Guideline

NHS
County Durham and Darlington
NHS Foundation Trust

COVID-19 Prescribing Guidance for Patients HOSPITALISED DUE TO COVID-19

General Information

- Send COVID-19 Anti-S protein Antibody serology (yellow top tube).
- Record in patient's notes the date of symptom onset if known and the date first tested positive for COVID-19.

Antibiotics

- ISARIC data showed risk of bacterial co-infection upon admission to hospital is rare - Co-Infections, Secondary Infections, and Antimicrobial Usage (isaric4c.net).
- Please review antibiotics when patients are identified as COVID-19 positive and stop unless clinical evidence of bacterial infection (purulent sputum/radiological evidence of bacterial pneumonia).
- Do not use CRP to guide initiation or escalation of antibiotics.
- Follow Trust guideline for treating concomitant infections with aim to:
  - limit treatment to 5 days
  - avoid broad-spectrum antibiotics (unless specified in Trust guideline)
  - review IV to oral switch daily (switch when clinical improvement and oral route available, should not be guided by CRP).
  - please note procalcitonin (PCT) test requires a consultant microbiologist approval.

updated-sapg-advice-on-hospital-ams-in-the-context-of-covid-19-july-2021.pdf

PRESCRIBING GUIDANCE

1. Corticosteroids

Eligibility Criteria:

- Adult patients hospitalised with COVID-19 confirmed or high clinical suspicion
- Requiring oxygen, non-invasive (NIV) and invasive ventilation, or Extracorporeal membrane oxygenation (ECMO)

Drug Choice and Dose:

- Oral Dexamethasone 6mg ONCE daily for 10 days (3x2mg tablets)
- If unable to take oral preparation –
  - INTRAVENOUS - Dexamethasone 5.94mg (1.8mL of 3.3mg per mL vial) ONCE daily for 10 days **or**
  - INTRAVENOUS - Hydrocortisone 50mg THREE times a day for 10 days
- If pregnant -
  - ORAL - Prednisolone 40mg ONCE daily for 10 days **or**
  - INTRAVENOUS - Hydrocortisone 80mg intravenously TWICE daily) for 10 days.

Consider adding a Proton Pump Inhibitor (PPI) e.g. Omeprazole 20mg DAILY.

STOP corticosteroids after 10 days or upon discharge from hospital. (NOTE - if discharged before end of 10 day course DO NOT continue).

Use of Dexamethasone in Patients with Diabetes:
Corticosteroid therapy impairs glucose metabolism. COVID-19 increases insulin resistance and impairs insulin production from pancreatic beta cells; this can precipitate hyperglycaemia even in patients without diabetes. Glucose levels above 10mmol/L have been linked to increased mortality in people with COVID-19. Admission blood glucose (BG) measurement in ALL patients.

- STOP Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g. Canaglifozin, Dapagliflozin, Empagliflozin) in **ALL** patients
- REVIEW Metformin in ALL patients: only stop if acute kidney injury (AKI) , lactic acidosis or eGFR less than 40ml/min
- Check ketones if blood glucose more than12mmol/L or known diabetes. URGENTLY consider Diabetic Ketoacidosis (DKA) or Hyperosmolar Hyperglycaemic State (HHS) and follow Trust guidance if confirmed
    - HHS - policy POL/MED/0004 HSS policy
    - DKA - policy POL/MedDiv/Diabetes/0003 DKA policy
- Patients with diabetes with requirement for insulin on dexamethasone
    - Check glucose at least every SIX hours.
- Patients without an insulin requirement on dexamethasone
    - Check blood glucose at least every SIX hours for first 24 hours of treatment. This can then be reduced to TWICE daily blood glucose IF blood glucose remains between 6.0 to 12.0mmol/L. **Continue with more frequent monitoring if blood glucose falls outside the 6.0 to 12.0mmol/L range**.

2. Antivirals

Eligibility Criteria REMDESIVIR:

- Patients aged 12 and over hospitalised with COVID-19 requiring low-flow supplemental oxygen – MUST NOT be used in patients not on supplemental oxygen or those on Continuous positive airway pressure (CPAP), High Flow Nasal Oxygen (HFNO). NOTE - Patients **NOT** on supplemental oxygen can be considered for remdesivir if they are immunocompromised).
- Symptom onset of less than 10 days (unless immunocompromised)
- ISARIC4C score 4 or greater prognostic-calculator (isaric4c.net)
- eGFR/CrCl greater than 30mL/min and Alanine Aminotransferase (ALT) less than 200units/L
- If aged 12-17 years, weight 40kg or over

Dose:

- Remdesivir 200mg STAT via INTRAVENOUS infusion, followed by 100mg daily for 4 days (5 day total course).
- Consider stopping remdesivir after 72 hours if clinical improvement and no longer requiring oxygen.
- Monitor bloods and STOP remdesivir if patient develops:
    - A raised ALT (greater than 200units/L)
    - AKI (CrCl less than 30mL/min)

- A 10 day course can be considered for significantly immunocompromised patients but this should be discussed at COVID-MDT/Respiratory/ITU consultant.
- Should be AVOIDED in pregnancy - Treatment of COVID-19 in pregnant patients (rcog.org.uk)
- Patients who present with another COVID-19 hospital admission after a course of remdesivir should be discussed with the Multidisciplinary Team (MDT) before a further course of remdesivir is prescribed.

3. Interleukin-6 (IL-6) inhibitors (sarilumab and tocilizumab)

Treatment with an IL-6 inhibitor should be discussed at COVID-MDT or with a Respiratory or Intensive Care Consultant.

Tocilizumab should be considered as first line treatment choice unless it is unavailable or contraindicated. Sarilumab may be considered as an alternative option assuming the inclusion criteria are met.

Eligibility Criteria:

- Adult patients hospitalised with COVID-19 confirmed (or where MDT has high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis).
- Only for patients currently prescribed (or have completed) a course of corticosteroids for COVID-19 such as dexamethasone (unless contra-indicated).
- Have NOT had another IL-6 inhibitor during this admission.
- Fits one of these criteria -
  - The patient needs supplemental oxygen (or has oxygen saturation of less than 92% on room air) **and** has a C-reactive protein level of 75 mg/L or more
    or
  - The patient is within 48 hours of starting HFNO, CPAP,NIV or invasive ventilation.

Exclusion Criteria:

- Known hypersensitivity to tocilizumab or sarilumab
- Pregnancy, unless clinically necessary and in consultation with a consultant obstetrician – see Treatment of COVID-19 in pregnant patients (rcog.org.uk)
- Reduced neutrophil count -
  - Sarilumab: neutrophil count less than 2.0 x 10^9/L
  - Tocilizumab: neutrophil count less than 1.0 x 10^9/L
- Reduced platelets -
  - Sarilumab: platelets less than 150 x 10^9/L
  - Tocilizumab: platelets less than 50 x 10^9/L
- Raised ALT -
  - Sarilumab: ALT greater than 200units/L
  - Tocilizumab: ALT greater than 400units/L

Dose:

A single dose of:

- TOCILIZUMAB 8mg/kg (max dose 800mg) by INTRAVENOUS infusion (follow ePMA dose-banding).
  or
- SARILUMAB 400mg by INTRAVENOUS infusion (using 2 x 200mg prefilled syringes)

A patient information leaflet must be given to all patients prescribed IL-6 inhibitor COVID-19 Patient Discharge Information Leaflet Tocilizumab Sarilumab (sps.nhs.uk) and please include the date and dose of IL-6 on the GP discharge letter.

Things to Consider:
There is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab. A consultant decision is required to ensure no concurrent infection that may be worsened by IL-6 inhibitor therapy.

Use with caution in patients with a pre-existing condition or treatment resulting in ongoing immunosuppression, or patients who have a history of recurrent or chronic infections.

A procalcitonin test requires microbiologist approval. Be vigilant for the development of infection following administration.

4. Neutralising Monoclonal Antibodies (nMABs) Casirivimab plus Imdevimab (Ronapreve®)

Treatment with Casirivimab plus Imdevimab (Ronapreve®) MUST be discussed at COVID-MDT and therefore are NOT stored on COVID-wards/ITU for use out of hours.

Currently the majority of inpatients have the Omicron variant and therefore are not eligible for Casirivimab plus Imdevimab (Ronapreve®) (see below).

Patients given Ronapreve must have the date/dose documented on the discharge letter for GP records as this may influence the timing of COVID-vaccinations.

Eligibility Criteria:
- PCR-confirmed SARS-CoV-2 infection and non-omicron variant - If genotype is UNKNOWN or OMICRON variant DO NOT use any nMAB (unless this is used as part of the RECOVERY trial).
- Patients hospitalised specifically for the management of acute symptoms of COVID-19.
- Negative for baseline serum anti-spike (anti-S) antibodies against SARS-CoV-2 (Immunocompromised patients or patients treated with Intravenous Immunoglobulin (IVIG)/ sub-cutaneos Immunoglobulin (SCIG) should have antibody status discussed with a respiratory consultant).

Exclusion Criteria:
- Children weighing less than 40kg
- Children aged under 12 years
- Hypersensitivity reactions to the active substances or any of the excipients
- Previously received treatment with casirivimab with imdevimab (Ronapreve®)at the 2.4g dose

Dose:
A single dose of:
- Casirivimab1.2g plus Imdevimab 1.2g (Ronapreve® 2.4g) by INTRAVENOUS infusion

Appendix 1: Summary of Evidence and Further Information

Dexamethasone

RECOVERY Trial demonstrated that dexamethasone decreased the need for invasive mechanical ventilation (IMV) and reduced deaths by one-third in ventilated patients (29.0% vs 40.7%) and by one fifth in other patients receiving oxygen only (21.5% vs 25.0%). See COVID-19 rapid guideline: Managing COVID-19 (magicapp.org) and CAS-ViewAlert (mhra.gov.uk) and Treatment of COVID-19 in pregnant patients (rcog.org.uk) for further prescribing information.

Remdesivir

Remdesivir is an antiviral and is most effective early in the disease course, when viral replication is a driver of disease. Antivirals are less likely to be effective in the later stages in the disease course when it enters the hyperinflammatory phase - this phase is often associated with the need for more respiratory support (HFNO/CPAP). In the ACTT-1 Study remdesivir shortened time to recovery significantly in patients on low flow supplemental oxygen and a symptom onset of <10 days. See COVID-19 rapid guideline: Managing COVID-19 (magicapp.org) and CAS-ViewAlert (mhra.gov.uk)) for further prescribing information.

IL6 Inhibitors

RECOVERY TRIAL - Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (a relative reduction in mortality of 14%). Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days and among those not receiving invasive mechanical ventilation at baseline, patient's allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death.

REMAP-CAP TRIAL – Tocilizumab reduced in-hospital mortality (ARR 8%, RRR 24%), and over 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support. Enrollment occurred within 24-48 hours of ITU admission, suggesting that the benefit of tocilizumab occurs specifically in patients who are experiencing rapid respiratory decompensation. Sarilumab showed similar benefits with a smaller sample size.

See COVID-19 rapid guideline: Managing COVID-19 (magicapp.org) and https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103194 and https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1 and Treatment of COVID-19 in pregnant patients (rcog.org.uk) for further prescribing information.

nMABs

Ronapreve binds to spike proteins on the SARS-CoV-2 virus blocking entry into host cells and inhibiting replication. The RECOVERY trial found it reduced the relative risk of mortality by 20% in hospitalised patients with COVID-19 (24% in the treatment group vs 30% in those who received standard care alone), who were negative for serum antibodies against SARS-CoV-2 (seronegative). See COVID-19 rapid guideline: Managing COVID-19 (magicapp.org) and CAS-ViewAlert (mhra.gov.uk) for further prescribing information.

Ronapreve is believed to be less effective against the Omicron variant and must only be used if genotyping results confirm a NON-Omicron variant - The Omicron variant is highly resistant against antibody-mediated neutralization – implications for control of the COVID-19 pandemic | bioRxiv. This test can be returned usually within 48h by a Variant of Concern (VOC) test but patients will only be eligible for VOC test if their CT value <30. Ronapreve must be discussed at COVID-MDT.

Appendix 2: Administration Information

1. Remdesivir

Full monograph available via Medusa IV Drug Guide and for further info see Veklury 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Remdesivir should be given in 250mL NaCl 0.9% (or 100mL NaCl 0.9% if fluid restricted – ARDS or renal failure) over 30-120 minutes.

Dilution Instructions:

Remdesivir dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag	Required volume of reconstituted remdesivir
200 mg (2 vials)	250 mL	40 mL	2 × 20 mL
	100 mL	40 mL	2 × 20 mL
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

Administration Instructions:

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

2. Tocilizumab

Full monograph available via Medusa IV Drug Guide and for further info see RoActemra 20mg/ml Concentrate for Solution for Infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

- Wear personal protective equipment including gloves, plastic apron and surgical face mask
- Calculate the volume of tocilizumab concentrate required.
- Remove the equivalent volume from a 100mL sodium chloride 0.9% infusion bag and discard.

- Draw up the required volume of tocilizumab from the vial and slowly add this to the prepared sodium chloride 0.9% bag.
- Complete this sequentially from each vial until the required dose has been added and results in a total volume of 100mL.
- To mix the solution, invert the bag gently to avoid foaming.
- Make sure the bag is appropriately labelled as per trust policy.
- It must be administered with an infusion set via a volumetric pump and should never be administered as an intravenous push or bolus.
- It should not be infused concomitantly in the same intravenous line with other drugs.
- Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted.
- The diluted solution MUST be given as an intravenous infusion.
- Start the infusion at 10mL per hour for the first 15 minutes then 130mL per hour for the subsequent 45 minutes.
- Total infusion time 60 minutes
- This should be followed by a 20mL sodium chloride 0.9% flush

3. Sarilumab

Full monograph available via Medusa IV Drug Guide and for further info see Kevzara 200 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Allow TWO x 200mg pre-filled sarilumab syringes to reach room temperature:

- Inject the contents of the TWO syringes into a 100mL sodium chloride 0.9% infusion bag.
- Invert bag at least 10 times to ensure thorough mixing
- Make sure the bag is appropriately labelled as per Trust policy.
- It must be administered with an infusion set including a low protein-binding 0.2 micron (or equivalent) filter via a volumetric pump
- It should not be infused concomitantly in the same intravenous line with other drugs.
- Only solutions which are clear to opalescent, colourless to pale yellow and free of visible particles should be diluted
- The diluted solution MUST be given as an intravenous infusion.
- Start the infusion at 10mL per hour for the first 15 minutes then 130mL per hour for the subsequent 45 minutes.
- Total infusion time 60 minutes
- This should be followed by a 20mL sodium chloride 0.9% flush.

4. Casirivimab 1.2g with imdevimab 1.2g (RONAPREVE® 2.4g)

Full monograph available via Medusa IV Drug Guide and for further info see Ronapreve 120 mg/mL solution for injection or infusion - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

- Remove the Ronapreve kit from the fridge
- This kit must have been supplied from pharmacy for a named patient
- Check the expiry of the kit. Please note: the expiry displayed on the outer packaging of the Ronapreve vial has been adjusted in accordance with national guidance. Please refer to this expiry instead of the expiry displayed on the glass ampoule which may be different.

- Withdraw 10mL from the 11.1mL vial containing casirivimab. After obtaining an independent check, add the withdrawn 10mL to a 250mL bag of sodium chloride 0.9%
- Withdraw 10mL from the 11.1mL vial containing imdevimab. After obtaining an independent check, add the withdrawn 10mL to the same 250mL bag of sodium chloride 0.9% already containing 1200mg of casirivimab
- Gently mix the filled infusion bag by slowly inverting 10 times. Do not shake the bag. Attach an infusion additive label to the bag
- Allow the infusion to equilibrate to room temperature (for approx. 30 mins prior to administration)
- Administer the prepared infusion over at least 30 minutes through an Intrapur© 0.2 micron in-line filter (supplied in kit).