclysis.** Gastrointest Endosc. 2011;73:1002–8.

Iron deficiency anemia (IDA) is a common problem in clinical practice and can be caused by iron malabsorption or blood loss. The etiological diagnosis of GI blood loss can be difficult, and the cause of bleeding frequently remains obscure when the small bowel is involved. After conventional endoscopy, the cause of anemia remains unknown in up to 40% of patients. Video capsule endoscopy (VCE) and CT-enteroclysis (CTE) can visualize the small bowel, however, their role in IDA is still to be fully elucidated. This single-center study from Italy evaluated prospectively the diagnostic efficacy of a systematic endoscopic approach to IDA, and compared the diagnostic yield of VCE and CTE in endoscopy-negative patients.
One hundred and eighty-nine consecutive patients (98 women) with IDA were enrolled. IDA was defined as serum hemoglobin concentration <12 g/dL for women and 13 g/dL for men, mean corpuscular volume (MCV) <80 fL, serum iron level <37 μg/dL, and ferritin level <30 μg/L. All patients had previously been investigated to exclude extra-intestinal causes of anemia. All patients underwent gastroscopy and colonoscopy plus ileoscopy. Endoscopy-negative patients were further evaluated by both CTE and VCE. VCE was not performed if a significant stenosis was revealed by CTE.
In 144 patients (76.2%), a potential cause of anemia was found (41.3% and 37%, respectively, for upper and lower endoscopy). CTE yielded a diagnostic rate of 22.2%, and the diagnoses were neoplasms, Crohn's disease, and polyps. VCE was superior to CTE (diagnostic rate 77.8%), especially where flat lesions were found (arteriovenous malformation [AVM]: 100% vs. 0%; small-bowel Crohn's disease: 88% vs. 50%, respectively). A comparable diagnostic accuracy was seen for neoplasms (85.7%). The most frequent finding at VCE was AVM (28%); other diagnoses were suspected Crohn's disease, polyps, suspected neoplasms, fresh blood, celiac disease and jejunal erosions. CTE and VCE allowed a diagnosis in 82.2% of 45 endoscopy-negative patients.
This study shows that in patients with IDA, a systematic approach including standard endoscopy, VCE, and CTE allows an overall diagnostic rate of 95.7%. VCE is superior to CTE when mucosal lesions are present, whereas the two techniques are comparable in the presence of neoplastic diseases.

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Gastroenterology India

Dhiman RK, Kurmi R, Thumburu KK, et al. **Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver**. Dig Dis Sci. 2010; 55:2381–90.

Minimal hepatic encephalopathy (MHE) impairs daily functioning or health-related quality of life (HRQOL) and may predict overt HE. This study compared the psychometric hepatic encephalopathy score (PHES) to critical flicker frequency (CFF) for the diagnosis of MHE, and determined the prognostic significance of MHE.
Patients with cirrhosis of liver without overt hepatic encephalopathy (HE; $n=100$) and matched healthy volunteers (83) underwent assessment for PHES and CFF. PHES has a range from +6 to −18 points. The cutoff between normal and pathological results in this test battery was set at −5 points. MHE was diagnosed if PHES was ≤−5 points. A Z score less than −2 was considered as abnormal for CFF.
PHES was between +5 and −8 points in healthy controls; 3 controls had pathological test result. MHE was detected in 48 (48%) patients (8 of 22 [36.4%] patients with Child-Turcotte-Pugh (CTP) class A, 27 of 60 [45%] patients with class B and 13 of 18 [72.2%] with class C; $p=0.056$). PHES correlated weakly with CTP score ($r=-0.272$, $p=0.006$). CFF was lower among patients with MHE (39.06 [3.66] Hz) compared to those without (41.39 [3.32] Hz; $p=0.001$) or controls (43.84 [2.3] Hz; $p=0.001$). CFF was altered in 21 (21%) patients. Seventeen of these 21 patients also showed impaired PHES; CFF provided additional information in only four patients while missing it in 31 patients who had abnormal PHES. Eighteen (39.1%) patients with MHE died as compared to 11 (22.9%) who did not have MHE. On univariate analyses, age, serum bilirubin level, CTP score and PHES were associated with poor survival. On multivariate analysis, only PHES≤−6 and

CTP score ≥8 predicted poor survival. The mean overall survival was 645 days in patients with PHES≥−6, vs. 490 days in patients with PHES≤−6 (hazard ratio 2.419; 95% CI, 1.014–5.769). The mean overall survival was 664 days in patients with CTP score <8, vs. 523 days with CTP score ≥8 (HR 2.466; 95% CI, 1.010–6.023). The probability of survival in patients with PHES≤−6 was 67.7% at 1 year, and 26.4% at 2 years, compared to 88.7% at 1 year and 74.6% at 2 years in patients with PHES>−6 (p=0.003). The accuracy of PHES≤−6 in predicting survival, was 0.65 (95% CI 0.53–0.78) while it was 0.64 (0.51–0.76) for CTP score ≥8.

This study reveals that PHES is a reliable tool for the diagnosis of MHE in an outpatient setting.

Puri R, Vilmann P, Sud R, et al. **Endoscopic ultrasound-guided fine-needle aspiration cytology in the evaluation of suspected tuberculosis in patients with isolated mediastinal lymphadenopathy.** Endoscopy. 2010;42:462–7.

Isolated mediastinal lymphadenopathy poses a diagnostic dilemma, with conventional investigations (computed tomography [CT]-guided cytology/biopsy and transbronchial fine-needle aspiration [FNA]) having a low diagnostic yield. This prospective study evaluated the utility of endoscopic ultrasound (EUS)-guided FNA for the diagnosis of isolated mediastinal lymphadenopathy in patients with suspected tuberculosis.

Sixty patients (mean age 39.8 years; 35 males) because of mediastinal lymphadenopathy of >1 cm on CT scan without any pulmonary lesion were evaluated by EUS. Fever was the most common symptom seen in 80% of the patients. None of the patients were HIV positive. EUS was performed on an outpatient basis under moderate sedation and a 22-gauge needle was used for EUS-FNA of the mediastinal lymph nodes. Air-dried and alcohol-fixed slides were sent for cytopathologic analysis. Forty-two patients had earlier undergone bronchoscopy and/or CT-guided FNA, which was non-diagnostic. On EUS, the size of mediastinal lymph nodes ranged from 8 to 40 mm (mean 26 mm); 60% revealed matted lymph nodes with a hypoechoic, inhomogeneous echotexture. Anechoic foci, suggestive of necrosis, were seen in 20 patients (33%). The most common location for EUS-FNA was subcarinal (n= 51; 85%). EUS-FNA established a diagnosis in 42 patients (tuberculosis 32, sarcoidosis 6, Hodgkin's disease 4). EUS-FNA had an overall diagnostic yield of 93% (sensitivity 71%, specificity 100%, PPV 100%, NPV 6%). In terms of tuberculosis, EUS-FNA had a sensitivity of 70%, specificity of 100%, PPV of 100%, and NPV of 50%.

The authors conclude that EUS-FNA cytology has a high diagnostic in the etiologic diagnosis of isolated mediastinal lymphadenopathy in patients with suspected tuberculosis.

Byrav DSP, Medhi B, Vaiphei K, Chakrabarti A, Khanduja KL. **Comparative evaluation of different doses of green tea extract alone and in combination with sulfasalazine in experimentally induced inflammatory bowel disease in rats.** Dig Dis Sci. 2011;56:1369–78.

Patients with inflammatory bowel disease (IBD) often use alternative medicine in addition to conventional therapy. Green tea is a rich source of polyphenols (flavanoids), which has antioxidant and anti-inflammatory effects. Tri nitro benzene sulfonic acid (TNBS) induced-IBD in animals mimics the human disease.

Thirty-six adult Wistar rats were divided into five groups: Group I –vehicle; Group II – TNBS + ethanol; Group III – two green tea-treated sub-groups: IIIA – TNBS + green tea (35 mg/kg), IIIB – TNBS + green tea (70 mg/kg); Group IV - TNBS + sulfasalazine (360 mg/kg), Group V – TNBS + sulfasalazine (360 mg/kg) + green tea. Colitis was induced by application of TNBS (20 mg in 0.5 mL 35% ethanol) into the descending colon. After 2 weeks of treatment, rats were killed for assessment of intestinal inflammation, histological analysis, myeloperoxidase (MPO) assay, malondialdehyde assay, and TNF-α estimation. In the TNBS-induced colitis group, all animals (100%) showed a histological score of 4. The green tea-treated group (group III) and Group V showed less inflammatory changes when compared to the TNBS-treated group. In group V, 83% of the animals showed normal histology and 16% of the animals showed a score of 1. Both green tea-treated subgroups (IIIA and B) showed reduction in MPO activity as compared to the TNBS-treated group (1.95 [0.16] and 1.62 [0.21] vs. 2.61 [0.44]; p<0.05). The sulfasalazine alone-treated group showed less MPO activity compared to the TNBS-treated group (1.33 [0.04] vs. 2.61 [0.44]; p< 0.05). Group V showed less MPO activity compared to the TNBS-treated group. The activity was less than the green tea alone group (1.62 [0.20]; p<0.05). Groups IIIA and IIIB showed a dose-dependent decrease in malondialdehyde activity compared to the TNBS group. Malondialdehyde activity and TNF-α were reduced in the sulfasalazine alone group (p<0.001) compared to the TNBS group. TNF- α was lower in the green tea group, but it was less effective than sulfasalazine alone and combination treatment.

This study concludes that green tea extract is effective in ameliorating TNBS-induced colitis. The combination of green tea extract with sulfasalazine showed greater efficacy than single-drug treatment.

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