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More on Covid-19 in Immune-Mediated Inflammatory Diseases.

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quires awareness among health care providers that syphilis is now common and that testing, correct treatment with benzathine penicillin, and advice from specialists are available.

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1. Panel on Opportunistic Infections in Adults and Adolescents

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More on Covid-19 in Immune-Mediated Inflammatory Diseases

TO THE EDITOR: In their letter, Haberman et al. (online April 29; July 2 issue)¹ provide data on a series of 86 patients with immune-mediated inflammatory disease who had either confirmed or highly suspected symptomatic coronavirus disease 2019 (Covid-19). It was reassuring to learn that the percentage of hospitalized patients in such a series (16%) was not higher than the percentage observed among patients with Covid-19 in the general New York City population (26%). However, the analyses according to the treatment received by the patients in their study series were

based on so-called floating numerators, which are quite unreliable.² The only suitable denominator for such analyses would have been the number of persons receiving a given treatment, biologics and Janus kinase (JAK) inhibitors as compared with other therapies or no treatment, in the reference patient population. Numbers similar to those analyzed in the letter can be derived from underlying populations with widely divergent risks of Covid-19 and consequent hospitalization (Table 1).

Providing signals of risks in patient subgroups is of major importance during the severe acute

Table 1. Relative Risks of Covid-19 According to Different Scenarios of Exposure to Biologics and Janus Kinase (JAK) Inhibitors.*

Exposure	Exposed Persons in Underlying Population <i>no.</i>	Incidence of Covid-19 among Ambulatory Patients (N = 72)	Relative Risk	Incidence of Covid-19 among Hospitalized Patients (N = 14)	Relative Risk
Scenario 1					
Biologics and JAK inhibitors	10,000	55/10,000	3.2	7/10,000	1.0
Other therapies or no treatment	10,000	17/10,000	Reference	7/10,000	Reference
Scenario 2					
Biologics and JAK inhibitors	5,000	55/5,000	10.0	7/5,000	3.4
Other therapies or no treatment	15,000	17/15,000	Reference	7/15,000	Reference
Scenario 3					
Biologics and JAK inhibitors	15,000	55/15,000	1.1	7/15,000	0.3
Other therapies or no treatment	5,000	17/5,000	Reference	7/5,000	Reference

* The simulations are based on data from Haberman et al.¹ regarding 86 patients with immune-mediated inflammatory disease who had either confirmed or highly suspected symptomatic Covid-19. Of 72 ambulatory patients, 55 were receiving biologics or JAK inhibitors when Covid-19 developed. Of 14 hospitalized patients, 7 were receiving biologics or JAK inhibitors when Covid-19 developed.

respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. However, inaccurate answers can be provided by neglecting basic epidemiologic principles.

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2. Victora CG. What's the denominator? *Lancet* 1993;342:97-9.

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TO THE EDITOR: Haberman et al. showed that the baseline use of biologics was not associated with worse Covid-19 outcomes in patients with immune-mediated inflammatory disorders. Whether patients with immune-mediated inflammatory disease who are treated with biologics are at increased risk for Covid-19 is unknown.¹⁻³ Here, we report the findings from a cohort of 6000 patients with inflammatory bowel disease at two academic centers (Nancy University Hospital in Nancy, France, and Humanitas University in Milan, Italy) located in severely affected areas. A total of 561 patients were treated with infliximab or vedolizumab involving repeat intravenous administration during the Covid-19 outbreak. Of these 561 patients, 13 tested positive for Covid-19 before these two centers had implemented preventive measures. After March 27 in Nancy and March 9 in Milan, none of the patients who were treated with biologics received a diagnosis of Covid-19 through April 30, 2020. We would infer from these data that patients who are treated with intravenous biologics are not at increased risk for Covid-19 if effective personal protective equipment is implemented for both patients and health care professionals.

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TO THE EDITOR: As epidemiologists, we appreciate the need for thoughtfully adjusted models in order to generate informative measures of associations. The general rule of thumb when constructing logistic-regression models is that the number of participants in the smaller of two outcome groups relative to the number of predictors estimated is at a ratio of 10 to 1.^{1,2} In the letter by Haberman et al., none of the reported odds ratios were from models satisfying this best practice; in fact, many counts of hospitalized patients with the exposure of interest were fewer than five, and several had counts of zero or one. It is unclear how the odds ratios and relatively narrow 95% confidence intervals were derived from models that additionally included several predictors for such exceptionally small counts.

Although these data are highly informative, the

associations are difficult to interpret and distract from the key message that there appeared to be no major differences in this patient population that contributed to hospitalizations for Covid-19. Given the urgent need for information for providers, it is essential that data are presented appropriately.

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1. Pavlou M, Ambler G, Seaman S, De Iorio M, Omar RZ. Review and evaluation of penalised regression methods for risk prediction in low-dimensional data with few events. *Stat Med* 2016;35:1159-77.

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THE AUTHORS REPLY: One of the most pressing questions in clinical practice is whether patients with immune-mediated inflammatory diseases should continue immunomodulatory medications during the Covid-19 pandemic. The argument for continuation is based on the premise that worse outcomes (hospitalization, intubation, and death) are related to uncontrolled overproduction of proinflammatory cytokines and their deleterious downstream effects.¹ It follows that patients receiving maintenance immunomodulatory therapies may be protected against severe Covid-19. Conversely, proponents of discontinuation cite the known risk of infections. This discrepancy has been met with a vacuum of data, and although many organizations have offered important recommendations, guidance has so far been supported by very-low-quality evidence.²

This scarcity of reporting is largely due to the necessary reassignment of physicians to the care of patients with Covid-19,³ which held true for

most authors of our study. Nevertheless, and however extraordinary, these circumstances should not be used as pretexts for ignoring scientific rigor, avoiding criticism, or not acknowledging honest mistakes. In our case, we had already recognized the partial submission of two supplementary tables containing exponentiated difference in proportions from a linear regression analysis, rather than odds ratios from logistic regression. This was further identified by Briggs et al. and, owing in part to their attentiveness, our analysis has now been adjusted; it is important to note that the conclusions of our work remain the same. We further note that a linear probability model serves as a useful sensitivity analysis for outcomes with small counts (relative to the number of predictors). Because this can lead to unstable solutions and convergence issues, we now show estimates for the linear model only when odds ratios are estimated for logistic regression. Small incident counts can lead to wide confidence intervals, decreasing the reliability of the estimates, and we therefore advise caution in the interpretation of our results.⁴ The Supplementary Appendix has been updated at NEJM.org.

The observation by Naldi and Cazzaniga, although of value, has two main challenges. First, it does not recognize the explicitly stated limited scope of our work, which focused on describing differences in medication use for incident cases of Covid-19 in our population. Second, although the proposed hypothetical approach is valid, it is certainly not the only suitable denominator.

Nevertheless, we agree that in order to answer these questions, prospective studies of incidence among patients with immune-mediated inflammatory diseases with adequate denominators should be pursued. We believe that the New York University cohort study and similar studies,⁵ including that of Peyrin-Biroulet and Danese, are good examples of ways to address these knowledge gaps.

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