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1. COVID-19 ANTIVIRAL DOMAIN

1.1.1. Presentation

Ivermectin is available as 3mg tablets.

1.1.2. Warnings

Nil.

1.1.3. Dosing

Dosing will be 0.2 mg/kg administered once daily via the enteral route, with a maximum daily dose of 24mg. Doses should be rounded to the nearest 3mg.

1.1.4. Duration of therapy

Ivermectin will be administered once daily for five days or until hospital discharge, whichever occurs first.

1.1.5. Preparation and administration

1.1.5.1. For patients who are able to swallow whole tablets

Preferred method of administration for patients who are able to swallow whole tablets is to administer tablets, swallowed whole.

1.1.5.2. For patients with swallowing difficulties or gastric feeding tubes

For patients with a gastric feeding tube:

1. Administer immediately after a bolus feed or stop the continuous feed

2. Flush the tube with 30mL of sterile water

3. Remove the plunger of an enteral syringe and place the tablets into the syringe. Replace the plunger

4. Draw 20 mL of water into the enteral syringe and allow the tablets to disperse. This may take several minutes. Shake gently if required.

5. Administer the dispersed tablets immediately into the enteral feeding tube

6. Rinse the enteral syringe with a further 10 mL of water to ensure the entire dose is given
7. If other medicines are given, flush the tube with at least 5 mL of water between each medication.

8. After the final medicine is given, flush the tube with 30 mL of water

1.1.6. Dose adjustment in renal or liver impairment

There are no recommendations for dose adjustment of ivermectin in patients with renal or hepatic failure.

1.1.7. Potential drug interactions

Ivermectin may enhance the anticoagulant effect of Vitamin K antagonists.

1.1.8. Discontinuation

An antiviral agent for COVID-19 should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.
2. **VITAMIN C DOMAIN**

2.1. **Vitamin C**

2.1.1. Presentation

Various presentations of ascorbic acid may be available. These include:

- 15g/50mL vial
- 25g/50mL vial
- 30g/100mL vial
- 500mg/5mL ampoule
- 750mg/5ml ampoule
- 1000mg/500ml ampoule

2.1.2. Warnings

Pressure may build up during storage of containers of ascorbic acid. At room temperature, the pressure may become excessive. When opening ascorbic acid, ampoules should be wrapped in a protective covering.

Some brands may contain a high content of sodium. This should be taken into account for relevant patients.

2.1.3. Dosing

Vitamin C will be administered intravenously via a central or peripheral venous cannula as bolus doses of 50mg/kg of estimated body weight. The maximum dose will be 7.5g (equivalent to 50 mg/kg for a 150 kg person).

Monitor patients for potential adverse events associated with rapid infusion rates (i.e. temporary faintness, nausea, lethargy, flushing, dizziness, or headache).
2.1.1. Duration of therapy

Vitamin C will be administered every 6 hours for 16 doses or until hospital discharge, whichever occurs first.

2.1.2. Preparation and administration

The appropriate dose of Vitamin C will be diluted in a 50ml or 100ml bag of 0.9% saline or D5W according to local pharmacy advice.

Vitamin C will then be administered at the following rate:

Table 1. Vitamin C infusion rate

<table>
<thead>
<tr>
<th>Estimated or measured weight</th>
<th>Duration of infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>30 minutes</td>
</tr>
<tr>
<td>60 – 120 kg</td>
<td>60 minutes</td>
</tr>
<tr>
<td>&gt;120 kg</td>
<td>90 minutes</td>
</tr>
</tbody>
</table>

2.1.3. Dose adjustment in renal or liver impairment

For the purposes of this trial, no dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy.

2.1.4. Potential drug interactions

Vitamin C is associated with factitious hyperglycemia when measured on standard hospital glucometers. If the patient is being treated with insulin or oral hypoglycemic agents, they may experience iatrogenic hypoglycemia. The risk of this is highest during the vitamin C intervention period, defined as the time from commencement of the first dose to 36 hours after the last dose.

Therefore, for patients in the vitamin C intervention period, before and during treatment for hyperglycemia with insulin or an oral hypoglycemic agent, we recommend glucose measurement with one of the following accurate methods:

- Hospital core lab instrument
- Point of care arterial blood gas machine with glucose measurements validated in the setting of high vitamin C concentrations, or
• Nova Biomedical StatStrip glucometer

In addition, in patients receiving insulin or oral hypoglycemic agents, from 36 hours to 7 days after the last dose of vitamin C, we suggest glucose monitoring as above. A standard glucometer is also acceptable if the difference between its value and that measured by a validated method listed above is low (e.g. ≤2 mmol/L on two occasions more than 4 hours apart). If a participant is discharged home less than 7 days after the last dose of vitamin C, we suggest the same approach using the participant’s glucometer, or if not available, a standard hospital glucometer.

2.1.5. Discontinuation

Vitamin C should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.
3. SIMVASTATIN DOMAIN

3.1. Simvastatin

3.1.1. Presentation

The following preparations are available:

- Simvastatin 10mg tablet
- Simvastatin 20mg tablet
- Simvastatin 40mg tablet
- Simvastatin 80mg tablet

3.1.2. Warnings

Do not crush or disperse the tablet if you are pregnant.

3.1.3. Dosing

Simvastatin will be administered at a dose of 80mg once-daily by the enteral route.

The first dose should be administered as soon as possible after assignment, ideally within four hours of randomization. Subsequent doses will be given each morning starting on the following study day. If for any reason a dose is not administered at the intended time, it should be administered subsequently within 12 hours of the intended time of administration.

3.1.4. Duration of therapy

Simvastatin will be administered once daily until ICU discharge or study day 28, whichever occurs first.

3.1.5. Preparation and administration

3.1.5.1. *For patients who are able to swallow whole tablets*

Preferred method of administration is tablets swallowed whole.

3.1.5.2. *For patients with swallowing difficulties*

For patients who are unable to swallow whole tablets and do not have a gastric tube in situ:
1. Crush the tablet with a mortar and pestle or a tablet crusher
2. Add 10 to 20mL of sterile water and mix well
3. Draw the mixture into an oral dispenser/syringe
4. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the oral dispenser/syringe, to ensure that all of the medicine is removed
5. Give the mixture immediately
6. Rinse the oral dispenser/syringe with a further 10mL of sterile water and give to the patient, to ensure the entire dose is given

If the person cannot swallow thin fluids (i.e. is at risk of aspiration), crush the tablet and mix with a spoonful of yoghurt or fruit puree.

3.1.5.2. For patients with gastric tubes

For patients with nasogastric, orogastric, percutaneous enterogastric (PEG), or percutaneous enterojunal (PEJ) tube in situ:

1. If relevant, stop the continuous feed
2. Flush the tube with 30mL of sterile water
3. Crush the tablet to a fine powder using a mortar and pestle or a tablet crusher
4. Add 10mL of sterile water to the powder and mix well (the tablet does not disperse easily)
5. Draw the mixture into the enteral syringe
6. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the enteral syringe, to ensure that all of the medicine is removed
7. Give the mixture (~30mL) immediately into the enteral feeding tube
8. Rinse the enteral syringe with a further 20mL of sterile water to ensure the entire dose is given
9. If other medicines are given, flush the tube with at least 5 mL of sterile water between each medicine

10. After the final medicine is given, flush the tube with 30 mL of sterile water

11. Restart the continuous feed immediately after dosing, if relevant

3.1.6. Dose adjustment in renal and liver impairment

Patients with known severe liver disease are excluded from the Simvastatin Domain.

There is no dose adjustment for renal failure of renal replacement therapy, however simvastatin must be ceased if there is renal failure that is caused or contributed to by rhabdomyolysis.

Liver function tests, serum creatinine kinase and renal function must be monitored at least once during the first 7 to 14 days after randomization and repeated between study day 21 and 28 if the patient is still receiving simvastatin.

3.1.7. Potential drug interactions

Simvastatin is generally contra-indicated with potent CYP3A4 inhibitors e.g. clarithromycin, tri-azole antifungals.

If a single dose of amiodarone (IV infusion of not more than one hour, or any enteral dose) is administered no change is required to simvastatin dose. However, if a patient receives more than a single dose of amiodarone, simvastatin dose should be reduced to 20 mg per day for the remainder of the course.

Other interactions include diltiazem, verapamil, amlodipine, ticagrelor.

3.1.8. Discontinuation

Simvastatin should be discontinued if there is development of a serious adverse event. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

In patients with suspected COVID-19 infection who receive an allocation status to receive simvastatin but subsequently test negative for COVID-19 infection after allocation may have treatment ceased unless the treating clinician believes that doing so would not be clinically
appropriate. This decision should take into account the known or suspected sensitivity for COVID-19 infection.
4. CYSTEAMINE DOMAIN

4.1.1. Presentation

Cysteamine bitartrate vials are provided frozen and should be immediately stored in a freezer between -15°C to -25°C.

Cysteamine bitartrate IV vials contain 500mg/vial; 2.5mL fill volume of cysteamine bitartrate (200mg/mL).

4.1.1.1. Packaging

Boxes (box size of 20cm (L) x 7cm (W) x 7cm (H) containing 30 vials of frozen cysteamine bitartrate (sufficient for 10 days of treatment (3 vials per day)). The box and insert are white.

4.1.2. Warnings

Cysteamine bitartrate should be stored frozen at -15°C to -25°C. Cysteamine bitartrate is temperature sensitive and the administration guide in section 4.1.5 should be strictly adhered to.

If preparing at the bedside, face shields should be worn in addition to standard PPE. There is no data supporting the safety of handling or preparation of cysteamine bitartrate by people who are pregnant or trying to conceive. Cysteamine bitartrate should be handled and prepared in line with local guidelines.

4.1.3. Dosing

Cysteamine will be administered every 8 hours at a dose of 5 mg/kg of estimated or measured body weight, with each administered dose not to exceed 500 mg. The IMP solution will be diluted in 50 or 100 mL of 0.9% NaCl and administered as an intravenous infusion over 10 minutes via a central or peripheral venous catheter.

If clinically significant hypotension occurs during infusion, the infusion rate should be slowed and, if necessary, ceased.

Monitor patients for:

- Suspected or proven allergic or hypersensitivity reaction sufficient to require interruption of infusion or treatment or both. These may include one or more of the following clinical findings - urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension
- Hypocalcemia* that is symptomatic or requires treatment or both

- Total neutrophil count less than $2.0 \times 10^9 /L$

- For any patients on glyceryl trinitrate – patients should be monitored for possible hypotension, which can be serious and may be indicated by headaches.

*Amifostine is an aminothiol drug that has been associated with hypocalcemia. As cysteamine is an aminothiol compound, hypocalcemia may be a potential side effect.

4.1.4. Duration of therapy

The duration of cysteamine administration is 10 days, i.e. 30 doses. Cysteamine may be ceased at the time of ICU discharge in patients who are discharged from ICU before completion of the 10-day course. Omission of three or more consecutive doses is a protocol deviation.

4.1.5. Preparation and administration

4.1.5.1. Instructions for thawing and storage

Vials of frozen cysteamine bitartrate IV containing 500mg; 2.5mL fill volume (200mg/mL)

Must be stored in a freezer at -15°C to -25°C

Thawing vials at room temperature
Approximately 25 mins (vials should be used within 6 hours of removal from freezer)

Do not refreeze vials once thawed - if unused please dispose of following trial procedure

Thawing vials in the refrigerator (2-8°C)
Approximately 40 mins (vials can be stored refrigerated at 2-8°C for up to 10 days before use)

Do not refreeze vials once thawed – if unused please dispose of following trial procedure

Thawed vials should be gently agitated for 30 seconds and checked for any particulates. If particulates present repeat agitation until the solution is clear.

The vial is then ready for dilution in 50 or 100mL 0.9% NaCl solution prior to administration.

Any vials where particulates are still present should not be given to a patient and should be quarantined (following trial procedure)
4.1.5.2. Preparation of 5mg/kg dose for IV administration

Cysteamine Bitartrate (200mg/mL) is a concentrated solution and should be diluted prior to administration intravenously (5mg/Kg of estimated/actual body weight, see dose banding table below) with each single administered dose not to exceed 500mg. Cysteamine bitartrate should be diluted in 50 mL or 100 mL 0.9% NaCl solution prior to administration and given as below.

The infusion may be made in an aseptic environment or at the bedside, depending on local regulations. If made at the bedside, administer infusion immediately after preparation and discard remaining vials following local guidance.

Calculate the volume (mL) of the thawed cysteamine bitartrate required (based on patient’s estimated/actual body weight) of 200 mg/mL cysteamine bitartrate drug product (see dose banding table below for guidance).

1. Cysteamine bitartrate is very sensitive to air, therefore care should be taken not to introduce air bubbles while drawing the solution from the vial into the syringe and on transferring into the infusion bag. Withdraw the required volume of cysteamine bitartrate using a needle and 1 mL or 5 mL syringe and add to a 50 mL or 100 mL 0.9% NaCl solution infusion bag (Baxter is the preferred infusion bag but is not essential to use).

2. The remaining contents of the vial should be disposed of in pharmaceutical waste.

3. Invert the infusion bag 10 times to ensure homogenous solution.

4. Inspect the bag. Only bags which are clear and free of visible particles can be infused.

5. It is recommended to administer cysteamine bitartrate as soon as it is diluted in the 50mL or 100mL 0.9% NaCl solution. However, if made in an aseptic environment and there is a situation where cysteamine bitartrate cannot be administered immediately, the 50mL or 100mL 0.9% NaCl bags with diluted cysteamine bitartrate can be stored in refrigerator at 2-8°C for a maximum of 24 hours prior to administration.

6. Attach the bag to the administration set and prime the line with the cysteamine bitartrate infusion then administer infusion intravenously over set at a flow rate to administer the entire bag within 10- minutes. Please note cysteamine bitartrate should not be given via the same line as betalactams (see Potential drug interactions).

7. Flush line at the same rate as the infusion with 20mL of 0.9% sodium chloride.
Table 2. Dose banding table for Cysteamine bitartrate

<table>
<thead>
<tr>
<th>Estimated or measured body weight (kg) Based on the upper weight in each 5kg band</th>
<th>Calculated dose in mgs (to give 5mg/Kg of body weight)</th>
<th>Required volume (mL) of 200mg/mL solution – rounded to nearest decimal point</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-40kg</td>
<td>200mg</td>
<td>1.0mL</td>
</tr>
<tr>
<td>41-45kg</td>
<td>225mg</td>
<td>1.1mL</td>
</tr>
<tr>
<td>46-50kg</td>
<td>250mg</td>
<td>1.3mL</td>
</tr>
<tr>
<td>51-55kg</td>
<td>275mg</td>
<td>1.4mL</td>
</tr>
<tr>
<td>56-60kg</td>
<td>300mg</td>
<td>1.5mL</td>
</tr>
<tr>
<td>61-65kg</td>
<td>325mg</td>
<td>1.6mL</td>
</tr>
<tr>
<td>66-70kg</td>
<td>350mg</td>
<td>1.8mL</td>
</tr>
<tr>
<td>71-75kg</td>
<td>375mg</td>
<td>1.9mL</td>
</tr>
<tr>
<td>76-80kg</td>
<td>400mg</td>
<td>2.0mL</td>
</tr>
<tr>
<td>81-85kg</td>
<td>425mg</td>
<td>2.1mL</td>
</tr>
<tr>
<td>86-90kg</td>
<td>450mg</td>
<td>2.25mL</td>
</tr>
<tr>
<td>91kg and over</td>
<td>475mg-500mg*</td>
<td>*Calculate the dose up to the extractable volume of the vial</td>
</tr>
</tbody>
</table>

*The total fill volume of each vial is 2.5 mL, however the total extractable volume varies between vials so for patients weighing 91kg and over use the maximum extractable volume from the vial.

4.1.6. Dose adjustment

For the purposes of this trial, no dose adjustment is made for impaired renal function or concomitant use of renal replacement therapy.

4.1.7. Potential interactions

Beta-lactam antibiotics are not contraindicated, but co-administration of cysteamine with beta-lactams should be avoided (as direct mixing in a line can affect the chemistry of the drugs and potentially reduce beta-lactam potency). Cysteamine is an antibiotic potentiator and is designed for co-administration with antibiotics but:

- Through different lines if given concomitantly
- Through different ports of the same line sequentially
• If only a single line is available/accessible, cysteamine and beta-lactams should be administered at different times (a few minutes apart)

Glyceryl trinitrate (GTN): Simultaneous administration with cysteamine may increase the vasodilatory and platelet aggregation-inhibiting effect of glyceryl trinitrate. If such combined treatment is considered necessary, the patient should be monitored for possible hypotension, which can be serious and may be indicated by headaches.

4.1.8. Discontinuation

Cysteamine bitartrate should be discontinued if there is development of a serious adverse event.

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE:

• Suspected or proven allergic or hypersensitivity reaction sufficient to require interruption of infusion or treatment or both. These may include one or more of the following clinical findings - urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension

• Hypocalcemia that is symptomatic or requires treatment or both

• Total neutrophil count less than $2.0 \times 10^9 /L$

Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.
APPENDIX 1. SUMMARY OF CHANGES FROM VERSION 1 TO VERSION 2

- Removal of Hydroxychloroquine. This agent has been removed from the COVID-19 Antiviral Domain of REMAP-CAP on the basis of results from the RECOVERY and WHO SOLIDARITY trials.

- Addition of Vitamin C and Simvastatin to reflect the addition of these domains to the platform.

- Clarification for duration of lopinavir/ritonavir, interferon, anakinra, and tocilizumab interventions to reflect the extension of these therapies to the Moderate Illness Severity State (i.e. patients not requiring organ support in ICU).

- Clarification of warnings regarding preparation for interferon, anakinra, and sarilumab.

- Clarification of preparation of infusions of interferon, anakinra, and sarilumab, particularly with reference to the use of Baxter Viaflex bags.

- Addition of a tocilizumab dose banding table, to be used at the discretion of sites to reduce wastage.

APPENDIX 2. SUMMARY OF CHANGES FROM VERSION 2 TO VERSION 2.1

- Updated advice about the preparation of IFN-β1a, anakinra, tocilizumab, and sarilumab by people who are pregnant or trying to conceive.

APPENDIX 3. SUMMARY OF CHANGES FROM VERSION 2.1 TO VERSION 3

- Removal of COVID-19 Immune Modulation Domain agents (anakinra, interferon-beta-1a, tocilizumab, and sarilumab). This domain has been closed.

- Removal of lopinavir/ritonavir from the COVID-19 Antiviral Domain, and addition of ivermectin to this domain.

- Addition of Cysteamine.