# Opportunistic Infection in immunocompromised IBD patients

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I have the following financial relationships to disclose:

Research grant support from NovoNordisk

** No products or services produced by this (these) company (companies) are relevant to my presentation.*

NASPGHAN

## Objectives

Recognize the importance of poorly controlled IBD as a general risk factor for infection in children with IBD

Understand the relationship between potency of immunosuppression and risk of infection in children with IBD

Recognize the manifestations of the most common opportunistic infections in immunosuppressed children with IBD

CDC categories of immunocompromised patients

1. Persons who are severely immunocompromised not as a result of HIV infection.
2. Persons with HIV infection
1. Persons with conditions that cause limited immune deficits (conditions include hyposplenism and renal failure, among others.)

Centers for Disease Control and Prevention. MMWR 1993;42

## 1. Persons who are severely immunocompromised not as a result of HIV infection

Severe immunosuppression can be the result of-

- congenital immunodeficiency
- leukaemia, lymphoma, generalised malignancy or therapy with alkylating agents
- ***antimetabolites***
- Radiation
- ***large doses of corticosteroids (2 mg/kg body weight, or 20 mg/day of prednisolone)***

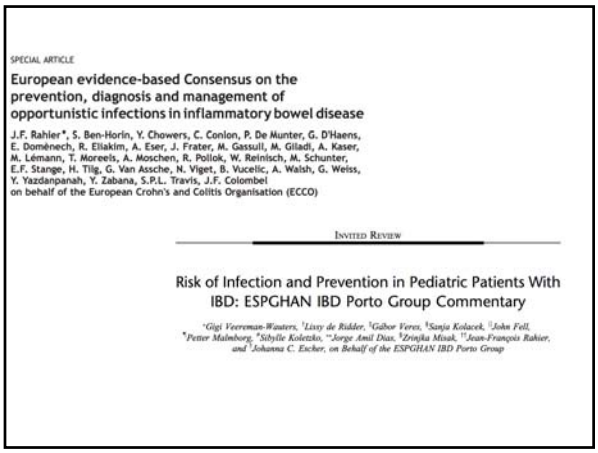
Centers for Disease Control and Prevention. MMWR 1993;42

## Definition of opportunistic infection:

"a serious and usually progressive infection by a micro-organism that has--

- limited (or no) pathogenic capacity under ordinary circumstances
- able to cause serious disease as a result of the predisposing effect of another disease or of its treatment".

SYMMERS. 1965.



SPECIAL ARTICLE

**European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease**

J.F. Rahier*, S. Ben-Horin, Y. Chowers, C. Conlon, P. De Munter, G. D'Haens, E. Domènech, R. Eliakim, A. Eser, J. Frater, M. Gassull, M. Giladi, A. Kaser, M. Lémann, T. Moreels, A. Moschen, R. Pollok, W. Reinisch, M. Schunter, E.F. Stange, H. Tilg, G. Van Assche, N. Viget, B. Vucelic, A. Walsh, G. Weiss, Y. Yazdanpanah, Y. Zabana, S.P.L. Travis, J.F. Colombel on behalf of the European Crohn's and Colitis Organisation (ECCO)

INVITED REVIEW

Risk of Infection and Prevention in Pediatric Patients With IBD: ESPGHAN IBD Porto Group Commentary

*Gigi Veereman-Wauters, †Lissy de Ridder, ‡Gábor Veres, §Sanja Kolacek, ||John Fell, ¶Petter Malmborg, #Sibylle Koletzko, **Jorge Amil Dias, ††Zrinjka Misak, ‡‡Jean-François Rahier, and §§Johanna C. Escher, on Behalf of the ESPGHAN IBD Porto Group

ECCO statements throughout this talk will be on a black background.

European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease.

Journal of Crohn's and Colitis (2009)

## Outline

1. Know the most important risk factors for infection in IBD patients, and apply one strategy to mitigate them.
1. Recognize Epstein-Barr virus infection and anticipate progression to severe disease.
2. Implement a clinical approach to CMV and severe ulcerative colitis.
3. Develop an approach to vaccinating children against varicella with IBD.

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## The most important risk factors are--

1. Potency of immune suppression.
2. Disease severity.
3. Malnutrition.

---

4. Old age-- >600 months
5. Duration of disease.

**Risk Factors for Opportunistic Infections in Patients With Inflammatory Bowel Disease**

MURAT TORUNER,* EDWARD V. LOFTUS JR,* W. SCOTT HARMSEN,‡ ALAN R. ZINSMEISTER,‡ ROBERT ORENSTEIN,§ WILLIAM J. SANDBORN,* JEAN-FREDERIC COLOMBEL,‖ and LAURENCE J. EGAN*,¶

## What are the risk factors for opportunistic infection?

Cases– patients with IBD and infection.

Controls– patients with IBD and no infection.

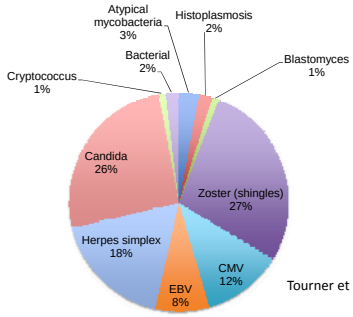
Caveat: study period before widespread use of infliximab

## Opportunistic infection definition

1. Viral (eg, cytomegalovirus, Epstein–Barr, herpes simplex, and varicella zoster)
1. fungal (eg, histoplasmosis, candidiasis, and blastomycosis),
1. bacterial (eg, tuberculosis and streptococcal) infections

Tourner et al, 2008

## Types of infections in IBD patients: herpes viruses and candida made up ~90% of infections




Tourner et al, 2008

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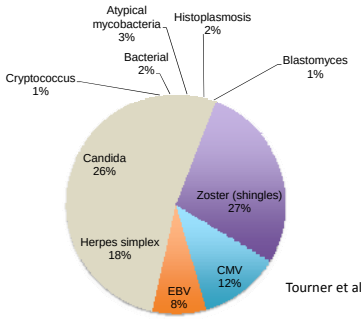


Tourner et al, 2008

## All immunosuppressives used in IBD are associated with increased risk of infection.

| Medication | OR (95% CI) | p value |
|---|---|---|
| Any medications | 3.9 (2.2-6.9) | <0.001 |
| Mesalamine | 1 (0.6-1.6) | ns |
| Glucocorticoids | 3.3 (1.8-6.1) | <0.001 |
| Thiopurines | 3.8 (2.0-7.0) | <0.001 |
| methotrexate | 4.0 (0.4-45) | 0.26 |
| Infliximab | 4.4 (1.1-17) | 0.03 |

Adjusted for age at first clinic visit

Tourner et al, 2008

## Risk of opportunistic infection increases with increased number of immunesuppressives

Tourner et al, 2008

| | OR (95% CI) | p value |
|---|---|---|
| Number of immunosuppressive meds | | |
| None | 1.0 (reference) | |
| One | 2.9 (1.5-5.3) | <0.001 |
| Two or three | 14.5 (4.9-43) | <0.001 |
| Combinations | | |
| No meds | 1 (reference) | |
| Glucocorticoids only | 2.2 (1.0–4.9) | 0.04 |
| Thiopurines only | 3.4 (1.5–7.5) | 0.002 |
| Infliximab only | 11.1 (0.8–148) | 0.07 |
| Thiopurines + glucocorticoids | 17.5 (4.5–68) | <0.001 |
| Thiopurines + infliximab | 1.6 (0.1-19) | 0.72 |
| Thiopurines+infliximab+glucocorticoids | Infinite* | <0.001 |

Adjusted for age at first clinic visit
*5 patients receiving three immunosuppressives developed infection. There were no controls receiving three immunosuppressives.

## The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT)

Cohort study of 6290 patients participating in registry.

Followed over time.

Determined the rate of serious infection and it's risk factors.

Lichtenstein et al. Clinical Gastroenterology and Hepatology, 2006

## Severe disease, potency of immune suppression are risk factors for infection in Crohn disease patients

| | Unadjusted OR (95% CI) | Adjusted OR 95% (CI) | P value |
|---|---|---|---|
| Caucasian | .67 (.39–1.16) | .54 (.31–.94) | 0.03 |
| Duration of disease | 1.03 (1.01–1.05) | 1.02 (1.01–1.04) | .011 |
| Severe disease at baseline | 3.15 (1.74–5.71) | 2.114 (1.103–4.05) | 0.024 |
| Corticosteroids | 2.65 (1.80–3.91) | 2.21 (1.46–3.34) | <0.001 |
| Immunomodulators | .96 (.66–1.42) | 0.78 (.52–1.18) | .24 |
| Infliximab use | 1.49 (1.01–2.19) | 0.99 (.64–1.54) | .97 |
| Narcotic use | 3.27 (2.19–4.87) | 2.38 (1.56–3.63) | <0.001 |

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Lichtenstein et al. Clinical Gastroenterology and Hepatology, 2006

## Infliximab use not associated with increased risk of serious infection after controlling for other factors.

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Lichtenstein et al. Clinical Gastroenterology and Hepatology, 2006

## Factors associated with increased risk of opportunistic infection.

Severe disease

Potency of immunosuppression.

Malnutrition

But….

These are collinear.

## What's a pediatric gastroenterologist to do?

## Case #1.

A 12 year old is referred to you for management of Crohn disease.

He is malnourished, on 30 mg of prednisone, infliximab every 6 weeks at 10 mg/kg, and azathioprine.

He continues to have abdominal pain, vomiting and is missing school.

How can we minimize the risk of infection in this patient?

An aggressive systematic search for why he is NOT responding to therapy.

Patient isn't responding– wrong therapy or wrong disease?
Remember: $C^3IS$

1. Does this patient have inflammatory Crohn disease?
2. Does this patient have celiac disease?
3. Does this patient have C. difficile or another intestinal infection?
4. Does this patient have irritable bowel syndrome?
5. Does this patient have a stricture?

$C^3IS$

You elect to perform an EGD and colonoscopy.

Endoscopy results

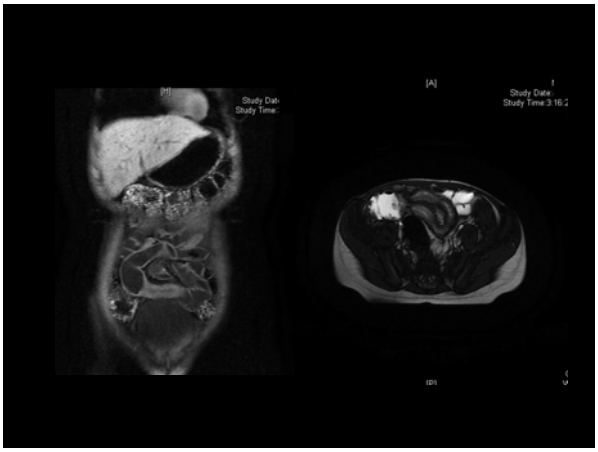
EGD is normal

Colonoscopy is normal

He has no perianal disease

Except…you are unable to intubate the TI. And you're good.

So, you order a MR enterography.



This patient has an ileal stricture

You refer the patient for small bowel resection.

He had an tight stricture with multiple small fistulae.

You are able to wean glucocorticoids.

But…now you have to decide what to do to prevent recurrence.

Immunosuppressives are hammers– make sure you're hitting a nail.

Assure symptoms are due to inflammatory disease.

Use the endoscope.

Noninvasive biomarkers?

- eg. fecal calprotectin, it may cost ~$500, may not be covered, and your patient may be sent to collections if they don't pay the bill (true story).

## Case #2.

A 12 year old boy with stable Crohn disease receiving an immunomodulator develops a fever and sore throat.

He has mild splenomegaly, several palpable lymph nodes in his posterior cervical chain.

Labs: AST, ALT are 75 and 50.

Atypical lymphocytes on peripheral smear

His symptoms resolve after 4 days.

## Case #2– alternate story.

A 12 year old boy with stable Crohn disease receiving an immunomodulator develops a fever and sore throat.

He is febrile and ill-appearing. With a diffuse follicular rash.

He has hepatosplenomegaly, several palpable lymph nodes in his posterior cervical chain.

Labs: AST, ALT are 550 and 300. He has thrombocytopenia and leukopenia.

## Case #2-alternate story.

Biopsy of skin rash demonstrates abnormal NK cell infiltrate

A bone marrow shows erythrophagocytosis.

Flow cytometry of the marrow aspirate shows NK cell lymphoma.

EBV serology is positive.

All biopsies are positive for EBV cells.

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3. Develop an approach to vaccinating children against varicella with IBD.

## ECCO statement

Screening for latent or subclinical EBV infection or chemoprophylaxis before onset of immunomodulator therapy is not recommended [EL2a, RG B].

In *severe clinical* EBV infection during immunomodulator therapy, antiviral therapy should be initiated and immunomodulator therapy discontinued [EL4, RG D].

In the event of EBV-related lymphoma during immunomodulator therapy, immunomodulators should be stopped.

In case of absent spontaneous regression or progression of lymphoma after interruption of immunomodulators chemotherapy should be considered [EL4,RGD]

As pediatricians we must be sophisticated about “severe” EBV disease.

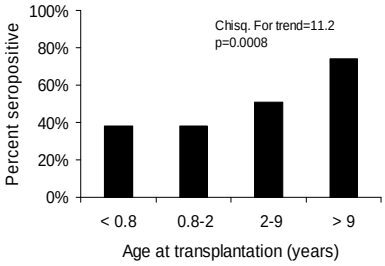
## Young age and potency of immune suppression are risk factors for severe EBV.

| | Relative Risk (95%CI) | P value |
|---|---|---|
| Tacrolimus | 3.1 (1.2-7.9) | 0.02 |
| Age* | 0.86 (0.75-0.98) | 0.03 |

*Age at transplantation (continuous)

Guthery et al. *Transplantation.* 2002

## Proportion of patients seropositive to EBV increases with increasing age



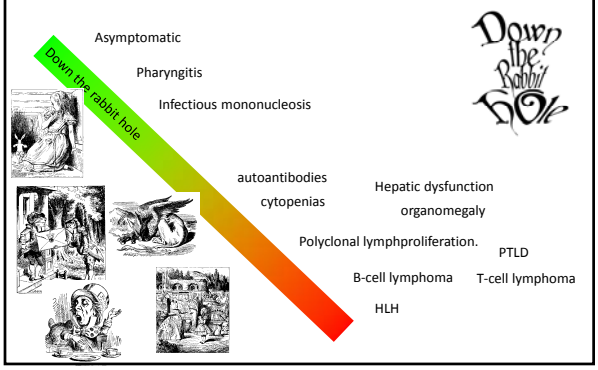

Guthery et al. *Transplantation.* 2002

Primary infection with EBV in the setting of immune suppression represents the most important risk factor for severe EBV.

EBV is acquired with increasing age.

## What is severe EBV?

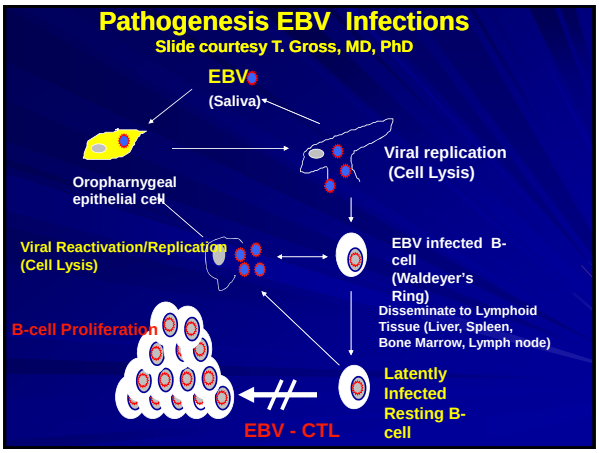
The spectrum of EBV infection is analogous to going down the rabbit hole.



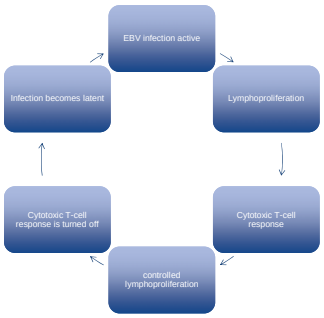

## What is severe EBV?

Severe EBV: the clinical manifestations of uncontrolled lymphoproliferation.

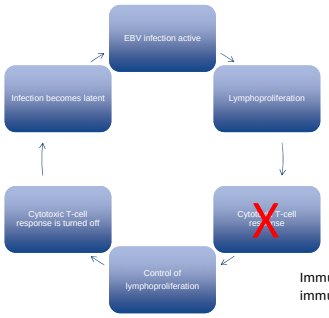
For immune suppressed IBD patients– best thought of in the context as EBV-PTLD.




Normal response to EBV infection or reactivation.



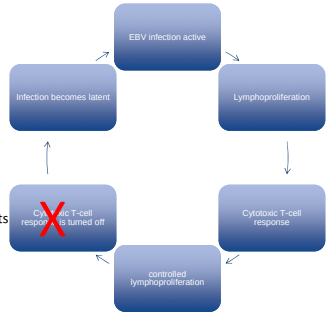

Absence of a T-cell response to EBV leading to uncontrolled lymphoproliferation.




Immunesuppressants
immunedeficiency

Probably, but rarely, relevant to IBD immune suppressed patients.


Absence of a signal to turn off T-cell response to EBV leading to uncontrolled T-cell activation.




Genetic defects
eg. XLP

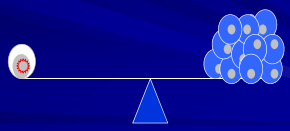
Probably not relevant to immune suppressed patients.


Genetic defects
XLP

## Immune Balance of EBV Infections Normal Host

EBV Infected B-cells 1/10,000 - 1/100,000

EBV-CTL 1-5/100



Yang, et al Blood 96:4055, 2000; Yang, et al Blood 95:241, 2000; Kuzushima, et al Blood 94:3094, 1999

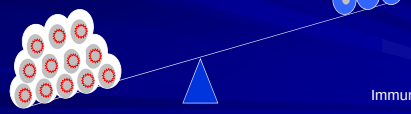
Slide courtesy T. Gross, MD, PhD

## Immune Imbalance of EBV Infections

EBV Infected B-cells 2/100

EBV-CTL ???? Insufficient Quantity

Insufficient Quality



Immunesuppressants

Yang et al, Blood 95:241, 2000

Slide courtesy T. Gross, MD, PhD

## PTLD - Clinical Presentations

- Infectious Mononucleosis (IM)- like PTLD - presents with tonsillar hypertrophy, hepatitis, cervical adenopathy
- Lymphomatous - masses (nodal or often extranodal)
- Septic-like or Fulminant PTLD - wide spread disease (fever, hypotension, hepatic dysfunction, pneumonitis)

Slide courtesy T. Gross, MD, PhD

Malatack, et al J Pediatr 1991; 118:667-675

## PTLD - WHO Classification

(Harris, et al Semin Diag Pathol 14:8, 1997)

- Early lesions
  - Reactive plasmacytic hyperplasia
  - Infectious mononucleosis-like
- Polymorphic PTLD
- Monomorphic PTLD
  - B cell neoplasms (DLBCL, Burkitt, myeloma)
  - T cell neoplasms
    - Can be difficult to distinguish from F-PTLD
  - Hodgkin Lymphoma and HL-like PTLD
    - Classical HL phenotype – CD45 (-), CD15(+) vs. Polymorphic B-cell PTLD – CD45 (+), CD15(-)

Slide courtesy T. Gross, MD, PhD

Case #3

A 14 yo female with known ulcerative colitis develops fever while on prednisone 40 mg daily and balsalzide 4.5 grams per day.

She has diarrhea with blood that awakens her from sleep, cannot attend school, and has severe pain.

Her PUCAI is 75=severe colitis

She is hospitalized.

Case #3.

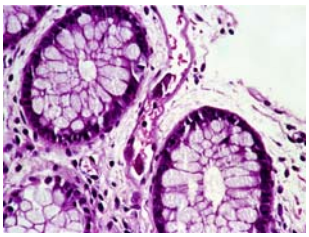
After 5 days of intravenous glucocorticoids and cessation of aminosalicylates her PUCAI is 70.

You elect to either enhance her immune suppression.

You perform a colonoscopy.

She has diffuse continuous colitis, from the rectum to cecum, mild friability in the TI.

Biopsies show this.



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1. Recognize Epstein-Barr virus infection and anticipate progression to severe disease.
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3. Develop an approach to vaccinating children against varicella with IBD.

## ECCO statement OI 4A

Screening for a latent or subclinical CMV infection is not necessary before starting immunomodulator therapy [EL2, RG B].

Latent or subclinical CMV infection is no contraindication for an immunomodulator therapy [EL2, RG B].

CMV colitis should be excluded, preferably by tissue PCR or immunohistochemistry, in immunomodulatory refractory cases of IBD before increasing immunomodulator therapy [EL3, RG C].

In case of severe colitis with CMV detected in the mucosa during immunomodulator therapy, antiviral therapy should be initiated and discontinuation of immunomodulators considered until colitis symptoms improve.

In case of systemic CMV infection immunomodulator therapy must be discontinued [EL2, RG B]

## CMV infection vs. CMV disease

CMV infection: detectable virus.

CMV disease: end-organ damage due to infection.

## Ulcerative colitis and CMV:

CMV is found in 20-40% of colonic biopsy specimens from severe UC.

In some studies, in patients with severe UC, CMV clears spontaneously without antiviral therapy.

Unclear if treating CMV disease alters course of severe UC.

No randomized trials of antivirals in patients with severe UC and CMV.

## Until more clarity exists….

Goal of finding CMV is to avoid enhancing immunosuppression in a patient with untreated tissue-invasive CMV disease.

ECCO guidelines are reasonable.

1. No need to screen asymptomatic patients.
2. Look for CMV prior to enhancing immune suppression.
3. Colonic biopsy tissues specimens are preferable.
4. Consider stopping immune suppression in severe colonic CMV
5. Stop immune suppression in systemic CMV infection.

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## Case #4

A newly diagnosed 10 year old boy with autoimmune hepatitis and ulcerative colitis requires immunesuppression.

His mother thinks he received the varicella vaccine.

Titers are obtained.

HAV nonimmune
HBV: HBsAgAb is positive, HBsAg is negative.
VZV: titers are negative.

Non-live vaccines are generally considered safe in patients with inflammatory bowel disease regard- less of immunomodulator therapy, but may be less effective.

Live attenuated vaccines are contraindicated in IBD patients on immunomodulator therapy (MMR, Typhoid Ty21a, Vaccinia, Yellow fever, live atte- nuated influenza vaccine, varicella, oral polio and BCG) [EL5, RG D].

Live-virus vaccines are probably safe in patients on less than 20 mg prednisone daily, or on higher doses provided they have been given for less than 14 days

Administration of live attenuated vaccines should be avoided for at least 3 months after treatment with immunomodulators is stopped.

## Hepatitis A vaccine current recommendations.

**All children at age 1 year (i.e., 12–23 months).**

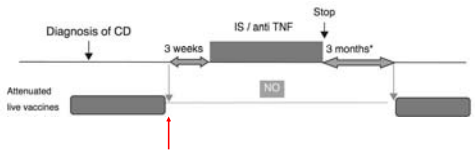
**Children and adolescents ages 2–18 who live in states or communities where routine Hepatitis A vaccination has been implemented because of high disease incidence.**

**Persons who have chronic liver disease**

http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#vaccine

## Approach to vaccinating varicella non-immune children.

Veereman-Wauters, JPGN 2012




Consider:
1. Not vaccinating
2. VZV Vaccination then enteral nutrition as primary therapy for three weeks without IS.

## Summary

Risk of opportunistic infection is increased in severe IBD, malnutrition, potent immune suppression.

These risks may be mitigated by treating malnutrition and assuring immune suppression is being used to treat inflammatory disease.

Severe EBV is manifested by uncontrolled lymphoproliferation– most effective therapy is stopping immune suppression

CMV should be excluded in severe UC patients prior to enhancing immune suppression to prevent worsening CMV

Consider vaccinating against VZV using enteral therapy prior to instituting immune suppression.

Don't forget hepatitis A vaccine– especially in patients with chronic liver disease.

End here.