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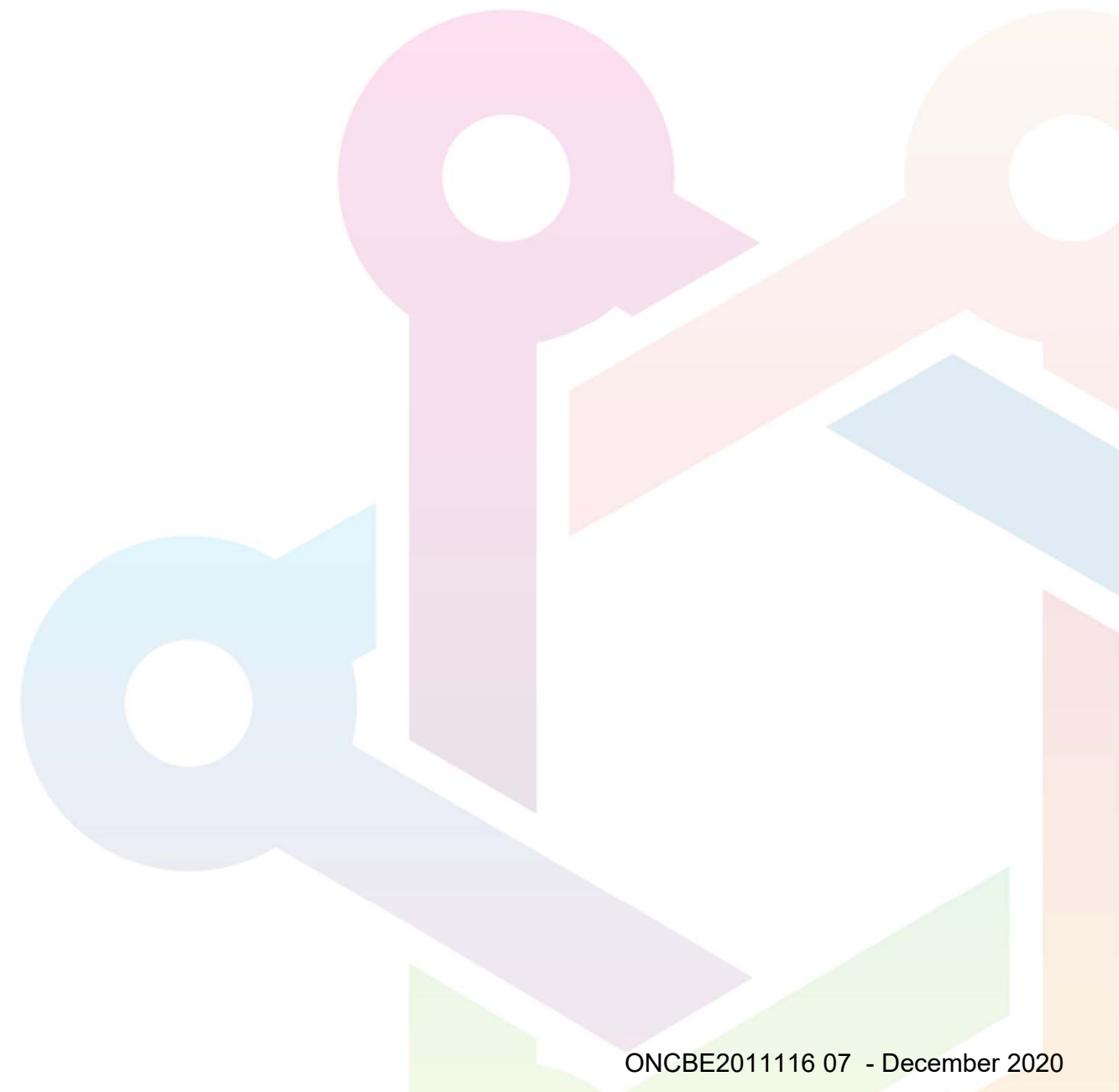www.immunoscienceacademy.be

Immune-related diarrhea and COVID-19 GI symptoms

Eric Van Cutsem MD, PHD
Digestive Oncology
University Hospitals Leuven
Leuven – Belgium

Overview

- Immune related (ir) diarrhea:
  - Mechanisms & clinical picture
  - Grading and management

- COVID-19 associated diarrea
  - Clinical characteristics
  - Pathogenesis
  - Prognostic Implications of COVID-19 Associated Diarrhea
  - Management of COVID-19 Associated Diarrhea

- Summary

ir AE-Diarrhea

Potential Mechanisms of Increased Immune System Activity

- Increasing T-cell activity against antigens that are present in tumors and healthy tissue

- Increasing levels of pre-existing autoantibodies (eg, in the thyroid gland)

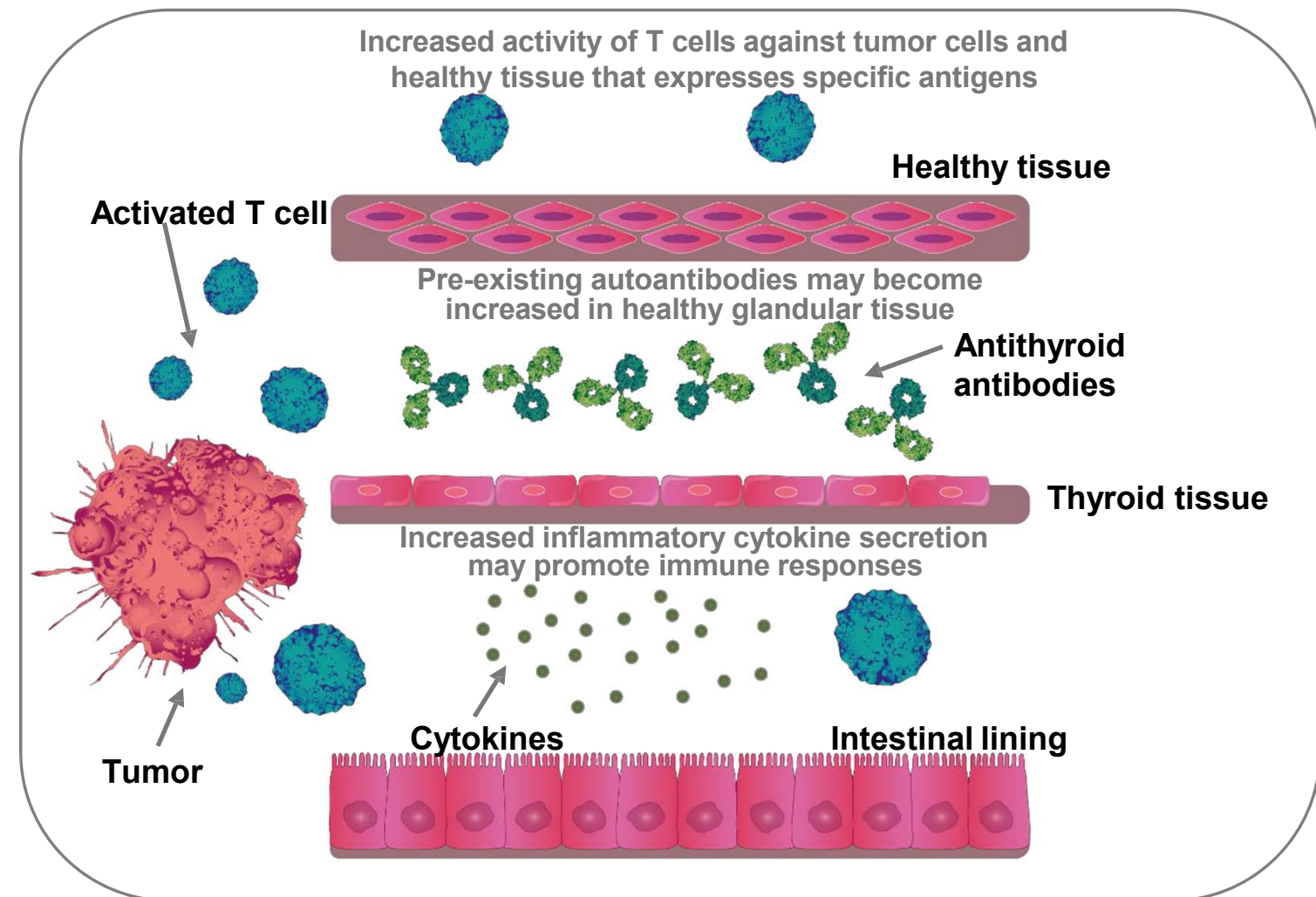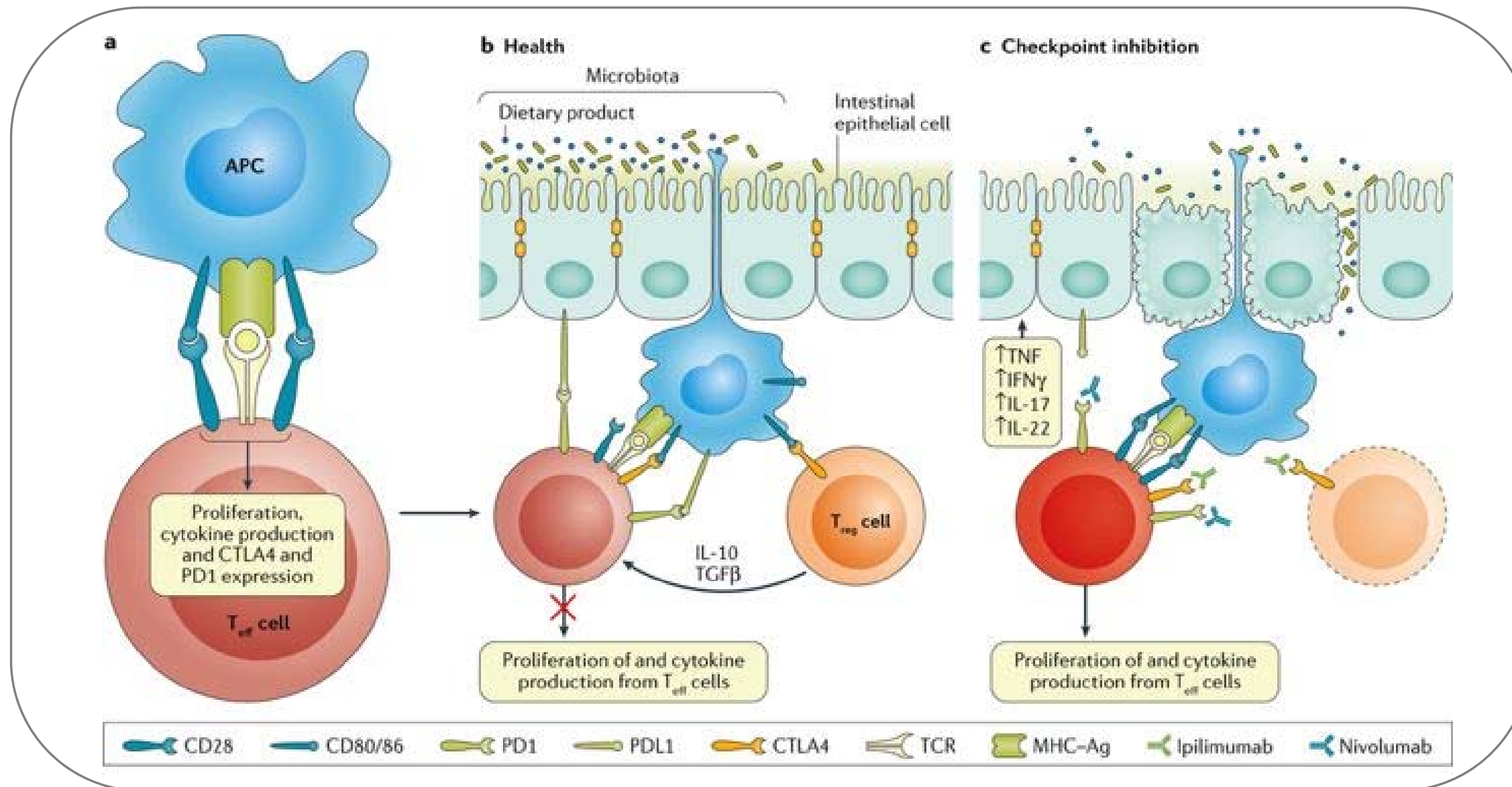- Increasing levels of inflammatory cytokines (eg, in the GI tract)

Increased activity of T cells against tumor cells and healthy tissue that expresses specific antigens

Healthy tissue

Activated T cell

Pre-existing autoantibodies may become increased in healthy glandular tissue

Antithyroid antibodies

Thyroid tissue

Increased inflammatory cytokine secretion may promote immune responses

Cytokines

Intestinal lining

Tumor

Figure adapted from Postow MA, et al. *N Engl J Med* 2018

ir AE, immuno-related adverse event, GI, gastrointestinal

Postow MA, et al. N Engl J Med 2018;378:158–168.

ir AE-Diarrhea

## The Role of CTLA4 and PD1 in T Cell Activation: GI Perspective

GI, gastrointestinal; irAE, immune-related adverse event.

Samaan MA et al. Nat Rev Gastroenterol Hepatol. 2018;15(4):222-234.

ir AE-Diarrhea: Disease History

- Diarrhea is common in patients undergoing treatment with checkpoint-blocking antibodies

- Patients should be informed that diarrhea/colitis does not typically begin with initiation of checkpoint blockade; instead, **it usually begins approximately 6 weeks into treatment**

- When a patient presents with mild diarrhea, clinicians should consider other etiologies that may be responsible, such as *Clostridium difficile* infection or other bacterial/viral pathogens

- Patients should be counseled on the importance of maintaining oral hydration

- Some clinicians find that the dietary restrictions similar to colitis is sometimes recommended, as well as antimotility agents (e.g: loperamide, oral diphenoxylate HCl and atropine sulfate 4 times a day) can be helpful

- If symptoms persist for more than 3 days, or increase, and/or no infectious causes are readily identified, the use of oral or intravenous corticosteroids are required
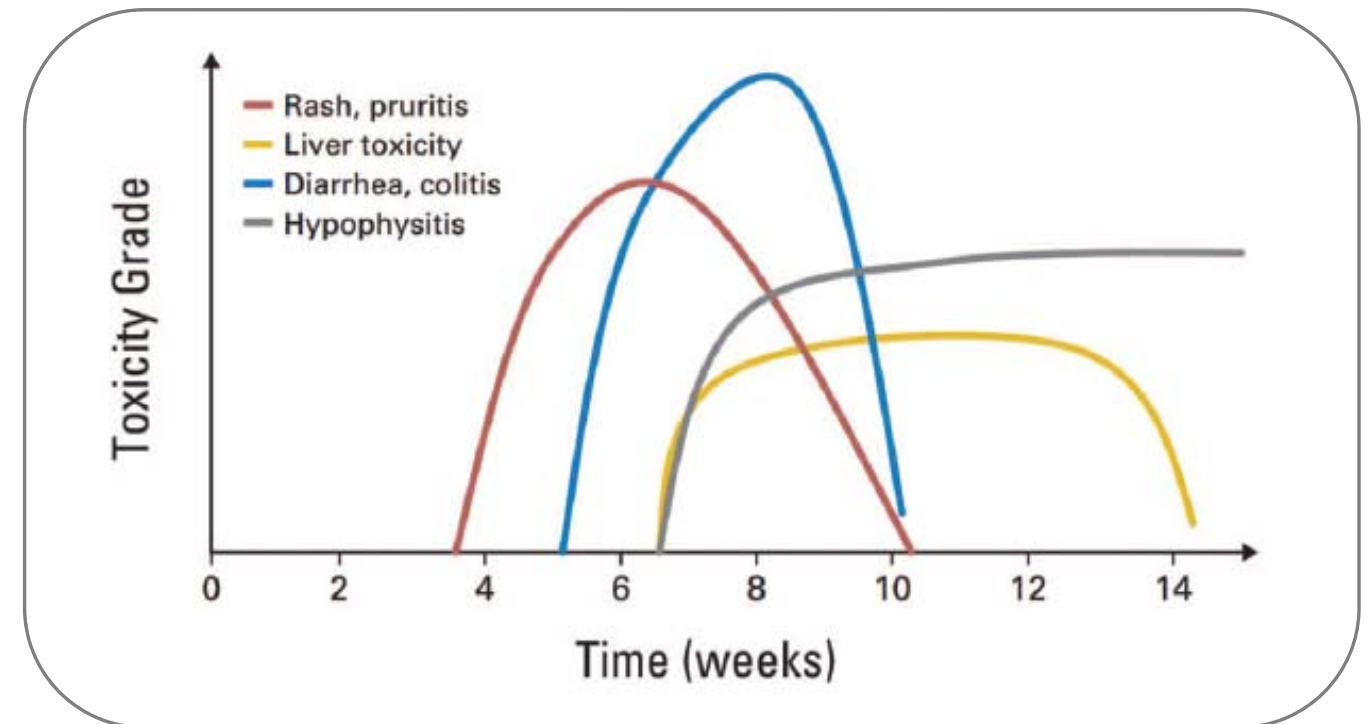
Ir AE, immune-related adverse event.

GI and Diarrhea Toxicity From Selected CPI Clinical Trials
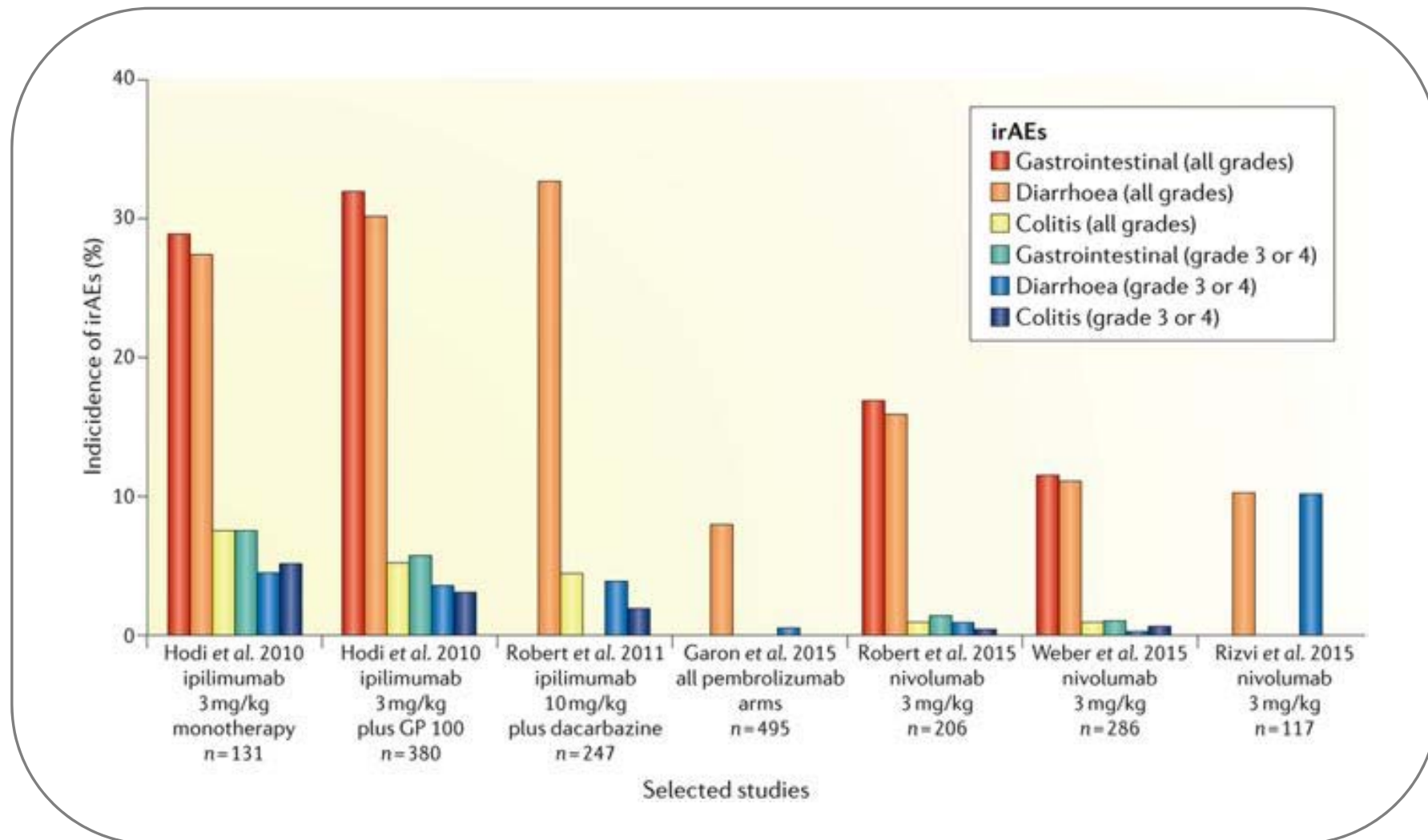
Diarrhea (all grades) have been reported ranging from 8% to 33%, and (grades 3-4) 1% to 10%

CPI, checkpoint inhibitor; GI, gastrointestinal; irAE, immune-related adverse event; GP 100, glycoprotein 100

Samaan MA et al. Nat Rev Gastroenterol Hepatol. 2018;15(4):222-234.

CTCAE Terms and Grades for GI Events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline and a mild increase in stoma output	Increase of 4-6 stools per day over baseline and a moderate increase in stoma output	Increase of ≥7 stools per day, incontinence, a severe increase in stoma output and limitations in self caring	Life-threatening consequences	Death

Adapated from Samaan MA et al. Nat Rev Gastroenterol Hepatol. 2018;15(4):222-234.

CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal.

Samaan MA et al. Nat Rev Gastroenterol Hepatol. 2018;15(4):222-234.

irAE Management Recommendations – ESMO

Gastrointestinal (Diarrhea & Colitis)			
Grade		**Grade**	

1	• Continue ICI
	
	• Symptomatic treatment (fluids, loperamide, low fiber/lactose)
	
	• If G1 and persists > 14 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea
		3 - 4	• Withhold ICI
			
			• If G2 and persists for > 3 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea
			
			• Do not wait for sigmoido/colonoscopy to start
			
			If no improvement in 72 hours or absorption concern, treat as G3/4. Steroid wean duration:
			
			   o Moderate: wean over 2–4 weeks
			   o Severe: taper over 4–8 weeks

2	• Withhold ICI
	
	• If G2 and persists for > 3 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea
	
	• Do not wait for sigmoido/colonoscopy to start
	
	If no improvement in 72 hours or absorption concern, treat as G3/4. Steroid wean duration:
	
	   o Moderate: wean over 2–4 weeks
	   o Severe: taper over 4–8 weeks		

ESMO, European Society for Medical Oncology; G, grade; ICI, Immune checkpoints; irAE, immune-related adverse event

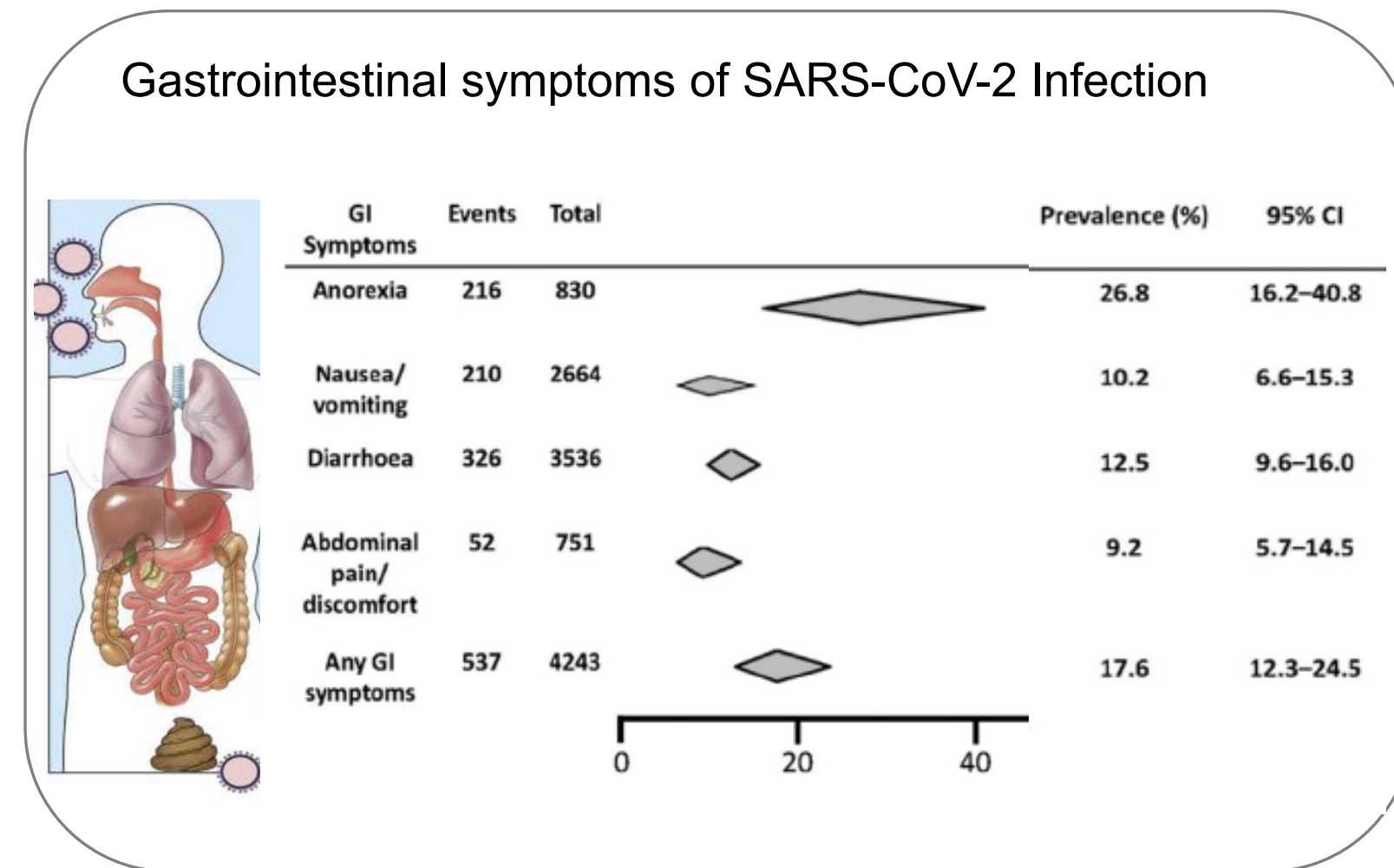| White	Continue ICI
Orange	Hold/Temporarily Hold ICI

Characteristics of COVID-19 – GI Symtoms

- COVID-19 is primarily a respiratory disease, however, increasing reports have reposted subgroups of patients with concurrent GI symptoms, notably diarrhea, anorexia, vomiting and nausea, onset of GI signs prior to respiratory symptoms,or only GI clinical signs with absence of respiratory symptoms[1,2]

- SARS-CoV-2 infections in the GI tract can cause bleeding and inflammation, which have an impact on the intestinal immune system and further influence the whole body's immune system, thus worsening the disease process of COVID-19 in the lungs and other organs[1]

- Additionally, the viral balance in the GI tract is disordered during SARS-CoV-2 infection, which could further impact the homeostasis of microbiota[1]

Gastrointestinal symptoms of SARS-CoV-2 Infection

GI Symptoms	Events	Total		Prevalence (%)	95% CI
Anorexia	216	830		26.8	16.2–40.8
Nausea/ vomiting	210	2664		10.2	6.6–15.3
Diarrhoea	326	3536		12.5	9.6–16.0
Abdominal pain/ discomfort	52	751		9.2	5.7–14.5
Any GI symptoms	537	4243		17.6	12.3–24.5

Adapted from Cheung et al. Gastroenterology 2020;159:81–95

GI, gastrointestinal

1. Zhang J et al., Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19, Genes & Diseases, https://doi.org/10.1016/j.gendis.2020.08.013. 2. COVID-19 (Coronavirus) and IBD: Resources for Healthcare Professionals https://www.crohnscolitisfoundation.org/coronavirus/professional-resources.

Characteristics of COVID-19 – Associated Diarrhea

- The WHO defines diarrhea as 3 or more loose/liquid stools per day or an increase in the number of evacuations compared with the usual. Given the subjective nature, there is marked heterogeneity in the estimates of patients with COVID-19 – associated diarrhea symptoms

- Some clinical studies have defined diarrhea as the passing of loose stools >3 times per day and a median symptom duration was 4 days

- Other studies report cases of patients that have experienced 3–4 days of diarrhea with several evacuations ranging from 5 to 8 per day

- Other report informs of diarrhea in a lower number of evacuations (3–4 per day) and associated with a low-grade fever. Interestingly, these symptoms disappeared after antiviral therapy (oral lopinavir and ritonavir), supporting the link between symptom and COVID-19 disease

- The first known case of COVID-19 in the United States also showed diarrheal symptoms for 2 consecutive days

- Unfortunately, in other remaining studies, diarrhea was not well characterized and no data were available regarding the total number of evacuations, consistency of the stools and duration of symptoms

WHO, World Health Organization

Pathogenesis of SARS-CoV – Associated Diarrhea

- SARS-CoV uses ACE2 and the serine protease TMPRSS2 for entry in lung AT cells

- ACE2 and TMPRSS2 are not only expressed in lung, but also the small intestinal epithelia. ACE2 is expressed in the upper esophagus, liver, and colon

- ACE2 is also necessary for the surface expression of aminoacid transporters of the small intestine. Aminoacids, like tryptophan, regulate the secretion of antimicrobial peptides by Paneth cells via mTOR pathway activation

- Antimicrobial peptides impact the composition and diversity of the microbiota. Disturbance of this pathway could drive inflammation (enteritis) and ultimately diarrhea

Proposed model for SARS-CoV-2-associated diarrhea
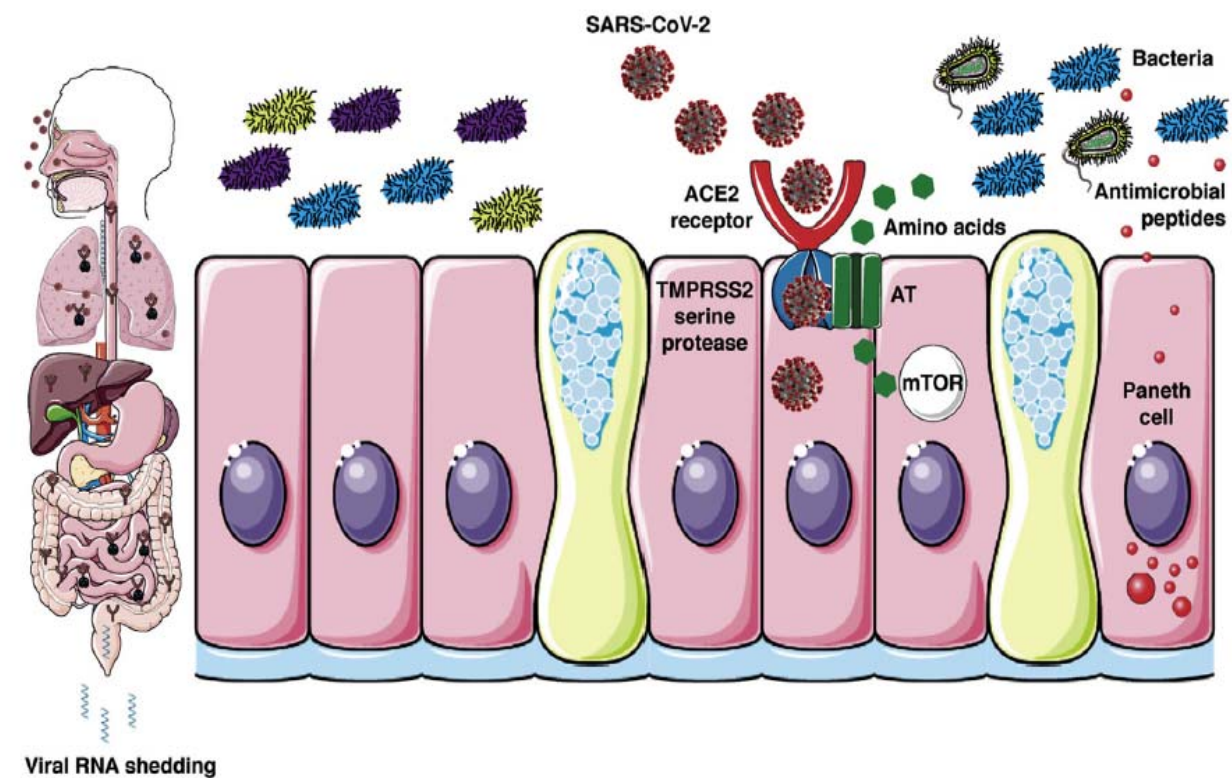
ACE2, angiotensin converting enzyme 2 ; AT, Alveolar Type; mTOR, mammalian target of rapamycin. TMPRSS2, Transmembrane Serine Protease 2.

D'Amico et al Clinical Gastroenterology and Hepatology 2020;18:1663–1672

Frequency of COVID-19 – Associated Diarrhea

- Clinical studies show that in COVID-19 patients with gastrointestinal symptoms, diarrhea was one of the most common, with a quite variable percentage of patients, ranging from 2% to 55% of cases. It may precede or trail respiratory symptoms[1,2]

- Other study reports two thirds of patients hospitalized with SARS-CoV-2 infection presented with at least 1 gastrointestinal symptom, and diarrhea as one of the most common, present in approximately one third of patients[3]

- The number of COVID-19 patients experiencing diarrhea is significant and cannot be overlooked[2]

1. Zhang J et al., Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19, Genes & Diseases, https://doi.org/10.1016/j.gendis.2020.08.013. 2. D'Amico et al Clinical Gastroenterology and Hepatology 2020;18:1663–1672. 3. Redd W eta al. Gastroenterology Vol. 159, No. 2

Prognostic Implications of COVID-19 – Associated Diarrhea

- Gastrointestinal symptoms are associated with more severe COVID-19 and worse outcomes[1]

- Additional studies reported prognosis implications:

  - A symptom analysis based on COVID-19 severity showed a greater diarrhea percentage in patients with severe disease compared with those with non severe disease, suggesting an association between presence of symptom and disease severity[2]

  - Likewise, COVID-19 patients with diarrhea, nausea, and vomiting were more likely to require mechanical ventilation and had acute respiratory distress syndrome compared with patients without gastrointestinal symptoms[2]

  - Presence of diarrhea as a presenting symptom is associated with increased disease severity and likely worse prognosis. Patients with diarrhea likely harbor increased viral load, which can potentially lead to an increased systemic response to the virus and associated respiratory complications from it. Early recognition of patients is needed for prompt management of this at-risk population[1]

  - However, other case series found that diarrhea was not associated with greater need for intensive care unit care or with poor prognosis[2]

Additional studies are needed to clarify the correlation between diarrhea and the outcomes of COVID-19 patients[2]

1. Ghimire S., Diarrhea Is Associated With Increased Disease Severity in COVID-19: Systematic Review and Meta-Analysis. ACG 2020 Virtual 2, https://www.eventscribe.net/2020/ACGPosters/PosterSpeakers.asp?goToLetter=G&pfp=PosterPresenter. 2. Amico, American College of Gastroenterology

Management of COVID-19 – Associated Diarrhea

- No evidence on the efficacy of antidiarrheal drugs is available, but adequate rehydration and potassium monitoring should be performed as in all patients with diarrhea

- Antibiotics and antivirals are often used for COVID-19 treatment, involving a likely alteration of the gut microbiota and therefore causing diarrhea

- It is therefore plausible that the gut microbiota could be a new therapeutic target and that probiotics could have a role in the management

- A rapid improvement in diarrea was also found after starting antiviral therapy (although no antiviral drug was specifically designed for the treatment of diarrhea, several molecules could have beneficial effects)

Recommendations for
Health Care Professionals
in the Management of Patients
With COVID-19 and Diarrhea

☞ Wear gloves, mask, protective gown, and goggles every time you visit a patient with diarrhea

☞ Pay attention to hand hygiene before and after visiting a patient with diarrhea, using alcoholic disinfectants or soap and water

☞ Patients with diarrhea should have a personal bathroom and bathroom sanitation should be performed several times per day

☞ All endoscopes and reusable accessories should be reprocessed with standard reprocessing procedures

Adapated from D'Amico et al Clinical Gastroenterology and Hepatology Vol. 18, No. 8

COVID-19 patients treated with ACE2 inhibitors

Numbers and proportions of patients taking ACE inhibitor according to patient characteristics

Category	Number in category	Prescribed ACE inhibitor (row%)
Total population	8 275 949	645 577 (7.80)
Male	4 115 973	375 509 (9.12)
Female	4 159 976	270 068 (6.49)
Age (Years)		
20-39	3 135 980	10 921 (0.35)
40-49	1 399 562	44 117 (3.15)
50-59	1 386 093	125 971 (9.09)
60-69	1 037 077	163 430 (15.76)
70-79	802 224	176 435 (21.99)
80 +	515 013	124 703 (24.21)

Adaptad from Hippisley-Cox et al., Heart 2020;106:1503–1511

HRs comparing risks of COVID-19 in users versus non-users of ACE inhibitor by ethnic group

	ACE inhibitor Adjusted HR (95%CI)	P value	ARB Adjusted HR (95%CI)	P value
White	0.66 (0.63 - 0.70)	<0.001	0.56 (0.52 - 0.62)	<0.001
Indian	0.74 (0.61- 0.90)	0.003	0.66 (0.52 – 0.82)	<0.001
Pakistani	0.83 (0.64 – 1.09)	0.182	0.78 (0.57 – 1.06)	0.114
Bangladeshi	0.97 (0.72 – 1.31)	0.847	0.74 (0.49 – 1.13)	0.164
Other Asian	0.81 (0.64 – 1.03)	0.084	0.96 (0.73 – 1.23)	0.726
Caribbean	1.05 (0.87 – 1.28)	0.480	0.70 (0.53 – 0.92)	0.010
Black African	1.31 (1.08 – 1.59)	0.005	1.24 (0.99 – 1.58)	0.062
Chinese	0.73 (0.30 – 1.79)	0.575	1.53 (0.77 – 3.01)	0.223
Other ethnic group	0.82 (0.67 – 1.05)	0.122	1.09 (0.86 – 1.39)	0.475

- Based on diarrhea etiopathogenesis and on the key role of ACE2, the use of ACE blockers is being investigated, as it could lead to a higher risk of developing COVID-19 diarrhea and COVID-19[2]

- One of these investigations studies whether patients treated with ACE2 inhibitors had altered risks of contracting severe COVID-19 disease and receiving associated intensive care unit (ICU) admission[1]

- ACE inhibitors has been associated with a significantly reduced risk of COVID-19 disease requiring hospital admission but were not significantly associated with risk of ICU care[1]

ARB, angiotensin receptor blocker

1. Hippisley-Cox J, Young D, Coupland C, et al. Heart 2020;106:1503–1511. 2. Amico. 2. D'Amico et al Clinical Gastroenterology and Hepatology Vol. 18, No. 8

Summary (1)

- Immune related adverse events:

  - The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue

  - Diarrhea is common in patients treated with CPI, it usually begins approximately 6 weeks into treatment.

  - Oral hydration, diet and antimotility agents can help, if symptoms persist for or increase, oral or intravenous corticosteroids are required

  .

Summary (2)

- COVID-19 infections:

Clinical picture
- Diarrhea is one of the most common COVID-19 gastrointestinal symptoms, ranging from 2% to 55% of cases of COVID-19 infections
- Several studies report cases of 3-8 evacuations per day and a median symptom duration of 4 days
- Onset of GI signs maybe prior to respiratory symptoms or appear also in absence of respiratory symptoms

- Gastrointestinal symptoms are associated with more severe COVID-19 and worse outcomes, and diarrhea could be associated with increased disease severity and worse prognosis

Pathogenesis

- ACE2 is crucial for SARS-CoV-2 cellular entry, and is expressed in the upper esophagus, liver, and colon. This could drive inflammation (enteritis) and ultimately diarrhea

Management
- Adequate rehydration and potassium monitoring should be performed, as in all patients with diarrhea
- Gut microbiota could be a new therapeutic target and probiotics could have a role in the management of COVID-19 diarrhea
- A rapid improvement in diarrea has been also found after starting antiviral therapy
- ACE inhibitors have been associated with a significantly reduced risk of COVID-19 disease requiring hospital admission but not significantly associated with risk of ICU care