North Carolina Society of Gastroenterology 2024 Annual Meeting

Bugs, Drugs & IBD: Managing Infection Risks

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Joint Providership

ASGE
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Disclosures:

- Janssen - Consultant

Types of Infections

OPPORTUNISTIC INFECTIONS

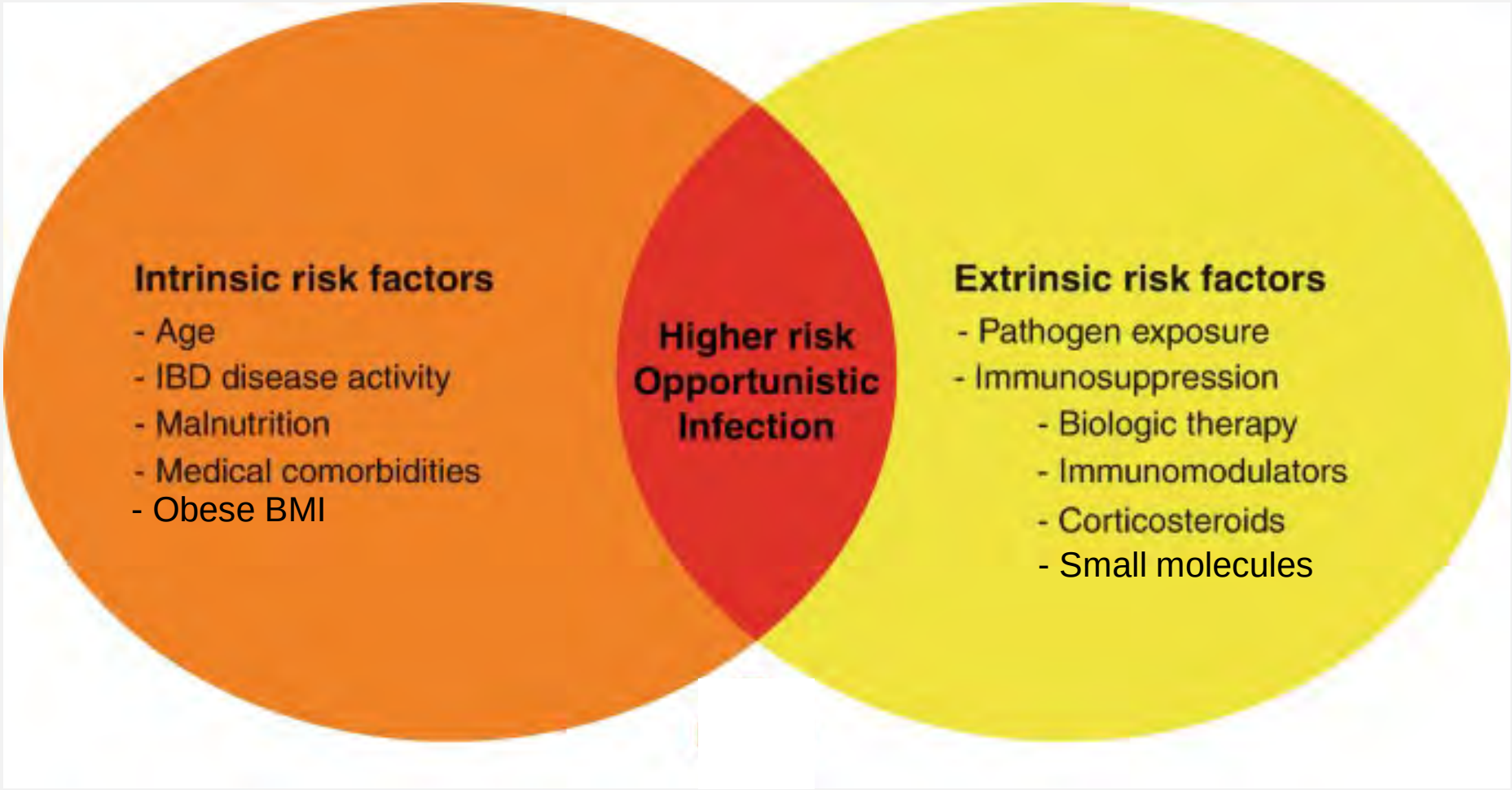
- Infection by an organism which has limited pathogenic capacity under ordinary circumstances

SERIOUS INFECTIONS

- Infection resulting in need for intravenous therapy or hospitalization, or which results in disability or death

Kucharzik T et al. JCC 2021; 15(6): 879-913

Infection Risk & IBD



Kucharzik T et al. JCC 2021; 15(6): 879-913
Martin S et al. IBD Nursing Manual 2019; 189-204

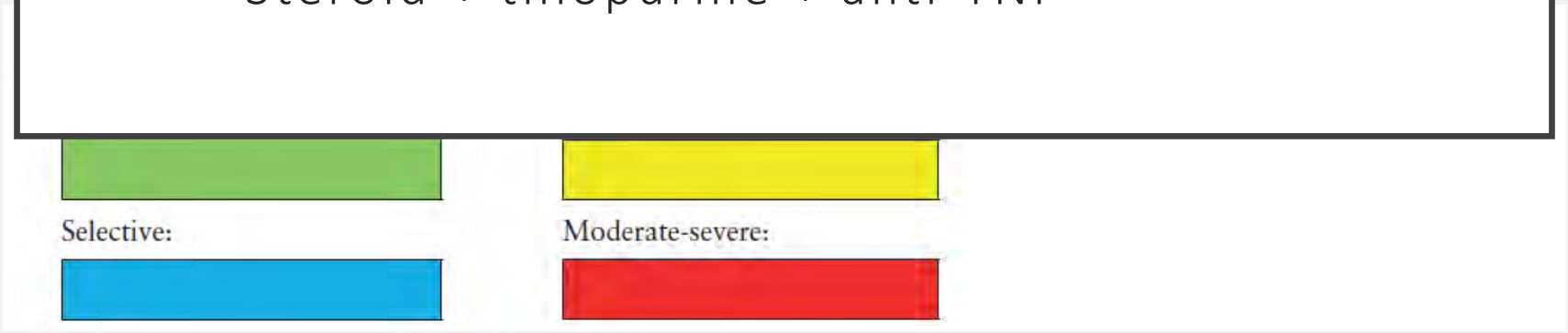
Immune Suppression & IBD Medications

Degree of immune suppression depends on:

- Mechanism of action
- Dose
- Duration
- Route of administration

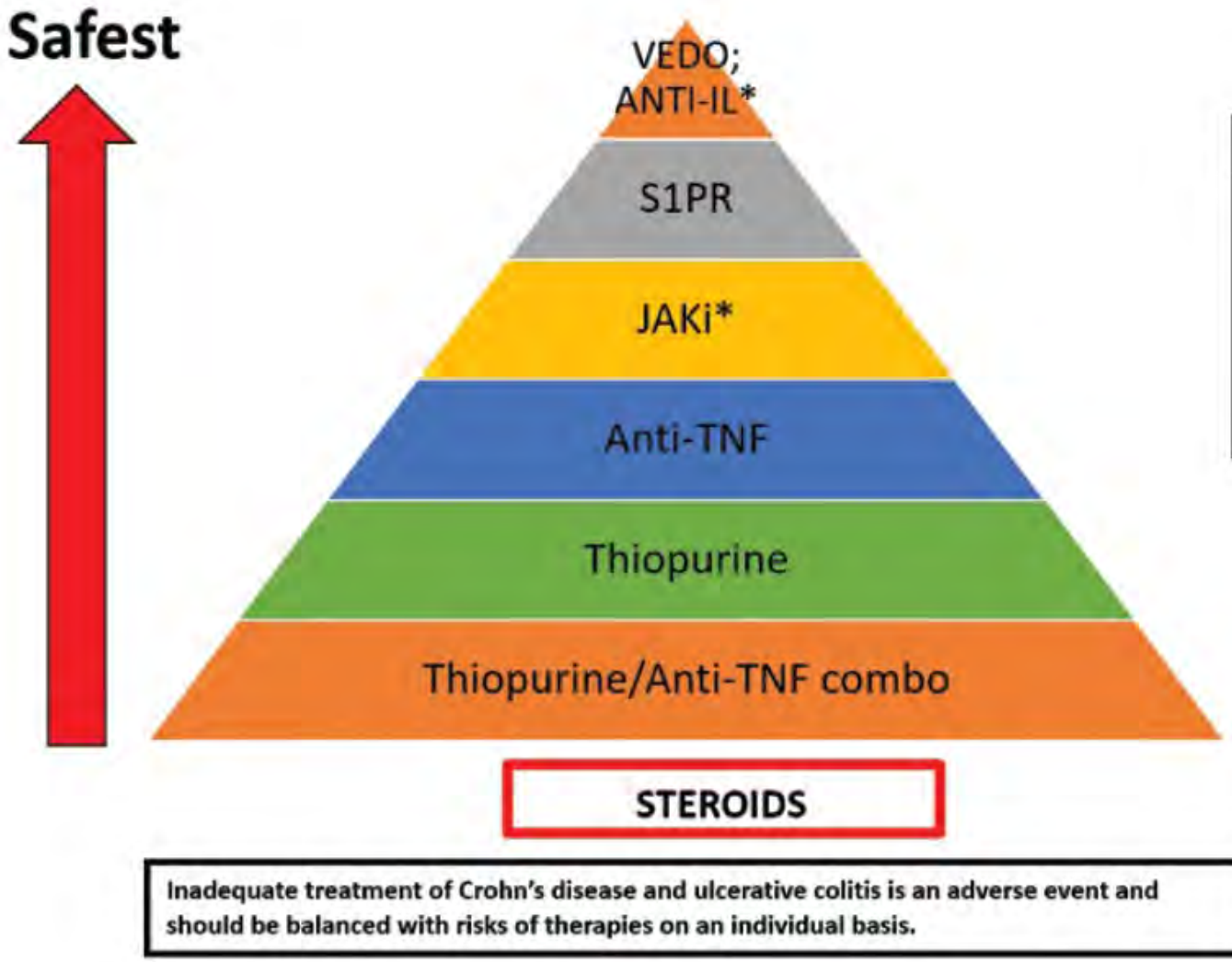
Highest risk of immune suppression/infection:

- Steroid + thiopurine
- Steroid + thiopurine + anti-TNF



Kucharzik T et al. JCC 2021; 15(6) 879-913

Immune Suppression & IBD Medications



Bhat S et al. Inflamm Bowel Dis July 2023: 1-15

Infections & IBD: Medical Decision Making

1. What is the nature/severity of the infection?

2. What is the patient's IBD disease activity status?

3. What medication(s) is the patient taking?

4. Are there complicating co-morbidities? (DM, HTN, CKD, malignancy)

Case 1

- 45 year old female with 6 year history of panulcerative colitis in stable clinical remission
- 5-6, loose, non-bloody BMs daily x 1 week
- PMHx: Frequent UTIs, recurrent *C. Diff*, dermatomyositis
- Meds: Mesalamine DR 4.8 g daily, Azathioprine 2 mg/kg daily
- Stool studies: ***C. Diff* PCR + toxin positive**; bacterial cx, parasites negative

C. Diff History	
1st episode	Hospitalized, Vancomycin
2nd episode	PCR/toxin +, Vancomycin 125 mg QID x 10 days
3rd episode	PCR/toxin +, Pulse taper vancomycin

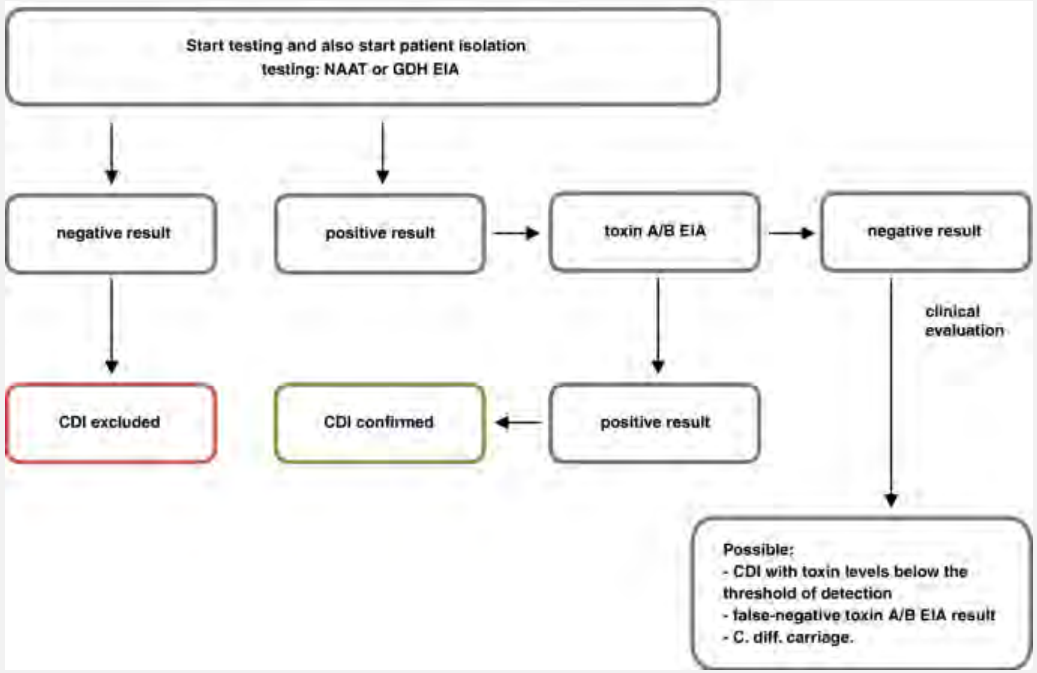
What treatment do you recommend next?
What can she do to prevent *C.Diff* recurrence?

Clostridioides difficile Infection (CDI) & IBD

- CDI occurrence is higher among patients with IBD than the general population, particularly those with UC; likely related to dysbiosis, ↓biodiversity

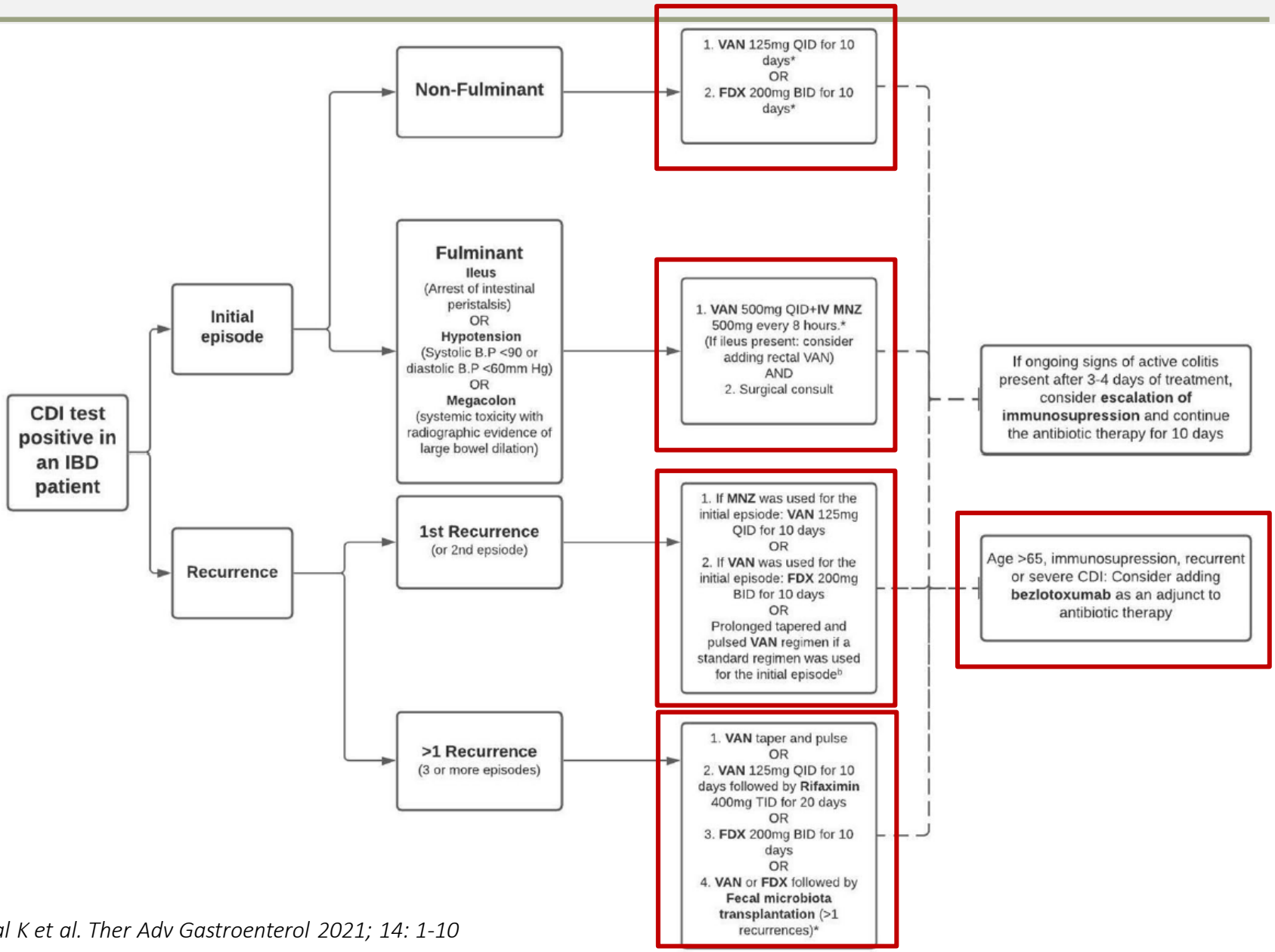
- Who to test: ≥ 3 unformed stools/ 24 hours without a clear explanation

- How to test:



Czepiel J et al. Eur J Clin Microbiol Infect Dis 2019; 38(7): 1211-1221

CDI Treatment Algorithm



Sehgal K et al. Ther Adv Gastroenterol 2021; 14: 1-10

Bezlotoxumab & FMT for Recurrent CDI in IBD

- Bezlotoxumab
  - Monoclonal IgG antibody against *C. Diff* toxin B
  - One time infusion 10 mg/kg IV over 60 minutes
  - 50 % relative reduction in incidence of recurrent CDI in IBD

- FMT
  - Cure rates 80-90%
  - Failure rates higher in IBD vs. non-IBD patients
  - Variable rates of IBD flare, generally low risk

Alhobayb T et al. Curr Opin Gastroenterol 2023; 39 (4): 257-262
Khanna S. Intest Res 2021; 19(3): 265-274

Case 1

- Treatment
  - Fidaxomicin 200 mg BID x 10 days
  - Bezlotoxumab 10 mg/kg IV infusion

- Doing well without documented C. Diff recurrence

Case 2

- 25 year old male with stricturing colonic and perianal fistulizing Crohn's disease complicated by ischiorectal abscess s/p recent right hemicolectomy
- Previous tx: infliximab (immunogenicity, skin issues), vedolizumab (ineffective)
- Significant arthralgias previously responsive to anti-TNF therapy
- Planning to initiate adalimumab + low dose methotrexate (MTX)

Data Review			
HBsAg	Negative	ALT	14
HBsAb	Positive	HBV DNA	Not detected
HB core Ab total	Positive	HCV Ab	Negative
HB core Ab IgM	Negative	Fibroscan	4.4 kPA, CAP 167 dB/m

Management of HBV status?
IBD treatment recommendations?

Hepatitis B Virus (HBV)

- Up to 1/3 of people worldwide may have been exposed to HBV

- Prevalence in IBD dependent on study population and IBD type
  - **Chronic hepatitis B:** **HBsAg (+)/HBcAb (+) 0.6 - 3.7%**
  - **Prior hepatitis B exposure:** **HBsAg (-)/ HBcAb (+) 1.6 - 17%**

- Increased risk of HBV reactivation (HBVr) on immune suppression

Axiaris G et al. World J Gastroenterol 2021; 27(25):3762-3779
Su J et al. Gastroenterol & Hepatol 2019; 15(11): 585-591

Immunosuppressive Drug Class & HBVr

Drug Class	Risk Estimate for HBsAg +	Risk Estimate for HBsAg-/anti-HBc +
TNF-α inhibitors	Moderate (1-10%)	Moderate (1%)
Anti-cytokines	Moderate (1-10%)	Moderate (1%)
Anti-integrin	Moderate (1-10%)	Moderate (1%)
JAK Inhibitors	Moderate (1-10%)	Moderate (1%)
S1PR Modulators	Limited data	Limited data
Corticosteroids - Prednisone ≥ 20 mg/d for ≥ 4 weeks - Prednisone 10-20 mg for ≥ 4 weeks - Prednisone <10 mg for ≥ 4 weeks - Prednisone < 10 mg for < 1 week	High (> 10 %) High (> 10 %) Moderate (1-10%) Low (< 1%)	Moderate (1-10%) Moderate (1-10%) Low (< 1%) Low (<1%)
Antimetabolites	Low (< 1%)	Low (<1%)

Axiaris G et al. World J Gastroenterol 2021; 27(25):3762-3779
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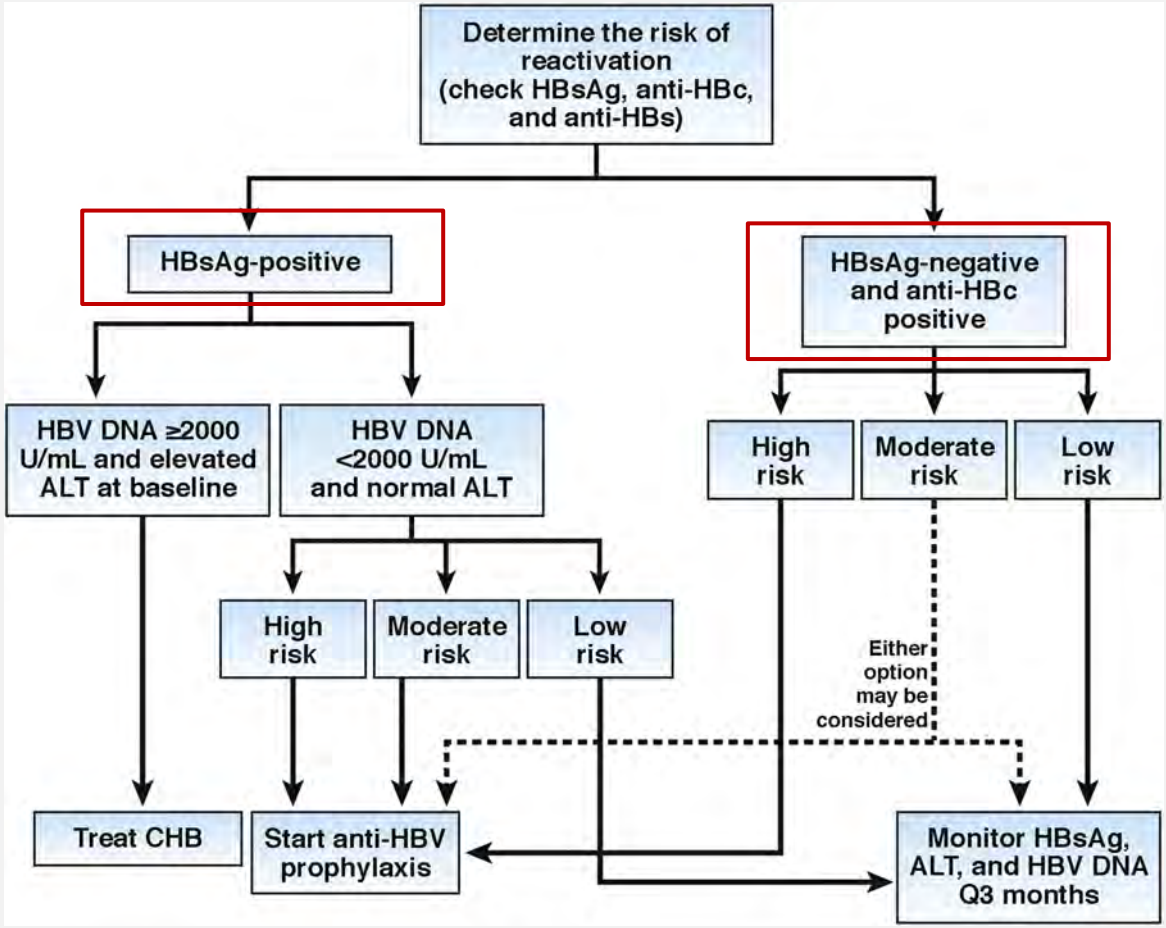
Hepatitis B Reactivation & Immune Suppression



- Prophylaxis → tenofovir or entecavir 2-4 weeks before introduction of immune suppression; continue at least 6-12 months after last dose of immune suppressant

Loomba R et al. Gastroenterology 2017; 152(6):1297-1309

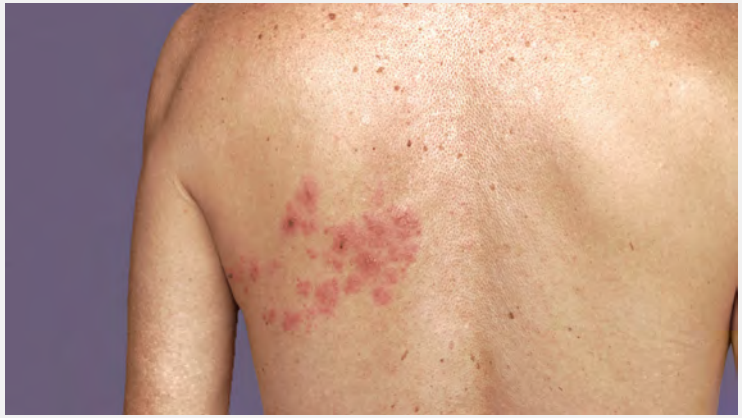
Case 2

- HBV management
  - HBsAg, HBV DNA and ALT monitored Q3 months
  - No hepatitis B reactivation

- IBD management
  - Adalimumab 40 mg Q 2 weeks + MTX 10 mg po weekly x 12 mos
  - MTX withdrawn at 12 months
  - Adalimumab levels decreased below target without antibody formation → increased to weekly dosing
  - Patient remains in clinical remission

Case 3

- 60 year old male with 20+ year history of left sided ulcerative colitis
- PMHx: Hyperlipidemia, remote history of pneumococcal PNA
- Previous tx: balsalazide, adalimumab
- Stable clinical remission > 1 year on tofacitinib 10 mg po BID
- Painful pruritic rash over left back x 2 days



Treatment recommendations?
Should he hold tofacitinib? How long?

Herpes Zoster (Shingles)

Reactivation of varicella zoster virus (VZV)

Can occur in those previously vaccinated or prior history of shingles

↑Risk

Systemic steroids

Thiopurines +/- anti-TNF

JAK inhibitors

S1PR modulators

Dx largely clinical based upon vesicular lesions in dermatomal distribution; can perform RT-PCR of lesions

Anti-viral tx recommended in immune suppressed even if lesions present > 72 hours

Consider holding immune suppression

Avoid contact w/pregnant or immune suppressed until lesions clear

Craviotto V et al. World J Gastroenterol 2021; 27(27): 4276-4297

Recombinant Herpes Zoster Vaccine (RZV)

- Non-live virus vaccine safe for immunocompromised
- Highly effective reducing herpes zoster risk and post-herpetic neuralgia
- Preferable to administer before immune suppression; can be given after

AICP RECOMMEDNATIONS		
Population	*Dosing*	
All immunocompetent ≥ age 50	2 doses	2-6 months apart
All immunocompromised ≥ age 19	2 doses	1-2 months apart

Craviotto V et al. World J Gastroenterol 2021; 27(27): 4276-4297
https://www.cdc.gov/vaccines/hcp/acip-recs/vaccspecific/shingles.html

Case 3

- Treatment
  - Valacyclovir x 10 days
  - Tofacitinib held until lesions crusted
  - No flare of IBD or post-herpetic neuralgia

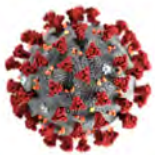
Case 4

- 30 year old male with recent diagnosis of stricturing ileocolonic Crohn's disease
- Fever, cough, congestion, loss of taste & smell x 3 days → dx'd w/COVID-19
- Reports looser stool, abdominal pain but unsure if due to IBD vs. COVID-19
- Meds: Prednisone 20 mg daily, infliximab 5 mg/kg x 2 induction doses
- Next infliximab induction dose due in 3 days

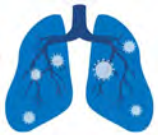
Do you delay infliximab dose?
Should steroids be stopped or dose reduced?
Other treatment recommendations?

COVID-19 (SARS-CoV-2)

SECURE-IBD REGISTRY
Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

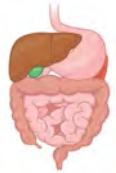


In general, IBD patients are NOT at increased risk



Severe COVID-19 risk factors:

Advanced age, # co-morbidities, systemic corticosteroids, anti-TNF + immune modulator, IBD disease activity



IBD patients are more likely to exhibit GI symptoms

Lin S et al. Gut 2022; 71(7): 1426-1439
Scalzo N et al. Ther Adv Gastroenterol 2023; 16: 1-16

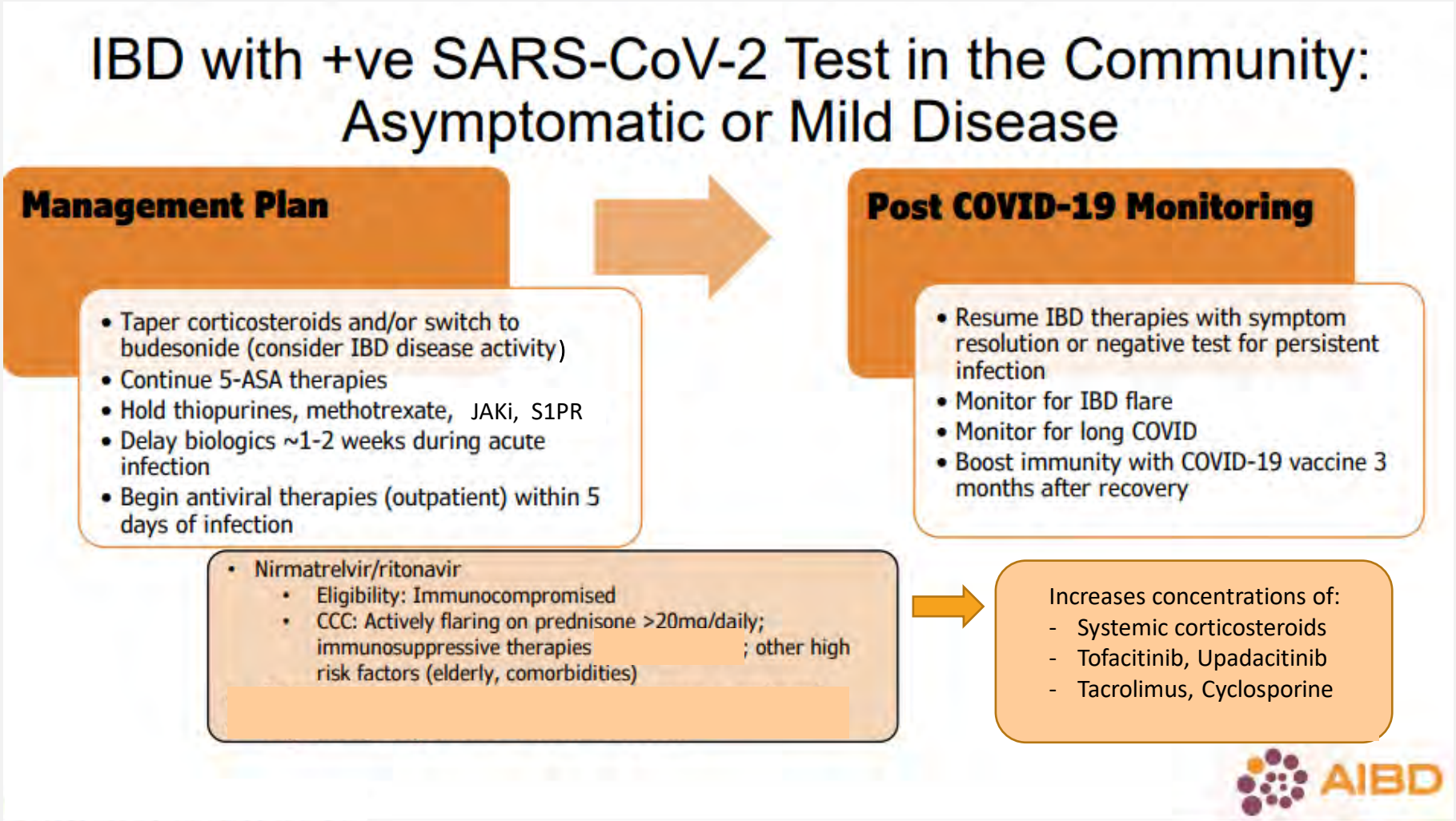
Impact of IBD Medications on COVID-19

	Hospitalisations	ICU admissions/Severe Covid	Mortality
Systemic steroids	RR 1.99 [95%CI 1.64 - 2.40]*	RR 3.41 [95%CI 2.28 - 5.11]*	RR 2.70 [95%CI 1.61 - 4.55]*
Immunomodulators	RR 0.89 [95%CI 0.37 - 2.10]	RR 0.71 [95%CI 0.17 - 3.02]	RR 1.18 [95%CI 0.23 - 6.01]
5-ASA	RR 1.02 [95%CI 0.83 - 1.26]	RR 1.03 [95%CI 0.74 - 1.43]	RR 1.09 [95%CI 0.65 - 1.82]
JAK-inhibitors	RR 0.48 [95%CI 0.30 - 0.76]*	RR 0.50 [95%CI 0.14 - 1.86]	RR 0.83 [95%CI 0.10 - 7.11]
Anti-TNF	RR 0.58 [95%CI 0.50 - 0.69]*	RR 0.50 [95%CI 0.33 - 0.78]*	RR 0.44 [95%CI 0.26 - 0.76]*
Anti-integrin	RR 0.66 [95%CI 0.56 - 0.78]*	RR 0.72 [95%CI 0.42 - 1.24]	RR 0.50 [95%CI 0.32 - 0.78]*
IL12/23 inhibitor	RR 0.44 [95%CI 0.36 - 0.54]*	RR 0.43 [95%CI 0.26 - 0.71]*	RR 0.55 [95%CI 0.28 - 1.11]

Clinical note:
1) The risk of IBD treatments on COVID-19 outcomes should be weighed up against IBD disease activity, and careful risk-benefit assessment regarding need for individual IBD treatments and risk of COVID-19 outcomes should be considered on an individual basis.
2) Classification of risk is based on limited published data

Lin S et al. Gut 2022; 71(7): 1426-1439

COVID-19 Management & IBD



Lin S et al. Gut 2022; 71(7): 1426-1439
Modified from Ungaro R, AIBD 2022

COVID-19 Vaccination in IBD Patients

COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised

Updated Oct. 18, 2023 Español Print

What You Need to Know

- CDC recommends the 2023–2024 updated COVID-19 vaccines: Pfizer-BioNTech, Moderna or Novavax to protect against serious illness from COVID-19.
- Everyone aged 6 months and older who is moderately or severely immunocompromised needs at least **1 dose of a 2023-2024 updated COVID-19 vaccine**. Depending on the number of doses you've previously received, you may need more than 1 dose of updated vaccine:
  - If you have not gotten any COVID-19 vaccines (not vaccinated), you should get 2-3 doses of updated COVID-19 vaccine.
  - If you got 1 previous Pfizer-BioNTech or Moderna COVID-19 vaccine you should get 1-2 doses of updated COVID-19 vaccine.
  - If you got 2 or more previous COVID-19 vaccines, you should get 1 updated COVID-19 vaccine.
- Talk to your healthcare provider about getting additional doses of updated COVID-19 vaccine.

Lin S et al. Gut 2022; 71(7): 1426-1439

https://www.cdc.gov/coronavirus/2019ncov/vaccines/recommendations/immuno.html

Case 4

- Infliximab delayed x 14 days
- Prednisone 20 mg daily continued
- Received nirmatrelvir/ritonavir x 5 days
- Progressive GI sx → pt increased prednisone to 40 mg daily
- Clinically improved after 3rd infliximab induction dose and commenced steroid taper

Infection Prevention Strategies

- Screening for infectious diseases before initiation of immune suppressants
  - Consider re-screening for latent TB and viral hepatidities based on risk
- Ensuring patients remain up to date with vaccinations
- Cautious use of systemic corticosteroids and combination therapy
- Consideration of *Pneumocystis jirovecii* prophylaxis in at risk individuals
  - 3 immune suppressants if one is a calcineurin inhibitor or anti-TNF
  - High dose steroids (≥ prednisone 20 mg daily for 4 weeks or more)

Kucharzik T et al. JCC 2021; 15(6): 879-913

Screening Tests for Serious & Opportunistic Infections

Disease Being Screened	Screening Test(s)	When to Screen
HBV	• HBsAg • Anti-HBc • Anti-HBs • HBV DNA if HBsAg-positive or anti-HBc–positive and/or anti-HBs–positive	Before immunomodulator, biologic, JAK inhibitor use
HCV	• HCV antibodies • HCV RNA (if anti-HCV–positive)	Before immunomodulator, biologic, JAK inhibitor use
Latent tuberculosis	• Tuberculin skin test or QuantiFERON-TB Gold assay • Consider T-SPOT.TB assay if QuantiFERON-TB Gold is indeterminate. • Chest radiograph	Before biologic, JAK inhibitor use
HIV	• 4th-generation antigen/antibody HIV-1/-2 immunoassay; if positive, obtain plasma HIV RNA level	Before immunomodulator, biologic, JAK inhibitor use
HPV	• Papanicolaou test or HPV test (if available)	Before immunomodulator, biologic, JAK inhibitor use
VZV	• Obtain history of chicken pox or shingles. • IgM/IgG anti-VZV	Before immunomodulator, biologic, JAK inhibitor, S1PR use
Epstein-Barr virus	• IgM/IgG anti–viral capsid antigen antibodies • IgM/IgG anti–Epstein-Barr nuclear antigen antibodies • IgM/IgG anti–early antigen antibodies • The Monospot test is not recommended for general use given its lack of specificity.	Before thiopurine use

Adapted from Lin E et at al. Gastroenterol Hepatol 2019; 15(11): 593-605

Recommended Vaccines for IBD Patients

Table 1. Recommended Vaccinations for Patients With IBD

Vaccines	Patient group	Frequency
COVID-19 (Moderna, Pfizer, Novavax)	• All adults	• Follow CDC recommendation for the general population
Influenza (Fluzone High Dose, Sanofi Pasteur; Flublok recombinant, Sanofi Pasteur; Fluad adjuvanted, CSL Sequirus)	• All adults, unless otherwise noted: standard dose • Adults on anti-TNF monotherapy: high-dose vaccine • Adults =65 y of age: high-dose, recombinant, or adjuvanted influenza vaccine • Those on systemic immunosuppresion should avoid live influenza vaccine (nasal)	• Annually
15-valent or 20-valent pneumococcal conjugate vaccine (PCV15 or PCV20) or pneumococcal polysaccharide vaccine (PPSV23)	• All patients =19 y of age receiving systemic immunosuppression[a]	• Vaccine-naive patients: PCV20 or PCV15, followed by PPSV23 8 wk later • Those previously vaccinated with PCV13 and PPSV23: 1 PCV20 dose at least 1 year after last dose of pneumococcal vaccine • Those =65 y of age: a dose of PCV20
RZV (adjuvanted non-live) (Shingrix, GlaxoSmithKline)	• All patients with IBD =19 y of age who are immunocompromised	• If on systemic immunosuppresion: 2 doses of RHZ vaccine 1-2 mo apart • If not on systemic immunosuppresion: 2 doses of RHZ vaccine 2-6 mo apart
HPV (9-valent) (Gardasil 9, Merck)	• All adults =18-26 y of age • Adults 26-45 y of age: shared decision between patient and provider	• 3-dose series at 0, 1-2, and 6 mo

Gastroenterology & Endoscopy October 2023

Recommended Vaccines for IBD Patients

Table 1. Recommended Vaccinations for Patients With IBD

Vaccines	Patient group	Frequency
Hepatitis A (Havrix, GSK; Vaqta, Merck)[b]	• All adults not previously vaccinated	• 2-dose series 6-12 mo apart
Hepatitis B (Heplisav-B, Dynavax; Engerix-B, GSK; Recombivax HB, Merck)[b]	• All adults with IBD. • Universal vaccination is recommended for adults 19-59 y of age	• Heplisav-B: 2-dose series at 0 and 1 mo • Engerix or Recombivax: 3-dose series at 0, 1, and 6 mo
Meningococcal A, C, W, y (MenACWY); Men B	• Adults who live in college residence halls and missed routine immunizations • Military recruits • Adults with asplenia, complement deficiency, or HIV	• MenACWY every 5 y • Men B 1 y after completing series and then every 2-3 y
Tetanus, diphtheria, pertussis (Tdap or Td)	• All adults • Pregnant patients	• If previously immunized: single dose of Tdap then Td or Tdap every 10 y • 1 dose of Tdap during third trimester of each pregnancy
MMR 2-dose live vaccine	• Patients not immune to MMR (if immune status is uncertain, obtain immunization history[c])	• 2-dose series, at least 4 wk apart • Contraindicated in those on systemic immunosuppresion
Varicella 2-dose live vaccine	• Check for documentation of 2 doses of varicella vaccine[d]	• All patients who are not immune: 2-dose series, 4-8 wk apart, =4 wk before immunosuppression, if therapy cannot be postponed • Contraindicated in those on systemic immunosuppression

Gastroenterology & Endoscopy October 2023

Avoid Live Virus Vaccines in Immunocompromised

NON-LIVE VIRUS (SAFE)	LIVE VIRUS (AVOID)
Inactivated influenza (parenteral)	Measles, mumps, rubella
Pneumococcal	Oral poliomyelitis (OPV)
COVID-19	Rotavirus
Hepatitis A	Varicella
Hepatitis B	Nasal influenza vaccine
Meningococcal	Live attenuated zoster (Zostavax)
Human papillomavirus	Yellow fever
Recombinant zoster (Shingrix)	Oral typhoid
Tetanus, diphtheria, pertussis	
Inactivated poliomyelitis (IPV)	
Typhoid Vi polysaccharide Ag/Monovalent whole cell typhoid	
Rabies	

Kucharzik T et al. JCC 2021; 15(6): 879-913

Recommendations for Live Virus Vaccines

Table 4. Suggested time frame between stopping immunosuppressants and live vaccination, considering drug elimination half-life.[2,218,429–432]

Drug	Elimination half-life	Stopping before live vaccines	Restart after live vaccines
Steroids [prednisone] >1 mg/kg, >14 days [children] >20 mg/day, >14 days [adults]	2–3 h	1 month	1 month
Thiopurines[a] [azathioprine and 6-MP[b]: approximately 2 h]	Several days [6-TGN[c]]	3 months	1 month
Methotrexate, low dose [adults]	3–10 h	1 month	1 month
Tofacitinib	3 h	1 month	1 month
Infliximab	7–12 days	3 months	1 month
Adalimumab	Approximately 2 weeks	3 months	1 month
Golimumab	Approximately 2 weeks	3 months	1 month
Certolizumab	Approximately 2 weeks	3 months	1 month
Cyclosporine[d,e]	8.4 h [10–27]	1 month	1 month
Tacrolimus[e]	23–46 h	1 month	1 month
Vedolizumab[f]	25 days	3–4 months	1 month
Ustekinumab	Approximately 19 days	3 months	1 month

I would suggest similar timeframes from S1PR modulators

Kucharzik T et al. JCC 2021; 15(6): 879-913

Useful Reference

Inflammatory Bowel Diseases, 2023, **XX**, 1–15
https://doi.org/10.1093/ibd/izad120
Advance access publication 14 July 2023
Review Article - Clinical

CROHN'S & COLITIS FOUNDATION

Safety and Monitoring of Inflammatory Bowel Disease Advanced Therapies

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CME/MOC Question:

In discussing potential biologic treatments with a newly diagnosed IBD patient, they inquire what measures can be taken to limit risk of infections.

Which of the following do you recommend?

A. Screening for infectious diseases before starting biologic therapy

B. Staying up to date with vaccinations

C. Cautious use of systemic corticosteroids

D. All of the above

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CME/MOC Answer

A. Screening for infectious diseases before starting biologic therapy

B. Staying up to date with vaccinations

C. Cautious use of systemic corticosteroids

D. All of the above

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