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Systemic Immunosuppressive Therapy for Inflammatory Skin Diseases in Children: Expert-Consensus-Based Guidance for Clinical Decision Making During the COVID-19 Pandemic

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Abstract:

Background/Objectives: The COVID-19 pandemic has raised questions about the approach to management of systemic immunosuppressive therapies for dermatologic indications in children. Given the absence of data to address concerns related to SARS-CoV-2 infection while on these agents in an evidence-based manner, a Pediatric Dermatology COVID-19 Response Task Force (PDCRTF) was assembled to offer time-sensitive guidance for clinicians.

Methods: A survey was distributed to an expert panel of 37 pediatric dermatologists on the PDCRTF to assess expert opinion and current practice related to three primary domains of systemic therapy: initiation, continuation, and laboratory monitoring.

Results: Nearly all respondents (97%) reported that the COVID-19 pandemic had impacted their decision to initiate immunosuppressive medications. The majority of pediatric dermatologists (87%) reported that they were pausing or reducing the frequency of laboratory monitoring for certain immunosuppressive medications. In asymptomatic patients, continuing therapy was the most popular choice across all medications queried. The majority agreed that patients on immunosuppressive medications who have a household exposure to COVID-19 or test *positive for acute infection* should temporarily discontinue systemic and biologic medications, with the exception of systemic steroids, which may require tapering.

Conclusions: The ultimate decision regarding initiation, continuation and laboratory monitoring of immunosuppressive therapy during the pandemic requires careful deliberation, consideration of the little evidence available, and discussion with families. Consideration of an individual's adherence to COVID-19 preventive measures, risk of exposure, and the potential severity if infected must be weighed against the dermatological disease, medication, and risks to the patient of tapering or discontinuing therapies.

Systemic Immunosuppressive Therapy for Inflammatory Skin Diseases in Children: Expert-Consensus-Based Guidance for Clinical Decision Making During the COVID-19 Pandemic

1. Introduction

The unprecedented set of circumstances related to the COVID-19 pandemic has raised questions about the approach to management of systemic immunosuppressive therapies for dermatologic indications in children. Given the absence of data to address concerns related to SARS-CoV-2 infection while on systemic immunosuppressive or immunomodulatory agents in an evidence-based manner, a Pediatric Dermatology COVID-19 Response Task Force comprised of 37 expert pediatric dermatologists from across the US and Canada was rapidly assembled and formally surveyed to offer time-sensitive guidance for clinicians. The process utilized herein is expert consensus-based and intended to guide, rather than specifically define, a rational approach to systemic treatment for inflammatory skin diseases in pediatric patients in the COVID-19 pandemic era.

2. Background and Rationale

The world has previously experienced outbreaks of infections from coronaviruses, with regional epidemics that threatened a global pandemic. In 2002, severe acute respiratory syndrome (SARS), and in 2011, Middle East respiratory syndrome (MERS) were newly identified respiratory-borne illnesses caused by the zoonotic coronaviruses SARS-CoV and MERS-CoV respectively.[1] By the end of 2019, an outbreak of a new respiratory illness termed the "Coronavirus Disease 2019" (COVID-19) was first identified in Wuhan, Hubei, China; the novel coronavirus, SARS-CoV-2 was quickly identified as the causative agent.[2] With the rapid dissemination of infection across the globe, clinicians are grappling with the question of whether patients treated with systemic immunosuppressive medications are at risk for worse outcomes with SARS-COV2 infection.

As of April 15, 2020, the COVID-19 pandemic has resulted in more than 1,900,000 cases and greater than 120,000 deaths worldwide, including 614,246 cases and 26,064 deaths in the United States.[3, 4] The reported prevalence and severity of the global COVID-19 pandemic in China, the US and Canada suggests the disease may be less frequent and milder in children than in adults. Children with COVID-19 less frequently present with fever, cough or shortness of breath compared to adults, making it difficult to collect accurate epidemiologic data regarding disease prevalence and transmission among children.[5,6] A recent publication by the Centers for Disease Control (CDC) reported on 149,760 laboratory-confirmed COVID-19 cases in the United States occurring in the timeframe between February 12 and April 2, 2020.[7] Only 2572 (2%) were in patients less than 18 years old with a median age of 11 years old. While few infected children required inpatient care and even fewer required intensive care, severe outcomes including 3 pediatric deaths were discussed in the report.[7]

At present, there is no evidence to support an increased risk of SARS-CoV-2 infection or increased severity of infection in children taking immunosuppressive medications for inflammatory skin diseases. Further, there is anecdotal evidence that some forms of immunosuppression can be used to modulate the COVID-19 related cytokine storm and trials have been initiated.[8] Nevertheless, the shared concern between patients and physicians is valid given the potential for immunosuppressive medications to inhibit relevant pathways critical for host immunity.

The objective of this consensus statement is to guide clinical decision-making to maintain optimal control of the inflammatory skin disease while minimizing the risk of infection and poor outcomes in children.

3. **Methods**

In response to the COVID-19 pandemic, the Pediatric Dermatology COVID-19 Response Task Force (PDCRTF) was created on March 30th, 2020. The goal of the Task Force is to address critical issues in

pediatric dermatology impacted by the pandemic, including the approach to systemic immunosuppressive therapies used to treat inflammatory skin diseases in pediatric patients. The PDCRTF is comprised of an expert panel of 37 pediatric dermatologists, representing 23 academic institutions, assembled from the membership of the Pediatric Dermatology Research Alliance (PeDRA) and Society for Pediatric Dermatology (SPD). A subset with expertise in use of systemic immunosuppressive therapy developed a survey to assess expert opinion and current practice related to three primary domains of systemic therapy: initiation, continuation, and laboratory monitoring. The survey closed 72 hours after launch and the results formed the basis of this consensus based guidance document. As none of the questions asked for information protected by the Health Insurance Portability and Accountability Act, the survey was exempt from review per the University of California San Francisco Institutional Review Board guidelines. Descriptive statistics were performed on the data and reported as percentages of the group.

4. Results

4.1 Demographics

A total of 37 expert pediatric dermatologists from the US and Canada ("the expert panel") completed the online survey (response rate 100%).

4.2 Prescriber Opinions and Current Practices Related to Initiation and Management of Immunosuppressive Medications

Nearly all respondents (97%) reported that the COVID-19 pandemic had impacted their decision to initiate immunosuppressive medications. The decision depended on the medication in question, the condition being treated, and family and patient preference. The patient's risk factors for contracting or having severe health consequences of COVID-19 while on the medication, compared to not treating their underlying condition, was also an important factor. **[Figure 1]**

Participants were asked how they would manage specific immunosuppressive medications in pediatric patients for dermatologic indications in different clinical circumstances during the COVID-19 pandemic. The results are shown in **Table 1** and **Table 2** and graphically in **Figure 2** and **Figure 3.**

4.3 Prescriber Actions Regarding their Patients on Immunosuppressive Medications

Prescriber contact: Fifty-four percent of the pediatric dermatologists surveyed proactively contacted patients to provide anticipatory guidance about COVID-19 symptoms and prevention. Only 30% proactively contacted patients to alter their immunosuppressive medications in light of the pandemic. Nearly all respondents (97%) had been contacted by at least one patient, parent, or caregiver about continuing or discontinuing an immunosuppressive medication during the pandemic.

Physicians who proactively contacted patients had concerns about a specific medication that they felt to be higher risk (57%). Fewer respondents contacted all of their patients on immunosuppressive medications, all patients on a certain immunosuppressive medication, or all patients with a specific dermatologic condition on immunosuppressive medications. **[Figure 4]** The majority of respondents who proactively contacted patients did so by phone calls from a physician in the practice (70%) **[Figure 5].** Those who did not contact patients proactively listed lack of resources or time (29%) or lack of data to drive the decision to contact (43%), while the remainder cited that responding to patient queries is adequate (29%). In addition, 40% of respondents reported not having a reliable way to track patients taking immunosuppressive medications.

Laboratory monitoring: The majority of pediatric dermatologists (87%) reported that they were pausing or reducing the frequency of laboratory monitoring for certain immunosuppressive medications in response to the COVID-19 pandemic.

5. Discussion: Evidence Plus Expert Consensus and Clinical Implications

Many dermatologists treat pediatric inflammatory and autoimmune skin diseases with therapies that have varying degrees of immune suppression. In many cases, these treatments are used "off label", with suboptimal data to inform best use, and practices vary widely even in normal circumstances. The COVID-19 pandemic has further complicated this difficult therapeutic decision-making process. While each child's management must be approached individually, we propose the following suggestions based on expert-consensus that may be used to guide decision making during the pandemic. The overarching goal is to protect the health of children and families while maintaining control of skin disease. This goal may be accomplished in part by well-considered, informed decisions about immunosuppressive therapies.

5.1 Approach to Patient Contact

The expert panel agreed that dissemination of general information to patients on immunosuppressive therapy, if resources are available, is important. However, specific advice should not be rendered by mass communication given the risk of misinterpretation of information by individual patients and families. Abrupt or reactive decisions to stop immunomodulatory therapy could have unintended consequences; particularly, inciting a flare of the underlying disease. The resultant utilization of urgent care centers, emergency departments, hospitals and laboratories risks placing undue burden on an already overwhelmed system and increasing exposure to SARS-CoV-2. It is important to address questions posed by patients and families with a discussion about what is known and unknown, allowing formulation of a shared decision. In order to help clinicians manage

the requests for information and to guide patients, the Task Force developed original educational content for patients and caregivers and resources for providers accessible via the SPD (https://pedsderm.net/) and PeDRA (www.pedraresearch.org) websites.

5.2 Approach to Initiation and Continuation of Therapy

The expert panel emphasizes that the decision to initiate therapy during the pandemic is context-dependent. Assuming a patient does not have COVID-19 or symptoms, 84% of experts surveyed said that the *decision to initiate* systemic immunosuppressive therapy depends on a patient's individual set of risk factors for contracting COVID-19 infection and the potential health consequences of infection while on the medication compared to the risks of not treating the underlying inflammatory skin condition. Though pre-treatment testing for COVID-19 infection would be ideal, especially given the probability of asymptomatic COVID-19 in children, widespread testing for asymptomatic individuals is not available. At present, testing practices vary by region and institution.

Hierarchical frameworks of disease based on functional consequences, short-term health impact and long-term sequelae of delaying treatment can prove very useful. Patients who may require early intervention to prevent permanent physical impairment or disfigurement from their underlying disease, such as erythrodermic pustular psoriasis or rapidly progressive linear morphea, would be candidates for treatment. In contrast, compromises may be made in initiation of treatment for patients with moderate to severe inflammatory skin diseases that may be acceptably, though not optimally, managed with topical and other home-based therapeutic options, such as atopic dermatitis. Variables to be considered include the medication in question, need for and frequency of laboratory monitoring, access issues, family/caregiver preferences, socioeconomic factors and ethical perspectives. Initiating appropriate therapy may also depend upon the ability of patient and close contacts to follow the recommendations of health authorities to shelter in place, follow social

distancing guidelines and practice aggressive hand hygiene and masking in order to reduce chances of exposure and infection.

Clearly, the complexity of medical decision-making regarding initiation of systemic immunosuppressive therapy cannot be distilled to medication factors alone. Though it is attractive to attempt to stratify the relative risk of immunosuppressive medications by mechanism of action and relative infection rate from clinical trials, there are few benefits and some flaws to this rationale. Data regarding the role of each component of the immune response, and by extension the relative safety or risk of any particular medication based on mechanism of action, is not fully known in relation to the novel coronavirus, SARS-CoV-2. Some immunosuppressive medications may even have a role in attenuating viral replication and SARS-CoV-2 induced cytokine storm.[9] Further, systemic therapies for inflammatory skin diseases in children, as compared to adults, have been studied far less in clinical trials. Therefore, access to comparative infection risk from pivotal trial data is limited for the majority of systemic and biologic therapies used off-label for pediatric inflammatory skin diseases. Even in available trial data, translating incidence of standard infections to risk of infection with SARS-CoV-2 should be done with caution.

5.3 Insight from SARS-CoV-2 and Immune System Pathways Relevant to Therapeutic Decisions

The mechanisms that lead to SARS-CoV-2 immunity are not fully established. However, experience with SARS and MERS as well as emerging data from COVID-19 patients are beginning to shed light on key immune pathways that likely contribute to viral clearance and long-term immunity.[10, 11, 12] From publications of COVID-19 patients in Wuhan, China, increased total neutrophils, low lymphocyte counts, high serum IL-6 levels and elevated C-reactive protein (CRP) correlated with disease severity and death.[2, 13] Additionally, pro-inflammatory cytokines linked to innate immune responses were highly elevated in patients who developed respiratory failure and required mechanical ventilation and ICU level care.[13] These clinical features suggested that a highly pro-inflammatory immune response may lead to disease progression and worse clinical outcomes. This early rise in serum

cytokine levels has also been observed in SARS-CoV and MERS-CoV infections suggesting a similar cytokine-storm mediated disease process in the late stage of acute lung injury from all of these related infections. [11, 12]

Effective innate immune responses to viral infection heavily relies on type I interferons (IFNs). Type I IFNs subsequently activate the JAK-STAT signaling pathway, leading to the expression of genes that block viral replication and dissemination.[14] In clinical trials, adult patients with rheumatoid arthritis had increased rates of viral infection (particularly to herpes simplex and herpes zoster) compared to placebo controls.[15,16] These results suggest that JAK inhibitors may impede effective viral clearance. However, JAK-dependent cytokines such as IL-6 may also play a role in the dysregulated immune response seen in seriously ill COVID-19 patients. As a result, numerous ongoing clinical trials are testing the efficacy of immune modulators (such as tocilizumab and sarilumab, IL-6 pathway inhibitors, and baricitinib, and JAK1/2 inhibitor) in COVID-19 patients after they have developed acute lung injury necessitating mechanical ventilation. [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28]

Inhibition of other immune pathways of interest to pediatric dermatologists, such as IL-4/IL-13, may have minimal impact on anti-viral immune responses to SARS-CoV-2. Dupilumab is an IL-4 receptor alpha (IL-4Rα) antagonist approved for atopic dermatitis. Results from the clinical trials showed comparable rates of cutaneous and non-cutaneous infections between the treatment arms and placebo control groups in adults and adolescents.[29, 30] These results are also consistent with preclinical observations in animal model systems where inhibition of or loss of the Th2 pathway has minimal effect on anti-viral immunity.[31, 32, 33, 34] Furthermore, dupilumab may help to reduce pulmonary risks in atopic dermatitis patients with concomitant asthma. These results collectively indicate that IL-4/IL-13 pathway inhibition likely plays a minimal role in generating an effective immune response to SARS-CoV-2.

5.4 Therapeutic Decisions Relative to Clinical Circumstances

In the absence of evidence specific to SARS-CoV-2, among the most critical decision points in *asymptomatic* patients is the stability of the underlying cutaneous disease and risk of a disease flare if undertreated. In some cases, if the underlying disease is chronic and stable, dose reductions or deferred injections/infusions can be considered during the pandemic in asymptomatic patients or those with mild non-specific URI symptoms of. Patients who are asymptomatic and presumably COVID-negative whose underlying skin disease is brittle or unstable should be continued on their medication regimen. In asymptomatic patients, continuing therapy was the most popular choice across all medications queried. This was especially notable for biologic agents, where more expert panelists selected to continue therapy in asymptomatic patients. Anti-TNF agents were the exception and scored more similarly to methotrexate and apremilast. One of the unintended consequences of temporarily stopping a biologic therapy is failure to regain response upon re-initiation, resulting in loss of disease control.

Responses to questions about systemic corticosteroids deserve special consideration. Roughly half (46%) of the panel would continue systemic corticosteroids in asymptomatic patients while 46% assert that the decision is context-dependent. Long-term (> 4 weeks) prednisone or prednisone equivalents at dosages at or greater than 10 mg/day are considered immunosuppressive in children (greater than 20mg/day in older adolescents and adults) and these patients may be at increased risk of infection.[35] Choices around corticosteroids are context-dependent given both their presumably high risk for infection but also the high risk of negative consequences of abrupt cessation such as adrenal crisis and disease flare. If the underlying disease has been otherwise stable, and the patient is in a high-risk environment for exposure to COVID-19, has suggestive symptoms, or a confirmed case, tapering the dosage appropriately and then stopping systemic steroids as clinically indicated is preferred. Patients recently tapered off corticosteroids should be assessed for residual adrenal suppression as they may need stress-dose steroids in the case of infection. Though the panel did not specifically address the question of polypharmacy, patients on more than one immunosuppressive therapy, especially if one of the medications is a systemic corticosteroid, may be at increased risk for

infection. Tapering or temporarily discontinuing at least one of the medications as clinically able is a reasonable step during the pandemic.

5.5 Patients with Household Exposure to COVID-19 or Confirmed COVID-19

The majority of the expert panel agreed that patients on immunosuppressive medications who have a household exposure to COVID-19 or test *positive for acute infection* should temporarily discontinue systemic and biologic medications, with the exception of systemic steroids, which as mentioned above may require tapering. For patients with confirmed infection, 24% of the expert panel would continue apremilast and 16% would continue dupilumab. These two medications may have been singled out as potentially reasonable to continue based on their immune modifying mechanism (apremilast) and potential to stabilize asthma (dupilumab, see above), important factors given the potential for pulmonary morbidity due to COVID-19. Dose reductions or decreased frequency of administration were less preferred strategies in confirmed cases.

5.6 Patients with URI Symptoms and Unknown COVID-19 Status

The risks and benefits of discontinuing therapy in the setting of URI symptoms needs to be considered on an individual basis, particularly for those patients who are being treated for very severe skin disease. Geography as related to disease epidemiology should influence decision making. Clinicians on the expert panel who practice in disease epicenters such as New York make therapeutic decisions on the assumption that any patient with URI symptoms has COVID-19, especially given lack of availability of outpatient testing. On the other hand, some experts emphasize the available data showing that COVID-19 appears to be mild and even sub-clinical in many children. If symptoms are mild and the patient has severe skin disease, having a discussion with the family and making a decision together about whether or not to continue is a sensible strategy.

5.7 Approach to Laboratory Monitoring

A large majority of the expert panel (87%) is pausing or reducing the frequency of laboratory monitoring for certain immunosuppressive medications. The necessity of obtaining laboratory values to assess the safety and toxicity of systemic therapies should be carefully considered and the frequency reduced if medically appropriate. Patients who have been on long-term stable doses of oral systemic agents without prior abnormalities are ideal candidates for reduced monitoring. These and other measures, such as reconsidering initiation or continuation of therapies that require frequent monitoring, may reduce utilization of medical facilities.

6. **Conclusion/Final Thoughts**

The ultimate decision regarding initiation, continuation and laboratory monitoring of immunosuppressive and immunomodulating therapy during the pandemic requires careful deliberation, consideration of the little evidence available, and discussion with families. Consideration of an individual's adherence to COVID-19 preventive measures, risk of exposure, and the potential severity if infected must be weighed against the dermatological disease, medication, and risks to the patient of tapering or discontinuing therapies. The global pandemic has brought to the forefront the importance of rational medical decision making and ethical decision analysis. Now more than ever, the values of beneficence and non-maleficence (do no harm) together with a respect for patient autonomy and shared decision-making underscore the provision of optimal patient care during a time of significant uncertainty. Partnering with patients and involving caregivers in decisions regarding therapies and interval reconsideration of decisions based on changing clinical contexts and evolving relative risk are key to optimizing outcomes.

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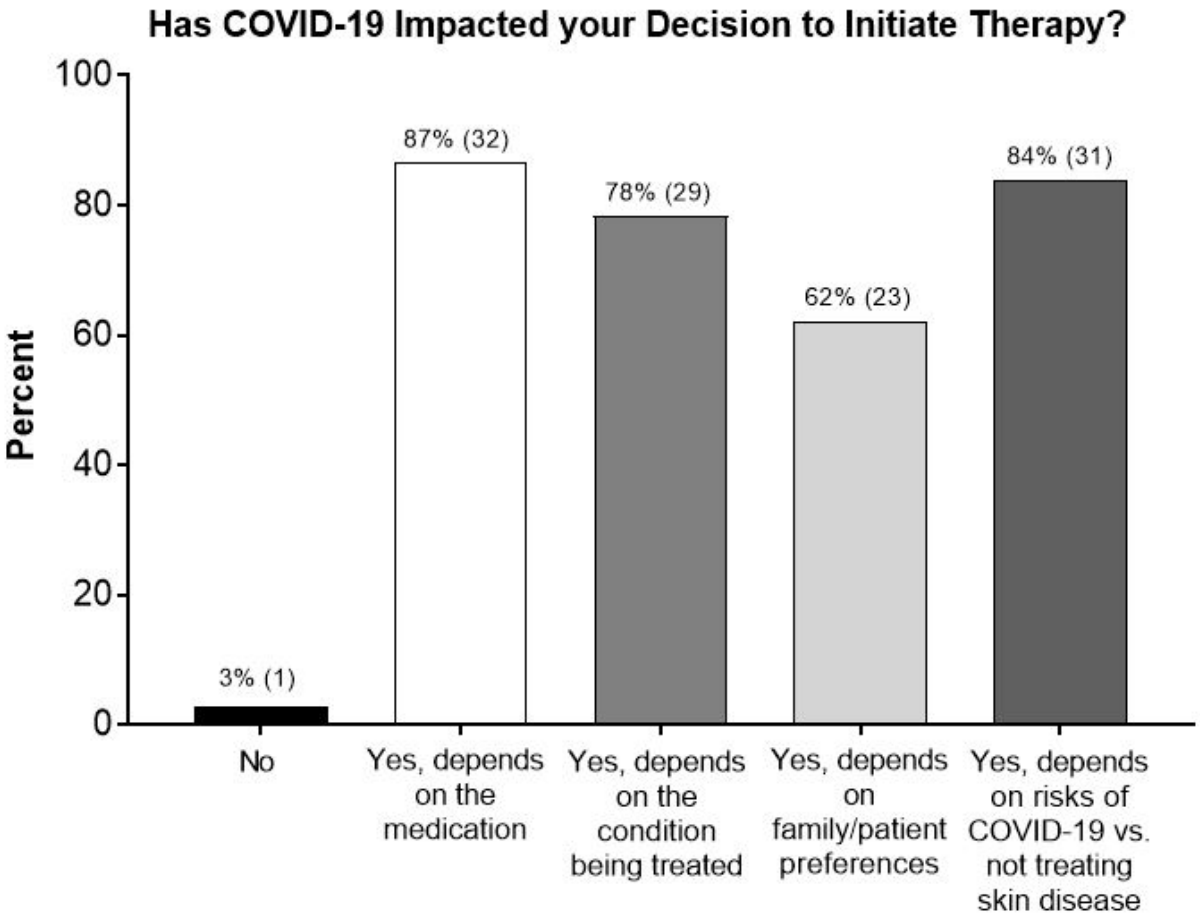

Figure 1. Expert panel survey responses to the question "Has the COVID-19 pandemic impacted your decision to initiate immunosuppressive medications?" Multiple selections were allowed.

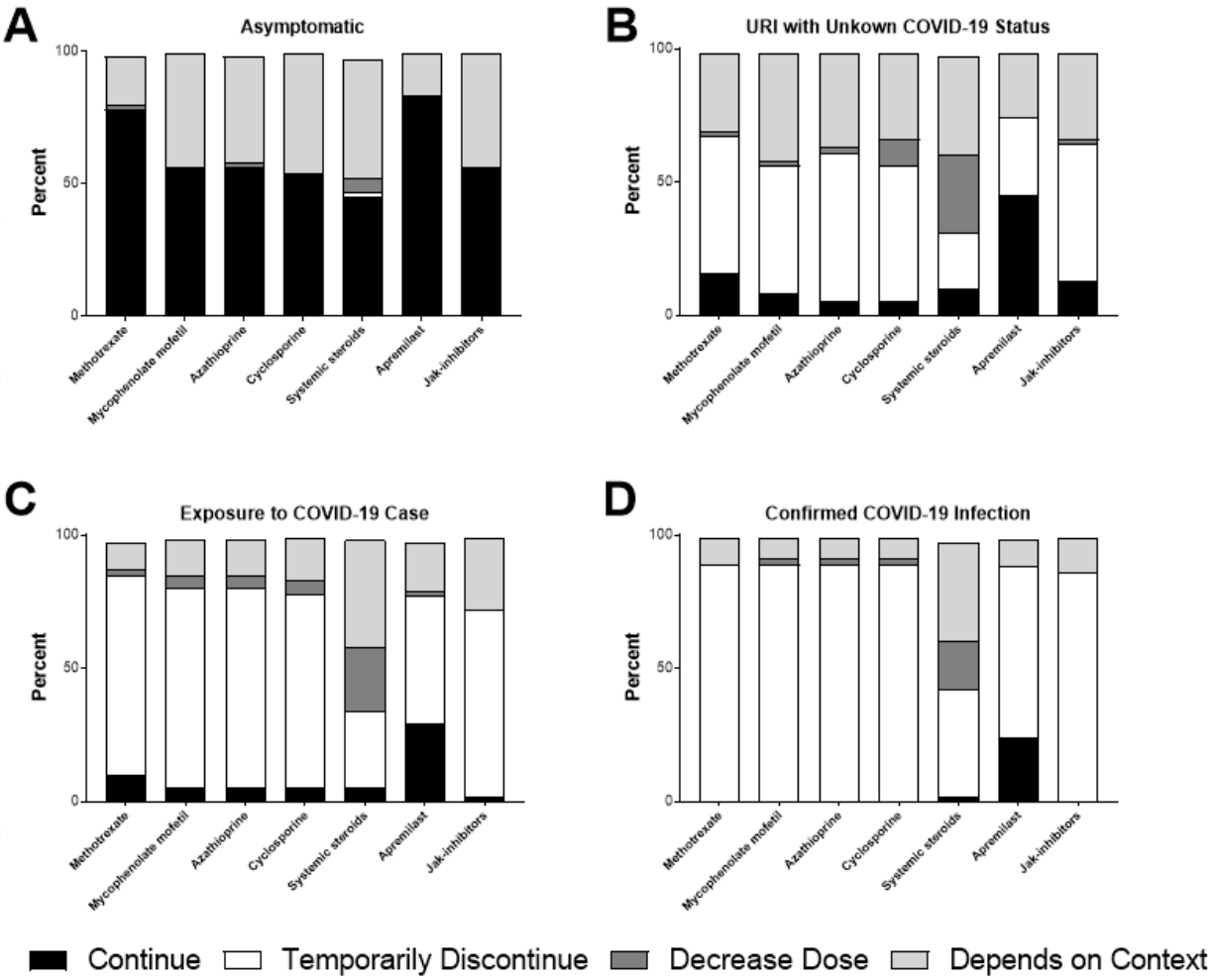

Figure 2. Expert panel responses for approach to individual systemic therapies by patient status. Only a single answer per drug and scenario was allowed.

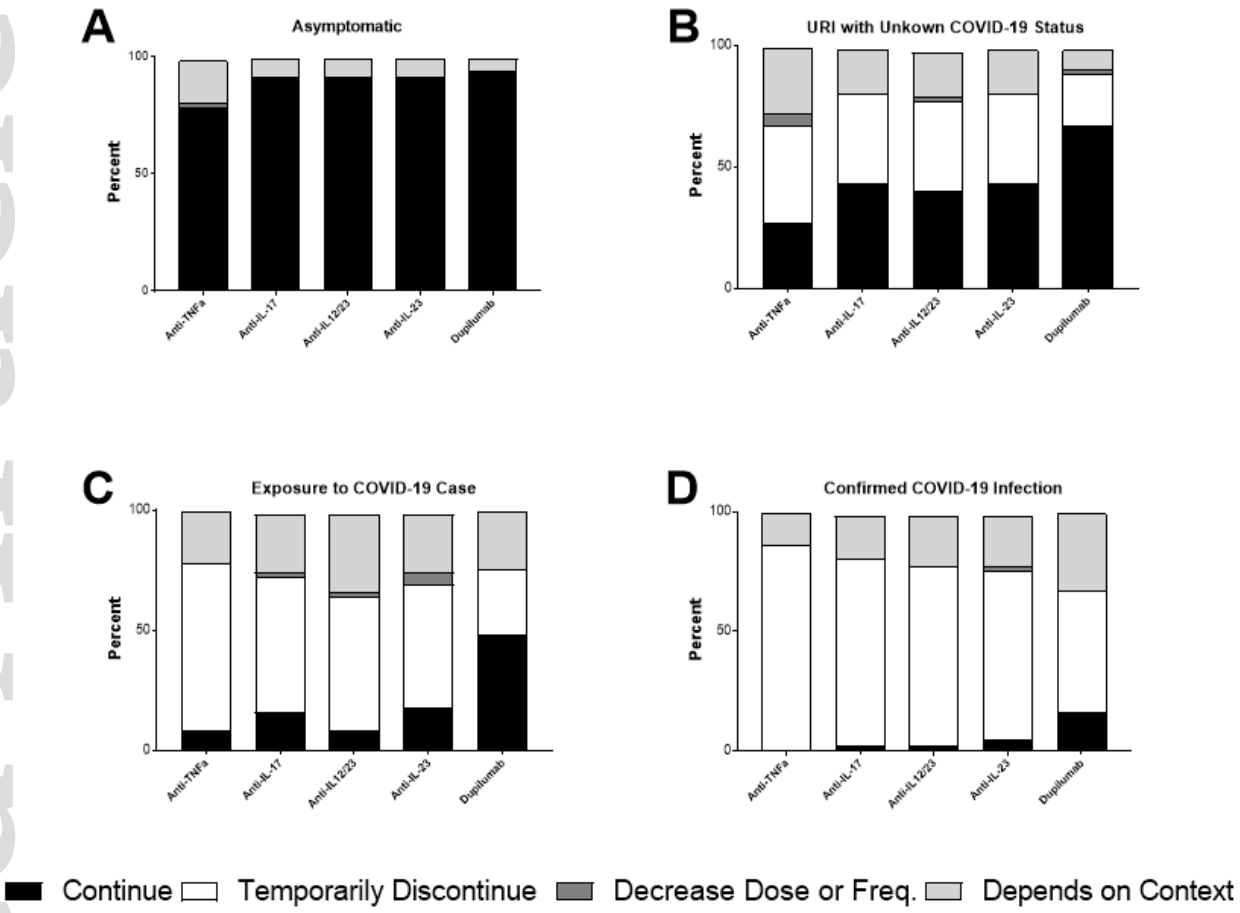

Figure 3. Expert panel responses for approach to individual biologic therapies by patient status. Only a single answer per drug and scenario was allowed.

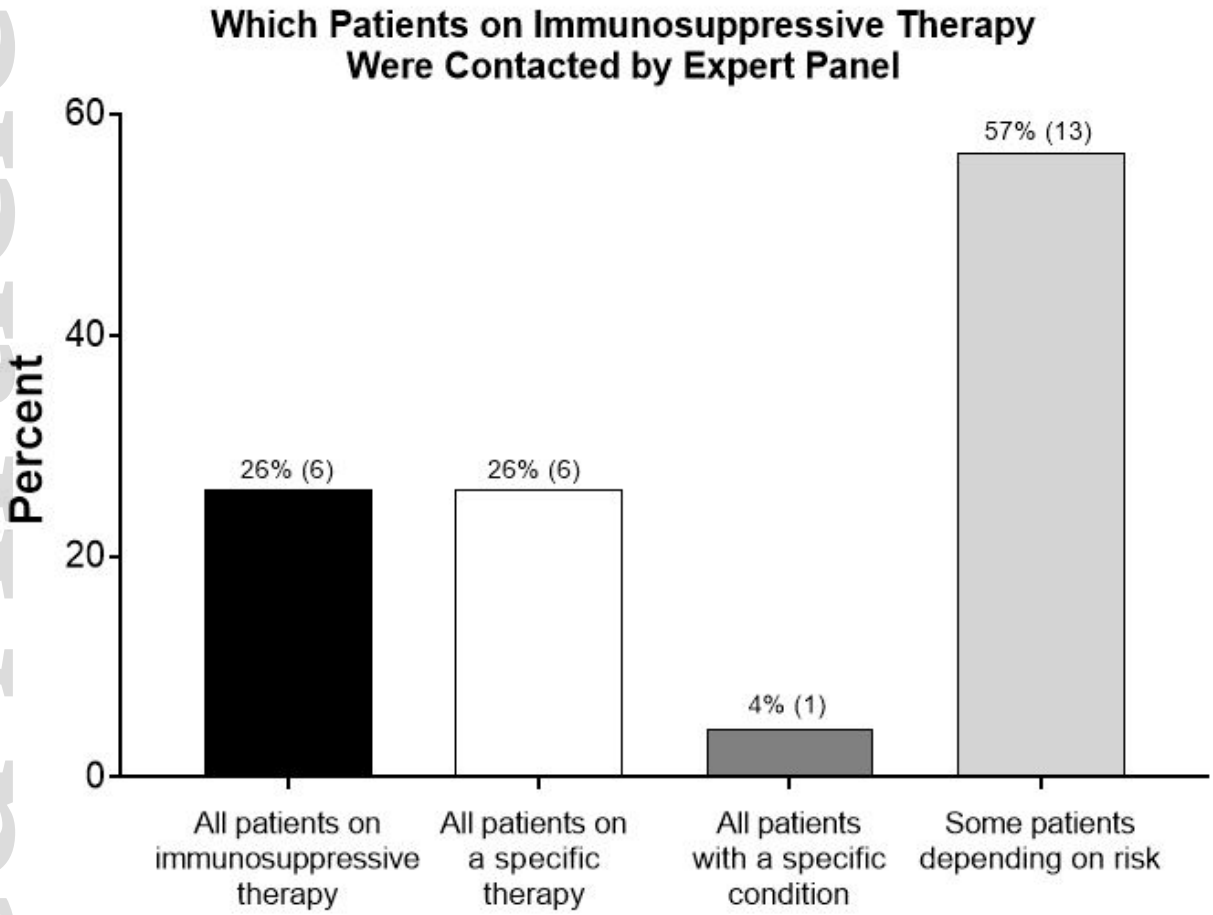

Figure 4. Percentage of the expert panel who proactively contacted patients on immunosuppressive therapy by the group they contacted. Multiple selections were allowed.

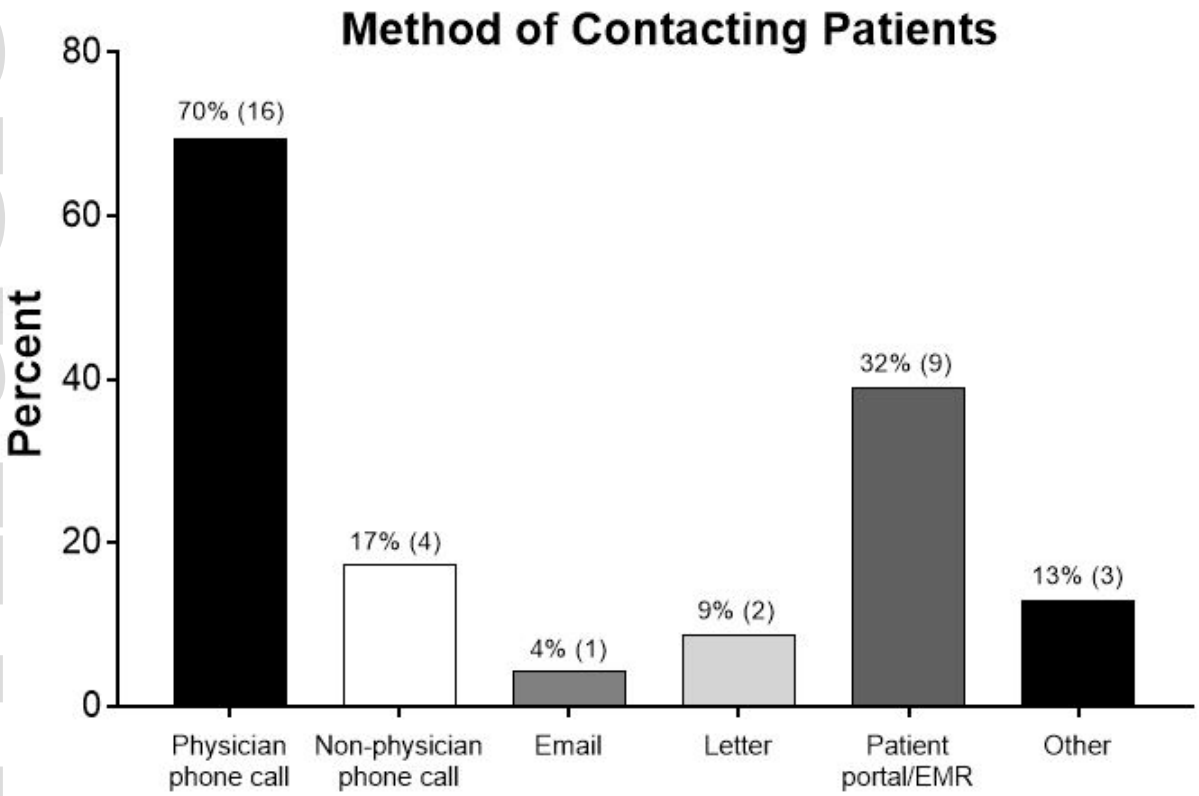

Figure 5. Percentage of the expert panel who proactively contact patients on immunosuppressive medications by method of contact. Multiple selections were allowed. “Other” methods included telehealth video-calls or bringing patients to an in-person visit.

		Patient Status			
Systemic Medications	**Response**	**Asymptomatic[1]**	**URI with unknown COVID-19 status[2]**	**Exposure to COVID-19 case[3]**	**Confirmed COVID-19 infection[4]**
Methotrexate	Continue	78%	16%	11%	0%
	Temporarily discontinue	0%	51%	76%	89%
	Decrease dose	3%	3%	3%	0%
	Depends on context	19%	30%	11%	11%
Mycophenolate mofetil	Continue	57%	8%	5%	0%
	Temporarily discontinue	0%	49%	76%	89%
	Decrease dose	0%	3%	5%	3%
	Depends on context	43%	41%	14%	8%
Azathioprine	Continue	57%	5%	5%	0%
	Temporarily discontinue	0%	57%	76%	89%
	Decrease dose	3%	3%	5%	3%
	Depends on context	41%	35%	14%	8%
Cyclosporine	Continue	54%	5%	5%	0%
	Temporarily discontinue	0%	51%	73%	89%
	Decrease dose	0%	11%	5%	3%
	Depends on context	46%	32%	16%	8%
Systemic steroids	Continue	46%	11%	5%	3%
	Temporarily discontinue	3%	22%	30%	41%
	Decrease dose	5%	30%	24%	19%
	Depends on context	46%	38%	41%	38%
Apremilast	Continue	83%	46%	30%	24%
	Temporarily discontinue	0%	30%	49%	65%
	Decrease dose	0%	0%	3%	0%
	Depends on context	16%	24%	19%	11%
Jak-inhibitors	Continue	57%	14%	3%	0%
	Temporarily discontinue	0%	51%	70%	87%
	Decrease dose	0%	3%	0%	0%
	Depends on context	43%	32%	27%	14%

Table 1. Expert panel responses for approach to individual systemic therapies by patient status. Only a single answer per drug and scenario was allowed

		Patient Status			
Biologic Medications	**Response**	**Asymptomatic[1]**	**URI with unknown COVID-19 status[2]**	**Exposure to COVID-19 case[3]**	**Confirmed COVID-19 infection[4]**
Anti-TNFα	Continue	78%	27%	8%	0%
	Temporarily discontinue	0%	41%	70%	87%
	Decrease dose or freq.	3%	5%	0%	0%
	Depends on context	19%	27%	22%	14%
Anti-IL-17	Continue	92%	43%	16%	3%
	Temporarily discontinue	0%	38%	57%	78%
	Decrease dose or freq.	0%	0%	3%	0%
	Depends on context	8%	19%	24%	19%
Anti-IL-12/23	Continue	92%	41%	8%	3%
	Temporarily discontinue	0%	38%	57%	76%
	Decrease dose or freq.	0%	3%	3%	0%
	Depends on context	8%	19%	32%	22%
Anti-IL-23	Continue	92%	43%	19%	5%
	Temporarily discontinue	0%	38%	51%	70%
	Decrease dose or freq.	0%	0%	5%	3%
	Depends on context	8%	19%	24%	22%
Dupilumab	Continue	95%	68%	49%	16%
	Temporarily discontinue	0%	22%	27%	51%
	Decrease dose or freq.	0%	3%	0%	0%
	Depends on context	5%	8%	24%	32%

Table 2. Expert panel responses for approach to individual biologic therapies by patient status. Only a single answer per drug and scenario was allowed

1. Patients who were asymptomatic (no signs or symptoms of COVID-19) and following recommended social distancing and hygiene practices
2. Patients who have symptoms of an upper respiratory tract infection (URI) with unknown COVID-19 status
3. Patients who have a household exposure to a confirmed COVID-19 case
4. Patients who have confirmed COVID-19 infection.