Prevention and Treatment of Opportunistic Infections in IBD Patients: Case Studies

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Case I

- Over next week, worsening symptoms with decreasing HCT, albumin and increasing bloody stools
- Infliximab added 5mg/kg on day 5
- Developed fever and dyspnea on day 11
- CXR-infiltrates and hypoxia requiring intubation
- Diagnosed with Pneumocystis Jiroveci Pneumonia (PJP), formerly pneumocystis carinii (PCP)
- Treated with Bactrim later changed to Atovaquone

Case I

- 38 year old female pediatric nurse with 7 year history of pan colitis doing well on mesalamine
- In remission for 5 years
- Recent flare treated with steroids (20mg/day) with transient improvement
- Worsening symptoms so admitted to her local community hospital
- C. diff negative
- Started on Solumedrol 20mg q 6h, increased to 50mg q 6h on day 3

Background

- Global increase in the incidence of IBD
- More patients on combination therapy: steroids, anti-metabolites and biologic agents
- Immune system suppression predisposes to opportunistic infections
- Increasing reports of Pneumocystis Jiroveci Pneumonia (PJP), formerly pneumocystis carinii (PCP) in IBD patients
- No evidence-based guidelines for prophylaxis

Pneumocystis Jiroveci Pneumonia

- Ubiquitous unicellular fungus
- Develops in patients with defects in T-lymphocyte immunity
- Exact incidence in IBD is unknown
- Higher mortality in non-HIV patients
- Absolute risk with biologic agents is debatable
- Risk increases with number of immune modulating agents
- Passive FDA reporting system identified 84 PJP cases between 1998-2003, 16 cases in IBD patients

Epidemiology of PJP in IBD Patients

- Case control study using administrative data from IMS Health Inc, LifeLink™ Health Plan Claims Database
  - 108,604 patients with IBD matched to four non-IBD patients
  - IBD patients had a 3.48-fold increased risk of PJP when compared to non-IBD patients
  - Incidence rate ratio, 4.49 (95% CI, 2.14-9.75) in CD patients compared to non-IBD patients
  - Incidence rate ratio, 2.40 (95% CI, 1.11-5.10) in UC patients compared to non-IBD patients
  - Incidence rate: 32/100,000 person-years vs. 4/100,000 person-years in non-IBD


Risk Factors for PJP in IBD

- High dose corticosteroid use
- Triple immunosuppressive therapy (steroids, anti-metabolites, anti-TNF agents)
- Immunosuppression with cyclosporine
- Lymphopenia (lymphocyte count <800, CD4+ <300)
- Low TPMT levels
- Advanced age
- Comorbidities, especially COPD
- Recent CMV infection


Recognizing PJP

- High degree of suspicion
- Triad of fever, hypoxia, cough
- Chest x-ray may show diffuse or no infiltrates
- Slow progression in HIV, more rapid in non-HIV cohorts culminating in respiratory failure with 30-50% mortality
- Histopathological staining of sputum samples
- PCR of sputum samples may be more sensitive
- Feasibility of oral washes in combination with PCR merits additional studies
- Beta-D-glucan and KL-6 may have less utility in non-HIV PJP due to smaller disease burden


PJP Prophylaxis

- Primary PJP prophylaxis is cost effective in Wegener’s granulomatosis when annual incidence is as low as 0.2%
- In an internet survey of US gastroenterology providers, only 11% prescribe PJP prophylaxis
- Prior experience with PJP and practice in an academic medical center were associated with PJP prophylaxis


PJP Prophylaxis

- Most cited reason for lack of prescribing prophylaxis was the lack of data or evidence-based guidelines to direct practice


ECCO Guidelines

- ECCO guidelines (2009) based on expert opinion
  - No vaccines for PJP
  - Recommend monitoring of cell counts
  - Primary prophylaxis with Bactrim for patients on triple therapy including biologic agents or calcineurin inhibitors
  - No consensus for dual therapy
  - Prophylaxis for steroid monotherapy debatable
  - No guidelines for primary PJP prophylaxis by US GI societies


PJP Prophylaxis and Treatment

- Trimethoprim-sulfamethoxazole (Bactrim) most commonly used because of cost, efficacy and side effect profile
- Other options include dapsone, atovaquone, pentamidine
- Treatment may be inpatient or outpatient depending on severity
- Corticosteroids indicated if PaO2 <70 mmhg, A-a gradient >35mmhg
- Involve infectious disease specialist early

Conclusions (1)

- PJP in IBD patients is a growing concern
- Fever is the principal and often the only initial manifestation of a serious infection
- Low incidence rates preclude feasibility of RCTs
- More case-control studies are needed
- Predictive models to identify patients at highest risk of PJP will be useful
- A case-by-case approach to identify at-risk groups that may benefit from prophylaxis is recommended

Conclusions (2)

- Bactrim prophylaxis for patients on triple therapy as recommended by ECCO
- Consider regular monitoring of lymphocyte counts for patients on dual agent or high dose steroid monotherapy
- Consider prophylaxis in high risk patients on triple immunosuppression OR monitor total lymphocyte and/or CD4+ counts closely
- Early recognition and treatment is essential

Vesicular Rash in a CD Patient on 6MP

- 55 year old female calls complaining of a rash on her neck that began 24 hours earlier
- She thinks it is shingles because her father had similar rash several years ago
- Diagnosed with Crohn’s Disease 12 years ago
- Limited ileocolic resection 8 years ago
- On 6MP for 8 years with surveillance colonoscopy showing few aphthous erosions in the neoterminal ileum
- Rash typical of shingles

Herpes Zoster Epidemiology

- At least 1 million people a year in the United States get shingles
- Rash usually lasts from 2 to 4 weeks
- Main symptom is pain, which can be quite severe
- Very rarely, shingles infection can lead to pneumonia, hearing problems, blindness, encephalitis or death
- Approximately 20% of patients can develop post-herpetic neuralgia

Herpes Zoster in IBD Patients

- Retrospective cohort study/nested case-control study using 1988-1997 data from the General Practice Research Database
- 7823 CD and 11,930 UC patients were matched on age, sex, and primary care practice to 79,563 randomly selected controls without CD or UC
- In the nested case-control study, 185 CD patients with zoster and 266 UC patients with zoster were matched on sex and year of birth to 1787 IBD patients without zoster

Herpes Zoster in IBD Patients

- In the cohort study, the incidence of zoster was higher in patients with CD and UC compared with controls
  - UC incidence rate ratio, 1.21; 95% CI, 1.05-1.40
  - CD incidence rate ratio, 1.61; 95% CI, 1.35-1.92
- In the nested case-control study, corticosteroids (adjusted odds ratio, 1.5; 95% CI, 1.1-2.2) or azathioprine/6-mercaptopurine (adjusted odds ratio, 3.1; 95% CI, 1.7-5.6) were both associated with zoster
- IBD patients, especially those on immunosuppressive medications, are at higher risk for herpes zoster compared with the general population


http://www.cdc.gov/vaccines/vpd-vac/shingles/vacc-need-known.htm
VZV Exposure History and Immunity

- History of VZV-related illness was accessed by epidemiological questionnaire, and serological testing for VZV-IgG was performed
- 121 IBD (86% CD, mean age 37 ± 12.8) patients were studied
- 87% of the patients were on immunomodulator therapy (anti-TNFs-71%)
- Previous exposure to VZV was reported by 104 patients, and 97/104 (93%) were VZV-IgG seropositive
- Seventeen patients, all seropositive, reported negative exposure history


- The calculated positive and negative predictive values for the reported history of VZV exposure were 93% and 0%
- Negative history of VZV exposure is a poor predictor of seronegativity
- History-positive patients may still be seronegative and exposed to VZV infection
- Suggest serological testing of all IBD patients with subsequent immunization of the seronegative patients before initiation of immunosuppressive therapy

VZV Vaccine

- Herpes Zoster vaccine first licensed in 2006
- Lyophilized preparation of a live, attenuated strain of varicella zoster virus (VZV)
- Herpes Zoster vaccine reduced the risk of shingles by 51% and the risk of post-herpetic neuralgia by 67%
- CDC recommends Herpes Zoster vaccine for use in people 60 years old and older to prevent shingles
- The CDC does not have a recommendation for routine use of shingles vaccine in persons 50-59 years old but the vaccine is approved by FDA for people in this age group

http://www.cdc.gov/vaccines/vpd-vac/shingles/vacc-need-know.htm

Vaccinating IBD Patients on Immunomodulators with Zoster Vaccine

- In 2008, the CDC determined that patients receiving low dose immunomodulators are not sufficiently immunosuppressed to create vaccine safety concerns and can receive VZV
  - Methotrexate (50-4mg/kg/week), azathioprine (≤ 3.0mg/kg/day), 6-mercaptopurine (51.5mg/kg/day)
- Study Design
  - On-going prospective open-label study
- Subjects
  - Patients ages 50 and older with IBD
    - Group A: Currently on low dose immunomodulator therapy, age 64 (51-76)
    - Group B: On 5-ASA therapy or no therapy, age 50 (61-76)


- Of the 21 patients enrolled thus far, 9 are on immunomodulator therapy
- None of the patients developed a varicella-like rash
- None of the patients noted an increase in IBD activity after administration of VZV
- Patients on immunosuppressive therapy did not increase VZV-specific antibody levels compared to the response noted in the immunocompetent group (p=0.13 vs p=0.01)
- Baseline antibody levels were not different between the two groups
- Although immunosuppressed patients were able to mount a statistically significant cytokine response following vaccination it was reduced compared to the immunocompetent group (p=0.04)

Immunocompetent patients with IBD who were vaccinated with VZV were able to increase their antibody response to the vaccine antigens.

Immunosuppressed patients with IBD who were vaccinated with VZV had much lower antibody responses to the vaccine antigens.

Additional studies are needed to determine the clinical significance of this blunted response and whether the immunological response is protective or requires an altered vaccination regimen.

Risk of VZV is increased in immunosuppressed IBD patients.

Up to 50% of adults born in tropical areas of the world have no history of primary infection.

Number of reports of severe, disseminated, and rarely fatal varicella infection in immunosuppressed IBD patients.

The risk of VZV infection is increased with all immunosuppressants, but corticosteroids and combination immunosuppression appear to be a particular risk.

Healthcare providers need to be aware of the various manifestations of primary and secondary VZV infection in immunosuppressed IBD patients.

Patients should be screened for VZV immunity and vaccinated prior to commencing immunosuppression.

38 year old woman with PJP
   - Intubated in ICU for 4 weeks
   - Survived and sent to rehab
   - Steroids tapered, PJP prophylaxis continued with atovaquone
   - Patient refused to take 6MP
   - UC flared with steroid taper and underwent colectomy

55 year old woman with Zoster
   - 6MP held and antiviral therapy (famciclovir) started
   - Rash resolved after one week
   - No post herpetic neuralgia
   - Received Herpes Zoster vaccine

Cases Followup

Conclusions: VZV in IBD Patients

Vaccinating IBD Patients on Immunomodulators with Zoster Vaccine

Conclusions: VZV in IBD Patients