Recommendations for treatment of patients with COVID-19 from the palliative care perspective V2.0

W. Nehls[1], S.Delis[1], B. Haberland[2], B.O. Maier[3], K. Sänger[1], G. Tessmer[4], L. Radbruch[5], C Bausewein[2]

1. Lungenklinik Heckeshorn, Klinik für Pneumologie, Helios Klinikum Emil von Behring, Berlin
2. LMU Klinikum, Klinik und Poliklinik für Palliativmedizin, München
3. Palliativmedizin und interdisziplinäre Onkologie, Med. Klinik III, St. Josefs-Hospital, Wiesbaden
4. Klinik für Pneumologie, Evangelische Lungenklinik, Berlin
5. Klinik für Palliativmedizin, Universitätsklinikum Bonn

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Introduction:

The current COVID-19 pandemic presents as a rapidly changing situation, touching palliative care at different aspects.

The Corona pandemic may lead to an accumulation of patients dying with breathlessness and anxiety in acute medical care which require competencies in the acute care setting that need to be supported by palliative care specialists (recommendation 1).

At the same time the provision of palliative care has to be maintained both in the inpatient and the home care setting despite of difficult operating conditions (recommendation 2)

In the current corona pandemic a number of questions need to be discussed, e.g. the definition of treatment goals, medical indications and assessment of the patient's will.

Recommendations on decision making related to resource allocation in the emergency and intensive care setting for patients with COVID-19 have been presented by the Working Group on Medical Ethics (Arbeitsgemeinschaft Ethik in der Medizin) in collaboration with other medical associations (including the German Association for Palliative Medicine) (https://www.divi.de/empfehlungen/publikationen/covid-19/1540-covid-19-ethik-empfehlung-v2/file).

The challenge of triage concepts in a scenario of limited intensive care capacities, including the potential consequence of discontinuation of intensive care that is no longer indicated because of deteriorating outcome prognosis has been discussed in detail in the position paper of the German Ethics Council (Deutscher Ethikrat) (https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/deutsch/ad-hoc-empfehlung-corona-krise.pdf).

As complex ethical dilemmata are to be expected, the definition of realistic patient-centred treatment goals requires palliative care expertise in the development of concepts as well as with individual clinical decisions.

Admission for inpatient treatment

With every inpatient admission the extent of potential treatment escalation should be defined, regardless of the actual specific health care situation.

The admitting physician should determine the extent of potential treatment escalation for every patient (see below for basic considerations on treatment escalation or treatment limitations).

Specifically, **clearly visible doctor's orders** have to be available for the following questions:	
Resuscitation	□ yes / □ no
Tracheal intubation	□ yes / □ no
Intensive care treatment	□ yes / □ no
NIV/High flow	□ yes / □ no

Other medical associations have recommended early endotracheal intubation for patients with acute respiratory failure from COVID-19 and without previously defined treatment limitations. If treatment limitations have been defined for invasive ventilation, patient preferences for non-invasive ventilatory support should be discussed early on.

This determination of treatment limitations may prevent patients receiving interventions that are not sensible in relation to severe comorbidities/underlying disease, helps palliative care patients to remain in their preferred place of care and supports the appropriate allocation of medical resources.

Decisions for or against medical interventions have to be carefully deliberated and present a major ethical challenge for the responsible physician. We recommend all services to check short-term options to support physicians with the ethical decision-making process on the site level. Members of the ethics committee, ethical counsellors, palliative care specialists and psychologists can be deployed at the hot spots (emergency room, isolation ward, intensive care etc) to support the decision-making processes in the pandemic. These support options should be available to staff as extensively and as early as possible.

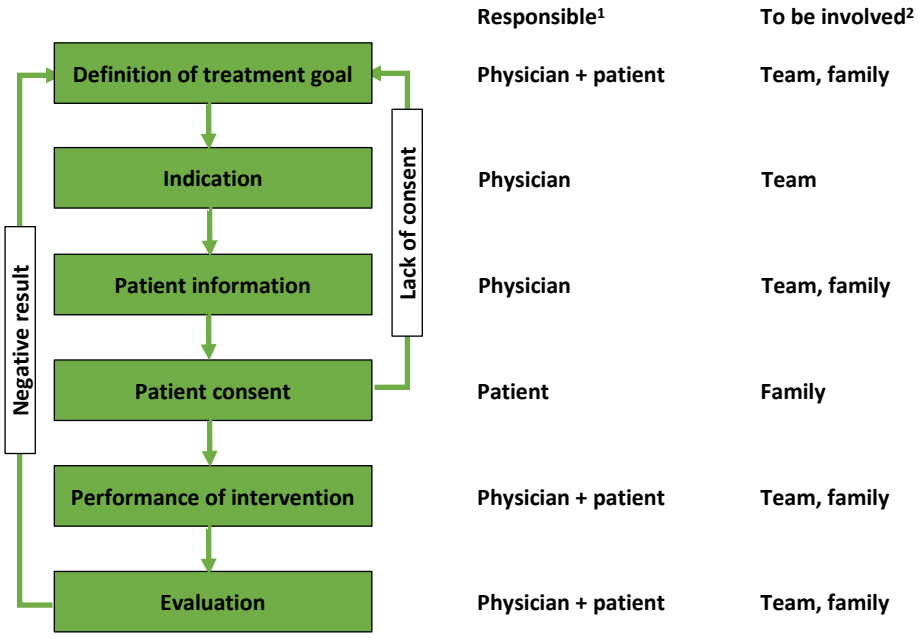
Basic considerations on treatment escalation or treatment limitations

Health care professionals treating a patient with acute COVID-19 infection with acute respiratory failure have to develop an awareness that this acute illness may represent the final stage of severe comorbidities. Palliative care with the aim of best possible relief of distressing symptoms is particularly relevant for these patients.

The following general principles should be considered for the decision-making process on the potential escalation of medical interventions. The mandatory prerequisite for any medical intervention is the medical indication, which has to be provided by the responsible physician based on the actual situation and knowledge of comorbidities. If a medical intervention cannot

achieve a realistic and patient-centered treatment goal, the intervention is not indicated and should not be offered to the patient. Identification of patient-centered treatment goals requires an evaluation of the preferences and priorities of the patient, either as the actual will of the patient, the mandated will (for example with an advance directive) or the presumed will of the patient. Treatment limitations should be determined as early as possible and should be discussed with the patient if possible, or with the surrogate decision maker. Family members should be informed about the decisions as well.

Figure: Algorithm for decision on and performance of medical interventions (Source: Guideline on palliative care for patients with incurable cancer, S3-Leitlinie Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung)



[1] The surrogate decision maker has to be involved if there are reasonable doubts about the decision-making capacity of the patient. This person is tasked with supporting the patient in the decision-making process and, if necessary, represent him in this process
[2] If medically advisable or requested by the patient

Recommendations for symptom control of patients with COVID-19

Clinical picture and leading complaints

The infection with COVID-19 is an acute disease with a clinical presentation of pneumonia and accompanying respiratory insufficiency. Thus, typical symptoms are breathlessness, cough, weakness and fever. In addition, anxiety, panic, restlessness and delirium have been described.

More specifically, patients who do not receive intensive care, with aggravating respiratory failure and high risk of dying, have a rapidly developing ARDS with acute and severe breathlessness and severe anxiety and panic, requiring rapid symptom control. The prognosis of these patients (without invasive ventilation) is limited to hours or a few days.

Symptomatic treatment of breathlessness of patients with COVID-19

If breathlessness persists despite optimal treatment of the acute disease, medical and non-medical measures should be used for symptom control (S3-Leitlinie Palliativmedizin).

Non-pharmacological interventions such as body positioning (leaning forward position, pillow support for arms etc), relaxation or cooling of the face with a cool towel (no hand-held fans to prevent dissemination of the aerosol) may alleviate mild breathlessness.

Oxygen or high flow oxygen may also relief breathlessness if intensive care and invasive ventilation are not indicated.

If breathlessness persists despite optimal treatment of the underlying disease, **pharmacological interventions** for symptom control should be implemented including the provision of oral or parenteral opioids. Slow-release opioids with constant drug levels show better symptom management than immediate-release application forms. However, with acute breathlessness and rapidly deteriorating patients rapid dose titration with immediate-release application forms applied regularly and as required should be preferred.

Avoidance of manipulations in the nasopharyngeal cavity

Manipulations in the nasopharyngeal cavity should be avoided, if possible, in patients with suspected or confirmed COVID-19 infection due to the high virus load in this area. To protect staff, this means that patients requiring support with taking oral medication, uncontrolled coughing or with secretions should not receive medications via the oral, transmucosal or intranasal route. Parenteral application routes should be preferred instead. The continuous application of opioids or midazolam usually requires an infusion pump. If no pump is available, medications can be injected subcutaneously or applied as a short infusion intravenously 4-hourly (see table B for dosages). In the home care setting, a subcutaneous needle can be left in place and family caregivers can be trained to provide repeated injections using that needle.

1. Recommendation for **opioid-naive patients able to take oral medications**

*Morphine slow release	10–0–10 mg**	(8.00 – 0 – 20.00)
Macrogol	1–0–0 package	
Supplement antiemetic if required: Haloperidol 0,5–1 mg at night and up to 2-hourly prn		
+ rescue medication as required, up to once per hour (immediate release opioids; 1/6 of the daily dosage)		
Morphine solution	2.5–5 mg**	(= 2-4 drops Morphine solution 2%)
alternatively Morphine i.v. short infusion/ s.c.		1–3 mg**
* or alternative opioids (Table A)/**rapid titration according to symptom intensity		

2. Recommendation for Patients already on opioids and able to take oral medications

- Increase dosage of slow-release opioids by 20%
- adapt rescue medication (immediate release opioids, 1/6 of daily dosage)
- **rescue medication as required, up to once per hour**
- continue constipation prophylaxis (f.e. Macrogol)

	Example:	**Increase by 20%**
*Morphine slow release	100–0–100 mg	**120–0–120 mg
+ * Morphine immediate release	30 mg prn	**40 mg prn up to once per hour.

Morphine dosages >240mg/d: change application route to parenteral (1/3 dosage - 10%)

* or alternative opioids (table A)/****rapid titration according to symptom intensity**

3. Recommendation for patients not able to take oral medications

Patients with **progressive respiratory failure and treatment limitations** in place (DNR/DNI) should receive parenteral opioids for relief of refractory breathlessness early on.

Opioid naive patients: ****Morphine 5-10** mg/24 h i.v./ s.c.

f.e. 50 mg *Morphine ad 50 ml NaCl 0.9%**,** concentration **1 mg/ ml,** ****Starting dose **0.4 ml/h**

Patients already on opioids:

Conversion of previous opioid dosage to continuous parenteral application (i.v. or s.c.)

Example: 150–0–150 mg Morphine p.o. equivalent to approx. 100 mg i.v./24 h

200 mg *Morphine ad 50 ml NaCl 0.9%**,** concentration **4 mg/ ml,** ****starting dose **1 ml/h**

*or alternative opioids (see table A) / ****rapid titration according to symptom intensity**

Table A: Equivalence dosages (C. Bausewein et al., Palliativmedizin pocketcard Set, 2016)

Opioid conversion table												
	Equivalence factor related to Morphine i.v.											
Tilidin/Naloxon p.o.	0,03	100	300	600								
Piritramid i.v.	0,7	5	15	30	45	60	75	90	150	225	300	450
Morphin p.o./rectal	0,3	10	30	60	90	120	150	180	300	450	600	900
Morphin s.c./i.v.	1	3,3	10	20	30	40	50	60	100	150	200	300
Hydromorphone p.o.	1,7	2	6	12	18	24	30	36	60	90	120	180
Hydromorphone s.c./i.v.	5	0,7	2	4	6	8	10	12	20	30	40	60
Opioid switch (rotation) requires a dose reduction of 30–50 %!												

Symptomatic treatment of cough

Patients with COVID-19 potentially suffer from dry cough, or from productive cough caused by bacterial superinfection. **Basic measures** include adequate ambient humidity, oral fluid intake, sucking sour candies or upright positioning of the upper body when sleeping as well as plant-based medicines (f.e. thyme cough solution 5-10 ml/8h).

Patients with productive cough should not receive anti-cough medications during daytime.

Pharmacological interventions

Morphine 3-5 mg p.o./4 h or continuously s.c./i.v. 5-10 mg/24 h

Noscapin 25–50 mg up to t.i.d.

Symptomatic treatment of death rattle

Death rattle will potentially occur in the final stage of life patients with COVID-19. Early provision of anti-secretory medication can prevent the development of secretions in the hypopharynx and trachea. However, already existing secretions will not be diminished. Repeated suction as well as parenteral fluids will increase secretions in dying patients.

Hyoscinebutylbromide continuously s.c./i.v. 40–80 mg/24 h and 20 mg prn up to once per hour

or

Glycopyrronium continuously s.c./i.v. 0.6–1.0 mg/24 h, 0.2 mg up to 2-hourly

Symptomatic treatment of restlessness and anxiety

Breathlessness is frequently related to restlessness and anxiety. Pharmacological interventions may be used to alleviate persisting signs of anxiety and restlessness. Patients with acute COVID-19 infection, respiratory insufficiency and the decision to limit invasive ventilation therapy require frequent assessment and rapid treatment of acute and exacerbating breathlessness and anxiety.

1. Recommendation for pharmacological treatment of anxiety and restlessness in patients with breathlessness, supplementing the opioid medication (example)

Lorazepam 1 mg p.o./s.l. (solution with 2 ml water if necessary) prn, up to once per 30 min

or

Midazolam 2.5-5 mg i.v. short infusion/s.c. prn, up to once per 30 min

2. Recommendation for the treatment of refractory anxiety and restlessness in patients with breathlessness

- early change to parenteral application route i.v. (or s.c.) continuously or 4-hourly - Midazolam-infusion pump (**in combination with morphine)** - starting dose: Midazolam 10 mg/24 h, titrate to effect
Example → 10 mg Midazolam ad 50 ml NaCl 0.9%, rate 2 ml/h *or* → Midazolam 2.5-5 mg short infusion/s.c. 4-hourly

Symptomatic treatment of acute agitation and delirium

Patients with COVID-19 infections frequently suffer from agitation or delirium caused by infection, hypoxemia or isolation. Agitation and delirium require timely interventions.

Potential causal factors have to be assessed and treated, including pain, constipation or full bladder.

Non-pharmacological interventions include assessment and treatment of potential causal factors, communication, provision of a quiet environment (well-lit and quiet room) and orientation for the patient (information on where and who the patient is, as well as on the actual situation he is in).

Predominantly **motor restlessness** (example) **Midazolam 2,5–5 mg** i.v. short infusion/s.c. prn, up to once per 30 min *or* **Lorazepam 0,5–1 mg** s.l./p.o. prn, up to once per 30 min *or* **Midazolam continuously** i.v. or s.c. 10 mg/24 h
Example → 10 mg Midazolam ad 50 ml NaCl 0.9%, rate 2 ml/h
Hallucinations and confusion **Haloperidol** 1-2 mg s.c. prn, up to once per 30 min *or* **Haloperidol** s.c. continuously 2–5 mg/24 h
Example → 5 mg Haloperidol ad 50 ml NaCl 0.9%, rate 2 ml/h

Palliative sedation

Patients with COVID-19 infection may require deep continuous sedation (palliative sedation) at the end of life to provide relief from **exacerbated breathlessness with fear of suffocation, anxiety and restlessness** to allow dying in peace. Palliative sedation is indicated when these symptoms are not alleviated (or alleviated not rapidly enough) with the interventions listed above.

Palliative sedation for refractory symptoms should be well documented. Following the initiation of palliative sedation residual symptom distress, level of sedation (with level of consciousness, vigilance) should be assessed regularly.

Medication	**Dosage**	**Comments**
Midazolam	Starting dose (example) 10–20 mg/24 hours s.c./i.v. Initial bolus of 1–5 mg s.c. or i.v. injection or short infusion, if required Maintenance dose 20–60 mg/24 h s.c./i.v.	For dosages ≥ 60 mg/24 h consider adding neuroleptic medication
Levomepromazine	Starting dose (example) 12.5–25 mg/24 hours s.c./i.v. Initially or as required bolus of 5–25 mg s.c./i.v. up to once per hour as short infusion if required Maintenance dose 12.5-100 mg/24 h (large range in the literature), alternatively regular bolus injections 2-3 times daily s.c./i.v. injection or short infusion	Supplemental medication if further dose increases of midazolam are not effective In addition to midazolam or for high dosages of midazolam ≥ 60 mg/24 hours

Specialist palliative care (palliative care unit, palliative care consultation service, specialist palliative home care service) should be contacted if palliative sedation with the recommended medications fails.

Table B: Recommendations for pharmacological symptom control for patients with COVID-19 and refractory breathlessness

Symptom		Continuous medication		PRN medication
		Slow-release p.o./ *or* **Continuous infusion pump i.v./s.c.**	**4-hourly i.v. short infusion/ s.c.** *(if infusion pump not available)*	***Symptom oriented Up to once per 30 min**
Breath-lessness *In combination with midazolam if required*	**Opioid-naive** Oral intake possible	*Morphine slow release p.o. 10–0-10 mg	*Morphine solution 2–5 mg 4-hourly (= 2-4 gtt morphine solution 2%)	*Morphine solution 2–5 mg *or* *Morphine i.v. short infusion/s.c.
	Opioid-naive i.v./s.c. application required	*Morphine 5-10 mg i.v./ s.c. / 24 h **Ex. 50 mg Morphine** ad 50 ml NaCl 0.9% concentration **1 mg/ ml.** ****starting dose 0,4 ml/h**	*Morphine 1-3 mg 4-hourly i.v. short infusion/ s.c.	*Morphine 1-3 mg i.v. short infusion/s.c.
	Already on opioids i.v./s.c. application required **(Ex.** Morphine 300 mg/ 24h p.o.)	**Ex. 200 mg Morphine** ad 50 ml NaCl 0,9% concentration **4 mg/ml**, ****starting dose 1 ml/h**	*Morphine 15 mg 4-hourly i.v. .short infusion/s.c.	*Morphine 10-15 mg i.v. slowly over 4 h short infusion/s.c.
Cough		*Morphine 5-10 mg/24 h s.c./i.v.	*Morphine liquid. 3-5 mg p.o./4 h Noscapin 25 – 50 mg up to t.i.d.	
Death rattle		Hyoscinebutylbromide s.c./i.v. 40–80 mg/ 24 h *or* Glycopyrrolate s.c./i.v. 0.6–1.0 mg/ 24 h		Hyoscinebutylbromide 20 mg up to once per hour Glycopyrrolate 0,2 mg up to 2-hourly
Restlessness/ Anxiety *Combination with morphine*	**Oral intake possible**	Lorazepam 1 mg s.l./p.o. (solution in 2 ml water if required)	Lorazepam 1 mg s.l./p.o. Midazolam 2,5-5 mg i.v. short infusion/s.c.	Lorazepam 1 mg s.l./p.o. Midazolam 2,5-5 mg i.v. short infusion/s.c.
	Parenteral application required	Midazolam 10 mg/24 h i.v./s.c. **Ex. 10 mg Midazolam** ad 50 ml NaCl 0,9% **2 ml/h**	Midazolam 2,5 - 5 mg short infusion/ s.c. 4-hourly	
Agitation and delirium	**Motor restlessness**	Midazolam 10 mg/24 h i.v./s.c. **Ex. 10 mg Midazolam** ad 50 ml NaCl 0,9% **2 ml/h**	Lorazepam 1 mg s.l./p.o. Midazolam 2,5-5 mg i.v. short infusion/s.c.	Lorazepam 1 mg s.l./p.o. Midazolam 2,5-5 mg i.v. short infusion/s.c.
	Hallucinations and delirium	Haloperidol 2–5 mg/24 h s.c. **Ex. 5 mg Haloperidol** ad 50 ml NaCl 0,9% **2 ml/h**	Haloperidol 1-2 mg s.c. 4-hourly	Haloperidol 1 - 2 mg s.c.

*Morphine as an example for other opioids, conversion using equivalent dosage ratios in table A if required

Rapid titration of continuous and prn medication if required

Tab. C Infusion pump dosages in relation to morphine daily dosages

Oral daily dosage of morphine	Infusion pump dosage	concentration mg/ ml	Infusion rate i.v.	Daily i.v./s.c. dosage of morphine
50 mg	50 mg/ 50 ml NaCl 0,9%	1 mg/ ml	0.6 ml/h	14.4 mg/ die
100 mg	100 mg/ 50 ml NaCl 0,9%	2 mg/ ml	0.6 ml/h	28.8 mg/ die
150 mg	100 mg/ 50 ml NaCl 0,9%	2 mg/ ml	1.0 ml/h	48 mg/ die
200 mg	100 mg/ 50 ml NaCl 0,9%	2 mg/ ml	1.4 ml/h	67.2 mg/ die
250 mg	100 mg/ 50 ml NaCl 0,9%	2 mg/ ml	1.8 ml/h	86.4 mg/ die
300 mg	200 mg/ 50 ml NaCl 0,9%	4 mg/ ml	1.0 ml/h	96 mg/ die
400 mg	200 mg/ 50 ml NaCl 0,9%	4 mg/ ml	1.4 ml/h	134.4 mg/ die