Guidance on the Management of Symptomatic Patients Dying from COVID-19

Principles

An experienced clinician needs to exclude reversible causes before the diagnosis of dying is made. Consider hospital admission for patients with respiratory distress of unknown cause – follow local pathways.

When caring for a patient dying from suspected or confirmed COVID-19, continue to use standard principles of holistic individualised care and symptom control. Many have mild respiratory symptoms and are already close to the end of life with other conditions so will require 'standard' palliative prescribing: see CD1 form (gold sheet) guidance.

Dying from Covid-19

Death from Covid-19 occurs via one or both of the following mechanisms:

- Type 1 Respiratory failure from Acute Respiratory Distress Syndrome (ARDS)
- Systemic shock from 'cytokine storm' that resembles bacterial septic shock

The most common terminal symptoms are: pyrexia, rigors, severe dyspnoea, cough, delirium and agitation. The terminal phase can be rapid, lasting just a few hours: symptoms can develop rapidly and can be very distressing. Rapid access to medication is vital and often involves larger doses than in 'standard' palliative care practice.

Medication Options

The medications most likely to provide effective symptom control are:

- Antipyretics for rigors and delirium
- Opioids for dyspnoea and cough
- Benzodiazepines for agitation
- Antipsychotics for delirium and agitation

The rapid onset of severe symptoms (and likely shortage of syringe drivers) means that stat doses of subcutaneous drugs may result in faster and better symptom relief.

Medication Route

- **Sub-cut**: If possible, insert a subcutaneous (SC) Saf-T-Intima safe needle system (alternatives: butterfly needle or paediatric venflon) to avoid multiple injections. These can last up to 72 hours but need to be changed earlier if there are signs of erythema or pain at the site.
- **Oral**: The oral route may not be available in the dying phase, but morphine sulfate oral solution can be helpful if given early.
- **Sublingual and buccal**: Lorazepam, morphine and oxycodone can be given sublingually (SL) and midazolam given buccally (BUC).
- **Rectal**: Viral shedding is thought to occur rectally, so the PR route is best avoided.

Pharmacokinetic Considerations

- Morphine, oxycodone and midazolam are effective for around 4 hours after SC, SL and BUC administration.
- Absorption of morphine, oxycodone and midazolam is similar via oral, SL and BUC routes: use similar doses.
- Hourly doses may be needed to ensure rapid symptom control.

- Levomepromazine is a sedating antipsychotic with a duration of action between 12 and 24 hours: a single dose of 25 to 50mg SC will give significant anxiolysis and sedation within 60 minutes.
- The combination of all three medications is therefore likely to provide optimal symptom control for 18 to 24 hours from a single SC administration.
- Avoid fentanyl and buprenorphine patches if possible due to the slow onset of action (>12 hours).
- Pyrexia exacerbates agitation and delirium. NSAIDs are the preferred antipyretics as they have a longer duration of action than paracetamol: they are unlikely to hasten death in the context of end of life care.
- Oxygen is rarely of benefit in the terminal phase: opioids and sedatives are usually more effective for management of symptoms in this context.

Medication and Dosing Rationale

- As nursing and medical staffing levels will be lower during the peak of the pandemic, the aim is to provide effective symptom control without relying on frequent medication administration.
- Larger than usual stat doses may be required for effective symptom control. The severe terminal anxiety and breathlessness that many patients experience may require higher doses of sedative medication in order to reduce conscious level more rapidly and deeply than in 'traditional' palliative care practice.
- In the absence of staff to administer SC drugs frequently, the use of 'standard' lower doses increases the risk of poor symptom control and unacceptable distress for patients and their families.
- Hourly doses may be needed to ensure rapid symptom control when staff are available.
- **Use CD1 form symptom guidance for usual first line when symptoms are mild-moderate and alternative prescribing sheet for when usual medications or syringe drivers are not available.**
- Oxygen therapy may improve breathlessness associated with hypoxia. A trial of oxygen (if possible) for respiratory distress could be considered for earlier symptom control in relevant patients. Opioids and sedatives are more appropriate for symptom management when patients are actively dying – only use oxygen if already shown benefit and therapy not causing distress for patient or family.

Quantity to Prescribe in Primary Care

When prescribing medication for imminent use in the home approximately 5 days' treatment should be adequate for most patients. Carers should be advised to contact the surgery on day 3 or 4 if further supplies are likely required and also to return any unused medication to a pharmacy or dispensary for safe disposal.

Pre-emptive Prescribing

The anticipatory prescribing of medication to be used at the end of life e.g. where medication is prescribed before the anticipated need, is discouraged during the Covid pandemic to avoid stock being held in patients' homes.

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Pharmacological Symptom Control for Patients Dying from Suspected or Confirmed Covid-19

An experienced clinician has decided that the person is imminently dying from COVID-19

If symptomatic from temperature > 37.5 C, give antipyretic (naproxen 500mg or paracetamol 1g) orally.
A tepid compress will also help. *Fans may encourage viral dispersion so are best avoided.*

If the patient is **severely distressed** by shortness of breath and / or agitated give the following together stat:

a) **Morphine 2.5 to 5 mg** (or Oxycodone 2.5 to 5 mg) SC or SL
b) **Midazolam 2.5 to 5 mg SC or BUC** (or Lorazepam 1mg SL)
c) **Levomepromazine 12.5 to 25 mg SC** (or Haloperidol 5mg SC)

Some patients dying from COVID-19 need the higher of these initial doses to achieve adequate relief of breathlessness and appropriate sedation. The lower doses may be more appropriate for the frail elderly.

If a patient has **mild to moderate distress**, initially give medication for most significant symptom (e.g. breathlessness - morphine, anxiety - midazolam, agitation - levomepromazine) as per CD1 form.

Prescribe the following p.r.n. drugs, with a low threshold for dose escalation if needed:

Shortness of breath: **Morphine 2.5 to 5 mg SC / SL hourly.** Or Oxycodone 2.5mg SC / SL hourly

Agitation/panic: **Midazolam 2.5 to 5 mg SC / BUC hourly** (max 80mg/24hrs).
Or Lorazepam 1mg sublingual 2-hourly

Agitation / delirium: **Levomepromazine 12.5 to 25 mg SC hourly** (max 250 mg/24 hrs)

If you need advice, contact St Barnabas Hospice on 0300 303 1754 or Thorpe Hall Hospice on 01733 225900. Advice from a Palliative Care specialist nurse or doctor is available 24/7: they will be pleased to help.

Dr Kat Collett and Palliative Medicine Consultants across Lincolnshire with thanks to Dr Barclay and Cambridge and Peterborough Palliative Medicine Consultants for allowing adaptation of their work.
NICE rapid guidance 163 and Association of Palliative Medicine guidance for COVID-19 also referenced (accessed 7.4.20).
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IN ALL CASES, EFFORTS TO FOLLOW FIRST LINE ADVICE FROM CD1 FORM SHOULD BE TAKEN; THIS ADVICE IS FOR EXCEPTIONAL CIRCUMSTANCES IF USUAL MANAGEMENT IS NOT POSSIBLE. USE IS OFF-LABEL.

Please call St Barnabas Hospice Lincoln for Specialist Advice 0300 303 1754 or Thorpe Hall 01733 225900

	Respiratory Distress/Breathlessness/Pain/Cough	Agitated Delirium	Secretions	Anxiety	Nausea
1st Line treatment unavailable (CD1 form AKA gold sheet)	Consider alternative opioid listed on CD1 form: • Morphine sulphate, Oxycodone or Alfentanil SC • Diamorphine – avoid unless need large doses as significant supply shortage Consider antimuscarinics if pre-existing smooth muscle pain Corticosteroids are unlikely to hasten death in context of EOLC Consider need for CSCI diuretic in fluid overload **Seek specialist advice:** Midazolam has some benefit in neuropathic pain Sodium Valproate by CSCI has been used in refractory neuropathic pain	If midazolam unavailable see benzodiazepine options listed under ANXIETY. If levomepromazine unavailable see SYRINGE DRIVER UNAVAILABLE section below for alternative anti-psychotic **Seek specialist advice:** Phenobarbital or sodium valproate for agitated delirium refractory to CD1 advice	Glycopyrronium 200-400mcg SC PRN 2 hrly (CSCI 600 micrograms to 2.4mg/24hrs) Available as 200micrograms/1ml, 600micrograms/3ml amps) Hyoscine Hydrobromide 400micrograms sc 1 hrly 1200- 1600micrograms/24hrs CSCI dilute with saline Caution: can cause agitation	Lorazepam available as 500mcg, 1mg, 2.5mg. Sublingual tablets **can be used in patients unable to swallow.** Oral tablets disperse in water 1mg/ml oral solution available Injection can be given sublingually Midazolam Oral mucosal solution 5mg/ml and 10mg/ml pre-filled syringes - buccal Injection may also be used in emergency buccal 10mg/2mls	Consider alternative anti-emetic listed on CD1 form: **Metoclopramide:** prokinetic for gastric stasis **Haloperidol:** if chemical cause renal failure, liver failure **Levomepromazine:** Broad spectrum **Cyclizine:** vestibular antihistamine, does not mix well in syringe driver **Ondansetron** may be used for gastric irritation 4- 8mg SC 4 hrly PRN or by CSCI seek advice
Syringe driver Unavailable If medication and teams available: consider regular administration of usual SC medications e.g. morphine, midazolam 4 hourly levomepromazine or haloperidol 12 hourly	MORPHINE: Zomorph capsule can be opened and administered directly in semi-solid food. Effect 12 hours Tablet and granules for suspension available **Similar preparations for OXYCODONE and Buccal, Intranasal and sublingual FENTANYL .** Immediate release **concentrated oral solution** e.g. Oramorph effect 4 hours 20mg/ml **(100mg/5ml) if reduced consciousness unable to swallow can be administered 0.5ml inside cheek** **Caution when calculating the required dose** FENTANYL: Slow release transdermal patch duration **72 hrs** Fencino, Matrifen, Mezolar, Opiodur **12mcg/hr (equivalent 30-45mg oral morphine sulphate in 24 hrs)** Also available in 25mcg/hr, 50 mcg/hr, 75mcg/hr 100mcg/hr BUPRENOPRPHINE: Slow release TD patch duration **7 days** Reletrans, Butec **5mcg/hr (equivalent 12mg oral morphine sulphate in 24 hrs)** Also available 10mcg/hr, 15mcg/hr and 20 mcg/hr. Sevodyne, BuTrans 5mcg/hr, 10mcg/hr and 20mcg/hr 24 hrs for effect so **immediate release medication will be needed** Caution: Fever & heat increase absorption TD	**Levomepromazine tablet 25mg may dispersed in small amount of water.** Levomepromazine Injection available and can be diluted for PO use in 30-50mls water. Olanzapine tablets includes orodispersible 2.5mg to 10mg daily Risperidone tablets may be dispersed in small amount of water 0.5mg-1mg at bedtime If sweating give Paracetamol 1g PO/PR PRN 4 hrly Dispersible tablets also available (4g/24hrs, 2-3g/24hrs in elderly/<50kg)	Hyoscine Hydrobromide 300micrograms SL tablets OR Transdermal patch 1mg per 72 hrs on hairless skin behind the ear. Patches can be halved or quartered. Maximum dose 2mg/24hrs Atropine SL 1% drops (ophthalmic drops) – 2 drops SL every 2-4 hrs	See above	See above for indication **Levomepromazine tablet 25mg may be halved if required and dispersed in small amount of water.** Half tablet 12.5mg nocte for nausea Injection available and can be diluted for PO use in 30-50mls water. Cyclizine: Tablet may disperse. Injection available and can be diluted for PO use 50mg TDS Haloperidol: 0.5mg to 1mg PRN 4 hrly Soluble tablet or oral liquid Metoclopramide Soluble tablet, oral liquid available. Injection available and can be diluted for PO use 30-50mls
Lay Carer/ Family available: Drug and non-drug measures	Medication: See **syringe driver unavailable** box above or **SC carers administration policy**. Also consider non pharmacological methods: • Lay semi prone (see positions leaflet on right). Elevate the head when sleeping, Cool atmosphere and humidify room air. • Loose clothing. Cooling the face by using a cold flannel. Oral fluids • DO NOT USE FANS unless person isolated as risk of aerosol. CBT. • Aromatherapy – Menthol- reduction in cough sensitivity. Expectorant – Eucalyptus			Leaflet 3: Breathing techniques to ease breathlessness Leaflet 4: Positions to ease breathlessness Leaflet 5: Thinking - Managing thoughts about breathlessness Leaflet 6: Relaxation Leaflet 7: Mindfulness	

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CD1 DIRECTION TO ADMINISTER DRUGS FOR SYMPTOM MANAGEMENT

Supply 10 ampoules for injection of:	
Morphine Sulphate	10mg/ml
Levomepromazine	25mg/ml
Midazolam	10mg/2ml
Hyoscine Butylbromide	20mg/ml
Water for injection	20ml

Patient's Name:

……

Drug sensitivities:

……

Drug allergies:

……

ANTICIPATORY DRUGS AS REQUIRED FOR SYMPTOM MANAGEMENT (PRN)

Seek advice if 2 or more doses have been ineffective or if benefit lasts less than 1 hour – the dose or drug may need changing.

Date	For the relief of:	Drug	Dose range	Route	Do not exceed max in range more	Seek specialist prescribing advice before exceeding:	Signature in full Print name below

DRUGS TO BE GIVEN SUBCUTANEOUSLY VIA A SYRINGE DRIVER OVER 24 HOURS

Please see guidance on reverse of form for administration within a dose range

Date	For the relief of:	Drug	Dose Range to be given over 24 hours	Route : Sub Cutaneous	Signature in full Print name below

TRANSDERMAL OPIOIDS (do not commence for unstable pain)

At end of life continue if already effective and ADD sub cut medications to manage symptoms

Date	Drug Name	Dose	Renewal	Signature in full Print name below

REVIEW BY APPROPRIATE CLINICIAN AS SYMPTOMS OR LOCATION OF PATIENT ALTER

PRESCRIBING GUIDELINES

The information within these guidelines is referenced to and should be used in conjunction with Palliative Care Formulary 5, Palliative Adult Network Guidelines 2016, Scottish Palliative Care Guidelines 2016 and the current British National Formulary.

Prescribing responsibility remains with the prescriber.

Maximum doses may be extended and some maximum doses only to be used **following discussion** with a Specialist Palliative Care Clinician. Be aware of drug accumulation in **renal failure** and seek guidance below for alternative analgesia.

Please note that only Morphine, Diamorphine, Oxycodone and Levomepromazine are licensed for subcutaneous use. It is accepted practice in palliative care to administer other appropriate drugs via the subcutaneous route.

It is recommended that **no more than 3 drugs** are combined in one syringe unless advised by Specialist Palliative Care Team. Drug compatibility information can be found in the PCF5 and **book.pallcare.info** and **www.palliativedrugs.com**

Match oral / SC / Syringe driver medication i.e. oxycodone prn - oxycodone in syringe driver.
PRN doses may vary according to the need of the individual patient. PRN doses will need titration in line with regular analgesia dose adjustments

SYMPTOM / MEDICATION	PRN	SYRINGE DRIVER	MAX DOSES
PAIN / BREATHLESSNES			
Morphine	2.5mg - 5 mg 2 hourly OR 1/6th of daily syringe driver dose, 2 hourly	If opioid naïve usual starting dose 5mg. Calculate previous 24 hours total oral morphine dose and divide by **2**.	Increase should not be more than by a maximum of 50%
Diamorphine *Useful if large doses of morphine required (p.r.n. or syringe driver)*	2.5mg - 5mg 2 hourly OR 1/6th of daily syringe driver dose, 2 hourly	Calculate previous 24 hours total oral morphine dose and divide by **3.** ***(More potent than morphine)***	
Oxycodone	2.5mg - 5 mg 2 hourly OR 1/6th of daily syringe driver dose, 2 hourly	Calculate previous 24 hours oral oxycodone and divide by **2**. *NB not compatible with Cyclizine.*	
Alfentanil *(If EGFR <30, if available, otherwise use oxycodone with caution - reduce dose and frequency)*	125micrograms hourly OR 1/6th of daily syringe driver dose, hourly	If opioid naïve usual starting dose 500micrograms. Calculate equivalent SC dose of Diamorphine and divide by **10**.	
ANTI-SPASMODIC / OBSTRUCTION (IF OBSTRUCTION PLEASE SEEK SPECIALIST ADVICE)			
Hyoscine Butylbromide	20mg 2 hourly prn	60mg	120mg
NAUSEA & VOMITING			
Levomepromazine *Dilute with water for injection. However if the site reacts, try 0.9% sodium chloride.*	3.125mg - 12.5mg 2 hourly prn	6.25mg - 25mg	50mg
Haloperidol	500 micrograms - 3 mg 2 hourly prn	1.5mg	10mg
Metoclopramide	10mg 2 hourly prn	30mg - 60mg	100 mg
Cyclizine *Needs to be well diluted to prevent crystallisation and/or skin irritation. Should **never** be diluted in 0.9% sodium chloride*	50mg 8 hourly prn	100 - 150mg	150mg
CONFUSION / AGITATION / DELIRIUM			
Midazolam *Can also be used 2nd line for breathlessness*	2.5mg - 5mg 2 hourly prn	5mg - 30mg	60mg (100mg*) **** Under specialist advice only***
Levomepromazine *Use first for delirium*	3.125mg - 12.5mg 2 hourly prn	6.25mg - 50mg *Consider sedating effect if used in higher doses*	150mg (250mg*) **** Under specialist advice only***
RESPIRATORY SECRETIONS			
Hyoscine Butylbromide *If prn effective consider commencing syringe driver*	10mg - 20mg 2 hourly prn	40mg -100mg	120mg
EPILEPSY / SEIZURES			
Midazolam	5 - 10mg 2 hourly prn	20 mg when unable to swallow anti-epileptic medication or no IV access (seek specialist advice)	

TERMINAL CRISIS EVENT **Eg significant distressing bleed**	***If any potential for terminal crisis event seek specialist advice***

If symptoms do not respond please seek early advice. Contact a Macmillan Specialist Palliative Care Nurse OR St Barnabas Hospice 0300-303 1754 OR Thorpe Hall Hospice on: 01733 225900