Serious Infections in Patients With Inflammatory Bowel Disease (IBD)

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These materials were created in conjunction with Pfizer Inc.

Contents

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Infections in Patients With IBD

Definitions of Infections

- **Serious infection event (SIE):** an infection that meets the US Food and Drug Administration definition for a serious adverse event, including an event that[1]:
  - Results in death
  - Is life-threatening
  - Requires hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability or incapacity
  - Requires medical or surgical intervention to prevent any of these specified outcomes
- **Opportunistic infection (OI):** an infection that occurs with higher frequency and severity in individuals with weakened immune systems[2]

1. Wheat CL, et al. *BMC Gastroenterol.* 2017;17(1):52. **2.** Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html. Accessed September 13, 2021.

Healthcare Burdens Associated With Infections in Patients With IBD

- In a retrospective analysis of Truven Analytics MarketScan data[a] of patients with IBD (N=63,759), pneumonia was the most common cause of infection-related hospitalizations, followed by sepsis, candidiasis, herpes zoster, *Clostridium difficile,* and intestinal and anorectal abscess

Unadjusted Incidence Rates of Infection and Infection With Hospitalization Among Elderly and Nonelderly Patients With IBD

	18–64 Years N = 54,971	65+ Years N = 8788
Infection (%)	10,515 (19.1)	2664 (30.3)
Incidence of infection per 100 PY [95% CI]	10.49 [10.29, 10.69]	16.95 [16.32, 17.61]
Infection with hospitalization (%)	3182 (5.8)	1193 (13.6)
Incidence of infection with hospitalization per 100 PY [95% CI]	2.86 [2.76, 2.96]	6.59 [6.22, 6.98]

Note: This study was limited to insured individuals and did not include direct Medicare patients or patients who did not have commercial insurance. The study was also limited by having only a partial measure of length of time patients had lived with IBD before entering the study.

[a]US-based commercial claims and Medicare supplemental database.
CD=Crohn's disease; CI=confidence interval; IBD=inflammatory bowel disease; PY=person-years; UC=ulcerative colitis.
Khan N, et al. *Inflamm Bowel Dis.* 2020;26(3):462-468.

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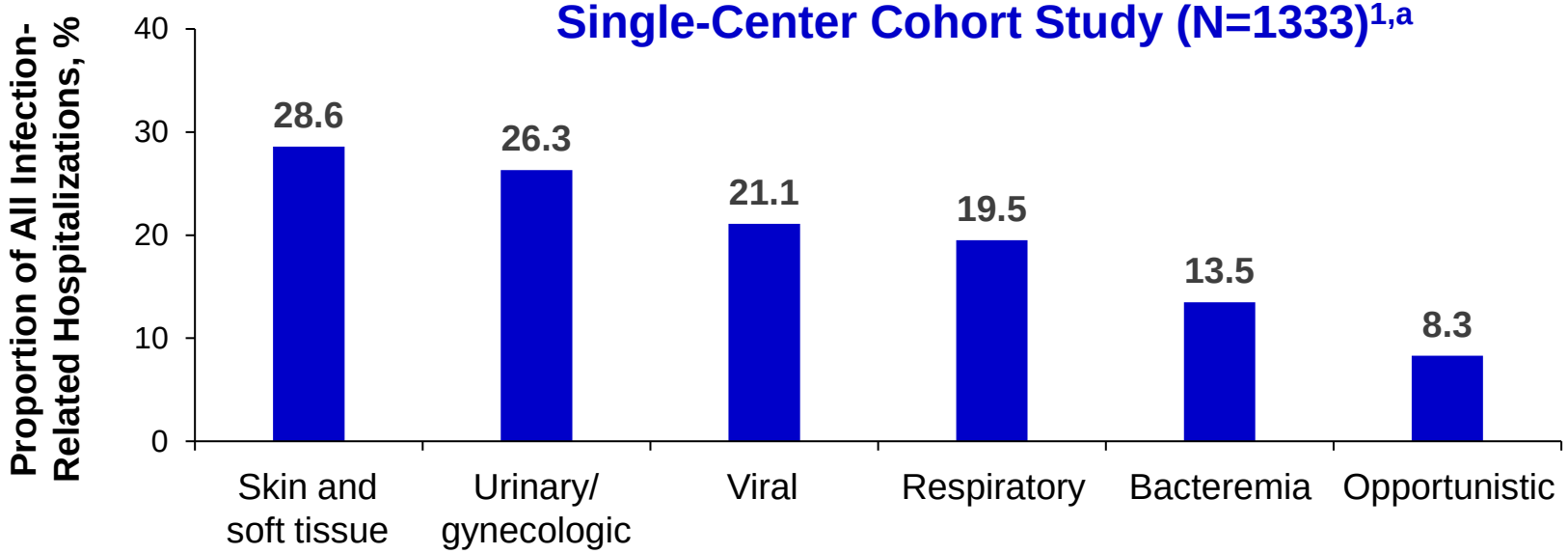
Serious Infections Requiring Hospitalization in Patients With IBD

Common Infections That Resulted in Hospitalization in a Prospective Single-Center Cohort Study (N=1333)[1,a]



Note: External validation of these study reports is essential for this study because the numbers of patients with infections by specific organ system or pathogen were low. The study results may not be generalizable to a population-based cohort because this study included patients from a single tertiary referral center.[1]

- A retrospective analysis using an inpatient database[b] found that ~34% of hospitalizations in patients with IBD were likely attributed to treatment-related serious infections, especially in older patients who may experience waning immunity or be on immunosuppressive therapy[2,c]

Note: All analyses are based on administration codes and CCS which can misclassify IBD diagnosis and causes of admissions and only focus on inpatient use without outpatient details. Readmissions causes were based on primary discharge diagnoses and grouped by system for ease of interpretation, which could also be potentially misclassified and somewhat biased due to reimbursement practices. NRD is limited to only within state boundaries and does not capture out-of-hospital mortality.[2]

[a]Included patients with IBD aged ≥18 years from a prospective-consented patient registry at Massachusetts General Hospital.
[b]Assessed data from the 2013 Nationwide Readmissions Database, a longitudinal, nationally representative sample of all-payer hospital inpatient stays from 21 state inpatient databases developed as part of a family of databases by the Healthcare Cost and Utilization Project; N=47,402 patients with index hospitalizations between January and June 2013 with a primary or secondary discharge diagnosis of IBD.
[c]Due to the use of claims data, the causes of infection (IBD or treatment related) were not reported in the publication. CCS=Clinical Classifications Software; IBD=inflammatory bowel disease.
1. Sasidharan S, et al. *Scand J Gastroenterol.* 2017;52(5):570-576. **2.** Nguyen N, et al. *Inflamm Bowel Dis.* 2018;24(4):916-923.

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Prevalence of Opportunistic Infections in Patients With IBD

- A large US-based retrospective cohort study reported an increased prevalence of OIs in patients with CD (17.8%) and UC (19.2%) compared with non-IBD controls (7%)
  - Rates of bacterial, fungal, and viral infections were all significantly higher in patients with IBD
- OIs with the highest occurrence in IBD patients were *Clostridium difficile* (for CD, PR: 11.5, 95% CI: 11.1-11.8; for UC, PR: 17.2, 95% CI: 16.8-17.7) and CMV (for CD, PR: 10.4, 95% CI: 9.4-11.6; for UC, PR: 14.6, 95% CI: 13.2-16.1)
- For IBD patients, aspergillosis, histoplasmosis, and pneumococcal disease are more prevalent in patients aged >65 years compared with younger adults (18-65 years)
- Candidiasis, influenza, HPV, and HSV were more prevalent in females with IBD than in males

Note: Limitations of this study include possible misdiagnosis of patients in the database, inability to validate diagnosis of OI, incomplete documentation on medications, lack of sociodemographic and geographic data, and rounding off of database, which may impact diseases with very low prevalence.

Prevalence of OIs in Patients With CD (N=27,300) and UC (N=24,690) vs Non-IBD (N=2,465,010)[1]

Organism	Prevalence[a]		
	CD	UC	Non-IBD
Clostridium difficile	2596	3905	227
Pneumococcal disease	294	303	89
Legionella	20	31	11
HPV	3901	4092	1967
Influenza	2322	2342	1468
HSV	1938	1914	1020
Candidiasis	5858	5703	1995
Histoplasmosis	104	93	23
Aspergillosis	72	86	17

[a]Prevalence reported per 100,000 population.

CD=Crohn's disease; CI=confidence interval; CMV=cytomegalovirus; HPV=human papillomavirus; HSV=herpes simplex virus; IBD=inflammatory bowel disease; OI=opportunistic infection; PR=prevalence rate; UC=ulcerative colitis.

Sheriff MZ, et al. *Inflamm Bowel Dis.* 2019; doi:10.1093/ibd/izz147.

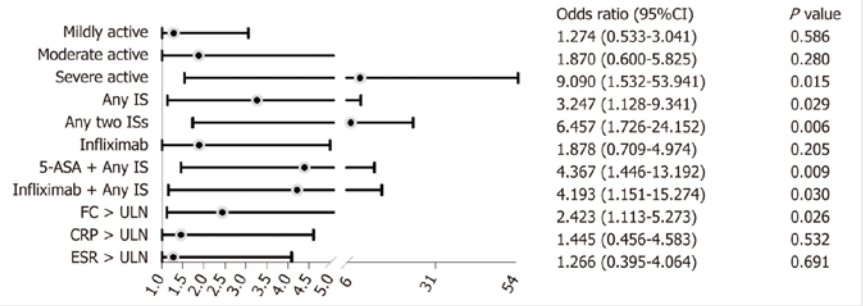
Risk Factors for Opportunistic Infections in Patients With IBD

- A retrospective case-control study of US patients with IBD (N=281,830) identified disease (UC vs CD), sex, and age as influential factors in both OI prevalence and type of OI contracted[1,a]
  - OI prevalence was 17.8% in CD and 19.2% in UC
  - Children (<18 yo) with IBD contracted more viral infections (eg, influenza and EBV) than adults (18-65 yo) with IBD
  - Elderly patients (>65 yo) with IBD had more fungal infections (eg, aspergillosis and histoplasmosis) and bacterial infections (eg, pneumococcal disease) than did adults (18-65 yo) with IBD
  - Cytomegalovirus prevalence was higher in males with IBD, whereas candidiasis, influenza, HPV, and HSV were more prevalent in females with IBD

Note: The study was limited by lack of validation of diagnosis of OIs, the inability to capture sociodemographic factors of these cases of OIs, and rounding of the database to 10, which can have a significant impact on the diseases with very low prevalence.

- In a single-cohort study of IBD patients in China (N=301), the risk of OI increased significantly in patients[2]
  - With severe IBD
  - Using immunosuppressants
  - With high levels of CRP or ESR

Risk Factors for OI in IBD Patients[2]



Note: This ex-US study was limited by a small sample size and was restricted to a single center. Also, this study was conducted in China and, therefore, the patient population may not be representative of other countries.

[a]This study used the Explorys search tool to identify a cohort of UC and CD within the period of March 2013 to March 2018.

5-ASA=5-aminosalicylic acid; CD=Crohn's disease; CI=confidence interval; CRP=C-reaction protein; EBV=Epstein-Barr virus; ESR=erythrocyte sedimentation; FC=fecal calprotectin; HPV=human papillomavirus; HSV=herpes simplex virus; IBD=inflammatory bowel disease; IS=immunosuppressant; OI=opportunistic infection; UC=ulcerative colitis; ULN=upper limit of normal; yo=years old.

1. Sheriff M, et al. *Inflamm Bowel Dis.* 2020;26(2):291-300. **2.** Gong SS, et al. *World J Gastroenterol.* 2019;25(18):2240-2250.

Risk of Infections With IBD Therapies

- Patients with IBD are at an increased risk of infection, which may be due to impaired innate mucosal immunity, concurrent malnutrition, and/or use of immunosuppressive therapies used to manage IBD[1]
- Therapies used to treat IBD may alter a patient's immunity by different mechanisms and to varying degrees[2]
- A case-control study of patients with IBD (N=10,838) who experienced a serious infection during follow-up (n=428) identified an elevated risk of serious infection in patients receiving TNF blocker or immunomodulator therapy[3]

  Note: The study was limited by the potential misclassification of outcomes and exposures, use of prescription records and outpatient claims to define exposure status, and the potential inability to generalize to forms of insurance outside of commercially available insurance. There was also a lack of clinical or laboratory information about patients and severity of illness.
- Across multiple RCTs, higher rates of infections have been reported in patients treated with JAK inhibitors[4,5]
  - Among OIs, HZ is of special concern for JAK inhibitors, which are associated with a higher risk of HZ infection[4,5]
- Pooled analyses of RCTs and postmarketing safety registries suggest a potential risk of OIs and SIs associated with certain biologics[6,7,b,c]
  - Among OIs, TB is of special concern for biologics that may increase the risk of development or reactivation of TB[6,b]
  - Targeted biologics, such as gut-selective anti-integrin therapies, are thought to have a favorable safety profile with a lower risk of infections compared with more systemic therapies[6-9]
- Whether combinations of therapies increase the risk of SIs in patients with IBD remains controversial[9]

Please see the Prescribing Information for each IBD therapy before use.

[a]Treatments studied included corticosteroids, AZA, 6-MP, MTX, infliximab, cyclophosphamide, and tacrolimus. [b]TNF blockers. [c]TNF blockers carry a boxed warning for SIs.
AZA=azathioprine; HZ=herpes zoster; IBD=inflammatory bowel disease; JAK=Janus kinase; 6-MP=6-mercaptopurine; MTX=methotrexate; OI=opportunistic infection; RCT=randomized controlled trial; SI=serious infection; TB=tuberculosis; TNF=tumor necrosis factor.

1. Mill J, Lawrance IC. *World J Gastroenterol.* 2014;20(29):9691-9698. **2.** Rahier JF, et al. *J Crohns Colitis.* 2014;8(6):443-468. **3.** Lee WJ, et al. *Inflamm Bowel Dis*. 2018;24(4):883-891. **4.** Ma C, et al. *Best Pract Res Clin Gastroenterol*. 2019;38-39:101606. **5.** Sabino J, et al. *Therap Adv Gastroenterol*. 2019;12:1756284819853208 **6.** Hindryckx P, et al. *Clin Pharmacol Ther*. 2017;102(4):633-641. **7.** Sandborn WJ. *Gastroenterol Hepatol (N Y).* 2016;12(7):438-441. **8.** Rubin DT, et al. *Am J Gastroenterol.* 2019;114(3):384-413. **9.** Wheat CL, et al. *BMC Gastroenterol.* 2017;17(1):52.

Infections of Special Interest

Herpes Zoster, Viral Hepatitis B, Tuberculosis, *Clostridium difficile*, SARS-CoV-2

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Prevalence and Risk of Herpes Zoster in Patients With IBD

- In the general population, ~30% develop HZ during their lifetime[1]
  - Incidence rate for HZ and risk of complications increase with age
  - Postherpetic neuralgia is the most serious complication (~15% of cases)

- Adult patients with IBD have an increased risk of HZ
  - A retrospective study using claims from ~50,000 patients from 2007 to 2010 estimated up to a 2-fold increase in HZ risk in the IBD population compared with the general population[2,a]

Note: Limitations of this study include the use of administrative claims data, which may lack complete clinical detail. Individual medical charts were not used to identify patients with autoimmune diseases. This study could not rule out the incidence of vaccine-related HZ events.

  - A separate retrospective cohort study[b,c] that analyzed claims from ~109,000 patients with IBD and ~435,000 controls from January 1997 to December 2009 reported the following[1]:
    - Incidence of HZ in patients with IBD (CD or UC) was 0.73 cases per 100, compared with 0.44 cases per 100 for the non-IBD population[1]
    - Risk increases with age and increases further with use of immunosuppressive therapies[1,c]: TNF blocker, corticosteroid, thiopurine, and combination TNF blocker and thiopurine therapy were independently associated with HZ

Note: Limitations of this study include the use of administrative claims data, which may lack complete clinical detail. Patients aged >65 years were not included in this study, which may constitute patient selection bias. This study could not assess length of medication exposure and HZ risk, because these data were not available.

[a]This retrospective study utilized data from the Multipayer Claims Database, which contains public and private data were obtained from beneficiaries who received healthcare coverage from United Healthcare, Medicare, or Medicaid. [b]This retrospective cohort study analyzed procedural and retail pharmacy claims covered by insurers contained in the IMS LifeLink Information Assets-Health Plan Claims Database. [c]Therapies studied included corticosteroids, immunomodulators, TNF blockers, and 5-ASAs.

5-ASA=5-aminosalicylic acid; CD=Crohn's disease; HZ=herpes zoster; IBD=inflammatory bowel disease; TNF=tumor necrosis factor; UC=ulcerative colitis.

1. Long MD, et al. *Aliment Pharmacol Ther.* 2013;37(4):420-429. **2.** Yun H, et al. *Arthritis Rheumatol.* 2016;68(9):2328-2337.

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Hepatitis B Virus Infection in Patients With IBD

- Incidence of HBV in patients with IBD is estimated to be similar to that in the general population[1]
- A retrospective, cross-sectional, observational study involving 500 patients with IBD at Rush University Medical Center (September 2010-January 2013) assessed the prevalence of HBV markers in patients with IBD (N=220)[2]
  - Present and/or past HBV infection was found in 3.6% of the 220 patients with serology data available

Note: This study may be limited by the availability of patient records. Results of this single-center study may not be generalizable to other settings.

- Reactivation of HBV depends on HBV status (highest risk if there is an active infection with detectable HBsAg, or even if anti-HBcAb is positive) and level of immunosuppression[3,4,a]
- A recent meta-analysis that included 2375 patients with IBD found that patients with IBD have an inferior response to hepatitis B vaccine compared with healthy controls without IBD[5]
  - In addition to the altered immune system in patients with IBD, the combination of multiple immunosuppressant medications with newer biologics could play a role in the observed low response rates to the hepatitis B vaccine

Note: Limitations of this retrospective study include the lack of thorough follow-up of patients, variability in the type of IBD and the medications used, and the inability to categorize results based on type of IBD, severity of disease, type of immunosuppressive treatment, or treatment duration. The study also could not compare the outcomes in patients on immunosuppression versus those not due to a lack of data segregated and/or classified to previously mentioned categories.

[a]Viral reactivation is defined by an increase of 1 log in viral load or reappearance of the virus after previous clearance.[2]

Anti-HBcAb=hepatitis B core antibodies; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IBD=inflammatory bowel disease.

1. López-Serrano P, et al. *World J Gastroenterol.* 2013;19(9):1342-1348. **2.** Musa RB, et al. *World J Gastroenterol.* 2014;20(41):15358-15366. **3.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **4.** Rojas-Feria M, et al. *World J Gastroenterol*. 2013;19(42):7327-7340. **5.** Kochhar GS, et al. *Inflamm Bowel Dis.* 2021;27(10):1610-1619.

Risk of HBV Reactivation in Patients With IBD

Reactivation of HBV infection can lead to fulminant or fatal hepatitis in patients with IBD treated with immunosuppressive therapies[1,2]

- Risk of HBV reactivation in patients with IBD varies depending on the type of immunosuppressive drug used and the HBV phase prior to treatment[3]
  - HBsAg-positive patients carry a higher risk for reactivation compared with HBsAg-negative anti-HBc–positive patients[4]
  - Higher HBV DNA levels before the start of immunosuppression confer an elevated risk of reactivation[4]

- Immunosuppressants may lead to an increase in the HBV DNA viral load due to an effect on the host immune response[5]
  - A multicenter study of patients with rheumatic disease or IBD (N=984; IBD n=160) receiving biologic therapy in Italy found HBV infection in 3% of patients with IBD; HBV reactivation was identified in an anti-HBs–positive patient with a titer of 6 IU/mL, suggesting that anti-HBs titer surveillance may be useful, because low anti-HBs titers could be predictive of HBV reactivation[6]

    Note: This was an ex-US study, so results may not reflect patients in the US.
  - In a retrospective cohort study based in Hong Kong (N=406 patients with IBD), the risk of HBV reactivation appeared to be low in patients receiving immunosuppressive therapy in the form of thiopurines unless there was concomitant use of steroids[7]

    Note: This was an ex-US study limited by some patients starting antiviral agents before the start of the study, possibly masking the true effect of immunosuppressants. Additionally, hospital records before 2000 are incomplete, and the cohort was modest in size.

Anti-HBs=hepatitis B surface antibody; anti-HBc=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IBD=inflammatory bowel disease.

1. Farraye FA, et al. *Am J Gastroenterol*. 2017;112(2):241-258. **2.** Rahier JF, et al. *J Crohns Colitis.* 2014;8(6):443-468. **3.** Restellini S, et al. *Liver Int*. 2017;37(4):475-489. **4.** Axiaris G, et al. *World J Gastroenterol*. 2021;27(25):3762-3779. **5**. López-Serrano P, et al. *World J Hepatol.* 2015;7(3):539-547. **6.** Ridola L, et al. *Ann Ist Super Sanita*. 2021;57(3):244-248. **7.** Chan H, et al. *BMC Gastroenterol.* 2016;16(1):100.

Prevalence and Risk of Tuberculosis in Patients With IBD

- After LTBI diagnosis in IBD patients participating in a retrospective cohort study, TB reactivation occurred at a rate of 0.98 cases per 100 patient-years of follow-up despite LTBI screening and treatment[1]
  - Most TB reactivation cases in patients taking biologics occur within the first year of therapy initiation
  - The risk for TB reactivation is assumed to be lower in patients receiving anti-integrin agents, given the gut-specific mechanism of action of these agents
  - TB reactivation associated with TNF blockers presented with higher rates of extrapulmonary and disseminated disease

Note: This study was limited by its retrospective design and limited sample size. Furthermore, most data collected from the patients in the cohort is specific to LTBI and TB treatment, with important information regarding IBD disease activity and management missing. Patients with indeterminate LTBI screening results (ie, indeterminate interferon gamma release assay results and negative repeat tuberculin skin test results) were also not included in the study analysis.

- In a meta-analysis of randomized controlled trials[b] of patients with CD receiving TNF blocker therapy, if TB infection incidence was 20 cases per 100,000 person-years, 1 TB case might be expected in a community of 5000 patients with CD within 1 year[2]
  - There was a determined risk difference between TNF blockers and placebo of 0.028 (95% CI: 0.0011-0.055; $P<0.05$)

Note: This study was limited by including only studies in English, which may limit the generalizability of the results, considering that the demographics and trends of CD and TB infection differ among different regions or populations. The included studies were mainly EMA- and FDA-regulated clinical trials conducted in Western countries. The TB screening methods of trials varied and often went unreported.

[a]Patient data were extracted from a prospectively maintained database from a large tertiary care center.[1] [b]Meta-analysis only included studies in English and randomized, placebo-controlled, double-masked trials with appropriate exposure in adult populations.[2]

CD=Crohn's disease; CI=confidence interval; EMA=European Medicines Agency; FDA=US Food and Drug Administration; IBD=inflammatory bowel disease; LTBI=latent tuberculosis infection; TB=tuberculosis; TNF=tumor necrosis factor.

1. Ramos G, et al. *Inflamm Bowel Dis*. 2018;24(10):2272-2277. **2.** Cao B, et al. *World J Gastroenterol.* 2018;24(25):2764-2775.

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Risk Factors for *C difficile* Infection in Patients With IBD

A retrospective cohort study (2010-2013) at Mount Sinai Hospital IBD Center (N=503) identified risk factors for recurrent *C difficile* infection among patients with IBD[1]

Risk Factor in Patients With IBD	Risk	*P* value
Recent antibiotic therapy[a]	Increased	<0.01
Proton pump inhibitor[b]	None	NS
5-ASA[b]	Increased	<0.001
Steroid[b]	Increased	<0.001
Immunomodulator[b,c]	None	NS
Biologic[b,d]	Increased	<0.01
Previous bowel resection	Decreased	<0.001

- Recurrent *C difficile* infection is defined as the return of *C difficile* infection-associated clinical symptoms and confirmatory stool test after successful completion of initial infection treatment[1]
- In the general population, recurrent *C difficile* infection is reported in 10% to 35% of patients[1]
  - Recurrent *C difficile* infection is associated with continued use of antibiotics after *C difficile* infection diagnosis, use of antacids, and older age
- Patients with IBD are 33% more likely to experience recurrent *C difficile* infection, and increased risk is associated with prior treatment with certain therapies[1]

- Serious infections with *C difficile* have also been observed in 3 patients receiving JAK inhibitor therapy for UC[2] or CD[3]

Note: This study relied on chart review as the primary data collection method and hence may be limited by factors such as missing data or the need for extrapolation. Because this was a single-center study, results may not be generalizable.

[a]Within 90 days of *C difficile* infection. [b]Within 60 days of *C difficile* infection. [c]Immunomodulators included azathioprine, MTX, and cyclosporine. [d]When stratified by type of biologic, more recurrent *C difficile* infection events were reported in patients on infliximab (34.3 vs 17.3%, *P* <0.01) but not adalimumab.

5-ASA=5-aminosalicylic acid; *C difficile=Clostridium difficile;* CD=Crohn's disease; IBD=inflammatory bowel disease; JAK=Janus kinase; MTX=methotrexate; NS=not significant; UC=ulcerative colitis.

1. Razik R, et al. *Am J Gastroenterol.* 2016;111(8):1141-1146. **2.** Sandborn WJ, et al. *N Engl J Med*. 2017;376(18):1723-1736 [supplemental appendix]. **3.** Panés J, et al. *Gut*. 2017;66(6):1049-1059.

Adverse Outcomes Associated With *C difficile* Infection in Patients With IBD

Adverse outcomes associated with *C difficile* infection in patients with IBD include[1]:

- Subsequent IBD flares
- Increased need to escalate IBD therapy
- Increased likelihood of failing IBD therapy
- Higher surgery rates
- Recurrent *C difficile* infection[2]
  - Patients with IBD are 33% more likely to experience recurrent *C difficile* infection

A nationwide population-based analysis (1998-2004) reported higher mortality rates and increased healthcare utilization among patients with *C difficile* infection and IBD (N=116,842; n=73,197 patients with CD, n=43,645 patients with UC)[3,a]

- In-hospital mortality was significantly higher among UC patients with *C difficile* infection compared with uninfected patients (OR: 3.79; 95% CI: 2.84-5.06)
- *C difficile* infection was associated with significantly longer duration of hospitalization for patients with CD and UC (65% and 46%, respectively) compared with patients without infection
- Similarly, hospital charges were higher for patients with *C difficile* infection (63% and 46% for CD and UC, respectively)

Note: This study may be limited due to its reliance on administrative diagnostic codes, which were not confirmed by laboratory data. Access to outpatient pharmacy data was also unavailable, and therefore the contribution of treatment-related predictor variables to risk of infection could not be assessed

[a]Study included 73,197 patients with CD and 43,645 patients with UC.

C difficile=Clostridium difficile; CD=Crohn's disease; CI=confidence interval; IBD=inflammatory bowel disease; OR=odds ratio; UC=ulcerative colitis.

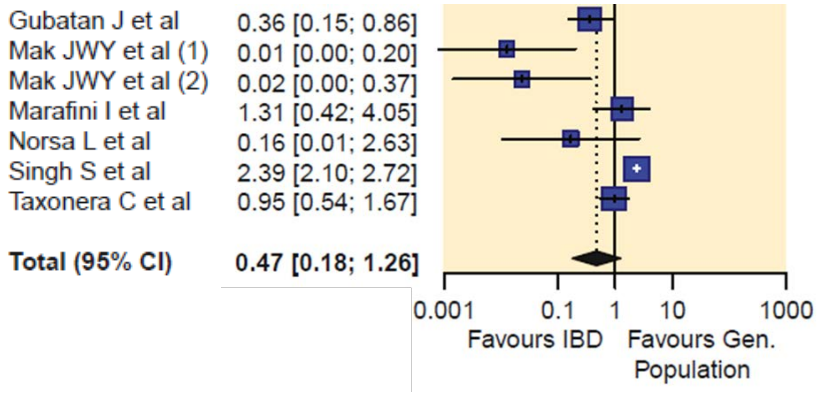
1. Khanna S, et al. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174. **2.** Razik R, et al. *Am J Gastroenterol.* 2016;111(8):1141-1146. **3.** Nguyen GC, et al. *Am J Gastroenterol.* 2008;103(6):1443-1450.

SARS-CoV-2 Infection in IBD

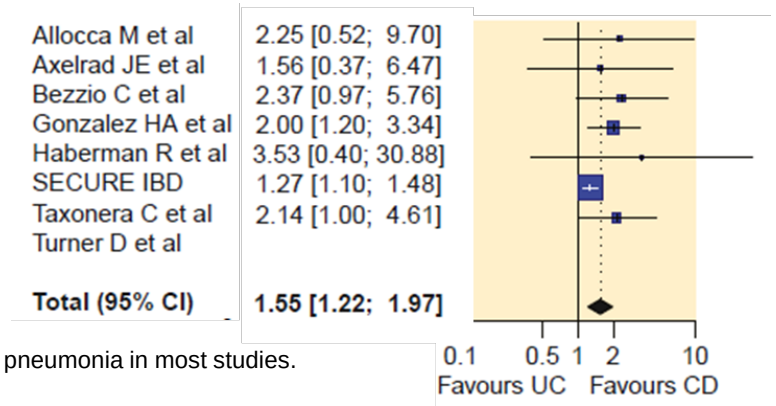
- Pooled relative risk of COVID-19 in patients with IBD was not different from that in the general population (0.47; 95% CI: 0.18-1.26; I^2=89%)
  - According to meta-analysis from December 2019 to July 2020, including 24 studies and data extracted from SECURE-IBD[a] on July 29, 2020, included in final analysis
- Incidence of COVID-19 was not significantly different between patients with UC and those with CD
  - UC: 4.55 (95% CI: 0.76-26.80) per 1000 cases
  - CD: 6.66 (95% CI: 1.49-29.35) per 1000 cases
- Overall, the risk of hospitalization was higher in patients with UC (1.55; 95% CI: 1.22-1.97; I^2=15%)

Note: Incidence in the included studies is reported from different geographical locations with different genetic compositions of the populations, medications used for IBD, comorbidities, and hygiene practices, which may affect the underlying risk of acquisition of SARS-CoV-2 infection.

Risk of COVID-19 in Patients With IBD Compared With the General Population



Risk of Hospitalization Due to COVID-19 in Patients With UC vs CD



Definitions used for COVID diagnosis were based on RT-PCR or clinical symptoms consistent with COVID-19 with radiologic evidence of pneumonia in most studies.
[a]SECURE-IBD is an international database to monitor and report on outcomes of COVID-19 in patients with IBD.
CD=Crohn's disease; CI=confidence interval; COVID-19=coronavirus disease 2019; IBD=inflammatory bowel disease; RT-PCR=real-time polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SECURE=Surveillance Epidemiology of Coronavirus Under Research Exclusion; UC=ulcerative colitis.
Singh AK, et al. *United European Gastroenterol J*. 2021;9(2):159-176.

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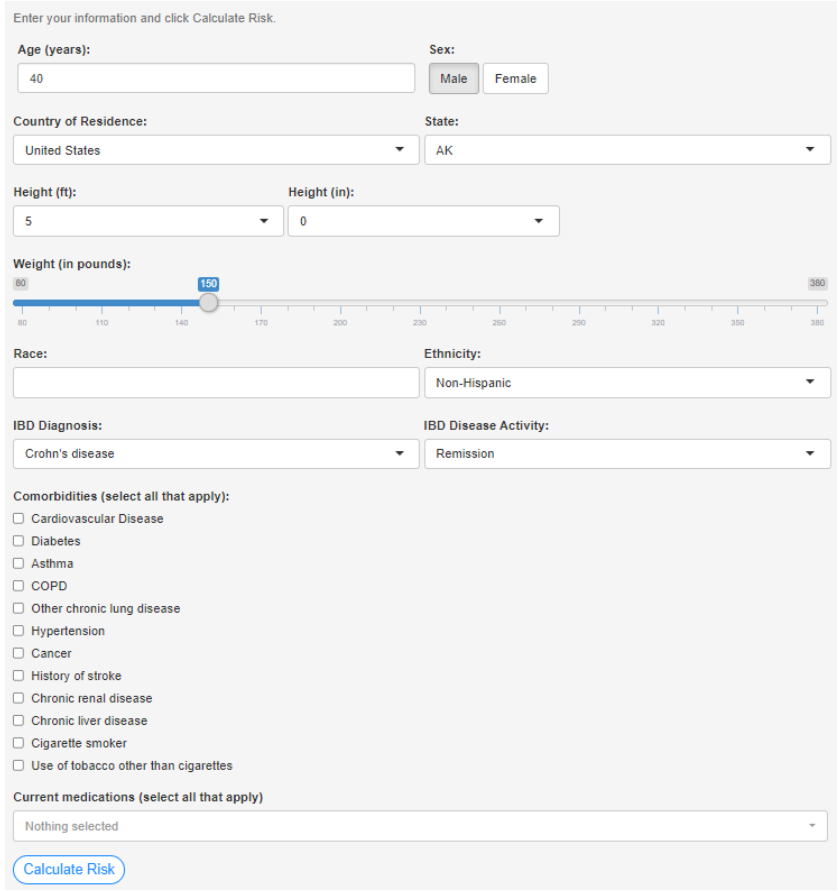
Risk Factors in IBD Patients With COVID-19

- Age, comorbidity, disease severity, and use of steroids have been associated with worse outcomes in IBD patients with COVID-19 (eg, ICU admission and mortality)[1]
- A COVID-19 risk calculator is available for physicians to assess risk of hospitalization, ICU admission, mechanical ventilation, or death in *unvaccinated* IBD patients with COVID-19, based on data from SECURE-IBD[2]

SECURE-IBD: COVID-19 Risk Calculator[2]



COVID-19=coronavirus disease 2019; IBD=inflammatory bowel disease; ICU= intensive care unit; SECURE=Surveillance Epidemiology of Coronavirus Under Research Exclusion.

1. Hunt RH, et al. *Dig Dis*. 2021;39(2):119-39. **2.** Sperger J, et al. *medRxiv*. Preprint posted online January 20, 2021. doi:10.1101/2021.01.15.21249889.

Guidelines for Managing Infections in Patients With IBD

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General Principles for Managing Risks of Serious Infections in Patients With IBD

- ✓ Minimize corticosteroid use[1]
- ✓ Collaborate with infectious disease specialists[2]
- ✓ Vaccinate all adult IBD patients in accordance with guidelines[3,a]
- ✓ Screen for HBV infection in all patients requiring immunosuppression, which includes patients with IBD, consistent with the AASLD and CDC guidelines[4,5,b]
- ✓ Consider preferential use of targeted therapy vs systemic therapy in patients with UC who have a higher risk of OI (eg, older patients)[8]

Vaccinations to Consider for Patients With IBD[3,a]
Inactivated seasonal influenza vaccine
Pneumococcal vaccination (PCV13 and PPSV23)
HAV
HBV (prior to starting TNF blocker therapies)
Haemophilus influenzae B
HPV
HZ
Tetanus
Pertussis

Please see the Prescribing Information for any therapies before use.

[a]CDC, ACIP, and IDSA. [b]For those who are immunocompromised, HCV screening can be considered.[6-7]

AASLD=American Association for the Study of Liver Diseases; ACIP= Advisory Committee on Immunization Practices; CDC=Centers for Disease Control and Prevention; HAV=hepatitis A virus; HBV=hepatitis B virus; HCV=hepatitis C virus; HPV=human papillomavirus; HZ=herpes zoster; IBD=inflammatory bowel disease; IDSA=Infectious Diseases Society of America; OI=opportunistic infection; PCV13=13-valent pneumococcal conjugate vaccine; PPSV23=23-valent pneumococcal polysaccharide vaccine; TNF=tumor necrosis factor; UC=ulcerative colitis.

1. Waljee AK, et al. *PLoS One*. 2016;11(6):e0158017. **2.** Rahier JF, et al. *J Crohns Colitis.* 2014;8(6):443-468. **3.** Farraye FA, et al. *Am J Gastroenterol*. 2017;112(2):241-258. **4.** López-Serrano P, et al. *World J Gastroenterol.* 2013;19(9):1342-1348. **5.** Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20. **6.** Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. 2013;62(18):362-365. **7.** AASLD, IDSA. http://www.hcvguidelines.org. Accessed September 20, 2021. **8.** Rubin DT, et al. *Am J Gastroenterol.* 2019;114(3):384-413.

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Management of Herpes Zoster in Patients With IBD

- Diagnosis can be made clinically based on the skin rash appearance, among other features; atypical, recurrent, or disseminated lesions should be tested with PCR analysis of the skin lesion
- Indications for antiviral therapy for primary varicella and HZ vary depending on the age of the patient, concomitant immunosuppressive therapy, and severity of disease
  - Clinicians should assess the vaccination status of all patients with IBD in order to vaccinate nonimmunized patients before any necessary immunosuppressive therapy
  - Treatment duration should be limited to 7 days in patients without immunosuppression and uncomplicated HZ (ie, without involvement of head and neck, no hemorrhagic lesions or 2 or more segments)
  - In patients treated with immunosuppressive therapy, intravenous acyclovir (8-12 mg/kg body weight every 8 hours for 7 days) should be initiated

Please see the Prescribing Information for any therapies before use.

HZ=herpes zoster; IBD=inflammatory bowel disease; PCR=polymerase chain reaction.

Schreiner P, et al. *J Crohns Colitis* 2021;15(2):316-325.

Guidelines for Management of HBV in Patients With IBD

Management of HBV in Patients With IBD

- All patients should be screened for HBV at diagnosis of IBD by testing HBsAg, anti-HBc, and anti-HBs[1,a]
- HBV vaccination is recommended in all HBV anti-HBc–seronegative patients[1]
  - Efficacy of HBV vaccination is impaired in patients with IBD; anti-HBs response should be measured after vaccination[1]
  - Patients positive for HBV should receive antiviral treatment for at least 6 months after discontinuation of immunosuppressive therapy[2]
- Regular monitoring of HBV DNA and ALT may guide treatment to minimize liver injury and improve patient outcomes[2-4]

Please see the Prescribing Information for any therapies before use.

[a]As recommended by the European Crohn's and Colitis Organisation.

ALT=alanine transaminase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IBD=inflammatory bowel disease.

1. Rahier JF, et al. *J Crohns Colitis*. 2014;8(6):443-468. **2.** Reddy KR, et al. *Gastroenterology*. 2015;148(1):215-219. **3.** Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed September 27, 2021. **4.** Rojas-Feria M, et al. *World J Gastroenterol*. 2013;19(42):7327-7340.

Recommendations for Management of the Risk of Tuberculosis in Patients With IBD

Clinicians should be aware of the risk of reactivation of TB or new TB infection in patients with IBD who are receiving immunosuppressive therapies for IBD[1-8]

General Recommendations for TB Risk Management

- Screen for active and latent TB before initiating advanced IBD therapies[1,3-8]
  - PPD skin testing (for immunosuppressed persons, ≥5 mm is considered a positive result, indicating hypersensitivity to TB protein)[9]
  - Interferon gamma release assays (QuantiFeron-TB Gold assay or T-Spot)[10]
- Perform chest x-ray[10]
- Perform annual TB risk assessment and consider re-testing if risk of exposure is ongoing, including travel to endemic region[9]
- Certain advanced IBD therapies should not be initiated or are not recommended to be used in those with active TB[2-8]

Please see the Prescribing Information for any therapies before use.

IBD=inflammatory bowel disease; PPD=purified protein derivative; TB=tuberculosis.

1. Hong SN, et al. *Aliment Pharmacol Ther*. 2017;45(2):253-263. **2.** Dassopoulos T, et al. *Gastroenterology.* 2013;145(6):1464-1478.e1-e5. **3.** Remicade [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2021. **4.** Humira [prescribing information]. North Chicago, IL: AbbVie Inc; 2021. **5.** Simponi [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2019. **6.** XELJANZ/XELJANZ XR [prescribing information]. New York, NY: Pfizer Inc.; October 2020. **7.** Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2021. **8.** Cimzia [prescribing information]. Smyrna, GA: UCB, Inc; 2019. **9.** Centers for Disease Control and Prevention. https://www.cdc.gov/tb/education/ssmodules/pdfs/Module3.pdf. Accessed September 27, 2021. **10.** Cornerstones Health. https://www.cornerstoneshealth.org/wp-content/uploads/2019/05/Checklist-for-Monitoring-Prevention-2018.pdf. Accessed September 27, 2021.

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Guidelines for Management of *C difficile* Infection in Patients With IBD

ACG Clinical Guidance for Managing *C difficile* Infection (CDI) in Patients with IBD
CDI Diagnosis in IBD
▪ Recommend 2-step testing algorithm for CDI (eg, PCR and toxin) in patients with IBD who present with an acute flare associated with diarrhea; this is because colonization by *C difficile* ($PCR^+/toxin^-$) is common in IBD
Treatment of CDI in IBD
▪ Suggest vancomycin 125 mg by mouth 4 times a day for a minimum of 14 days in patients with IBD and CDI ▪ Consider fecal microbiota transplantation for recurrent CDI in patients with IBD
IBD Therapy Considerations With CDI
▪ Immunosuppressive IBD therapy should not be held during anti-CDI therapy in the setting of disease flare, and escalation of therapy may be considered if there is no symptomatic improvement with treatment of CDI

ACG=American College of Gastroenterology; CDI=*C difficile* infection; IBD=inflammatory bowel disease; PCR=polymerase chain reaction.

Kelly CR, et al. *Am J Gastroenterol; 2021;116(6):1124-1147.*

Considerations for Vaccination and Disease Management in the Setting of COVID-19

- The IOIBD recommends patients with IBD to be vaccinated against SARS-CoV-2 at the earliest opportunity[1]
  - SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving immune-modifying therapies
  - Vaccinated patients with IBD should be counselled that vaccine efficacy may be decreased when receiving systemic corticosteroids
- The Crohn's and Colitis Foundation, ECCO, and IOIBD recommend against discontinuation of immunosuppressive and biologic therapies in patients with IBD without symptoms suggestive of COVID-19[2]

Patients with IBD who have confirmed COVID-19[3,a]	Intervention until COVID-19 symptoms are completely resolved for ≥72 hours ▪ Reduce prednisone dose ▪ Discontinue or delay dosing of immune-based therapies
Patients with IBD who have severe or progressive COVID-19[3,a]	Consider treatments that have efficacy in both the bowel symptoms of IBD and systemic inflammation of COVID-19 ▪ Taper or discontinue prednisone ▪ Discontinue all immune-based IBD therapies ▪ If available, treat COVID-19 with antiviral or other anti-inflammatory/anti-cytokine therapies

[a]Based on a 2020 expert opinion article published by the ACG in the Red Section of the *American Journal of Gastroenterology*.[1]

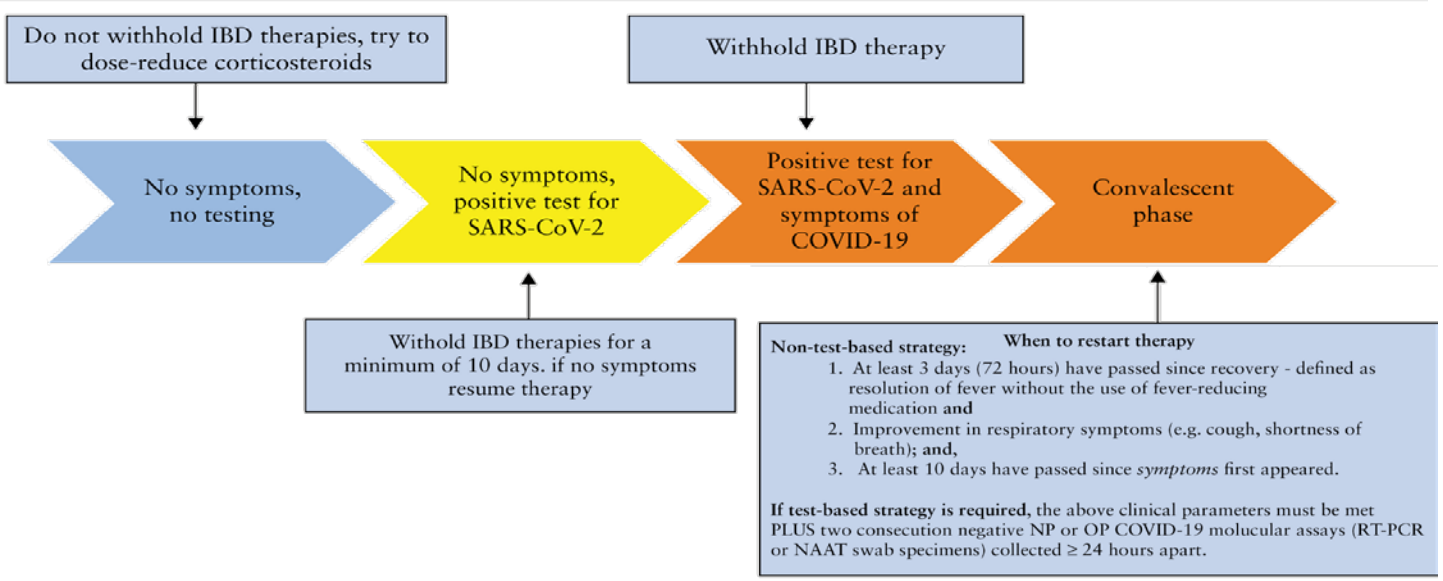
COVID-19=coronavirus disease 2019; ECCO=European Crohn's and Colitis Organization; IBD=inflammatory bowel disease; IOIBD=International Organization for the Study of Inflammatory Bowel Disease; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

1. Siegel CA, et al. *Gut.* 2021;70(4):635-640. **2.** Naseer M, et al. *World J Metaanal.* 2020;8(5):383-399. **3.** Lichtenstein GR, Rubin DT. *Am J Gastroenterol*. 2020;115(10):1566-1569.

IOIBD Guidance on Re-initiating IBD Therapy in Patients Who Withheld Immunosuppressant Medications During COVID-19

- For patients with IBD who have had immunosuppressant therapy withheld due to COVID-19, the IOIBD recommends a symptoms-based strategy to determine timing to re-initiate IBD therapy
- The timing of re-starting IBD immunosuppressant therapy should be influenced by the clinical severity of both IBD and COVID-19
  - For those with mild COVID-19 and a history difficult to control IBD, earlier re-start of IBD therapy may be considered (eg, re-start after 10 days)
  - For those with severe COVID-19 and a well-controlled IBD, a delay in IBD therapy re-initiation may be desired (eg, re-start after >28 days)

IOIBD Recommendations on Management of IBD Therapy in the Setting of COVID-19



[a]Based on a 2020 expert opinion article published by the ACG in the Red Section of the *American Journal of Gastroenterology*.[1]
COVID-19=coronavirus disease 2019; IBD=inflammatory bowel disease; IOIBD=International Organization for the Study of Inflammatory Bowel Disease; NAAT=nucleic acid amplification test; NP=nasopharyngeal; OP=oropharyngeal; RT-PCT=reverse transcription-polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Siegel CA, et al. *J Crohns Colitis*. 2020;14(14 suppl 3):S769-S773.

Summary

- Patients with IBD, especially those treated with immunosuppressants, have a heightened risk of infections
  - Risk for HZ increases with age and increases further with use of immunosuppressive therapies
  - Risk of HBV reactivation in patients with IBD varies depending on the type of immunosuppressive drug used and the HBV phase prior to treatment
  - Screen patients with IBD for active and latent TB before initiating advanced IBD therapies
  - Patients with IBD are more likely to experience recurrent *C difficile* infection, and increased risk is associated with prior treatment with certain therapies
  - Age, comorbidity, disease severity, and use of steroids have been associated with worse outcomes in IBD patients with COVID-19
- Consider vaccinating patients with IBD to protect against vaccine-preventable infections
  - ACG recommends vaccinating all adult patients with IBD in accordance with guidelines

Please see the Prescribing Information for any vaccine before use.

C difficile=*Clostridium difficile*; HBV=hepatitis B virus; HZ=herpes zoster; IBD=inflammatory bowel disease; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TB=tuberculosis.

Resources and References

Available Resources

Checklists for Monitoring and Care of Patients With Inflammatory Bowel Disease (IBD)

- Crohn's & Colitis Foundation (Health Maintenance Checklist for Adult IBD Patients)
- Cornerstones Health (IBD Checklist for Monitoring & Prevention)

US Department of Health and Human Services

- Centers for Disease Control and Prevention (CDC)
  - Advisory Committee of Immunization Practices (ACIP)
- Vaccines.gov

Society Guidelines

- American Association for the Study of Liver Diseases (AASLD)
- American College of Gastroenterology (ACG)
- American Gastroenterological Association (AGA)
- Infectious Diseases Society of America (IDSA)
- European Crohn's and Colitis Organisation (ECCO)

References

- American Association for the Study of Liver Diseases, Infectious Diseases Society of America. HCV testing and linkage to care. http://www.hcvguidelines.org. Accessed November 4, 2019.
- Axiaris G, Zampeli E, Michopoulos S, Bamias G. Management of hepatitis B virus infection in patients with inflammatory bowel disease under immunosuppressive treatment. *World J Gastroenterol*. 2021;27(25):3762-3779.
- Barnes EL, Kochar B, Long MD, et al. Modifiable risk factors for hospital readmission among patients with inflammatory bowel disease in a nationwide database. *Inflamm Bowel Dis*. 2017;23(6):875-881.
- Cao BL, Qasem A, Sharp RC, Abdelli LS, Naser SA. Systematic review and meta-analysis on the association of tuberculosis in Crohn's disease patients treated with tumor necrosis factor-α inhibitors (Anti-TNFα). *World J Gastroenterol*. 2018;24(25):2764-2775.
- Centers for Disease Control and Prevention. AIDS and opportunistic infections. https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html. Accessed July 12, 2018.
- Centers for Disease Control and Prevention. Hepatitis B questions and answers for health professionals. https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm. Accessed October 11, 2019.
- Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep*. 2013;62(18):362-365.
- Chan HC, Wong VW, Wong GL, Tang W, Wu JC, Ng SC. Prevalence of hepatitis B and clinical outcomes in inflammatory bowel disease patients in a viral-endemic region. *BMC Gastroenterol.* 2016;16(1):100.
- Cimzia [prescribing information]. Smyrna, GA: UCB, Inc; 2019.
- Cornerstones Health. IBD checklist for monitoring & prevention. https://www.cornerstoneshealth.org/wp-content/uploads/2019/05/Checklist-for-Monitoring-Prevention-2018.pdf. Accessed October 11, 2019.
- Dassopoulos T, Sultan S, Falck-Ytter YT, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology.* 2013;145(6):1464-1478.e1-e5.
- Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2021.
- Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol*. 2017;112(2):241-258.
- Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2013;108(8):1268-1276.

References

- Gong SS, Fan YH, Han QQ, Lv B, Xu Y. Nested case-control study on risk factors for opportunistic infections in patients with inflammatory bowel disease. *World J Gastroenterol.* 2019;25(18):2240-2250.
- Hindryckx P, Novak G, Bonovas S, Peyrin-Biroulet L, Danese S. Infection risk with biologic therapy in patients with inflammatory bowel disease. *Clin Pharmacol Ther*. 2017;102(4):633-641.
- Hunt RH, East JE, Lanas A, et al. COVID-19 and gastrointestinal disease: implications for the gastroenterologist. *Dig Dis*. 2021;39(2):119-139.
- Hong SN, Kim HJ, Kim KH, et al. Risk of incident *Mycobacterium tuberculosis* infection in patients with inflammatory bowel disease: a nationwide population-based study in South Korea. *Aliment Pharmacol Ther.* 2017;45(2):253-263.
- Humira [prescribing information]. North Chicago, IL: AbbVie Inc; 2021.
- Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol*. 2021;116(6):1124-1147.
- Khan N, Vallarino C, Lissoos T, Darr U, Luo M. Risk of infection and types of infection among elderly patients with inflammatory bowel disease: a retrospective database analysis. *Inflamm Bowel Dis.* 2020;26(3):462-468.
- Khanna S, Shin A, Kelly CP. Management of *Clostridium difficile* infection in inflammatory bowel disease: expert review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol*. 2017;15(2):166-174.
- Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology*. 2018;155(2):337-346.
- Kochhar GS, Mohan BP, Khan SR, et al. Hepatitis-B vaccine response in inflammatory bowel disease patients: a systematic review and meta-analysis. *Inflamm Bowel Dis.* 2021;27(10):1610-1619.
- Lee WJ, Lee TA, Calip GS, Suda KJ, Briars L, Schumock GT. Risk of serious bacterial infection associated with tumor necrosis factor-alpha inhibitors in children and young adults with inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(4):883-891.
- Lichtenstein GR, Rubin DT. Coronavirus and patients with inflammatory bowel disease: management strategies for the practicing clinician. *Am J Gastroenterol*. 2020;115(10):1566-1569.
- Long MD, Martin C, Sandler RS, et al. Increased risk of herpes zoster among 108 604 patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013;37(4):420-429.
- López-Serrano P, de la Fuente Briongos E, Alonso EC, Pérez-Calle JL, Rodríguez CF. Hepatitis B and immunosuppressive therapies for chronic inflammatory diseases: when and how to apply prophylaxis, with a special focus on corticosteroid therapy. *World J Hepatol.* 2015;7(3):539-547.

References

- López-Serrano P, Lázaro Pérez-Calle J, Sánchez-Tembleque MD. Hepatitis B and inflammatory bowel disease: role of antiviral prophylaxis. *World J Gastroenterol.* 2013;19(9):1342-1348.
- Ma C, Jairath V, Vande Casteele N. Pharmacology, efficacy and safety of JAK inhibitors in Crohn's disease. *Best Pract Res Clin Gastroenterol*. 2019;38-39:101606.
- Mill J, Lawrance IC. Preventing infective complications in inflammatory bowel disease. *World J Gastroenterol.* 2014;20(29):9691-9698.
- Musa RB, Gampa A, Basu S, et al. Hepatitis B vaccination in patients with inflammatory bowel disease. *World J Gastroenterol.* 2014;20(41):15358-15366.
- Naseer M, Poola S, Dailey FE, Akin H, Tahan V. Implications of COVID-19 for inflammatory bowel disease: opportunities and challenges amidst the pandemic. *World J Metaanal.* 2020;8(5):383-399.
- Nisar MK, Rafiq A, Östör AJK. Biologic therapy for inflammatory arthritis and latent tuberculosis: real world experience from a high prevalence area in the United Kingdom. *Clin Rheumatol*. 2015;34(12):2141-2145.
- Nguyen NH, Ohno-Machado L, Sandborn WJ, Singh S. Infections and cardiovascular complications are common causes for hospitalization in older patients with inflammatory bowel diseases. *Inflamm Bowel Dis.* 2018;24(4):916-923.
- Nyboe Andersen N, Pasternak B, Friis-Møller N, Andersson M, Jess T. Association between tumour necrosis factor-α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. *BMJ.* 2015;350:h2809.
- Panes J, Sandborn WJ, Schreiber S, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut.* 2017;66(6):1049-1059.
- Park SH, Yang SK, Lim YS, et al. Clinical courses of chronic hepatitis B virus infection and inflammatory bowel disease in patients with both diseases. *Inflamm Bowel Dis.* 2012;18(11):2004-2010.
- Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. *Medicine (Baltimore).* 2011;90(6):359-371.
- Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2014;8(6):443-468.
- Ramos GP, Stroh G, Al-Bawardy B, Faubion WA, Papadakis KA, Escalante P. Outcomes of treatment for latent tuberculosis infection in patients with inflammatory bowel disease receiving biologic therapy. *Inflamm Bowel Dis*. 2018;24(10):2272-2277.

References

- Razik R, Rumman A, Bahreini Z, et al. Recurrence of *Clostridium difficile* infection in patients with inflammatory bowel disease: the RECIDIVISM study. *Am J Gastroenterol*. 2016;111(8):1141-1146.
- Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219.
- Remicade [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2021.
- Restellini S, Chazouillères O, Frossard JL. Hepatic manifestations of inflammatory bowel diseases. *Liver Int*. 2017;37(4):475-489.
- Ridola L, Zullo A, Laganà B, et al. Hepatitis B (HBV) reactivation in patients receiving biologic therapy for chronic inflammatory diseases in clinical practice. *Ann Ist Super Sanita*. 2021;57(3):244-248.
- Rojas-Feria M, Castro M, Suárez E, Ampuero J, Romero-Gómez M. Hepatobiliary manifestations in inflammatory bowel disease: the gut, the drugs and the liver. *World J Gastroenterol*. 2013;19(42):7327-7340.
- Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol.* 2019;114(3):384-413.
- Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):e44-e100.
- Sabino J, Verstockt B, Vermeire S, Ferrante M. New biologics and small molecules in inflammatory bowel disease: an update. *Therap Adv Gastroenterol*. 2019;12:1756284819853208.
- Sandborn WJ. The present and future of inflammatory bowel disease treatment. *Gastroenterol Hepatol (N Y).* 2016;12(7):438-441.
- Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis [supplementary appendix]. *N Engl J Med.* 2017;376(18):1723-1736.
- Sasidharan S, Yajnik V, Khalili H, et al. Genetic risk factors for serious infections in inflammatory bowel diseases. *Scand J Gastroenterol.* 2017;52(5):570-576.
- Schreiner P, Mueller NJ, Fehr J, et al. Varicella zoster virus in inflammatory bowel disease patients: what every gastroenterologist should know. *J Crohns Colitis* 2021;15(2):316-325.
- SECURE-IBD. COVID-19 risk calculator. https://covidibd.org/covid-19-risk-calculator/. Accessed September 2, 2021.
- Seto WK. Hepatitis B virus reactivation during immunosuppressive therapy: appropriate risk stratification. *World J Hepatol.* 2015;7(6):825-830.
- Sheriff MZ, Mansoor E, Luther J, et al. Opportunistic infections are more prevalent in Crohn's disease and ulcerative colitis: a large population-based study. *Inflamm Bowel Dis.* 2020;26(2):291-300.

References

- Siegel CA, Christensen B, Kornbluth A, et al. Guidance for restarting inflammatory bowel disease therapy in patients who withheld immunosuppressant medication during COVID-19. *J Crohns Colitis*. 2020;14(14 suppl 3):S769-S773.
- Siegel CA, Melmed GY, McGovern DPB, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut.* 2021;70(4):635-640.
- Simponi [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2019.
- Singh AK, Jena A, Kumar-M P, Sharma V, Sebastian S. Risk and outcomes of coronavirus disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *United European Gastroenterol J*. 2021;9(2):159-176.
- Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;18(1):69-81.
- Sperger J, Shah KS, Lu M, et al. Development and validation of multivariable prediction models for adverse COVID-19 outcomes in IBD patients. *medRxiv*. Preprint posted online January 20, 2021. doi:10.1101/2021.01.15.21249889
- Waljee AK, Wiitala WL, Govani S, et al. Corticosteroid use and complications in a US inflammatory bowel disease cohort. *PLoS One*. 2016;11(6):e0158017.
- Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
- Wheat CL, Ko CW, Clark-Snustad K, et al. Inflammatory bowel disease (IBD) pharmacotherapy and the risk of serious infection: a systematic review and network meta-analysis. *BMC Gastroenterol.* 2017;17(1):52.
- XELJANZ/XELJANZ XR [prescribing information]. New York, NY: Pfizer Inc.; October 2020.
- Yun H, Yang S, Chen L, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. *Arthritis Rheumatol.* 2016;68(9):2328-2337.
- Zhang T, Lin QY, Fei JX, et al. *Clostridium difficile* infection worsen outcome of hospitalized patients with inflammatory bowel disease. *Sci Rep*. 2016;6:29791.