Impatto del COVID-19 sulle Malattie Infiammatorie Croniche Intestinali

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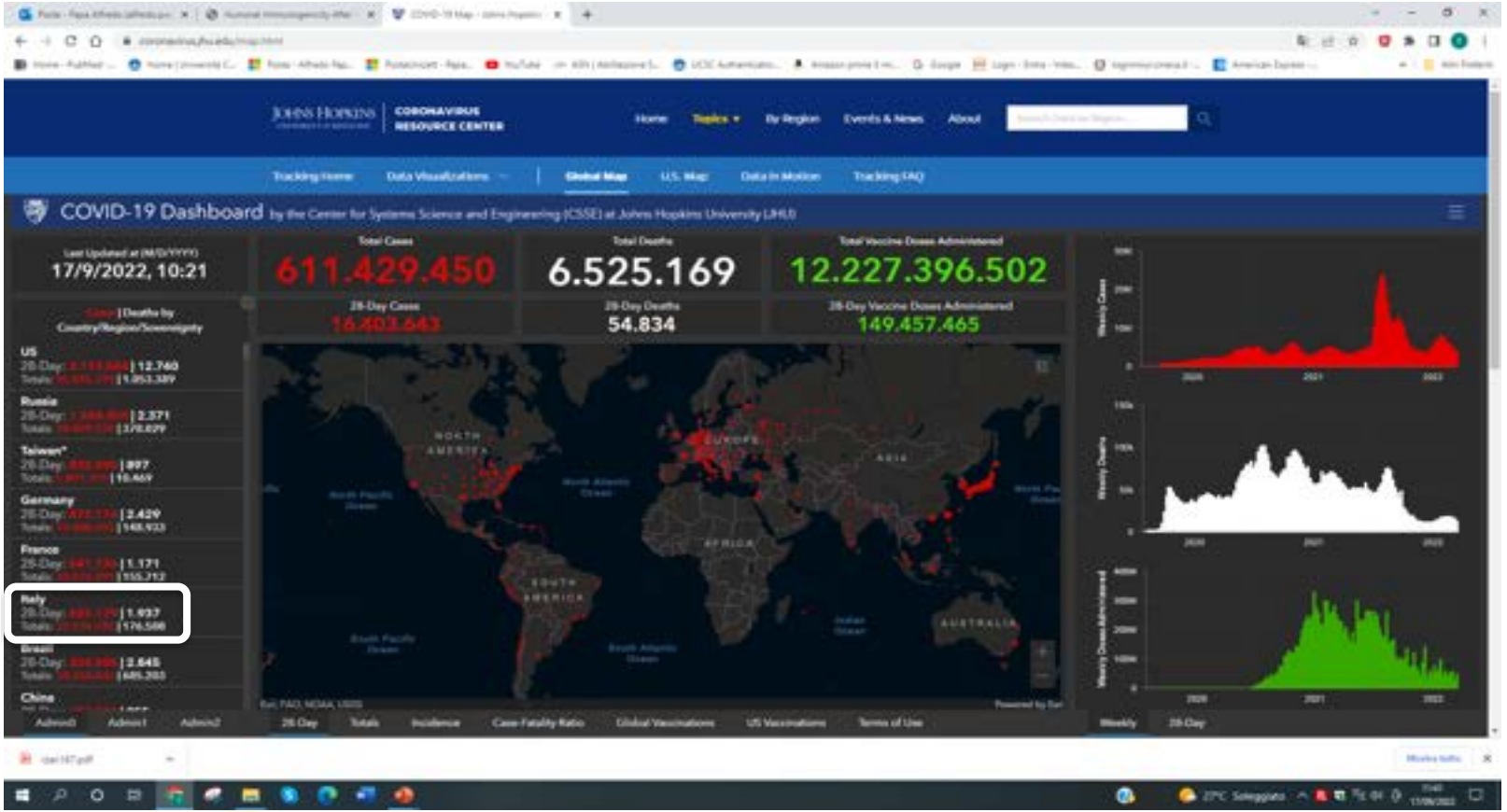
Epidemiologia COVID-19



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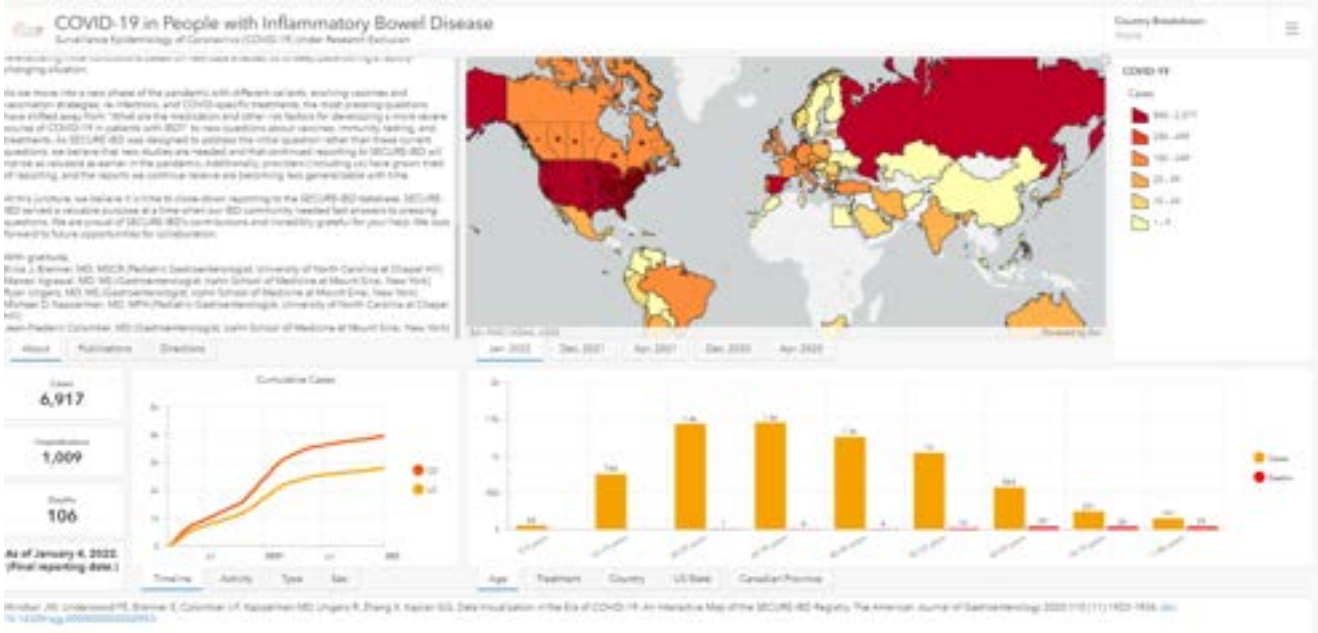
https://coronavirus.jhu.edu/map.html

SECURE-IBD registry



Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study

Table 2 Association between potential risk factors and COVID-19-related pneumonia

Risk factor	OR	95% CI	P value
Age >65 years	5.87	1.15 to 29.66	**0.03**
CCI score >1	2.91	1.06 to 9.21	**0.04**
UC diagnosis	2.72	1.06 to 6.99	**0.03**
Active IBD	10.25	2.11 to 49.73	**0.003**
Corticosteroids	4.94	0.95 to 25.55	0.05
Thiopurines	1.21	0.22 to 6.40	0.82
Anti-TNF	1.18	0.47 to 2.97	0.71
Vedolizumab	0.53	0.16 to 1.73	0.29

Bold indicates $p < 0.05$.
CCI, Charlson Comorbidity Index; TNF, tumour necrosis factor.

Table 3 Association between potential risk factors and COVID-19-related death

Risk factor	OR	95% CI	P value
Age >65 years	19.6	2.95 to 130.6	0.002
CCI score >1	16.66	1.80 to 153.9	0.01
Active IBD	8.45	1.26 to 56.56	0.02
UC diagnosis	2.95	0.31 to 27.73	0.34
Corticosteroids	6.28	0.89 to 44.24	0.064
Anti-TNF	0.40	0.04 to 3.78	0.42

CCI, Charlson Comorbidity Index; TNF, tumour necrosis factor.

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Bezzio C et al. GUT 2020

Epidemiology and the Impact of Therapies on the Outcome of COVID-19 In Patients with Inflammatory Bowel Disease

Table 1. Outcomes of COVID-19 in patients with IBD according to treatment with anti-TNF-α antibodies or steroids

Database/study/case report (country)[ref]	Total pts. with IBD with COVID-19 (CD/UC/IBDU)	Total inpatients	Total pts with severe outcomes (ICU/VU/death)	Patients in treatment with anti-TNF-α (%)	Severe outcomes (ICU/VU/death) in pts in treatment with anti-TNF-α (%)	Patients in treatment with steroids (%)	Severe outcomes (ICU/VU/death) in pts in treatment with steroids (%)
SECURE-IBD database (worldwide) (3)	1,069 (604/465)	352 (33%)	96 (9%)	60 (19%)	8 (3%)	56 (66%)	22 (26%)
Bezzio et al. (Italy) (4)	79 (32/47)	22 (28%)	6 (8%)	NA	1 (3.4%)	NA	2 (22.2%)
Rodriquez-Lago et al. (Spain) (5)	40 (13/23/4)	21 (53%)	2 (5%)	3 (8%)	0	4 (10%)	0
Allocca et al. (Italy—France) (6)	15 (9/6)	5 (33%)	0	1 (6%)	0	2 (13%)	0
Taxonera et al. (Spain) (7)	12 (7/5)	8 (67%)	1 (8%)	2 (67%)[a]	0	0	0
Gubatan et al. (USA) (8)	5 (3/2)	NA	1	NA	NA	NA	NA
Khan et al. (USA) (9)	36	NA	NA	3 (8.3%)	NA	NA	NA
Mazza et al. (Italy) (10)	1 UC	1	1	0	0	1	1
Tursi et al. (Italy) (11)	1 CD	1	0	1	0	0	0

CD, Crohn's disease; COVID-19, coronavirus disease; IBDU, inflammatory bowel disease unclassified; ICU, intensive care unit; NA, not available; pts, patients; SECURE, Surveillance Epidemiology of Coronavirus Under Research Exclusion; TNF, tumor necrosis factor; UC, ulcerative colitis; VA, ventilator use.

[a]Three patients affected by COVID-19 were under treatment with anti-TNF-α: one pt with adalimumab, one pt with golimumab plus methotrexate, and one pt with adalimumab plus methotrexate: the first 2 patients were admitted to hospital.

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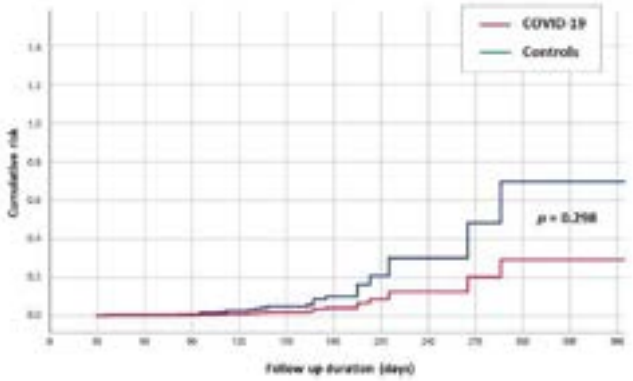
Papa A et al. Am J Gastroenterol 2020

Article

Impact of SARS-CoV-2 Infection on the Course of Inflammatory Bowel Disease in Patients Treated with Biological Therapeutic Agents: A Case-Control Study

Variable	All Patients (n = 285)	SARS-CoV-2 + ve Patients (n = 95)	Controls (n = 190)	*p*-Value
Age (years)	42 (30–55)	40 (30–55)	42 (32–44)	0.476
Sex (male)	158 (55.4%)	49 (51.6%)	109 (57.4%)	0.354
IBD diagnosis				
- CD	192 (67.4%)	64 (67.4%)	128 (67.4%)	0.724
- UC	93 (32.6%)	31 (32.6%)	62 (32.6%)	
Biological therapeutic agents				
- Adalimumab	130 (45.6%)	42 (44.2%)	88 (46.3%)	0.975
- Infliximab	90 (31.6%)	30 (31.6%)	60 (31.6%)	
- Ustekinumab	32 (11.2%)	11 (11.6%)	21 (11.1%)	
- Vedolizumab	33 (11.6%)	12 (12.6%)	21 (11.1%)	



Cumulative risk of IBD recurrence in patients with COVID-19 vs. non-infected IBD patients

Variable	Multivariate *p*-Value	Hazard Ratio (95% Confidence Interval)
SARS-CoV-2 infection *	0.298	0.42 (0.08–2.15)
ΔCRP	0.017	1.14 (1.02–1.27)
Biological agent discontinuation	0.033	7.27 (1.17–45.18)

p-values < 0.05 were considered statistically significant. Abbreviations: IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CRP, C-reactive protein. * SARS-CoV-2 diagnosis was forced in the analysis.

Multivariate analysis to determine factors associated with IBD recurrence

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Papa A, et al. Biomedicines 2022

Article

Impact of SARS-CoV-2 Infection on the Course of Inflammatory Bowel Disease in Patients Treated with Biological Therapeutic Agents: A Case-Control Study

Clinical characteristics of the 95 SARS-CoV-2 positive IBD patients

Variable	Crohn's Disease (n = 64)	Ulcerative Colitis (n = 31)	*p*-Value
COVID-19 severity *			
- Asymptomatic - Mild - Severe	22 (34.4%) 41 (64.1%) 1 (1.6%)	11 (35.5%) 17 (54.8%) 3 (9.7%)	0.168
Sex (male)	33 (51.6%)	16 (51.6%)	1.000
Age (years)	39 (27–53)	43 (34–58)	0.090
Disease duration (years)	9 (5–15)	8 (4–17)	0.605
Extraintestinal manifestations	8 (25.0%)	54 (21.3%)	0.637
Previous surgery	44 (68.8%)	0	<0.001
Active smoker	21 (32.8%)	8 (25.8%)	0.487
Biological therapeutic agents			
- Adalimumab - Infliximab - Ustekinumab - Vedolizumab	34 (53.1%) 15 (23.4%) 10 (15.6%) 5 (7.8%)	8 (25.8%) 15 (48.4%) 1 (3.2%) 7 (22.6%)	0.003
Steroids	3 (4.7%)	2 (6.5%)	0.718
Mesalamine	1 (1.6%)	14 (45.2%)	<0.001
Immunosuppressants	2 (3.1%)	0	1.000
Extraintestinal manifestations	17 (26.6%)	6 (19.4%)	0.442
CRP level (mg/dL) at the start of f-u	0.5 (0.5–2.7)	0.5 (0.5–3.7)	0.336
CRP level (mg/dL) at the end of f-u	0.5 (0.5–3.1)	0.7 (0.5–2.8)	0.500
ΔCRP (mg/dL)	0.0 (0.2–0.0)	0.0 (0.5–1.2)	0.107
Discontinuation of treatment with biological agents	29 (45.3%)	17 (54.8%)	0.384
Discontinued doses	2 (2–2)	2 (1–2)	0.003
F-u duration (weeks)	20.3 (15.8–26.0)	23.3 (18.0–27.4)	0.304
Disease recurrence	6 (9.4%)	5 (16.1%)	0.335

Values represent absolute numbers (%) or medians (interquartile range), and *p*-values < 0.05 were considered statistically significant. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; f-u, follow-up. * COVID-19 severity was categorized as asymptomatic (no symptoms), mild (requiring no oxygen supplementation or hospitalization), and severe (requiring hospitalization or oxygen supplementation).

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Papa A, et al. Biomedicines 2022

SARS-CoV-2 infection as a potential trigger factor for de novo occurrence of inflammatory bowel disease

Antonio Tursi[a,b,*], Loris Riccardo Lopetuso[c,d,e], Lorenzo Maria Vetrone[a], Antonio Gasbarrini[a,f] and Alfredo Papa[a,f,*]

Table 1. Characteristics of patients with inflammatory bowel disease (IBD) onset after SARS-CoV-2 infection

Author (Ref.)	Sex	Age (years)	COVID-19 symptoms	Therapy for COVID-19	Time from SARS-CoV-2 negativity to IBD diagnosis (months)	Type of IBD	Type of IBD treatment
Calabrese *et al.* [5]	F	19	Fever, nausea, vomiting, bloody diarrhea, loss of taste and smell, anemia	HCQ	1	UC	Oral BEC and MES
Taxonera *et al.* [6]	F	NA	Fever, sore throat, myalgia, bloodless watery diarrhea	HCQ, LOP-RIT, AZI	4	UC	Oral and topic MES
Imperatore *et al.* [7]	M	55	Pneumonia	CS, AZI, HEP	4	UC	NA
Aydin *et al.* [8]	M	50	Fever, dyspnea and pneumonia	HCQ and AZI	1	UC	Oral and topic MES
Senthamizhselvan *et al.* [9]	F	33	Sore throat, fever, myalgia	ACE	<1	CD	CS and sulfasalazine
Tursi *et al.* [10]	F	47	Weakness, myalgia and diarrhea	ACE	3	CD	Oral BUD

ACE, acetaminophen; AZI, azithromycin; BEC, beclomethasone dipropionate; BUD, budesonide; CD, Crohn's disease; CS, systemic corticosteroids; HCQ, hydroxychloroquine; HEP, heparin; LOP–RIT, lopinavir–ritonavir; MES, mesalamine; UC, ulcerative colitis.

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EJGH 2022

Questioni aperte riguardanti la vaccinazione per il SARS-CoV-2 nei pazienti con MICI

1) La vaccinazione è sicura nei pazienti con MICI?
2) La vaccinazione è efficace nei pazienti con MICI?
3) Quali trattamenti sono associati ad una ridotta immunogenicità alla vaccinazione per il SARS-CoV-2?
4) E' necessaria una differente schedula vaccinale per i pazienti con MICI (come ad esempio dosaggio incrementato, rapporto temporale con la terapia infusionale, dosi aggiuntive)
5) Sono le risposte immunitarie umorale e cellulare nei pazienti con MICI di uguale durata e qualità rispetto alla popolazione generale?
6) E' una piattaforma vaccinale preferibile rispetto ad un'altra nei pazienti con MICI?

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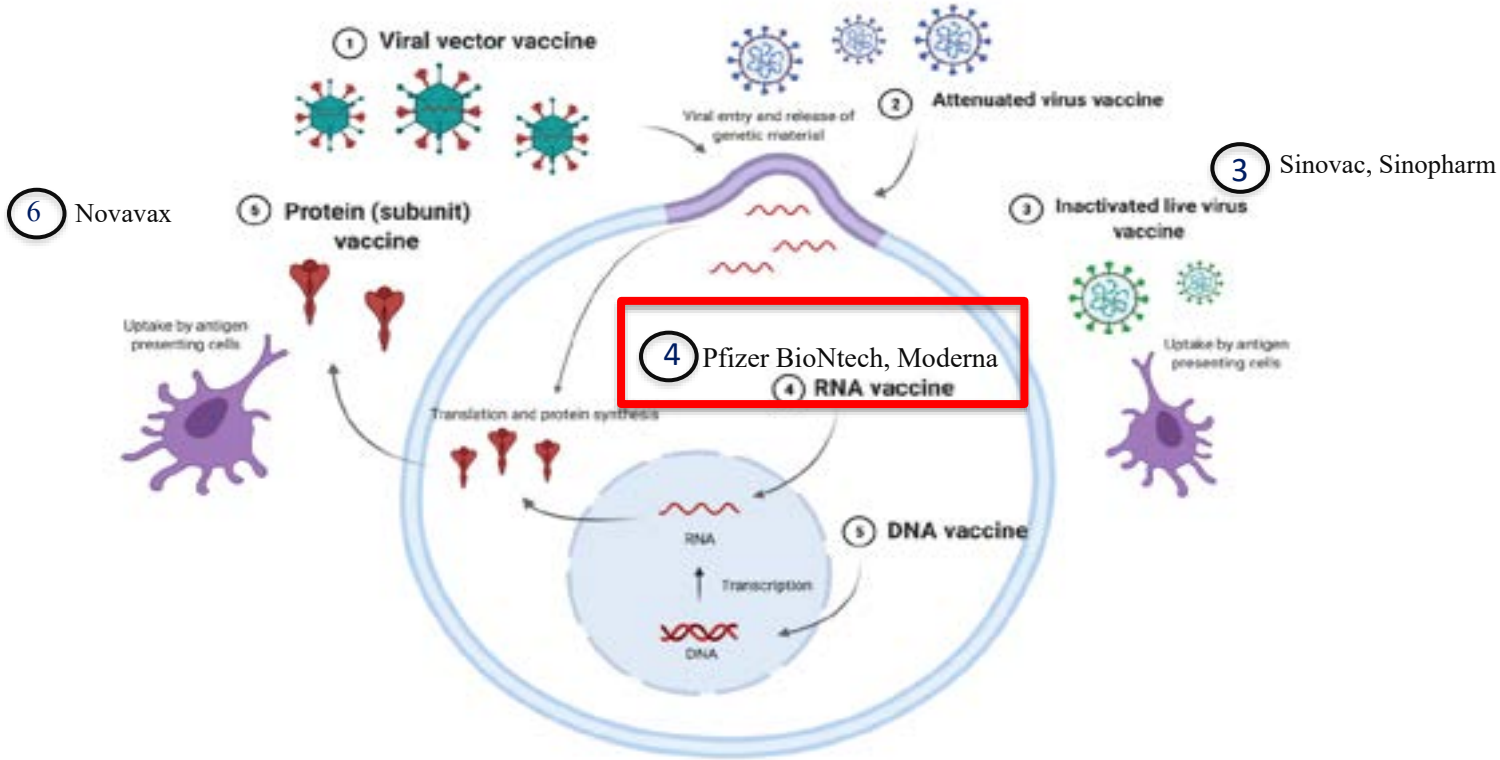
Modalità d'azione delle diverse piattaforme vaccinali rispetto al ciclo di replicazione virale

1 AstraZeneca/Oxford, Johnson&Johnson, Sputnik V.



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SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting

- Patients with IBD should be vaccinated against SARS-CoV-2
- The best time to administer SARS-CoV-2 vaccination in patients with IBD is at the earliest opportunity to do so
- SARS-CoV-2 vaccines including messanger RNA vaccines, replication-incompetent vector vaccines, inactivated vaccines and recombinant vaccines are safe to administer to patients with IBD
- SARS-CoV-2 vaccination should not be deferred because a patient with IBD is receiving immune-modyfing therapies
- Patients with IBD vaccinated with SARS-CoV-2 should be counselled that vaccine efficacy may be decreased when receiving systemic corticosteroids

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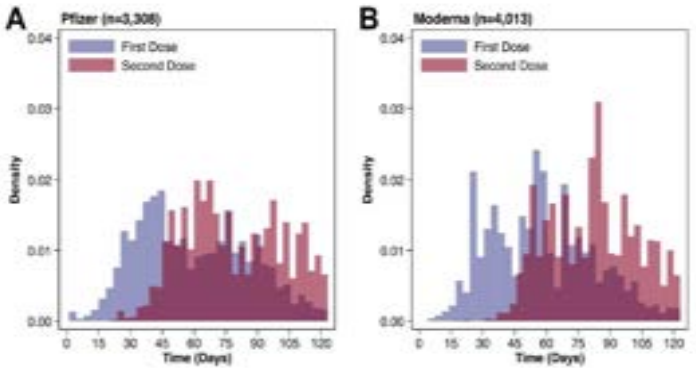
Siegel CA, *et al*. *Gut* April 2021 Vol 70 No 4

Efficacia del vaccino Pfizer/Moderna rispetto a diversi outcomes



Distribuzione delle dosi di vaccino per ciascun brand, relativo alla data indice della campagna vaccinale (VHA, Veterans Health Administration)

Table 2. Raw Proportion of Outcome Events, Stratified by Effective Vaccination Status[a,b] and Vaccine Manufacturer

Variable	No.	SARS-CoV-2 infection n (%)	Severe SARS-CoV-2 infection n (%)	All-cause mortality n (%)
Unvaccinated state	14,697	197 (1.34)	47 (0.32)	97 (0.66)
Pfizer				
Partially vaccinated	3194	7 (0.22)	2 (0.06)	5 (0.16)
Fully vaccinated	2873	3 (0.10)	1 (0.03)	0 (0.00)
Moderna				
Partially vaccinated	3918	7 (0.18)	1 (0.03)	4 (0.10)
Fully vaccinated	3380	4 (0.12)	2 (0.06)	2 (0.06)

Table 4. Vaccine Effectiveness for Primary and Secondary Outcomes in Inverse Probability Weight-Adjusted Models

Variable	Vaccination status	Person-time, d	Outcome events	Incidence rate (per 1000 person-days)	Vaccine effectiveness (vs unvaccinated state), %[a]
SARS-CoV-2 infection	Unvaccinated (Ref)	2,801,990.10	416.84	0.146	…
	Partially vaccinated	256,445.62	27.97	0.109	25.1
	Fully vaccinated	443,805.61	12.66	0.029	80.4[b]
Severe SARS-CoV-2 infection	Unvaccinated (Ref)	2,882,437.00	108.23	0.038	…
	Partially vaccinated	254,436.67	6.04	0.024	36.8
	Fully vaccinated	425,365.65	4.78	0.011	70.1
All-cause mortality	Unvaccinated (Ref)	2,945,906.30	241.50	0.082	…
	Partially vaccinated	266,056.47	15.76	0.059	27.8
	Fully vaccinated	381,159.52	3.98	0.010	87.3

Ref, reference.
[a] Calculated as: [1 − incidence$_{vaccinated}$/incidence$_{unvaccinated}$] × 100.
[b] The associated comparison in Cox's regression analysis was statistically significant.

Khan N and Mahmud N, Gastro 2021

Adverse Events Following SARS-CoV-2 mRNA Vaccination Among Patients with Inflammatory Bowel Disease

- This study evaluated post-mRNA vaccination adverse events (AE) in 246 vaccinated adults with IBD.
- AE frequency was similar to that reported in the general population. AE were more common among younger patients, and those with prior COVID-19.
- AE were less common in individuals receiving biologic therapy.

Adverse events after each vaccine dose stratified by biologic use (purple: no biologic; green: any biologic). AEs are graded by severity (darker colors represent more severe AE). AE are also tracked by duration. ("Biologic" refers to use of anti-TNFα, anti-integrin, anti-IL112/23, or JAK-inhibitor)

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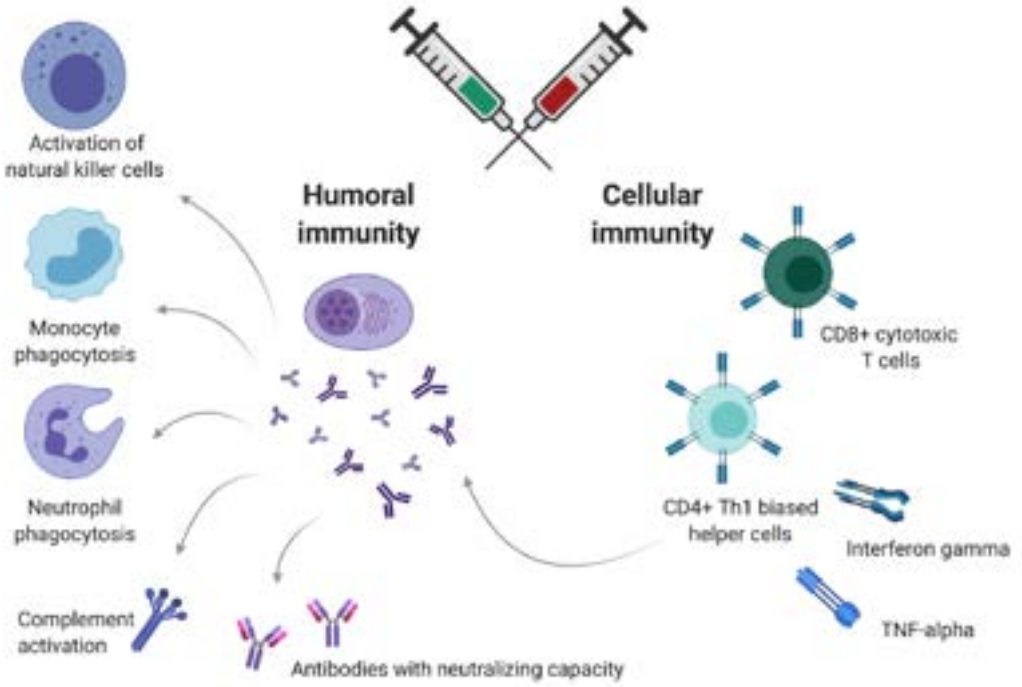
Botwin GJ, et al. Am J Gastroenterol. 2021

Attivazione del sistema immunitario dopo il vaccino anti-covid



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Humoral Immunogenicity After Vaccination Against SARS-CoV-2 Infection in Inflammatory Bowel Disease Patients Under Immunosuppressive Therapy: Should We Prioritize an Additional Booster Injection?

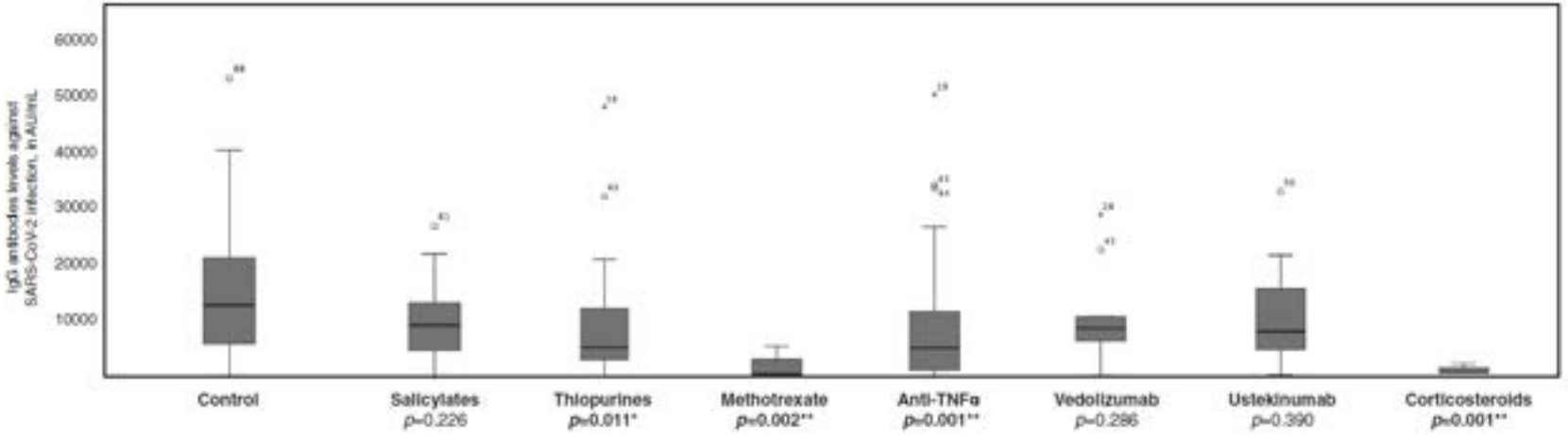

Figure 1. Comparison of immunoglobulin G (IgG) antibody levels against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between the control group and patients treated with different inflammatory bowel disease medications. *$P < .05$; **$P < .01$. AU, arbitrary units; TNFα, tumor necrosis factor α.

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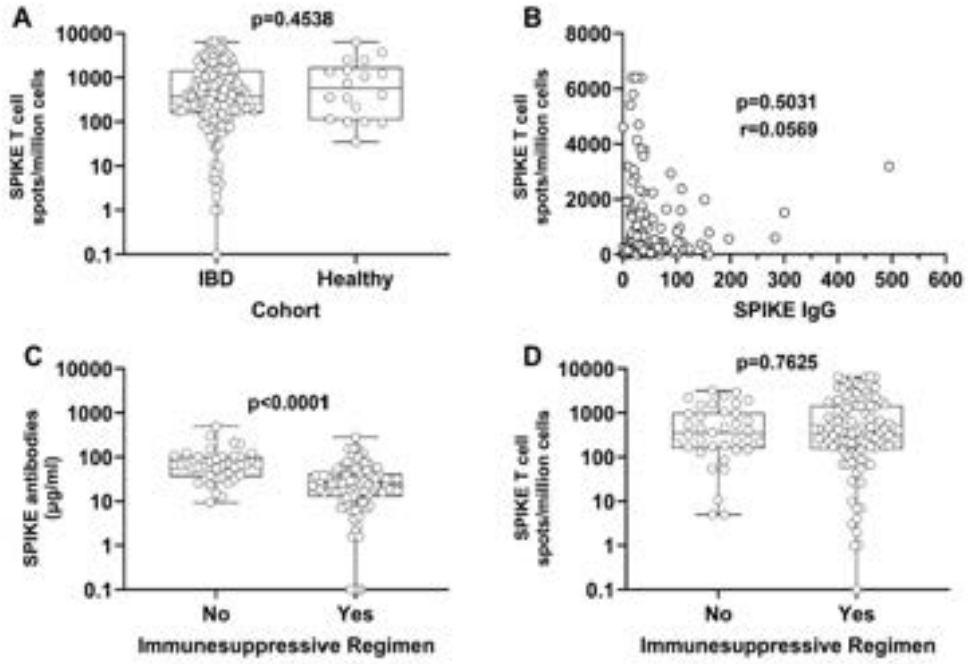
Silva VM et al. IBD 2022

Higher Cell-Mediated Immune Responses in Patients With Inflammatory Bowel Disease on anti-TNF Therapy After COVID-19 Vaccination



Caldera F et al., IBD 2022

COVID-19 vaccine-induced antibody and T-cell responses in immunosuppressed patients With Inflammatory Bowel Disease after the third vaccine dose (VIP): a multicentre, prospective, case-control study

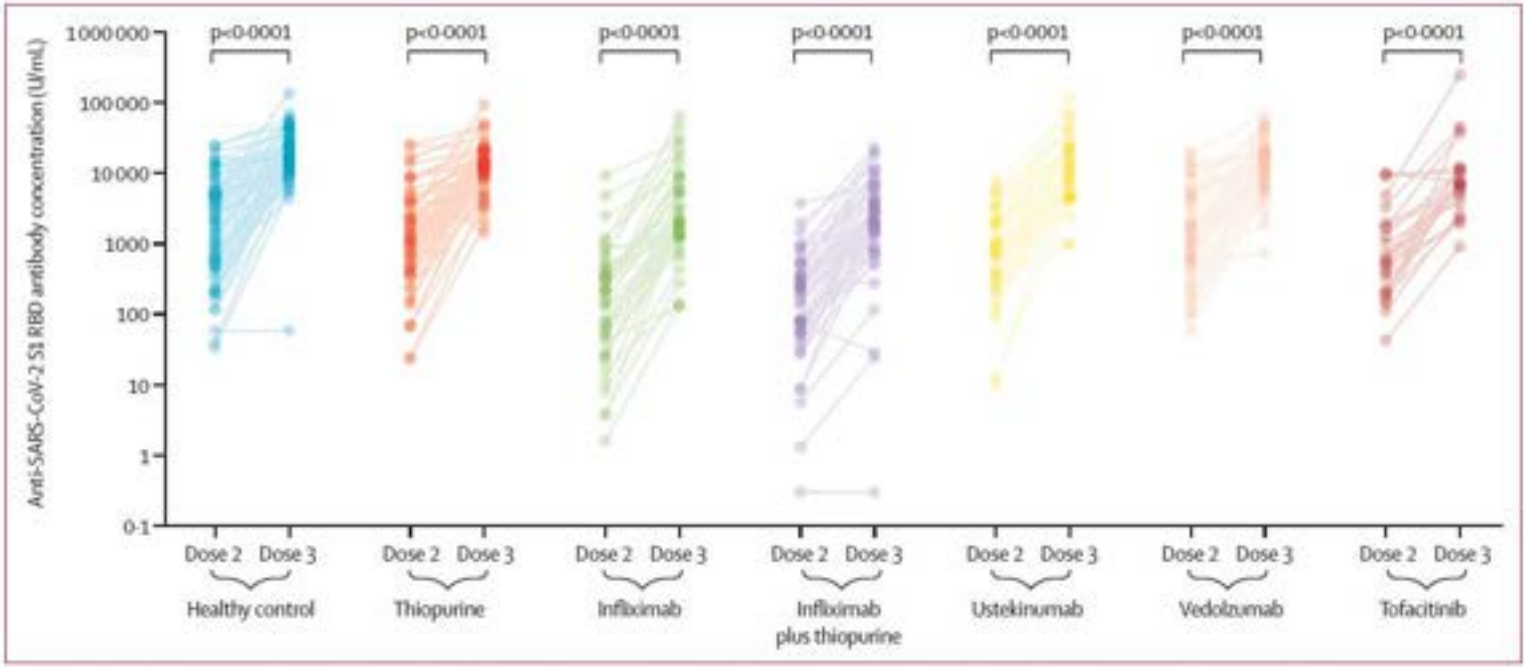


Figure 1: Ladder plots showing anti-SARS-CoV-2 S1 RBD antibody binding after two doses and three doses of COVID-19 vaccine, stratified by study treatment group

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Alexander JL et al., Lancet GH 2022

COVID-19 vaccine-induced antibody and T-cell responses in immunosuppressed patients With Inflammatory Bowel Disease after the third vaccine dose (VIP): a multicentre, prospective, case-control study

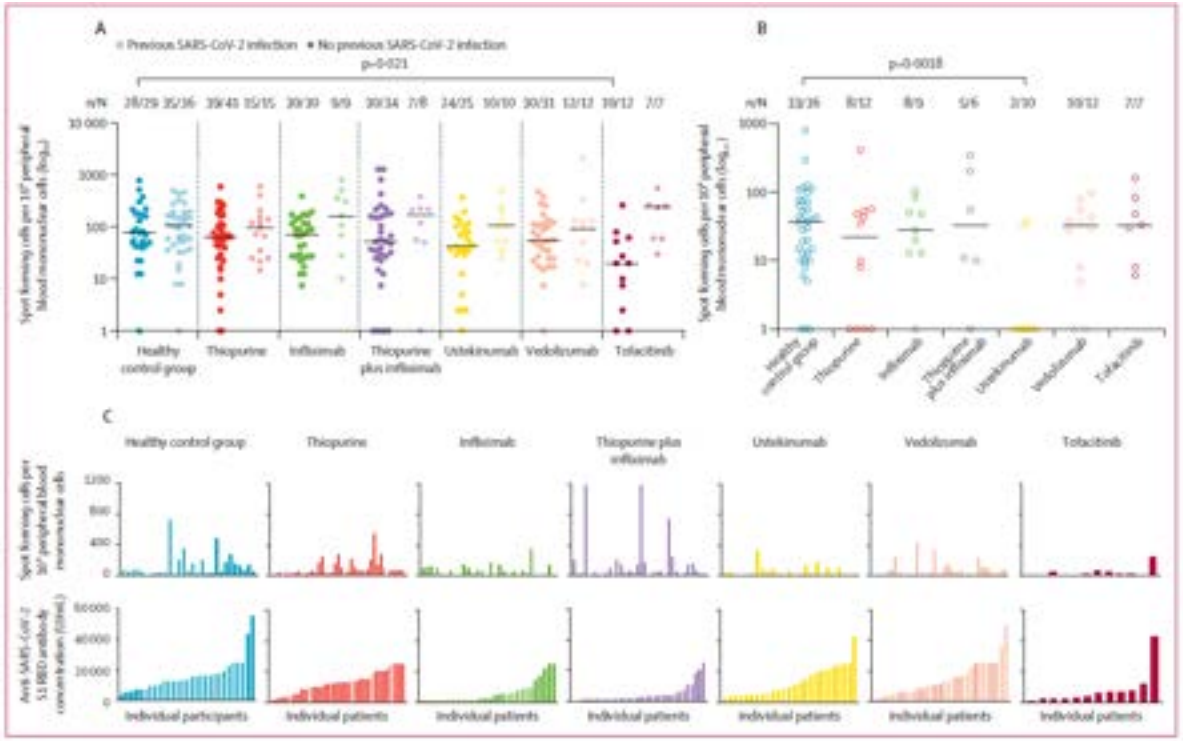
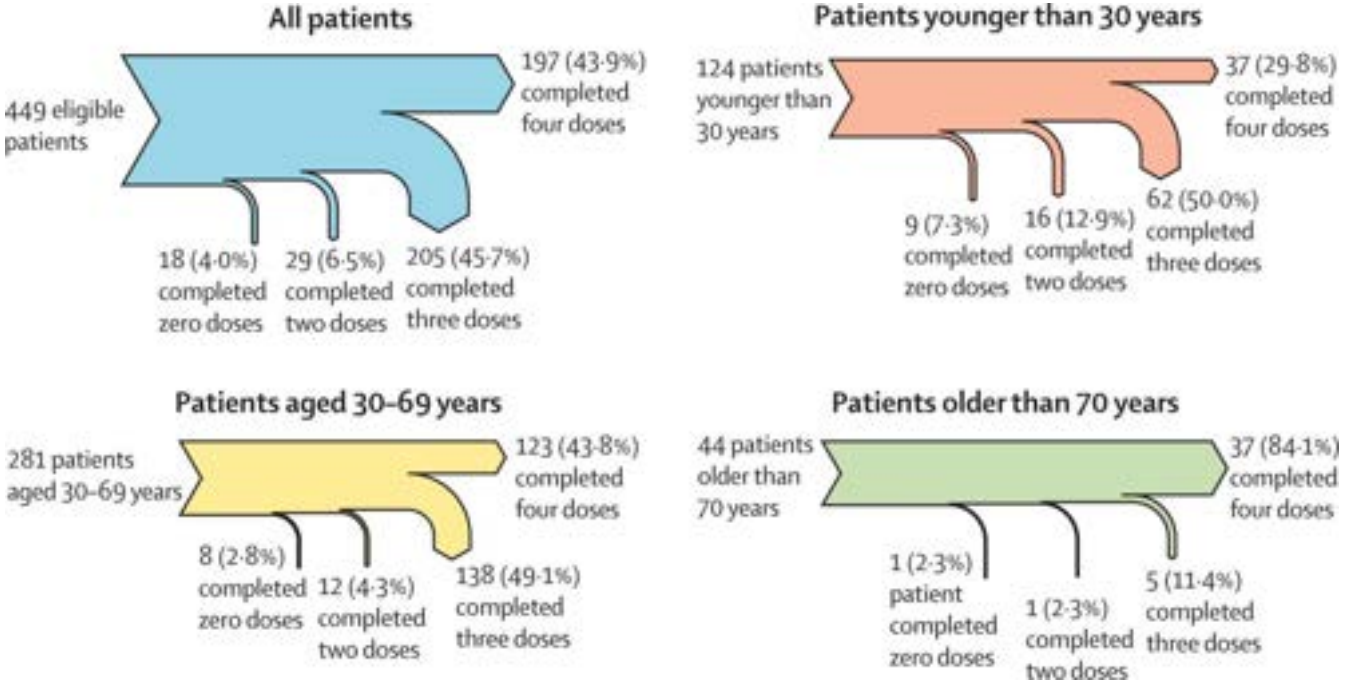


Figure 4: T-cell immunity against SARS-CoV-2 spike and nucleocapsid in the healthy control group and patients with IBD who are triple vaccinated against COVID-19

(A) T-cell responses against SARS-CoV-2 spike mapped epitope pool. (B) T-cell responses against SARS-CoV-2 nucleocapsid mapped epitope pool. For panels A and B, statistical significance was determined using a Kruskal-Wallis multiple comparison test with Dunn's correction; previously infected donors were assayed for nucleocapsid T-cell responses; the number of study participants in each group with a positive T-cell response to the peptide pools is shown, and n/N=number of T-cell responders/number of individuals tested. Midlines on both A and B are the geometric means. (C) Individual donor T-cell responses to the spike mapped epitope pool and matched data for serum S1 RBD binding antibodies, plotted by ascending antibody binding titer for SARS-CoV-2 infection-naive healthy control group (n=29) and SARS-CoV-2 infection-naive patients with inflammatory bowel disease taking thiopurine (n=41), infliximab (n=30), thiopurine plus infliximab (n=34), ustekinumab (n=25), vedolizumab (n=31), or tofacitinib (n=12). RBD=receptor binding domain.

Alexander JL et al., Lancet GH 2022

Decrease in uptake of SARS-CoV-2 vaccine in patients with inflammatory bowel disease



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Lancet Gastroenterol Hepatol **2022**

A recommended paradigm for vaccination of rheumatic disease patients with the SARS-CoV-2 vaccine

Haralampos M. Moutsopoulos

Table 1
Suggested recommendations on SARS-CoV-2 vaccination in ARD patients under immunosuppressive/immunomodulatory agents.

1. Clinical remission prior to vaccination is desirable.
2. Initiation of immunosuppressive therapy should be delayed until the vaccination is completed, if possible.
3. Anti-metabolites, calcineurin and JAK inhibitors should be held 10 days before and 10 days after each vaccination dose.
4. Prednisone dosage (>0.5 mg/kg body weight) or an equivalent synthetic steroid dose, should be decreased to <10 mg/daily for 10 days before and after each vaccination dose (if possible).
5. Patients on rituximab therapy should be vaccinated either one month prior to initiation of the therapeutic scheme or 6–8 months after the rituximab infusion.
6. Patients on intravenous monthly pulse cyclophosphamide/methyl prednisone therapy should be vaccinated either prior to therapeutic scheme or one month after the completion of 6 months pulse therapy.
7. Immunization should be performed after the anti-cytokine drug therapy has reached baseline sera levels (if possible).
8. If some patients are reluctant to follow the above precautions, they should be vaccinated without withholding their immunoregulatory/immunosuppressive therapy.
9. In all cases, regardless of adherence to these recommendations, antibody titers against SARS-CoV-2 should be checked 2–4 weeks after the final vaccination dose and at 3 and 6 months thereafter.

Journal of Autoimmunity 121 (2021) 102649

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COVID-19 and the management of patients with inflammatory bowel disease: a practical decalogue for the post-pandemic phase

Recommendation	Practical accomplishment
Educate patients to continue to comply with the general rules for the prevention of COVID-19 according to the indication of the WHO.	Remind patients at all times (outpatient visits, phone calls, chat, email, etc.) to comply with the recommendations for pandemic control provided by the WHO.
Do not discontinue undergoing biological therapy or delay new prescriptions.	Continue prescribing subcutaneous biological therapy and outpatient infusions. Start biological therapy, if indicated, without any delay.
Prescribe steroids only if they are strictly needed and consider a rapid tapering of their dosage.	Use steroid therapy judiciously.
Keep your patients in follow-up by preferring remote methods: telemedicine, internet, social media.	Use telemedicine with its different applications for the follow-up of patients in stable remission and therapy.
Prefer non-invasive methods to monitor disease activity.	Use calprotectin, patients' reported outcomes and intestinal ultrasound as non-invasive tools for treat-to-target strategy.
Advise patients to seek psychological support if necessary.	Offer patients psychological support and the possibility of using mindfulness techniques even remotely. In more severe cases, ask for a consultation with the psychiatrist.
Schedule (or re-schedule) endoscopic examinations if you recognize a non-deferrable indication, giving priority to the most urgent cases.	Gradually resume normal endoscopic procedures for patients with IBD using a prioritization criterion assessed on a case-by-case basis. Use the appropriate PPE to protect patients and healthcare professionals from the risk of contagion.
Infusion clinic: consider testing for SARS-CoV-2 all patients.	Resume (or continue) the activity of the infusion clinic, ensuring the safety of healthcare professionals and patients. Recommended PPE, spacing and subjecting patients to serological tests for SARS-CoV-2 on first access or return to the clinic after lockdown.
Schedule (or re-schedule) surgical interventions, giving priority to the most urgent cases.	Promote urgent surgery postponed for the lockdown, if possible, test the patient with naso-pharyngeal swab for SARS-CoV-2 before hospitalization; gradually insert all the scheduled interventions in the list.
Continue educational initiatives (not necessarily related to COVID-19) by involving patient associations.	Patient associations should offer webinars, videos, chats and other informative material to inform patients about the recommendations to be followed in "real time" to safely continue their treatments and diagnostic controls.

IBD, inflammatory bowel disease; PPE, personal protective equipment; WHO, World Health Organization.

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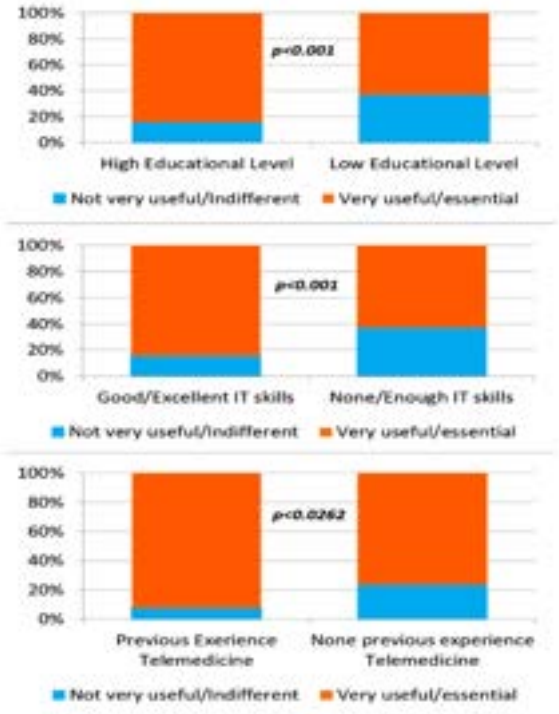
Papa A et al., Ther Adv Gastr 2020

Evaluation of factors associated with trust in telemedicine in patients with inflammatory bowel disease during COVID-19 pandemic: a multicenter cross-sectional survey



376 IBD patients from Rome (Policlinico Gemelli) and S. Giovanni Rotondo (CSS)

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F Bossa …and A Papa. Eur Rev Med Pharmacol Sci 2022

Conclusioni

- ✓ L'epidemiologia del COVID-19 ed i fattori di rischio per outcomes sfavorevoli nei pazienti con IBD non differiscono da quelli della popolazione generale.
- ✓ La terapia steroidea e la malattia attiva rappresentano i principali fattori prognostici negativi mentre la terapia con anti-TNF-α (ed altri biologici) sono associati a decorso clinico favorevole.
- ✓ La vaccinazione contro il SARS-CoV-2 e le dosi booster sono raccomandate nei pazienti con IBD.
- ✓ La risposta sierologica al vaccino anti-SARS-CoV-2 è ridotta nei pazienti in terapia con steroidi, immunosoppressori ed anti-TNF-α mentre è sovrapponibile alla popolazione generale nei pazienti in terapia con ustekinumab e vedolizumab.
- ✓ La risposta cellulo-mediata al vaccino anti SARS-CoV-2 è simile nei pazienti con IBD rispetto alla popolazione generale e non sembra essere influenzata dalle terapie (ad eccezione degli anti-JAK)
- ✓ L'epidemia da COVID-19 ha dato impulso a nuove modalità di gestione clinico-terapeutica: telemedicina, maggior ricorso al monitoraggio non-invasivo (calprotectina/eco anse), shift da farmaci endovena ad orali-sottocute

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