COVID-19 rapid guidelines; areas of uncertainty

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## Frequency of blood testing for drug monitoring and association with disease outcomes (July 2020)

### Research Questions

1. What is the impact on disease outcomes of increasing the time between blood tests for drug monitoring (e.g., when receiving methotrexate or mycophenolate) in patients who are shielding, but stable on treatment?
2. What is the impact on disease outcomes of patients who are unable to attend blood monitoring (due to shielding) and therefore do not receive immunosuppressants (e.g., methotrexate or mycophenolate) and only receive steroids alone?

### Research question narrative

After the development of NICE’s COVID-19 rapid guidelines on [rheumatological autoimmune, inflammatory and metabolic bone disorders](https://www.nice.org.uk/guidance/ng167) (NG167), [gastrointestinal and liver conditions treated with drugs affecting the immune response](https://www.nice.org.uk/guidance/ng172) (NG172) and [interstitial lung disease](https://www.nice.org.uk/guidance/ng177) (NG177) it was identified that there was uncertainty in whether it was safe to increase the length of time between blood tests for patients who are stable on treatment (defined as patients with 3-monthly blood tests that have been stable for more than 2 years in NG167) and what treatment(s)/doses should be offered to patients who are not stable, but are unable to attend for blood monitoring and the follow-on impacts on disease outcomes. Current recommendations in NG167, NG172 and NG177 are as follows:

NG167 – “5.1 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.”

NG172 – “2.8 For patients who are stable on treatment, assess whether it is safe to do less frequent blood tests for drug monitoring. Take into account the patient’s age and any comorbidities.”

NG177: “5.8 Discuss with the patient the risks and benefits of being on an immunosuppressant with blood monitoring requirements. For patients with a condition that is responsive to immunosuppressants who are unable to attend for blood monitoring, think about offering prednisolone alone.”

These recommendations, however, were based on expert consensus and it is unclear what impact these recommendations could have on disease outcomes. If data show these potential changes to monitoring/treatments for patients on immunosuppressants result in poor outcomes, the recommendations made in NG167, NG172 and NG177 will need to be re-visited and updated according to the new evidence.

## Modifying doses of steroids and association with disease and COVID-19 outcomes (July 2020)

### Research questions

1. Is use of high-dose steroids associated with increased risk of COVID-19 infection?
2. What dose of steroids leads to the best outcomes during a COVID-19 infection?
3. What is the impact on disease outcomes of patients not being offered increased doses of steroids during periods where they are unwell?

### Research question narrative

There seems to be consensus across specialties that treatment with steroids should not be stopped when patients are at risk or directly affected by COVID-19, as stopping steroids can be harmful. However, it has been suggested that those on steroids and more specifically those receiving high-doses of steroids (exact definition of ‘high-dose’ is unclear) are at an increased risk of being affected by COVID-19 and if affected are at an increased risk of poorer outcomes.

This is potentially problematic as patients on maintenance steroids usually receive an increased dose if they become unwell. There have therefore been some conflicting opinions as to what dose of steroids should be given if a patient becomes unwell. For example, the Society for Endocrinology state that short-term administration of high-dose glucocorticoids is “never harmful” and should be used to treat adrenal crisis and the BTS guidance for interstitial lung disease continues to advise increasing the dose of steroids during disease flare-ups to reduce the risk of adrenal crisis, but the latter also specifically states that higher dose steroids should be avoided due to associated poorer outcomes if concurrent COVID-19 infection ensues.

In contrast, the NHSE rheumatology guidance specifically advises against any increase in dosage of steroids if patients become unwell in all patients with rheumatic disease. There is therefore uncertainty in several of the recommendations that NICE has published in the COVID-19 rapid suite of guidelines related to the use and appropriate dosage of steroids if a patient become unwell.

The relevant NICE COVID-19 rapid guidelines on [rheumatological autoimmune, inflammatory and metabolic bone disorders](https://www.nice.org.uk/guidance/ng167) (NG167), [community-based care of patients with chronic obstructive pulmonary disease (COPD)](https://www.nice.org.uk/guidance/ng168) (NG168) and [interstitial lung disease](https://www.nice.org.uk/guidance/ng177) (NG177) have current recommendations related to the use of steroids as follows:

NG167 – 4.8 “Only use methylprednisolone for treating major organ flares. Think about using oral corticosteroids and refer to NHS England’s clinical guide on the management of patients with musculoskeletal and rheumatic conditions on corticosteroids.”

NG168 – 2.5 “Tell patients established on inhaled corticosteroids 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 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 destabilising COPD management.”

NG177 – 5.9 “Offer the lowest dose of prednisolone possible, if patients have been on prednisolone before, use the last dose that controlled their symptoms.”

These recommendations, however, were based on expert consensus and it is unclear what impact these recommendations could have on disease outcomes. If data show these potential changes to doses of steroids during periods of illness result in poor outcomes, the recommendations made in NG167, NG168 and NG177 will need to be re-visited and updated according to the new evidence.

## Risk stratification for patients treated with drugs affecting the immune system (July 2020)

### Research questions

1. In patients receiving drugs affecting the immune system (e.g., patients with gastrointestinal/liver conditions and/or patients with dermatological conditions) and who have been infected by COVID-19, what factors are associated with an increased risk of poor outcomes?
2. Compared to individuals infected by COVID-19 who are not receiving drugs affecting the immune system, do individuals infected by COVID-19 who are receiving drugs affecting the immune system have an increased risk of severe illness from COVID?

### Research question narrative

Many of the patient groups that were the focus of the COVID-19 suite of rapid guidelines received letters indicating that they are at high risk of severe illness from COVID-19 and that they should shield to protect themselves from the virus. However, it is obvious that not all patients will have the same risk of severe illness from COVID-19 and therefore it may not be necessary for them to shield. This is important as current advice on shielding limits the ability of individuals to shop for themselves, see family/friends and potentially attend/receive routine healthcare, all of which could result in patients experiencing poor outcomes, despite not being exposed to COVID-19.

It would therefore be helpful if care teams could have a better understanding of which patients are most at risk of severe illness from COVID-19 and which patients have a lower risk of severe outcomes. Therefore some patients could be reclassified and given less restrictive advice to practice self-isolation and/or social distancing to reduce the risk of COVID-19 infection. For example, early data presented by Higgins et al. (The risk of SARS-CoV-2 in immunosuppressed IBD patients) indicated that IBD patients, including those on immunosuppressive therapies were not having COVID-19 infections at higher rates compared to the non-IBD population.

Such risk stratification was identified as an area of uncertainty in two of NICE’s COVID-19 rapid guidelines, specifically [dermatological conditions treated with drugs affecting the immune response](https://www.nice.org.uk/guidance/ng169) (NG169) and [gastrointestinal and liver conditions treated with drugs affecting the immune response](https://www.nice.org.uk/guidance/ng172) (NG172), which prevented the guideline developers/clinical experts from making any specific recommendations about when or in what types of patients modification of shielding advice could be made by the care team.

## RRT circuit clotting in acute kidney injury patients with COVID-19 (July 2020)

### Research questions

1. What is the prevalence of renal replacement therapy circuit clotting in acute kidney injury patients who have been infected with COVID-19?
2. What factors other than coagulopathy are associated with renal replacement therapy circuit clotting in acute kidney injury patients who have been infected with COVID-19?

### Research question narrative

The proposed research questions are based on areas of uncertainty in the evidence base that was used to inform NICE’s COVID-19 rapid guideline on [acute kidney injury in hospital](https://www.nice.org.uk/guidance/ng175) (NG175). A recommendation was included in the guideline to make treating clinicians aware of the possible occurrence of renal replacement therapy circuit clotting based on some anecdotal reports (<https://www.era-edta.org/en/covid-19-news-and-information/#toggle-id-21>) of this event happening in patients with COVID-19. The current recommendation is as follows:

NG175 - “9.3 Be aware of the anecdotal reports of renal replacement therapy circuit clotting because of the increased risk of coagulopathy in patients with COVID-19.”

However, it is unclear if renal replacement circuit clotting is an event that is associated with COVID-19 and if there are other factors in COVID-19 patients that may contribute to the occurrence of this event. It will therefore be important to obtain evidence of this outcome so the current recommendation can include additional information that allows patients who are at risk of being affected to be better identified so that interventions can be put in place to avoid its occurrence.