Systematic review of immunosuppressant guidelines in the COVID-19 pandemic

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Abstract

Aims: Individuals taking immunosuppressants are at increased susceptibility to viral infections in general. However, due to the novel nature of the COVID-19, there is a lack of evidence about the specific risks of the disease in this patient group. This systematic review aims to summarize the current international clinical guidelines to highlight areas where research is needed through critical appraisal of the evidence base of these guidelines.

Methods: We conducted a systematic review of clinical practice guidelines about the usage of immunosuppressants during the COVID-19 pandemic. Electronic databases including MEDLINE and the websites of relevant professional bodies were searched for English language guidelines that were published or updated between March 2020 and May 2020 in this area. We assessed the quality and consistency of guidelines. The evidence base underpinning these guidelines was critically appraised using GRADE criteria.

Results: Twenty-three guidelines were included. Most guidelines ($n = 15$, 65.2%) informed and updated evidence based on expert opinion. The methodological quality of the guidelines varied, ranging from 'very low' to 'moderate'. Guidelines consistently recommended that high-risk patients, including those who are taking high doses of steroids for more than a month, or a combination of two or more immunosuppressants, should be shielding during the outbreak. Most guidelines stated that steroids usage should not be stopped abruptly and advised on individualized risk–benefit analysis considering the risk of the effect of COVID-19 infection and the relapse of the autoimmune condition in patients.

Discussion: Clinical practice guidelines on taking immunosuppressants during the COVID-19 outbreak vary in quality. The level of evidence informing the available guidelines was generally low. Given the novel nature of COVID-19, the guidelines draw on existing knowledge and data, refer to the use of immunosuppressants and risks of serious infections of other aetiologies and have extrapolated these to form their evidence base.

Keywords: clinical guidelines, COVID-19, immunosuppression

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Introduction

The novel coronavirus SARS-CoV-2 has spread rapidly across the globe since its discovery in Wuhan, China in December 2019, and was declared a pandemic by the World Health Organization (WHO) in March 2020.[1] COVID-19 is highly transmissible between humans and in moderate to severe cases causes bilateral interstitial pneumonia with associated respiratory failure. High levels of transmission with significant impact relating to COVID-19 have forced governments worldwide to introduce social distancing or lockdown measures. Among those considered most at risk, who are being asked to take even stricter shielding measures, are patients taking immunosuppressant medications.[2,3]

Immunosuppressants, including corticosteroids, cytokine-targeted therapies, monoclonal antibodies and antimetabolites, are commonly prescribed

for a wide variety of chronic conditions such as inflammatory bowel disease (IBD) and rheumatological, neurological and dermatological conditions as well as for the prevention of solid organ rejection in transplant recipients. The prevalence of immunosuppressant use is difficult to ascertain; however, in the US it has been estimated at 2.7–6.2%.[4,5] The rationale behind shielding advice for patients taking immunosuppressant medications is their increased susceptibility to viral infections in general.[6]

However, due to the novel nature of COVID-19 there is a lack of available evidence about the specific risks of the disease in this patient group. Since the onset of the outbreak, governing bodies and professional societies have produced guidelines to support clinicians in the management of patients taking immunosuppressant medications – both for COVID-19-free patients in the community in the context of the pandemic and for patients with active COVID-19 disease. These guidelines and recommendations are mainly based on available evidence of viral illnesses in immunosuppressed patients, as sufficient evidence specific to COVID-19 is yet to emerge.

This article aims to systematically search the current guidelines available and summarize for clinicians in this area. We also highlight areas where further research is needed by critically appraising the literature cited in these guidelines.

Search strategy/methods

In light of urgent need for evidence synthesis, a focused review of published guidelines was carried out using internet search engines Google and Google Scholar, PubMed, and the websites of relevant national and professional societies, such as the National Institute of Clinical Excellence (NICE) and The British Society for Rheumatology. Search terms used included 'immunosuppressants' and its derivatives, 'guidelines', 'COVID-19' and 'coronavirus'. Guidelines published in English for use by clinicians or healthcare professionals were included, but guidance or recommendations written and published for patients and the general public were not included. Guidelines which included recommendations for the management of patients who were routinely taking immunosuppressant medications were selected. All publications returned were published or updated between March 2020 and May 2020. The relevant data were collected from the full published guidelines and entered into a summary table. Searches were carried out on 16 May 2020 and rerun on 23 May 2020 to search for any new guidelines. The PRISMA flowchart for guideline inclusion is shown in Figure 1.

Two reviewers (FBP and TWH) independently assessed the guidelines, and discrepancies were resolved by consulting with another reviewer (PKM).

Public and patient involvement was not specifically sought as this is the review of existing evidence around the use of immunosuppressant agents.

Critical appraisal of guidelines

The following Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Criteria (https://training.cochrane.org/grade-approach) were used to assess the level of evidence of individual guidelines. Level of evidence was classified as 1: 1a, Systematic reviews (with homogeneity) of randomized controlled trials; 1b, Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials; Level of evidence 2: 2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up); 2c, 'Outcomes' research; ecological studies; Level of evidence 3: 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; Level of evidence 4, Case series and poor-quality cohort and case-control studies; Level of evidence 5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.

We re-categorized the level of overall evidence included in these guidelines as very low (GRADE 5 evidence), low (GRADE evidence level 3a–4), moderate (GRADE evidence level 2a–2c) and high (GRADE evidence level 1a–1c). Where evidence indirectly related to COVID-19 has been generalized, it has been downgraded. For example, a cohort study on the susceptibility to viral infections (not specifically SARS-CoV-2) associated with immunosuppressant use has been

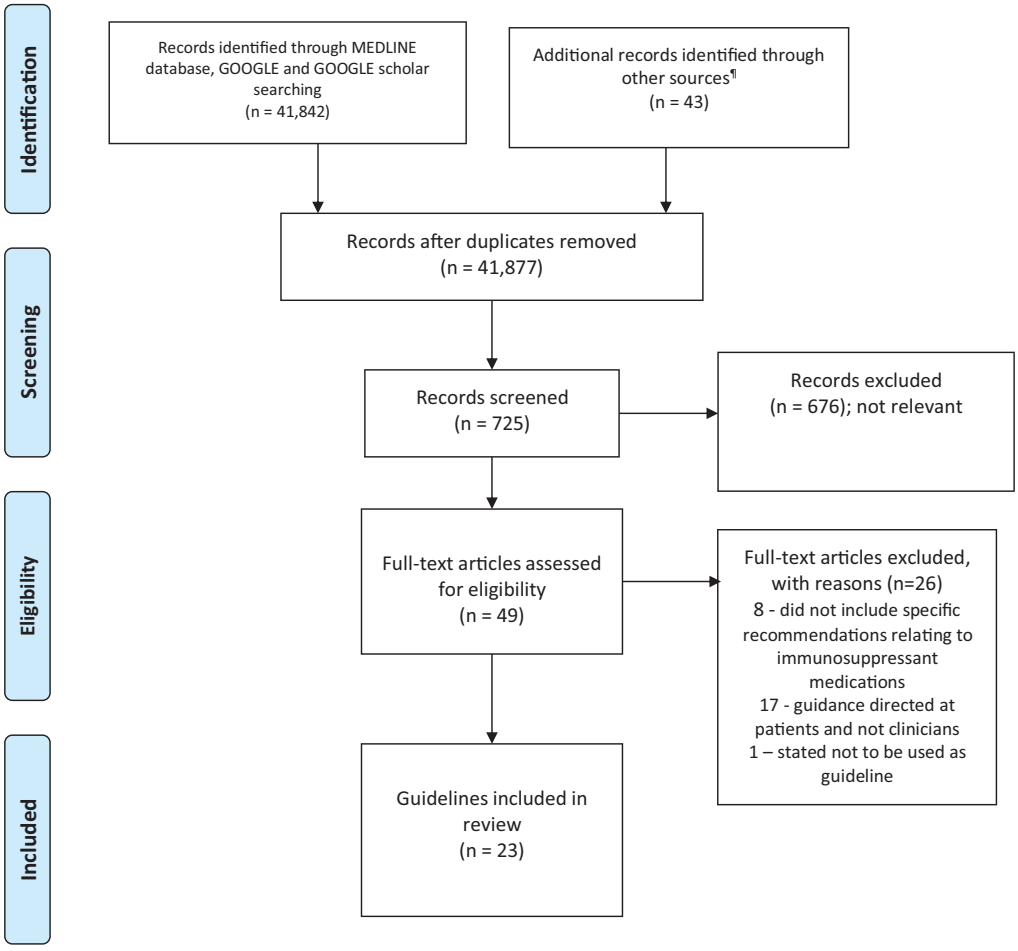

Figure 1. PRISMA 2009 flow diagram.
Royal College of Physicians website (https://www.rcplondon.ac.uk/), National Institute for Health Care & Excellence (NICE) (www.nice.org.uk), Association of British Neurologists (https://www.theabn.org/), British Society for Rheumatology (https://www.rheumatology.org.uk/).
From: Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6: e1000097. doi:10.1371/journal.pmed1000097.
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downgraded from moderate to low. Where evidence was not cited to support recommendations, we have downgraded as very low, as it is likely to be an expert opinion.

Results

Twenty-three guidelines developed for clinicians managing patients taking immunosuppressive medications during the coronavirus pandemic were identified, of which 15 were from the United Kingdom, four from the United States, two from Australia and two were international guidelines.

Summary of individual guidelines

UK

The UK guidelines for patients on immunosuppressants in COVID-19 are summarized in Table 1. The NICE has issued several guidelines relevant to patients taking immunosuppressant medicines during the COVID-19 pandemic. NICE guideline 169 *COVID-19 rapid guideline: dermatological conditions treated with drugs affecting the immune response*[7] recommends that in COVID-19-free patients, a risk–benefit analysis should be performed when considering continuing the treatment with immunosuppressant agents or starting

Table 1. Summary of UK guidelines for patients on immunosuppressants in COVID-19.

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
NICE guideline 167: COVID-19 rapid guideline: rheumatological, autoimmune, inflammatory and metabolic bone disorders[8]	April 2020	5	In patients known or suspected to have COVID-19: • continue hydroxychloroquine and sulfasalazine. • do not suddenly stop prednisolone. • only give corticosteroid injections if the patient has significant disease activity and there are no alternatives, and refer to NHS England's clinical guide on the management of patients with musculoskeletal and rheumatic conditions on corticosteroids. • temporarily stop other disease-modifying antirheumatic drugs, JAK inhibitors and biological therapies, and tell them to contact their rheumatology department for advice on when to restart treatment. The half-life of some drugs means that immunosuppression will continue for some time after stopping treatment. Corticosteroids: • Advise patients taking prednisolone that it should not be stopped suddenly. • Only use methylprednisolone for treating major organ flares. Think about using oral corticosteroids. Biological treatments: • Assess whether patients having intravenous treatment can be switched to the same treatment in subcutaneous form. If this is not possible, discuss with the patient an alternative subcutaneous treatment. • Assess whether maintenance treatment with rituximab can be reduced to one pulse or the duration between treatments increased. Drug monitoring: • Assess with each patient whether it is safe to increase the time interval between blood tests for drug monitoring, particularly if 3-monthly blood tests have been stable for more than 2 years. • Patients starting a new disease-modifying antirheumatic drug should follow recommended blood monitoring guidelines. When this is not possible, they should contact the relevant specialist for advice. • Think about pooling drug monitoring resources between local organizations.	Very low
NICE guideline 169: COVID-19 rapid guideline: dermatological conditions treated with drugs affecting the immune response[7]	April 2020	5	Patients not known to have COVID-19: When deciding whether to start or continue treatment with a drug that affects the immune system, discuss the risks and benefits with the patient, their parents or carer, and take into account the following in the context of COVID-19. • Is it essential to start this drug immediately? • Is it essential to continue this drug? • If treatment is needed, is there an alternative with a better risk profile? • Is the required monitoring and review feasible? • Can monitoring be done remotely or at a frequency that minimizes the risk to the patient's safety and wellbeing? • Are there any changes to the dose, route of administration or mode of delivery that could make hospital attendance or admission less likely? Assess whether it is safe to increase the time interval between blood tests for drug monitoring in patients who are stable on treatment. Take into account the patient's age and any comorbidities. Patients known or suspected to have COVID-19: • Be aware that patients taking drugs that affect the immune system may have atypical presentations of COVID-19. For example, patients taking prednisolone may not develop a fever. • continue topical treatments. • think about treating new-onset dermatological conditions with topical treatments rather than new systemic treatments that affect the immune system. • do not suddenly stop oral corticosteroids. • continue hydroxychloroquine, chloroquine, mepacrine, dapsone and sulfasalazine. • consider temporarily stopping all other oral immunosuppressive therapies, novel small-molecule immunosuppressants, biological therapies and monoclonal antibodies, and contact the dermatology department for advice on when to restart treatment. The half-life of some drugs means that immunosuppression will continue for some time after stopping treatment. When deciding whether to stop treatment, discuss the risks and benefits with the patient, or their parent or carer, and take into account: • whether COVID-19 is confirmed. • the severity of the COVID-19. • the risks and benefits of stopping or continuing treatment. • the severity of the dermatological condition. • the effect of stopping treatment on other conditions, for example the effect on asthma of stopping dupilumab other risk factors such as age and comorbidities, for example respiratory or cardiovascular conditions.	Very low

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
***NICE guideline 166*:** COVID-19 rapid guideline: severe asthma[9]	April 2020	5	Corticosteroids: • Tell patients, or their parent or carer, to continue using inhaled corticosteroids because stopping can increase the risk of asthma exacerbation. Tell them there is no evidence that inhaled corticosteroids increase the risk of getting COVID-19. • Tell patients on maintenance oral corticosteroids, or their parent or carer, to continue to take them at their prescribed dose because stopping them can be harmful. • Tell patients, or their parent or carer, that if they develop symptoms and signs of an asthma exacerbation, they should follow their personalized asthma action plan and start a course of oral corticosteroids if clinically indicated.	Very low
***NICE guideline 168*:** COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD)[10]	April 2020	5	Corticosteroids: • Explain to patients there is no evidence that treatment with inhaled corticosteroids (ICS) for COPD increases the risk associated with COVID-19. • Tell patients established on ICS to continue to use them, and delay any planned trials of withdrawal of ICS. While there is some evidence that use of ICS in COPD may increase the overall risk of pneumonia (see the 2014 MHRA drug safety update on inhaled corticosteroids: pneumonia), do not use this risk alone as a reason to change treatment in those established on ICS and risk destabilizing COPD management. • Tell patients on long-term oral corticosteroids that they should continue to take them at their prescribed dose, because stopping them can be harmful. Advise patients to carry a Steroid Treatment Card.	Very low
British Society of Gastroenterology: Guidance for management of inflammatory bowel disease during the COVID-19 pandemic[25]	April 2020	2a, 5 2b, 3b (indirect)	Corticosteroids: • Should be avoided if possible but will still be necessary for some who should then observe 'shielding' while prednisolone dose is ⩾20 mg daily. • High-dose steroids are an established risk factor for respiratory tract infection and opportunistic infection in IBD and septicaemia. • Rapid tapering (10 mg/week) should be considered where possible. This must be balanced against the risks of extending steroid exposure overall by decreasing dose too quickly. • Should not be stopped suddenly without advice. • Consider using budesonide MMX (9 mg/day 8 weeks) or beclometasone (5 mg/day 4 weeks) for patients with flaring UC (important to assess after 2 weeks) • Consider using exclusive enteral nutrition for patients with flaring CD. • Consider budesonide (Entocort, Budenofalk, 9 mg/day 8 weeks) for active small bowel and ileo-caecal CD. Immunomodulators (azathioprine, mercaptopurine, tioguanine, methotrexate, tacrolimus, mycophenolate mofetil): • No current evidence of increased risk of COVID-19 infection. • Initiation of monotherapy may not be appropriate. • Combination therapy with biologics should be made on careful discussion of risk and benefit on a case by case basis. • Older patients (>60 years) or those with significant comorbidity who are in sustained remission on thiopurines may wish to consider stopping after appropriate discussion with their IBD team. Anti-tumour necrosis factor therapy (adalimumab, infliximab, golimumab, certolizumab): • No current evidence of increased risk of COVID-19 infection. • Consider initiation with monotherapy (therefore consider adalimumab to promote home care and lower risk of immunogenicity relative to infliximab). • Use early therapeutic drug monitoring where possible, highlighting those appropriate for later combination immunosuppression where necessary. • Enforced intravenous to subcutaneous switching is not recommended. Anti-interleukin-12/23p40 therapy (ustekinumab). • No current evidence of increased risk of COVID-19 infection. • One advantage of ustekinumab is a one off intravenous induction dose followed by subcutaneous maintenance dosing (minimal impact on infusion suite). Anti-$\alpha 4\beta 7$ integrin therapy (vedolizumab). • No current evidence of increased risk of COVID-19 infection. • Unlikely to increase the risk of COVID-19 complications, although caution should be exercised in applying existing trial data to COVID-19.	Moderate

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
			Janus kinase inhibitors (tofacitinib): • No current evidence of increased risk of COVID-19 infection. 5-Aminosalicylic acid derivatives (mesalazine) • No current evidence of increased risk of COVID-19 infection. • In UC patients with uncontrolled symptoms, oral 5-aminosalicylic acid dose should be optimized with or without the addition of topical (rectal) 5-aminosalicylic acid. Shielding advice: Highest risk group who should be advised to shield includes: • IBD patients who either have a comorbidity (respiratory, cardiac, hypertension or diabetes mellitus) and/or are ⩾70 years old and are on any 'moderate risk' therapy for IBD and/or have moderate to severely active disease. • IBD patients of any age regardless of comorbidity and who meet one or more of the following criteria: – Intravenous or oral steroids ⩾20 mg prednisolone or equivalent per day (only while on this dose) – Commencement of biologic plus immunomodulator or systemic steroids within previous 6 weeks – Moderate to severely active disease not controlled by 'moderate risk' treatments – Short gut syndrome requiring nutritional support. Moderate risk group, stringent social distancing advised: • Patients on the following medications: Anti-TNF (infliximab, adalimumab, golimumab, certolizumab) monotherapy, biologic plus immunomodulator in stable patients, Ustekinumab, Vedolizumab, Thiopurines (azathioprine, mercaptopurine, tioguanine), Methotrexate, Calcineurin inhibitors (tacrolimus or ciclosporin), Janus kinase (JAK) inhibitors (tofacitinib), Immunosuppressive trial medication, Mycophenolate mofetil, Thalidomide, Prednisolone <20 mg/day. Low-risk group, social distancing advised: • Patients on the following medications: 5-ASA, rectal therapies, orally administered topically acting steroids (budesonide or beclometasone).	
Association of British Neurologists: Guidance on COVID-19 for people with neurological conditions, their doctors and carers[22]	2020	5	General advice related to immunosuppression in neurology patients in individuals without symptoms of COVID-19 infection: • People with neurological conditions should not stop or alter their medication without prior discussion with their neurology team. • Individuals taking azathioprine, mycophenolate mofetil, methotrexate with or without prednisolone should continue to take their tablets as normal. Evidence is limited, but these medications may increase the risk of COVID-19 infection and its complications. However, in almost all cases this risk is outweighed by the benefits of the medication in reducing the chance of a relapse of the neurological condition. • For those taking an immunosuppressive drug (azathioprine, mycophenolate mofetil or methotrexate) combined with prednisolone, there is an increased risk. The level of risk is uncertain; however, any of these drugs combined with a daily prednisolone dose of 10 mg or above is considered high risk, and self-isolation is recommended. Combining prednisone up to 9 mg with an immunosuppressive agent increases the risk to medium. Steroids increase risk of diabetes, hypertension and high BMI, which are associated with poor outcomes after COVID-19. Infliximab/Rituximab/Ocrelizumab: • These infusions moderately increase the risk of viral infections, so individuals may be more prone to COVID-19 and its complications. In many patients this risk is outweighed by the benefits of rituximab in suppressing otherwise progressive or severe neurological disease, and the treatment should continue as normal. In all cases the consultant should review the timing of retreatment and delay treatment if possible or consider alternative options. Some immunomodulatory drugs (for example tocilizumab) are in trial to treat the complications of COVID-19 infection. This fact alone does not mean their use as disease-modifying therapies is safe. Each case will need to be considered individually with specialist medical oversight. Some immunotherapies require frequent attendance at hospitals, for instance monthly infusions of natalizumab for multiple sclerosis. As this would be incompatible with social distancing, the administration of such therapies may not be feasible at the height of the epidemic. Individual neurology departments will advise on local arrangements for service delivery.	Very low

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
British Transplant Society: Guidance on the management of transplant recipients diagnosed with or suspected of having COVID-19[11]	March 2020	2b, 4, 5 2a (not COVID-19 specific)	Patients with COVID-19 not requiring hospital admission: • Each patient should be considered individually regarding the risk of immunosuppression dose reduction. • Stop antiproliferative agents (MMF/azathioprine). • Review total burden of immunosuppression and consider reduction of CNI. • High or increased dose steroid is NOT recommended at this stage. • Consider restarting immunosuppression 14 days after onset of symptoms if symptom free in absence of anti-pyretics for minimum of 3 days. • Consider early monitoring of graft function when safe to do so and risk of transmission to others is low. Unwell patients with COVID-19 who are admitted to hospital: • Stop antiproliferative agents (MMF/azathioprine). • Consider reducing or stopping CNI. • Consider increasing steroids if currently taking them. • There is no evidence for benefit of high-dose steroids at this stage. • Oxygen therapy to achieve saturations over 94% (unless COPD). • Regular observations, especially saturations, to monitor for rapid deterioration. • Conservative fluid administration. • Consider adjunctive antibiotics if superadded bacterial infection is suspected. • Early discussion of ceilings of care. Patients who are progressively unwell and require ventilatory support: • Stop antiproliferative agents (MMF/azathioprine). • Dramatically reduce or stop CNI. • Consider high-dose steroids in discussion with ITU team. • Ventilatory support in line with local or national guidance. • Adjunctive support or antivirals in line with local practice or clinical trials.	Moderate
Association of British Neurologists: ABN guidance on the use of disease-modifying therapies in multiple sclerosis in response to the threat of a coronavirus epidemic[23]	April 2020	5	It is safe to start or continue interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide and dimethyl fumarate. They probably all confer a very slight increase risk in viral infections, but usually far less than posed by a return of disease activity. While some argue that the risk of viral infections can be predicted by total lymphocyte count, the literature is not clear, so we do not recommend any change to the current monitoring guidelines for these drugs. We currently view natalizumab as safe to use, and the safest high-efficacy therapy, because COVID-19 is not a neurotropic virus. The risk of acquiring coronavirus infection is probably moderately increased on fingolimod. For those already taking it, the risk of rebound disease probably outweighs the risk of infection. For those with disease breakthrough on first-line therapies, fingolimod has the advantage over ocrelizumab of being able to be stopped in the event of a coronavirus infection. The risk of acquiring coronavirus infection is probably moderately increased after ocrelizumab. If a patient needs a high-efficacy drug, and they are not eligible for natalizumab, it is an option to consider. But it will leave a patient with persistently higher risk of infection throughout the anticipated period of the COVID-19 epidemic. For those already on ocrelizumab, we recommend delaying further infusions until the risk of coronavirus infection is clarified or has passed. The risk of viral infections is significantly higher in the three to six months after alemtuzumab and cladribine. We recommend these drugs are not started during the coronavirus epidemic; natalizumab and ocrelizumab are safer options for active disease. For those who have already started treatment, we recommend delaying the second round of both treatments until the risk of coronavirus infection has passed. For patients with active COVID-19 infection: It is not necessary for people with mild symptoms of COVID-19 to stop their DMT. In cases of MS with severe COVID-19 infection (for instance requiring admission) we recommend pausing all injectables and oral medication, and delaying infusions.	Very Low

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
British Society for Rheumatology: COVID-19 – Identifying patients for shielding in England[12]	March 2020	5 1b, 2a, 2b (indirect)	Patients to shield: • Corticosteroid dose of ⩾20 mg (0.5 mg/kg) prednisolone (or equivalent) per day for more than four weeks. • Cyclophosphamide at any dose orally or within last six months IV. • Corticosteroid dose of ⩾5 mg prednisolone (or equivalent) per day for more than 4 weeks plus at least one other immunosuppressive medication, biologic/monoclonal or small molecule immunosuppressant (e.g. JAK inhibitors). • Any two agents among immunosuppressive medications, biologics/monoclonals or small molecule immunosuppressants with any co-morbidity. Patients to self-isolate: • Well-controlled patients with minimal disease activity and no co-morbidities on single agent broad spectrum immunosuppressive medication, biologic/monoclonal** or small molecule immunosuppressant. • Well-controlled patients with minimal disease activity and no co-morbidities on single agent broad spectrum immunosuppressive medication plus Sulphasalazine and/or hydroxychloroquine. • Well-controlled patients with minimal disease activity and no co-morbidities on a single-agent broad-spectrum immunosuppressive medication at standard dose (e.g. Methotrexate up to 25 mg per week) ***plus*** single biologic (e.g. anti-TNF or JAKi). Patients to social distance: • Single-agent 5-ASA medications (e.g. mesalazine). • Single-agent 6-mercaptopurine. • Only inhaled or rectally administered immunosuppressant medication. • Hydroxychloroquine. • Sulphasalazine. We do NOT advise that patients increase steroid dose if they become unwell.	Moderate
British Society for Rheumatology: Covid-19 Guidance for Rheumatologists[14]	May 2020	5	Patients on long-term glucocorticoids (steroids, prednisolone) should not stop these abruptly. Starting or escalating treatment during COVID-19: • A discussion on treatment decisions should take place, including consideration that deferring starting treatment (biologics or DMARDs). • Co-morbidities significantly increase the risk of serious infection with COVID-19, and any decision to start treatment in patients >70 years, or for those with pre-existing diabetes mellitus, lung disease, IHD or hypertension must be considered carefully. • For patients starting DMARDS, consider using those with a shorter half-life. If appropriate, opt for sulfasalazine and/or hydroxychloroquine rather than methotrexate or leflunomide. • For patients starting biologic or small molecule or switching biologic drugs, please discuss carefully with them; the risk of infection is highest in the first 4–6 months after starting treatment. • If there is significant disease activity and the patient understands the risk, then it is acceptable to move forward with these drugs. Otherwise, we recommend considering postponing starting treatment for 2–3 months. • We advise considering the use of drugs with the shortest half-life (e.g. Etanercept, JAKi).	Very low
British Association of Dermatologists: Dermatology Advice Regarding Medication Acting on the Immune System: Adults, Paediatrics and Young People[15]	April 2020	5	High risk – to be advised to shield: • Any two agents within the following classes: immunosuppressive medications (e.g. ciclosporin, azathioprine as below),1 biologics/monoclonals (e.g. anti-TNFs, IL17 agents as below) or novel small-molecule immunosuppressants (e.g. apremilast). • Corticosteroid dose of ⩾20 mg (or 0.5 mg/kg) prednisolone (or equivalent) per day for more than 4 weeks. • Corticosteroid dose of ⩾5 mg prednisolone (or equivalent) per day for more than 4 weeks plus at least one other immunosuppressive medication, 1 biologic/monoclonal2 or novel small-molecule immunosuppressants (e.g. JAK inhibitors). • Cyclophosphamide at any dose orally or if received IV dose within last 6 months. • Rituximab or infliximab when prescribed primarily for skin conditions (e.g. psoriasis or pemphigus). Advised to shield (moderate risk) only if other concerns or high-risk circumstances/co-morbidities5 (individual decision by clinician): • Well-controlled patients with minimal disease activity and no co-morbidities on single agent, standard oral immunosuppressants, biologic/monoclonal2 or novel small-molecule immunosuppressants. • Well-controlled patients with minimal disease activity and no co-morbidities5 on a single biologic (e.g. anti-TNF, IL17 agent) plus methotrexate at a standard dose. • Well-controlled patients with minimal disease activity and no co-morbidities5 on single-agent standard oral immunosuppressant1 plus hydroxychloroquine or sulfasalazine.	

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
			Social distancing only: • Medications on the following list alone or in combination: • Topical skin treatments (creams, gels etc). • Hydroxychloroquine. • Chloroquine. • 5-ASA medications (e.g. mesalazine). • Sulphasalazine. • Only inhaled or rectally administered immunosuppressant medication, for example, steroid inhalers. • Omalizumab. • Acitretin, alitretinoin and isotretinoin.	Very low
The Renal Association: Stratified Risk for Prolonged Self Isolation for Adults and Children who are Receiving Immunosuppression for Disease of Their Native Kidneys[16]	March 2020	5	Group 1 (highest risk with one of the following should all be advised to self-isolate for at least 12 weeks): • Those currently receiving intravenous induction immunosuppressive medication for autoimmune disease, for example, receiving CYCLOPS/Euro lupus regimens or have received cytotoxics/rituximab/other biologic within the last 6 months. • Those who are currently receiving cyclophosphamide orally. • Those who have received a corticosteroid dose of > or = to prednisolone 20 mg/day or 35 mg/m^2/day for more than 4 weeks within the last 6 months. • Those who have received >5 mg/day, or >0.25 mg/kg/day, prednisolone (or equivalent) for >4 weeks plus at least one other immunosuppressive medication within the last 6 months. • Those who have current nephrotic range proteinuria or who have a history of frequently relapsing nephrotic syndrome. • Those whose overall cumulative burden of immunosuppression (IS) is high over a number of years even if their current IS is in stable maintenance phase, for example, patients who have received repeated courses of cyclophosphamide/biologics/or repeated high-dose corticosteroids. • Those who are currently on stable (possibly modest) maintenance IS but whose additional factors make them vulnerable to a severe course in COVID-19, for example, a. those over 70 years of age, those whose AI disease has affected their CVS/Respiratory systems such as lung fibrosis, those with any non-autoimmune underlying co-morbidity of respiratory/cardiovascular system, hypertension or diabetes mellitus, and those with CKD stage 3 or above. • Those who have previously manifested adverse infectious complications of immunosuppression, for example, those with recurrent CMV or chest infections. Group 2 (intermediate risk: if one of the following risk factors exist: these patients are not currently advised to self-isolate but may be moved in to Group 1 at a later stage, as understanding develops): • Those with well-controlled disease activity and no co-morbidity who are on a single oral immunosuppressive drug. • Those known to have low IgG levels even if not currently on immunosuppression. • Those who despite completing biologic induction treatment more than 6 months previously remain B-cell depleted. • Patients who despite achieving disease remission remain on maintenance low-dose prednisolone. Group 3 (may not require self-isolation in the first instance but should follow all hygiene measures and social distancing as per standard government guidelines): • Patients less than 60 years who are generally well and whose disease has been stable for >6 months who are on Hydroxychloroquine alone.	Very Low
The Renal Association: Guidance for clinicians with patients receiving immunosuppression treatment for autoimmune conditions of their native kidneys during COVID-19[17]	April 2020	5 1b, 2b, 3a (indirect)	Some kidney patients, particularly those on steroids, intravenous cyclophosphamide and biologics, will be significantly immunosuppressed and should therefore be considered 'high risk'. This is particularly true in the induction phase of their treatment. All patients should be triaged on arrival before any infusion to exclude symptoms of active COVID-19 infection and to check for raised temperature. Patients should plan to complete standard induction medication unless directed otherwise by their renal team. When considering which induction regimens to use, whilst there may be theoretical risks in the long term about vaccination responses after rituximab, there is evidence that cyclophosphamide is a more potent immunosuppressant and requires more hospital attendances for intravenous dosing, so is potentially more likely to be associated with increased risk of infections. Patients should stay on their maintenance immunosuppression and steroids provided infection free. Immunosupressive therapy needs to be reviewed on a case-by-case basis balancing the risk of inadequately treated disease, or acute relapse, against the risk of the effect of COVID-19 infection in the individual patient. Patients on long-term glucocorticoids (steroids, prednisolone) SHOULD NOT stop these abruptly. Patients receiving hydroxychloroquine SHOULD CONTINUE this as it may afford some protection against COVID-19 (as yet unproven in clinical trials).	Moderate

(Continued)

Table 1. (Continued)

Guideline	Date	Graded level of evidence	Recommendation	Quality of evidence (based on GRADE principles)
			If units are unable to deliver intravenous induction medication due to staff shortages or patients being unable to attend hospital: • In vasculitis: If at all possible to maintain hospital visits (and recognizing the risks during COVID-19) and given the risks of uncontrolled disease, the ongoing use of IV cyclophosphamide-based induction regimens may be preferable to oral ones but rituximab affords fewer hospital visits and less monitoring. • If intravenous infusions are not available, it may be necessary to use only oral induction – ideally these would be monitored by clinicians familiar with their use. Oral cyclophosphamide is an alternative to IV cyclophosphamide (but is associated with higher infective complications). Oral mycophenolate mofetil can be considered but the evidence supports use only in patients deemed low risk of relapse with GFR >15 ml/min and without rapidly deteriorating renal function, and requires concomitant steroid dosing, though high-dose steroids should be avoided if possible in COVID-19. • In lupus: oral mycophenolate mofetil can be used as a well-established alternative to IV cyclophosphamide in induction therapy. • If possible to administer rituximab, it may be worth considering the Rituxilup protocol which is steroid sparing. • In general, in order to reduce infection risk, clinicians are recommended to reduce steroids promptly in line with protocols found in the PEXIVAS trial and the Aura-LV Trial. MAINTENANCE PHASE OF IMMUNOSUPPRESSION TREATMENT: • If well, all patients should continue to take their maintenance medication unless directed otherwise by their renal team. • In individual cases where there has been prolonged disease quiescence and the risk of severe COVID-19 infection is felt to be high for a given patient, clinicians may consider modifying maintenance immunosuppression regimens on a case-by-case basis. • In the case of long-acting rituximab maintenance regimens, delaying intervals between rituximab infusions could be considered for patients where the risk of disease flare is deemed low and the risk of 3 adverse outcomes with COVID-19 infection is high. • There is currently no evidence on the impact of rituximab on the severity of COVID-19 infection. Clinical Guidance for Managing Patients with or Suspected of having Covid-19: • There is emerging evidence in the transplant population that some patients on immunosuppressive therapy for solid organ transplants have a worse prognosis. • Therefore, in some cases based on the risk of COVID-19 and the current state of their underlying autoimmune disease, the renal unit may recommend that immunosuppressive therapy be paused, or significantly reduced, for the duration of the infection (14 days after onset of symptoms if symptom free in the absence of anti-pyretics for a minimum of 3 days). • For those on maintenance glucocorticoids (steroids, prednisolone), treatment should not be stopped abruptly and advice should be sought from their treating team. • High-dose steroids may be associated with prolonged viral shedding and possible poor outcome. There is no evidence to support their therapeutic use in COVID-19 and they should be not be initiated unless for other therapeutic indications.	
NHS England: Clinical guide for the management of Rheumatology patients during the coronavirus pandemic[29]	April 2020	5	Regarding risk: • All of the (immunosuppressants) listed would put an individual at an increased risk. • The presence of additional risk factors would put them at a high risk or very high risk. These risk factors include: high doses; use of multiple immunosuppressants; active disease; presence of other co-morbidities, such as interstitial lung disease/pulmonary fibrosis, pulmonary hypertension/pulmonary arterial hypertension, glomerulonephritis/renal impairment (any cause), neutropaenia, liver disease, diabetes mellitus, ischaemic heart disease, other underlying lung disease (such as asthma, chronic obstructive pulmonary disease [COPD]), pregnancy and older age. • Some patients with very active disease, for example, newly diagnosed and on IV cyclophosphamide, may be at very high risk. Patients must not suddenly stop prednisolone. Patients can continue hydroxychloroquine and sulfasalazine if they are infected with coronavirus. If a patient is infected with coronavirus, they should temporarily stop their conventional DMARD and biological therapy.	Very low
Health Protection Scotland: Search criteria for highest risk patients for shielding.[28]	May 2020	5	Highest risk groups include: • Corticosteroids ⩾20 mg/day for >4 weeks • Those identified by a clinician as requiring shielding or on a single agent: cyclophosphamide, rituximab, infliximab, cladribine, alemtuzumab, or others identified by specialties • Corticosteroids ⩾5 mg/day for >4 weeks AND one other immunosuppressive medication, DMARD or biologic • Two immunosuppressants (DMARD/biologic) and a co-morbidity.	Very low

Level of evidence 1: 1a, Systematic reviews (with homogeneity) of randomized controlled trials; 1b, Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials; 2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up); 2c, 'Outcomes' research; ecological studies; 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; 4, Case series and poor-quality cohort and case-control studies; 5, Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[44,45]

a drug which affects the immune system. For immunosuppressive therapies that require monitoring, it advises on ways to reduce hospital visits – either by reducing the frequency of monitoring or by choosing or switching to a drug which does not require monitoring. For patients with known/suspected COVID-19, it recommends that corticosteroids should not be stopped abruptly. Hydroxychloroquine, chloroquine, sulfasalazine, mepacrine and dapsone can be continued, whilst consideration should be given to stopping all other immunosuppressive agents including novel small-molecule immunosuppressants, biological therapies and monoclonal antibodies.

NICE guideline 167 'COVID-19 rapid guideline: rheumatological, autoimmune, inflammatory and metabolic bone disorders'[8] provides similar guidance for these patient groups. It additionally emphasized that clinicians should be aware of atypical presentations of COVID-19 (e.g. lack of fever with corticosteroids or interleukin-6 inhibitors), and consider possible medication changes such as dosage, route and frequency of administration for those patients with confirmed COVID-19 disease. Steroids, hydroxychloroquine and sulfasalazine should be continued but other disease-modifying anti-rheumatic drugs, JAK inhibitors and biological therapies should be stopped temporarily.

NICE guidelines 166 and ***168*** 'COVID-19 rapid guideline: severe asthma'[9] and 'COVID-19 rapid guideline: community-based care of patients with chronic obstructive pulmonary disease (COPD)'[10] gives the same advice on oral corticosteroids – those patients taking oral maintenance steroids should not stop them abruptly. NICE states that its guidelines are produced from existing guidelines and advice from specialists.

Many professional societies in the UK, including the British Society of Gastroenterologists, Association of British Neurologists, British Transplant Society and British Society of Rheumatologists have produced guidelines relevant to their patient groups. Guidance from **The British Transplant Society** (BTS), entitled 'Guidance on the management of transplant recipients diagnosed with or suspected of having COVID19',[11] divides recommendations depending on the severity of the COVID-19 disease. It recommends that all patients with COVID-19 should have their anti-proliferative medications including mycophenolate mofetil and azathioprine withheld, regardless of disease severity. For patients with mild COVID-19 symptoms, who do not require hospital admission, it recommends reviewing the total burden of immunosuppression and considering reducing the dose of calcineurin inhibitors (CNIs) and recommends *against* the use of high or increased dose of steroids. However, this guideline does not specify whether maintenance doses of steroids should be continued. For patients requiring hospital admission, it recommends early consideration of suitability for and escalation to critical care, considering increasing the dose of steroids and stopping or reducing the dose of CNI. For the sickest patients, requiring ICU admission, it recommends reducing CNI dose dramatically or stopping it and considering high doses of steroids. BTS guidance advises that if medicines are withheld or reduced, this should be continued for 2 weeks from the onset of symptoms and can be resumed provided that the patient has been apyrexial for 3 days. BTS used a combination of laboratory-based research and cohort studies on coronaviruses to produce its recommendations.

The **British Society for Rheumatology** (BSR) have produced a risk-stratification tool[12] to identify patients who should be advised to shield. It advises that high-risk patients who should be advised to shield include those who are taking >20 mg/day prednisolone (or equivalent steroid) for at least 4 weeks, cyclophosphamide (any dose), >5 mg/day prednisolone (or equivalent steroid) in combination with $\geqslant 1$ other immunosuppressant medication or a combination of any two immunosuppressants, and patients who also have an additional risk factor that would put them at increased risk (e.g. age >70, diabetes, hypertension, ischemic heart disease, lung disease and renal impairment patients). The risk stratification table is only designed to determine which patients should be advised to take additional shielding measures and does not offer guidance on changing or stopping medications in the context of the pandemic. It is based on evidence comprising case reports of COVID-19 from China and a systematic literature review of research relating to general infection risk in patients taking immunosuppressant medications, which comprises randomized controlled trials (RCTs), observational and cohort studies.[13] BSR guidelines advise

against increasing steroid doses during an acute illness. In guidance published on their website,[14] with regards to starting or escalating disease, the BSR recommends selecting a drug with a shorter half-life such as etanercept or one a with lower risk of susceptibility to infection such as sulfasalazine or hydroxychloroquine where possible. They recommend careful consideration of risk when starting biologics or small molecules, and discussing the risk and benefit of treatment in detail with each individual patient, with consideration given to delaying starting a new treatment for 2–3 months. Evidence used to inform these recommendations is not provided, therefore it is assumed to be expert opinion.

This guideline has updated advice on shielding in October 2020; according to this update shielding has been paused in the UK; however, shielding may continue or be reinstated depending on local restrictions or lockdowns depending on the area.

The **British Association of Dermatologists** (BAD) have produced a similar risk stratification table[15] to aid clinicians in deciding which patients should be advised to shield, self-isolate or follow social distancing guidelines as per the general population. The guidance for high-risk patients, who should be advised to shield, does not differ significantly from that given by BSR. High-risk patients are those taking a combination of two immunosuppressant medications, taking $\geqslant$20 mg/day prednisolone or equivalent corticosteroid for $>$4 weeks, those on $\geqslant$5 mg/day prednisolone for $>$4 weeks in combination with another immunosuppressant medication and any patient taking cyclophosphamide, rituximab or infliximab. BAD have not included advice about withholding, starting or switching between medications in their guidance. The evidence base used to inform this guidance has not been stated by BAD.

The **Renal Association** (RA) has published two documents: a risk stratification guide,[16] similar to those described above, specific to patients taking immunosuppressive therapies for autoimmune disease of their native kidneys, and general guidance for clinicians caring for such patients.[17] The criteria for patients who fall into the highest risk category, who should be advised to shield, is broadly similar to BSR and BAD guidelines. Patients who are taking $\geqslant$20 mg/day prednisolone for $>$4 weeks or taking $\geqslant$5 mg/day prednisolone for $>$4 weeks in combination with another immunosuppressant, and anyone taking cytotoxic agents, cyclophosphamide, rituximab or other biologic are considered as high risk according to the RA guideline. In addition, this guideline has cited patients whose long-term burden of immunosuppression is high, that is, those who have had repeated courses of biologics, cyclophosphamide or high-dose steroids over 'a number of years', and those who are taking immunosuppressive agents with modest dose and have a co-morbidity or risk factor of age $>$70, lung fibrosis, hypertension, diabetes and patients with a history of morbidity relating to their immunosuppression (e.g. recurrent CMV or chest infections). Evidence used to inform the risk stratification tool is not cited by the RA.

General guidance for clinicians treating patients with systemic lupus erythematosus (SLE) or vasculitis is divided into the induction and maintenance phases of treatment. Regarding the induction phase, the RA guideline does not advise swabbing asymptomatic patients for COVID-19 prior to starting treatment but does state that patients should be triaged for symptoms and have their temperature checked. It advises that patients should complete the full induction regime, but when choosing an induction regime, the increased level of immunosuppression combined with additional hospital visits associated with cyclophosphamide should be considered as posing a potential increased risk to patients. Despite this, for vasculitis they recommend using IV rather than oral cyclophosphamide as it is associated with lower infective complication rates. Where IV inductions are not available, oral mycophenolate mofetil (MMF) is recommended due to lower risk for patients with an eGFR $>$15, instead of cyclophosphamide, and this is supported by a single non-inferiority trial.[18] Similarly, the guidance supports the use of MMF for induction regimes for lupus, informed by a systematic review of the literature.[19] If a rituximab regime is used it advises using one which is steroid sparing, a recommendation supported by a single prospective, single-centre, observational cohort trial.[20] In using steroids, it recommends reducing the dose as soon as possible to reduce risk of infection.

With regards to maintenance therapy, the guideline states that steroids should not be stopped abruptly and that patients who are infection free

should continue their usual steroids, immunosuppressants and hydroxychloroquine. Clinicians are advised to consider reducing the frequency of rituximab infusions in patients whose risk of disease flare is low and risk relating to COVID-19 is high. The RA cite a single RCT, the MAINRITSAN2 trial,[21] to support the use of lower doses of rituximab regimes, though it acknowledges that there is currently no evidence that rituximab increases risk of COVID-19. In the event of COVID-19 infection the RA guideline advises individualized risk–benefit analysis 'balancing the risk of inadequately treated disease, or acute relapse, against the risk of the effect of COVID-19 infection in the individual patient'.[17] Similarly, steroids should not be stopped abruptly, but the guideline also advises against the uses of high-dose steroids. Whilst the guideline cites several trials to support its recommendations on specific drug choices or dosing, it does not state the source of the evidence that has informed the more general guidance. Furthermore, the evidence used relates to infection risk in general and is not specific to COVID-19.

The **Association of British Neurologists** (ABN) have produced two guidelines; the first entitled 'Guidance on COVID-19 for people with neurological conditions, their doctors and carers',[22] and a second specific to patients with multiple sclerosis (MS) entitled 'ABN guidance on the use of disease-modifying therapies in multiple sclerosis in response to the threat of the coronavirus pandemic'.[23] The first general guideline[22] recommends that COVID-19-free patients with neurological conditions should continue taking immunosuppressive medicines. Patients taking an immunosuppressant medication combined with prednisolone $\geqslant$10 mg/day are recognized as high risk and the guideline recommends that these patients should be advised to shield. Treatment with infliximab, rituximab and ocrelizumab infusions should be continued as the risk of untreated progressive neurological disease outweighs that of COVID-19, but where possible reinfusion could be delayed, or an alternative option considered. In the event of COVID-19 infection, the guideline advises that patients can continue to take their hydroxychloroquine and sulfasalazine; however, they should stop their disease-modifying antirheumatic drug (DMARD) or biologic unless they have myasthenia gravis (MG) or a neuromyelitis optica spectrum disorder. The evidence used to inform these guidelines is not stated.

The MS-specific guideline[23] advises on each individual drug. It advises that interferon beta 1a, interferon beta 1b, glatiramer, teriflunomide and dimethyl fumarate are all safe to use and can be continued or started during the pandemic. It also recommends that natalizumab is safe to use as COVID-19 is not a neurotropic virus (although acknowledge a single case-report where COVID-19 was detected in cerebrospinal fluid) and extended licensing has been granted by NHS England so that it can be used for more patients in place of other, higher risk therapies during the pandemic. For fingolimod, the guideline recognizes a 'moderately' increased risk of COVID-19 but advises for patients established on the drug that it is likely that the risk of discontinuation and disease relapse is higher. Similarly, it advises the risk of COVID-19 is moderately increased with ocrelizumab, and it should only be used when the patient requires a high-efficacy drug but does not meet the criteria for natalizumab. For those on established ocrelizumab treatment, it is recommended that repeated infusions should be delayed where possible. A Swedish study looking at outcomes after interrupted rituximab treatment[24] is used to inform this recommendation. If the risk of viral infection is high in the first 3–6 months after starting alemtuzumab or cladribine, the guideline advises against commencing these drugs during the pandemic, and if a patient is already on these medicines the next round of treatment should be delayed. For patients with active COVID-19 infection, the guideline recommends that if symptoms are mild then disease-modifying treatments (DMTs) should not be withheld. In the event of more severe infection, requiring hospital admission, it recommends 'pausing all injectables and oral medication, and delaying infusions'. Recommendations are detailed regarding reducing the frequency of blood test monitoring for all drugs. The ABN cited other guidance it has used to help inform this guideline, including that from the Italian MS Society and the European Society for Blood and Bone Marrow Transplantation.

The **British Society of Gastroenterologists** (BSG) has published guidelines for the management of IBD during the COVID-19 pandemic.[25] Included is a risk stratification table, comparable

to those published by BSR and BAD, which identifies those patients who are at highest risk and should be advised to shield. IBD patients at highest clinical risk include those taking a 'moderate risk' immunosuppressant therapy (such as anti-TNFs, CNIs, methotrexate, MMF or prednisolone <20 mg/day) who also have another co-morbidity (respiratory, cardiac, hypertension or diabetes mellitus, age >70), and those without comorbidities taking prednisolone ⩾20 mg/day, IV steroids or having commenced a biologic and immunomodulatory or steroid within the last 6 weeks. The guideline advises that a drug must be stopped for 3 months before it can be deemed to have undergone full clearance and advises against the switching of therapies purely to alter the risk category. It advises that medications should not be stopped, and access to injectable treatments and infusion suite services and home-care provision of subcutaneous medicines should be maintained. The rationale for continuing treatment is that 'active disease is associated with an increased risk of infection, exposure to steroids (increased risk from infection), hospitalization and major surgery', evidenced by a large, prospective observational study and a case-control study.[26,27] BSG outline some therapy-specific considerations in the guideline. Steroids should be avoided where possible and rapid tapering used if prescriptions are necessary, although they should not be stopped abruptly. It states that there is no current evidence of increased risk of COVID-19 infection with the use of immunomodulators (azathioprine, MMF, methotrexate, tacrolimus), anti-interleukin-12/23p40 therapy (ustekinumab), anti-α4β7 integrin therapy, JAK inhibitors (tofacitinib), 5-aminosalicylic acid derivatives (mesalazine) and anti-TNF therapies (adalimumab, infliximab). With regards to anti-TNF therapies, if initiating therapy, it suggests adalimumab may be preferable as preparations can be given at home.

Health Protection Scotland have amalgamated the guidance from the RA, BAD, BSG, BSR, and ABN to produce an immunosuppressive therapy flowchart,[28] and therefore essentially reiterates those high-risk groups described earlier. **NHS England** have produced the 'Clinical guide for the management of Rheumatology patients during the coronavirus pandemic'.[29] The advice regarding immunosuppressants states that prednisolone should not be stopped suddenly, and that if patients have active COVID-19 infection they can continue hydroxychloroquine and/or sulfasalazine but should temporarily stop DMARDs and biologics. They advise against the use of increased steroid doses with acute COVID-19 illness. The NHS England description of those who are at highest clinical risk and should be advised to shield is in line with the advice given by BSR. Evidence used to inform the guideline is not stated.

United States

The American guidelines for patients on immunosuppressants in COVID-19 are summarized in Table 2. Comparable to the UK, professional societies in the US have produced guidance on the use of immunosuppressants in their patient groups. The **American Gastroenterology Association** (AGA) have published 'AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic'.[30] The guideline acknowledges concerns that patients with IBD might be at increased risk due to the use of immunosuppressive therapies, 'some of which have well-described risks of other viral infections', but states that based on the limited data available, referring to the IOIBD database,[31] there is currently no evidence that patients with IBD are at increased risk. It advises that patients without active COVID-19 infection should remain on their usual therapies with the aim of maintaining remission and therefore reducing the likelihood of hospital admission. The guideline advises that all IBD patients should practice strict social distancing measures, referring to the experience of the Wuhan IBD Center[32] to demonstrate that this approach can protect patients from contracting the infection. It advocates for the continued delivery of infusion therapies, albeit with procedures in place to reduce infection risk including temperature screening and distancing measures. For patients who have tested positive for COVID-19, but are asymptomatic, the guideline advises reducing doses of prednisolone to <20 mg/day, temporarily withholding methotrexate, thiopurines and tofacitinib and delaying monoclonal antibody treatments for 2 weeks.

In the patient with confirmed COVID-19 disease, the guideline recommends that thiopurines, methotrexate, tofacitinib, anti-TNF agents and

Table 2. Summary of American guidelines for patients on immunosuppressants in COVID-19.

American Academy of Dermatology: Guidance on the use of medications during COVID-19 outbreak[33]	April 2020	3, 4, 5	Patients on systemic immunosuppressive agents who have not tested positive or exhibited signs/symptoms of COVID-19: • There is insufficient evidence to recommend discontinuation of systemic immunosuppressive agents at this time. Physicians should use their clinical judgments to stop or continue the patients on these drugs. Patients on systemic immunosuppressive agents who have tested positive for COVID-19 or exhibit signs/symptoms of COVID-19: • We recommend physicians discontinue or postpone the systemic immunosuppressive agents until the patient recovers from COVID-19, consistent with guidelines on the management of patients with active infections on systemic non-biologic and biologics therapy. Patients who have halted systemic immunosuppressive therapy after testing positive for COVID-19: • We recommend physicians can re-initiate the systemic immunosuppressive therapy after ensuring the patients have completely recovered from COVID-19. Patients being considered for systemic immunosuppressive agents: • We recommend physicians assess the risk *versus* benefits in lower-risk patients before initiating immunosuppressive agents on a case-by-case basis, recognizing that anyone may develop serious complications from COVID-19 infection.	Low
American Gastroenterology Society: AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary[30]	April 2020	4, 5 2b (indirect)	The patient with inflammatory bowel disease who is not infected with SARS-CoV-2: • The general recommendation is to stay on IBD therapies with a goal of sustaining remission. • Patients should be advised to maintain their current regimens and to avoid relapse due to nonadherence. • Patients with IBD should practice strict social distancing, work from home, have meticulous hand hygiene, and separate themselves from known infected individuals. • The IOIBD consensus supports ongoing use of infusion centers, provided that the center had a COVID-19 screening protocol in place. Infusion centers should have a protocol that includes prescreening of patients for exposure or symptoms of COVID-19, fever checks at the door, adequate spacing between chairs (minimum of 6 feet), masks and gloves used by providers and provided to patients, and adequate deep cleaning after patient departure. • Elective switching to injectable therapies is not recommended. • Switching to home infusions may seem appealing to limit exposure, but this is not recommended. The patient with IBD who is infected with SARS-CoV-2 but without manifestations of COVID-19: • Patients should be actively moved to lower doses of prednisone (<20 mg/d) or transition to budesonide when feasible. • Thiopurines, methotrexate, and tofacitinib should be held temporarily. • The available monoclonal antibody therapies (anti-TNF therapies, ustekinumab, or vedolizumab) should have their dosing delayed for 2 weeks while monitoring for development of COVID-19. • Restarting therapy after 2 weeks if the patient has not developed manifestations of COVID-19 is reasonable. The patient with IBD who has confirmed COVID-19 with or without bowel inflammation: • Adjustment of the medical therapy for IBD is appropriate, based on the understanding of the immune activity of the therapy and whether that therapy may worsen outcomes with COVID-19. • Taper steroids or switch to oral budenoside. • Continue 5-ASA, rectal therapies, and budenoside. • Hold thiopurines, methotrexate and tofacitinib. • Delay biologics for 2 weeks or until symptoms resolve.	Low
American Society of Clinical Oncology: COVID-19 Patient Care Information [35]	May 2020	3a, 5	IMMUNOSUPPRESSIVE THERAPY: Can/should potentially immunosuppressive therapy (except allogeneic stem cell transplantation) be stopped, delayed, or interrupted? There is no little direct evidence to guide decisions around changing or withholding immunosuppressive therapy in patients with cancer. Routinely withholding critical anti-cancer or immunosuppressive therapy is not recommended. The balance of potential harms that may result from delaying or interrupting treatment *versus* the potential benefits of possibly preventing or delaying COVID-19 infection is very uncertain. Clinical decisions should be individualized and consider factors such as the risk of cancer recurrence/progression if therapy is delayed, modified or interrupted; the number of cycles of therapy already completed; and the patient's tolerance of treatment. However, the following practice points should be considered: • For patients in deep remission who are receiving maintenance therapy, stopping chemotherapy may be an option. • Some patients may be able to switch chemotherapy from IV to oral therapies, which would decrease the frequency of clinic visits but would require greater vigilance by the health care team to be sure that patients are taking their medicine correctly.	Low

(Continued)

Table 2. (Continued)

			Decisions on modifying or withholding chemotherapy should include consideration of the indication for chemotherapy and the goals of care as well as where the patient is in the treatment course and their tolerance of treatment. For example, the risk/benefit assessment for proceeding with chemotherapy in patients with untreated extensive small-cell lung cancer is different from that for patients on maintenance pemetrexed for metastatic non-small-cell lung cancer. Consider whether home infusion of chemotherapy drugs is medically and logistically feasible for the patient, medical team and caregivers. In some settings, delays or modifying adjuvant treatment may pose a higher risk of compromised disease control and long-term survival than in others. Prophylactic growth factors as would be used in high-risk chemotherapy regimens as well as prophylactic antibiotics may be of potential value in maintaining the overall health of the patient and make them less vulnerable to potential COVID-19 complications. In cases where the absolute benefit of adjuvant chemotherapy may be quite small, and where non-immunosuppressive options are available (e.g. hormonal therapy in ER+ early-stage breast cancer), risk of infection with COVID-19 may be considered as an additional factor in weighing the different options available to the patient.	
American College of Rheumatology: Guidance for the Management of Adult Patients with Rheumatic Disease During the COVID-19 Pandemic[34]	April 2020	2a, 3b, 5	General recommendations for patients with rheumatic disease: • If indicated, glucocorticoids should be used at the lowest dose possible to control rheumatic disease, regardless of exposure or infection status. • Glucocorticoids should not be abruptly stopped, regardless of exposure or infection status. Recommendations for ongoing treatment of stable patients with rheumatic disease in the absence of infection or known SARS-CoV-2 exposure and in patients with SLE: • HCQ/CQ, SSZ, MTX, LEF, immunosuppressants (e.g. tacrolimus, CSA, MMF, AZA), biologics, JAK inhibitors and NSAIDs may be continued. • Denosumab may still be given, extending dosing intervals to no longer than every 8 months, if necessary to minimize health care encounters. • For patients with a history of vital organ-threatening rheumatic disease, immunosuppressants should not be dose-reduced. • In newly diagnosed (SLE), HCQ/CQ should be started at full dose, when available. Recommendations for the treatment of newly diagnosed or active rheumatic disease in the absence of infection or known SARS-CoV-2 exposure: • For patients well-controlled on HCQ/CQ, this DMARD should be continued, when available; when unable to access (including in patients with active or newly diagnosed disease), switching to a different conventional synthetic DMARD (either as monotherapy or as part of combination therapy) should be considered. • For patients well-controlled on an IL-6 receptor inhibitor, this DMARD should be continued, when available; when unable to access the agent, switching to a different biologic should be considered. • For patients with moderate to high disease activity despite optimal conventional synthetic DMARDs, biologics may be started. • For active or newly diagnosed inflammatory arthritis, conventional synthetic DMARDs may be started or switched. • If indicated, low-dose glucocorticoids (⩽10 mg prednisone equivalent) or NSAIDs may be started. • In patients with systemic inflammatory or vital organ-threatening disease (e.g. lupus nephritis or vasculitis), high-dose glucocorticoids or immunosuppressants (e.g. tacrolimus, CSA, MMF, AZA) may be initiated. Following SARS-CoV-2 exposure: HCQ/CQ, SSZ, and NSAIDs may be continued. Immunosuppressants (e.g. tacrolimus, CSA, MMF, AZA), non-IL-6 biologics, and JAK inhibitors should be stopped temporarily, pending a negative test result for COVID-19 or after 2 weeks of symptom-free observation. In select circumstances, as part of a shared decision-making process, IL-6 receptor inhibitors may be continued. Documented or presumptive COVID-19: • Regardless of COVID-19 severity, HCQ/CQ may be continued, but SSZ, MTX, LEF, immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped or held.	Moderate

Level of evidence1: 1a, Systematic reviews (with homogeneity) of randomized controlled trials; 1b, Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials; 2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up); 2c, 'Outcomes' research; ecological studies; 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; 4, Case series and poor-quality cohort and case-control studies; 5, Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[44,45]

ustekinumab should all be temporarily withheld, whilst systemic corticosteroids should be avoided and discontinued if possible. It advises that aminosalicylates and oral budenoside are safe and can be continued. There is some discussion regarding research into whether some drugs, such as anti-TNF agents, may be used in the treatment of COVID-19 as their anti-cytokine effects might prevent the progression to respiratory failure. The guideline acknowledges that this data is not yet available but refers readers to get up-to-date information from https://clinicaltrials.gov/.

The **American Academy of Dermatology** (AAD) have also produced guidance on the use of medications during the COVID-19 outbreak.[33] For patients not infected with COVID-19, the AAD do not recommend routinely discontinuing medicines but considering risk *versus* benefit in each individual patient, taking into account severity of dermatological condition and risk factors for severe manifestations of COVID-19 disease (including age >60, cardiovascular disease, hypertension, diabetes). For patients with COVID-19 disease the guidance recommends discontinuation of systemic immunosuppressants until recovery, in line with their own existing guidelines on immunosuppressive medications and infections in general. When considering initiation of systemic immunosuppressive therapies, it recommends careful consideration of risk and benefit, and delaying initiation where possible. Three Chinese studies are cited to provide evidence of co-morbidities which can put patients at increased risk of severe manifestations of COVID-19 disease, otherwise the guidelines appear to be based on existing knowledge/guidance surrounding the use of immunosuppressants and susceptibility to infection in general.

In their publication 'Guidance for the Management of Adult Patients with Rheumatic Disease During the COVID-19 Pandemic',[34] the **American College of Rheumatology** (ACR) sets out guidelines for clinicians on managing rheumatology disorders. The guidelines were created from a taskforce of 10 rheumatologists and four infectious diseases specialists working in the US, and are based on collective expert opinion informed by a review of the available literature, acknowledging a low level of available evidence on the subject. Guidelines are laid out specific to drug class. For glucocorticoids, it recommends continuing steroid treatment, avoiding abrupt withdrawal and using the lowest effective dose to control disease. Conventional synthetic DMARDs (sulfasalazine, hydroxychloroquine, chloroquine, leflunomide and methotrexate) are described as low risk, particularly when used as monotherapy, and therefore it recommends their continuation in the absence of COVID-19 infection. However, leflunomide, methotrexate and sulfasalazine should be discontinued with active infection. It advises that hydroxychloroquine/chloroquine should be continued for SLE, even in the context of active COVID-19 infection. The guideline draws on existing evidence that biologics and JAK inhibitors are associated with increased risk of serious infection but that their discontinuation is associated with disease flare in rheumatoid patients, and concludes with the recommendation to 'continue all immunosuppressants (e.g. tacrolimus, cyclosporine, mycophenolate mofetil, or azathioprine), biologics, and JAK inhibitors in patients with stable rheumatic disease in the absence of COVID-19 (disease or) exposure'. After some discussion relating to ongoing research into the potential benefits of immunosuppressant medicines in preventing cytokine-mediated disease manifestations, the guideline recommends that with currently available evidence all non-IL-6 biologics, immunosuppressants and JAK inhibitors should be withheld in patients with COVID-19 infection or exposure. Although it is clear that an extensive literature review has been undertaken to inform these guidelines, the ACR themselves describe the level of evidence used as 'low', given that much of the data relates to infectious diseases of other aetiologies and are not specific to COVID-19.

The **American Society of Clinical Oncology** have produced guidelines for the care of cancer patients during the coronavirus pandemic.[35] Regarding immunosuppressive therapies, they advise that there is currently no direct evidence to guide changing or withholding therapies during the pandemic, referring to a systematic review of the literature.[36] Therefore, they recommend against routinely withholding immunosuppressive treatments. Like many of the other societies, they do suggest some practical points that could help mitigate risk, including switching from IV to oral therapies to reduce hospital visits and stopping chemotherapy maintenance in patients who are in deep remission.

Table 3. Summary of Australian guidelines for patients on immunosuppressants in COVID-19.

National Covid-19 Clinical Evidence Taskforce Australian guidelines for the clinical care of people with COVID-19[38]	May 2020	5	Steroids for people with asthma or COPD and COVID-19 • Use inhaled or oral steroids for the management of people with co-existing asthma or COPD and COVID-19 as patient would normally for viral exacerbation of asthma or COPD. Do not use a nebulizer.	Very low
Gastroenterological society of Australia. Principles for Clinicians caring for Patients with IBD during the COVID-19 pandemic[37]	March 2020	5	Patients should be continued on the minimum level of immunosuppressive or biologic therapy to control disease activity and minimize risk of flares. Some patients with long-term stable disease may be able to be considered for a 'drug holiday'. If infusions can be performed outside of the hospital, or in a location in the hospital that minimizes risk of exposure to patients, then this should be implemented. For appropriate patients in long-term stable remission, infusion intervals lengthening may be considered. There are inadequate data available to recommend switching from intravenous to subcutaneous preparations of biologic agents. For patients who contract COVID-19, consider holding therapies that may impact the ability of T-cell-mediated viral clearance (thiopurines, anti-TNF agents, anti-IL23 agents, tofacitinib, and vedolizumab for patients with prominent COVID-19-related GI symptoms). Typical symptom duration is 3–5 weeks, and a pause in therapy of this duration is unlikely to precipitate a major flare. For patients flaring, it is important to treat their underlying disease regardless of their COVID-19 status, and this includes initiation of steroids or anti-TNF agents in the setting of severe disease. Exclusive enteral nutrition (EEN) may be an alternative to consider for patients with flares of Crohn's disease.	Very low

Level of evidence1: 1a, Systematic reviews (with homogeneity) of randomized controlled trials; 1b, Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials; 2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up); 2c, 'Outcomes' research; ecological studies; 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; 4, Case series and poor-quality cohort and case-control studies; 5, Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[44,45]

Australia

The Australian guidelines for patients on immunosuppressants in COVID-19 are summarized in Table 3. The **Gastroenterological Society of Australia** (GESA) have produced a guideline for clinicians caring for patients with IBD during the COVID-19 pandemic.[37] It advises using the lowest dose of maintenance immunosuppressive therapy possible to maintain disease control and considering a 'drug holiday' for patients with long-term stable disease. It advocates continuing infusion therapies with additional cautionary measures but suggests increasing intervals between infusions where possible. For patients who contract COVID-19, the guideline advises to 'consider' withholding therapies that might affect T-cell-mediated viral clearance including thiopurines, anti-TNF agents, anti-IL23 agents and tofacitinib. For patients undergoing a disease flare it recommends that disease control is vitally important, regardless of COVID-19 status, and therefore initiation of steroids or anti-TNF agents may be appropriate. GESA describe their guidelines as principles that are not prescriptive; they have been developed *via* a consensus of opinion among their faculty. As such, the evidence level informing these guidelines is low.

The Australian group, the **National Covid-19 Clinical Evidence Taskforce** have produced 'Australian guidelines for the clinical care of people with COVID-19',[38] which includes a small subsection on steroids for patients with asthma and COPD. It recommends the use of oral or inhaled steroids for these patients with COVID-19, as would normally be prescribed for any viral exacerbation. The group cite the NICE guidelines[9,10] to support this recommendation.

Other international guidelines

The international guidelines for patients on immunosuppressants in COVID-19 are summarized in Table 4. The **International MG/COVID**

Table 4. Summary of international guidelines for patients on immunosuppressants in COVID-19.

International Organization for the Study of Inflammatory Bowel Disease: Management of Patients with Crohn's Disease and Ulcerative Colitis During the COVID-19 Pandemic: Results of an International Meeting[40]	April 2020	5	5-ASA: • Patients taking 5-ASA therapy should not discontinue therapy or reduce the dose to prevent SARS-CoV-2 infection. • Patients taking 5-ASA therapy should not stop therapy if they test positive for SARS-CoV-2 but don't have COVID-19. • Patients taking 5-ASA therapy should not stop therapy if they develop have COVID-19. Oral budenoside: • Patients taking oral budenoside therapy should not discontinue therapy or reduce the dose to prevent SARS-CoV-2 infection. Oral prednisolone: • Patients taking prednisone therapy (⩾20 mg/d) should reduce the dose of therapy to prevent SARS-CoV-2 infection. • Patients taking prednisone therapy (⩾20 mg/d) should discontinue therapy (taper as appropriate) to prevent SARS-CoV-2 infection. • Patients taking prednisone therapy (⩾20 mg/d) should discontinue therapy (taper as appropriate) if they test positive for SARS-CoV-2 but don't have COVID-19, or if they develop COVID-19. Thiopurines: • Patients taking azathioprine/6MP should not discontinue therapy or reduce the dose to prevent SARS-CoV-2 infection. • Patients taking azathioprine/6-MP should stop therapy if they test positive for SARS-CoV-2 but don't have COVID-19, or if they develop COVID-19. Tofacitinib: • Patients taking tofacitinib should not discontinue therapy or reduce the dose to prevent SARS-CoV-2 infection. • Patients taking tofacitinib should stop therapy if they test positive for SARS-CoV-2 but don't have COVID-19, or if they develop COVID-19. Combination therapy: • Patients taking combination therapy with an anti-TNF and thiopurine/methotrexateshould stop the thiopurine/methotrexateif they test positive for SARS-CoV-2 but don't have COVID-19, or if they develop COVID-19. Clinical trials: • Patients taking clinical trials drugs should not discontinue therapy to prevent SARS-CoV-2 infection. • Patients taking clinical trials drugs should stop therapy if they test positive for SARS-CoV-2 but don't have COVID-19, or if they develop COVID-19. Approach to active disease: • A patient with moderately to severely active Crohn's disease or ulcerative colitis (new diagnosis or relapsing disease) should be treated with the same therapies you would choose in the pre-COVID-19 era. TREATMENT OF IBD AFTER SARS-COV-2 INFECTION OR COVID-19: • In an IBD patient who tests positive for SARS-CoV-2 and whose IBD meds have been stopped because of this, IBD meds can be restarted after 14 days (provided they don't develop COVID-19). • In an IBD patient who develops COVID-19 and whose IBD meds have been stopped, IBD meds can be restarted after COVID-19 symptoms resolve. • In an IBD patient who develops COVID-19 and whose IBD meds have been stopped, IBD meds can be restarted after 2 nasopharyngeal PCR tests are negative.	Very low

(Continued)

Table 4. (Continued)

International MG/COVID-19 Working Group: Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic[39]	March 2020	5	Patients on existing therapies for MG/LEMS: • MG/LEMS patients should continue their current treatment and are advised not to stop any existing medications, unless specifically discussed and approved by their healthcare provider. • There is no scientific evidence to suggest that symptomatic therapies like Pyridostigmine or 3,4 Diaminopyridine increases the risk of infection and should not be discontinued unless there are other clinical reasons to do so. • Even though strong evidence is lacking, it is recommended that MG patients already on immunosuppressive medications should practice extra-vigilant social distancing, including avoiding public gatherings/crowds, avoiding crowded public transport and where possible use alternatives to face-to-face consultations (e.g. telemedicine), if clinically appropriate. • When altering or stopping an existing immunosuppressive therapy that carries a potential for increased disease activity and/or MG exacerbation or crisis, people with MG and their MG healthcare providers should consider specific risks (e.g. age, comorbid health conditions, location) and benefits. Infusion therapies, intravenous immunoglobulins and plasma exchange: • Certain infusion therapies in MG may require travel to hospitals or infusion centers and we strongly recommend that this decision be made based on regional incidence of COVID-19 and risk/benefit of the therapy for the individual patient. The healthcare provider should be able to give region-specific advice, and where possible consider switching to home infusion. • There is currently no evidence to suggest that intravenous immunoglobulin (IVIG) or therapeutic plasma exchange (PLEX or TPE) carry any additional risk of contracting COVID-19. However, the use of IVIG has to be based on individual patient need and indiscriminate use should be avoided. • In general, PLEX and IVIG should be reserved for patients with acute exacerbations. However, the panel recognizes that there are some patients receiving these as maintenance therapy, who should continue these, but extra precautions may need to be taken because of the need for travel to and from a healthcare facility. • There is currently no evidence to support that targeted C5-complement inhibition using eculizumab, a monoclonal antibody increases susceptibility to COVID-19 infection or its outcome. Blood tests for existing therapies: • Weigh risks and benefits of routine blood monitoring at this time. Some of the MG therapies require frequent blood work monitoring and decisions regarding the ongoing need for testing, which requires patient to leave their home, should be individualized and based on regional COVID-19 incidence. What to consider when starting an immune therapy in patients with MG/LEMS: • Before starting a B-cell-depleting therapy (e.g. rituximab), healthcare providers should consider the risk of worsening myasthenia or crisis and the risk of contracting the viral infection. • It may be advisable to delay initiation of cell-depleting therapies, until the peak of the outbreak is over in their region. However, the risk of not starting the cell-depleting therapy in occasional patients may outweigh the risk of severe COVID-19 infection and this has to be discussed with the patient in detail.	Very low

Level of evidence1: 1a, Systematic reviews (with homogeneity) of randomized controlled trials; 1b, Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials; 2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low-quality randomized controlled trials (e.g. <80% follow-up); 2c, 'Outcomes' research; ecological studies; 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; 4, Case series and poor-quality cohort and case-control studies; 5, Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.[44,45]

Working Group has published 'Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic'.[39] The MG/LEMS guideline acknowledges that there is a lack of available evidence on how immunosuppressant medicines affect the risk of contracting or the severity of COVID-19, however, recognizing the likelihood of an increased risk; the guideline was produced by 'an international working group of MG experts'. The guideline advises that patients on immunosuppressants and symptom-control therapies (including pyridostigmine) for MG/LEMS should not stop taking them, but should practice 'extra vigilant social distancing'. If a clinician is considering stopping an immunosuppressant then the risk of increased disease activity or myasthenic crisis must be weighed against the risks associated with contracting COVID-19, which might be higher in patients with certain comorbidities. It advises that treatment infusions that require travel to hospital are based on individual risk–benefit analysis and 'regional incidence' of COVID-19, and the same advice is given regarding blood monitoring. The guideline states that there is currently no evidence that IVIG infusions or the monoclonal antibody, eculizumab, increase the risk of contracting or suffering a more severe form of COVID-19. Before starting a B-cell-depleting therapy such as rituximab it recommends considering the risk of contracting COVID-19 *versus* the risk of worsening MG, and suggests delaying commencing treatment until the peak of the outbreak is over in that region. Overall, these guidelines are non-specific with the general message being 'use clinical judgement on a case-by-case basis'. They are informed by expert opinion alone, and therefore the grading of evidence is low.

The **International Organization for the Study of Inflammatory Bowel Disease** (IOIBD) have produced guidance for publication entitled 'Management of Patients with Crohn's Disease and Ulcerative Colitis During the COVID-19 Pandemic: Results of an International Meeting'.[40] The IOIBD used a RAND panel of international IBD experts to produce a series of statements. The resulting statements include advocating for continued administration of infusion therapies, provided the infusion centre has COVID-19 screening procedures in place. It recommends reducing or discontinuing steroids to prevent contracting COVID-19 but advises against reducing or stopping other IBD therapies in patients without COVID-19. With regards to patients who develop COVID-19 disease, the panel agreed that aminosalicylates can be continued, but that methotrexate, azathioprine, steroids, anti-TNF agents, tofacitinib and clinical trial medicines should be withheld (or tapered in the case of steroids). They recommend that discontinued therapies can be restarted after symptoms resolve or 14 days after a positive test in asymptomatic patients.

Evidence summary of guidelines

A summary of guidelines and level of evidence base for these guidelines are presented in Tables 1–4. It also outlines details on recommendations for management of immunosuppressive agents during the COVID-19 pandemic. These guidelines were also critically appraised on their level of evidence-base on the recommendations and described as a final grade for the quality of evidence as 'high', 'moderate', 'low' or 'very low' based on the strength and quality of underlying evidence for the critically important outcomes based on the GRADE principles. Of the 23 guidelines included, 15 (65.2%) were graded as 'very low', three (13.0%) were 'low', and five (21.7%) were 'moderate'. No guidelines were found to be underpinned by a 'high' level of evidence.

Discussion

This article summarizes international guidelines relating to the use of immunosuppressive medications for chronic conditions during the COVID-19 pandemic. On several points, there is general agreement amongst the guidance. For example, all advise against routinely discontinuing immunosuppressant medications in the absence of COVID-19 infection, and with respect to shielding guidance there is consistency regarding those who are at highest clinical risk. The guidance from the British Society for Rheumatology, British Association of Dermatologists and the Renal Association is summarized in Table 1, and all identify patients taking $\geqslant$20 mg prednisolone/day for $>$4 weeks or $\geqslant$5 mg prednisolone/day combined with another immunosuppressant, patients taking a combination of any two or more immunosuppressants, and patients who are taking cyclophosphamide, rituximab or another biologic as being most at risk. The Association of British Neurologists deviate here slightly, advising that an immunosuppressant medicine combined with

⩾10 mg prednisolone/day constitutes high risk whereby patients should be advised to shield. Whilst there is much consensus across the guidelines, there are discrepancies.

Logically, there are variances in the guidance from different medical specialties, due to the difference in relative risk that withholding immunosuppressive treatment would pose to the patient depending on the chronic condition for which they are prescribed. For example, discontinuation of immunosuppressive therapy for a patient with IBD could result in disease flare requiring hospitalization or emergency surgery,[26,27] whereas discontinuation in a patient with a dermatological condition might result in a disease flare but is unlikely to lead to hospital admission or emergency intervention. This would perhaps explain why the British Gastroenterology Society and American Gastroenterology Association recommend that all patients without COVID-19 infection should continue their usual immunosuppressive therapies, whilst the American Association of Dermatologists recommend a risk *versus* benefit analysis for each individual patient when deciding whether to continue or withhold treatments during the coronavirus pandemic. The American guidelines for patients on immunosuppressants in COVID-19 are summarized in Table 2.

Given the novel nature of COVID-19, the guidelines draw on existing knowledge and data pertaining to the use of immunosuppressants and risks of serious infections of other aetiologies and have extrapolated these to form their evidence base. The Australian and international guidelines for patients on immunosuppressants in COVID-19 are summarized in Tables 3 and 4. Many guidelines drew on expert opinion including those from the Gastroenterological Society of Australia, the International MG/COVID Working Group and British Society for Rheumatology. Some guidelines have used more extensive methodology including systematic review of the literature and data from large RCTs, including those from the American College of Rheumatology and British Society of Gastroenterologists. However, even these guidelines have generalized data from studies on the effect of immunosuppressants on infection risk in general or in relation to other viruses. As a result, the highest level of evidence awarded to any guideline was 'moderate' and 78.3% ($n = 18$) of the guidelines were found to be informed by a 'low' or 'very low' quality of evidence.

This is a fast-moving field with emerging evidence regarding the hospitalization and mortality rate associated with immunosuppressant usage. For example, a prospective case series identified 86 individuals with underlying immune-mediated inflammatory disease who had either confirmed or highly suspected COVID-19 infection. Some 72% were receiving biologics or JAK inhibitors, and of these 16% were hospitalized with one death in the ED department and one developing acute respiratory distress syndrome and remaining on ventilation at the time of publication. The hospitalized patients were older, more likely to be on steroids or conventional DMARDS but less likely to be on a biologic or JAK inhibitors.[41] In addition, the Global Rheumatology Alliance – which is collecting data on COVID-19 cases in rheumatic disease patients worldwide – published its first report on 600 patients with underlying rheumatic disease who developed COVID-19 in May 2020. Some 46% of these patients were hospitalized and 9% died. Steroids >10 mg per day were associated with higher odds of hospitalization (2.05) whereas use of anti-malarials, NSAIDs, and conventional DMARDS either alone or in combination with biologics or JAK inhibitors were not associated with higher risk of hospitalization (OR 0.94, 0.64, 1.23, 0.74). Anti-TNF use was associated with a lower risk of hospitalization (OR 0.4) according to this report.[42] Finally, a UK population-based cohort study linked primary care electronic health records with COVID-19 reported deaths found a slight increase in risk of death in rheumatic diseases with HR of 1.17. This study reported that asthmatics who had required treatment with steroids within the last 12 months had a higher HR for death of 1.24 compared with 1.03 in those without steroids consumption.[43]

There are several strengths to this study. We have systematically reviewed the currently available guidelines written in English on the use of immunosuppressive medicines during the coronavirus pandemic. Although we have found a wide range of guidelines available from professional societies and governing bodies internationally, some are lacking in specific detail that would aid clinicians, and we have also demonstrated that at present there is limited evidence to inform these guidelines.

This study has some limitations to note. As we only reviewed guidelines in English language there might be further published guidelines in other

languages that were not included. This might explain why our search did not return any European guidelines, especially as given the urgent nature of our subject it is unlikely that English translations would be readily available. This manuscript is a systematic review of guidelines and hence is based on published guidance. We did not include original research papers in this review. In addition, at the time we accomplished this study, there were no published RCTs of immunosuppressive usage in COVID-19 and therefore no high-quality evidence was accessible to inform these guidelines. Consequently, the highest level of evidence awarded to these guidelines was moderate, and this was an inherent limitation imposed to our study. Therefore, our study is limited with regard to recommendation from the findings.

This systematic review has highlighted gaps and uncertainties regarding the use of long-term immunosuppressive medicine during the coronavirus pandemic. Areas where future or currently ongoing research could be directed include:

- The relative risk of contracting SARS-CoV-2 in patients taking immunosuppressive medicines;
- The clinical course of COVID-19 disease in these patients, including disease severity and mortality as compared with the general population;
- The consequences of withholding immunosuppressive therapies at the point of diagnosis with COVID-19 disease, including whether that mitigates disease severity and improves outcomes or results in chronic disease relapse, with consequential morbidity and mortality.

Conclusion

New evidence surrounding COVID-19 is continually emerging and we would anticipate that some of these questions will be answered as the pandemic progresses. Following the publication of robust data and evidence, clinical guidelines on the subject should be reviewed and updated. In the interim, our rapid focused systematic review and critical appraisal of current international guidelines provide a useful resource for all clinicians who are managing patients who routinely use immunosuppressants for the benefit of patients and to help clinicians to make better decisions.

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Supplemental material

Supplemental material for this article is available online.

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