19. Palliative and end-of-life care

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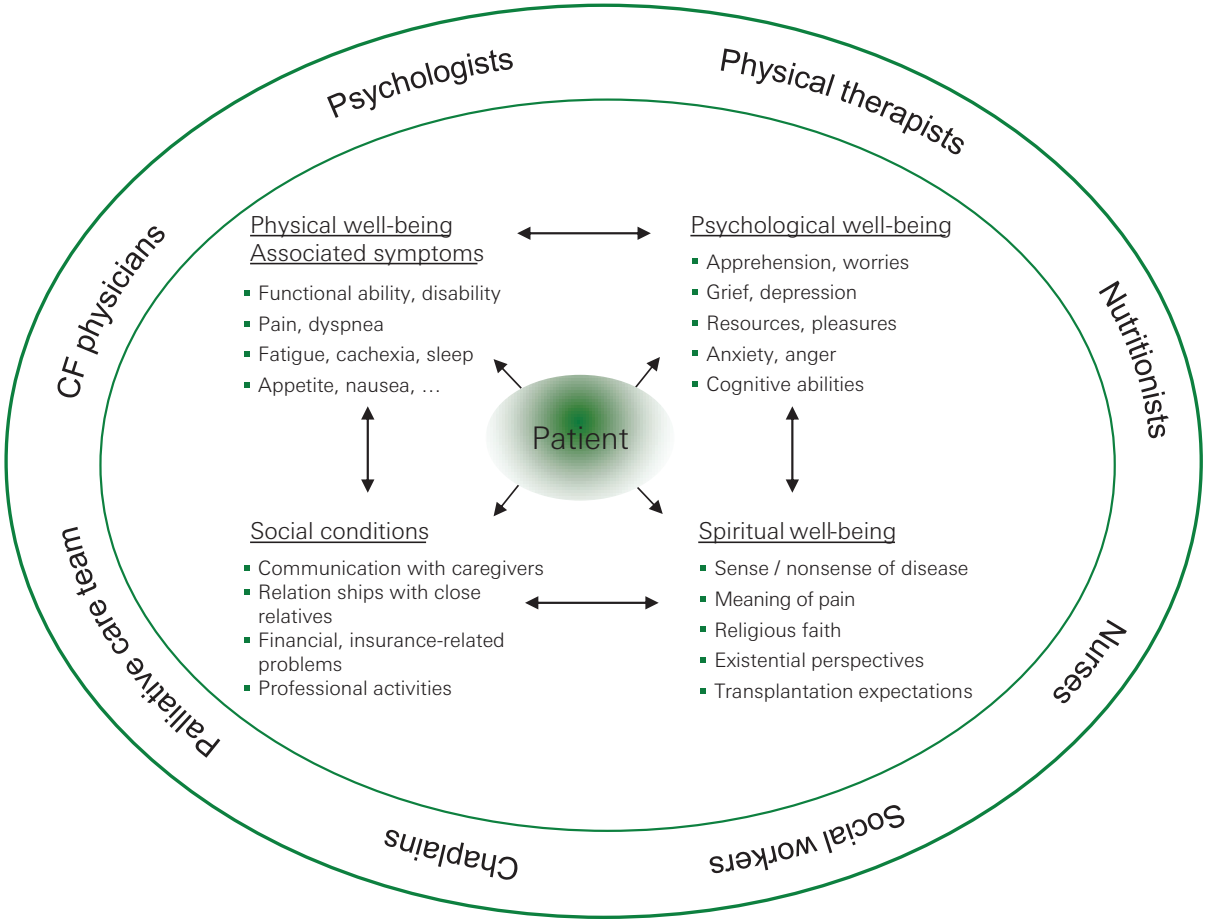
1. INTRODUCTION

- Palliative care is a multidisciplinary approach to improve the quality of life of patients and close relatives facing a life-threatening illness. It focuses on the prevention and relief of pain and suffering by means of an **early identification** and a **multidimensional assessment (Figure 1)** of medical, psychosocial and spiritual issues.
- **Palliative care is an essential component of CF care with which the CF team should be familiar.**
  - Palliative care should be integrated in the standard, multidisciplinary CF care trajectory. This becomes even more relevant with the aging of the CF population.
  - Palliative care should be available at any point along the course of disease, as soon as the patient experiences physical, psychosocial and/or spiritual needs.
  - For CF patients on a lung transplant waiting list, palliative care can be provided without compromising eligibility for transplant.
- The main barriers to access palliative care are:
  - Mistaken concept that palliative care is only reserved for end-of-life patients.
  - The CF clinical course is variable and unpredictable → recognition of the terminal phase may be difficult.
  - Difficulty of prognostication of an eventual lung transplantation.
- The Swiss association of palliative care (Palliative.ch) site http://www.palliative.ch/fr/home/ provides contact details of available palliative care teams.

2. ADVANCE DIRECTIVES (ADS) AND ADVANCE CARE PLANNING (ACP)

- Discussions about the evolution of the disease and end-of-life issues are a difficult but crucial and beneficial process for patients, close relatives and health providers:
  - They provide knowledge of the person's desires and needs, and they allow to respect the patient's individual wishes at the end of life.
  - They improve communication between the various partners.
- They are especially challenging for CF patients because of the unpredictable character of the disease course.
  - Only a minority of CF patients reports such discussions with the physician and completes any documentation related to ACP and/or ADs.
  - Some CF physicians are reluctant to discuss end-of-life issues with their patients. The main obstacles are difficulty of prognostication, conflicting needs of preparation for possible transplantation and simultaneously palliative care, concerns about removing hope from the patient and insufficient training and time to approach these issues.
  - However, the majority of CF adults report feeling comfortable talking about ACP with their close relatives and physicians, regardless of disease severity. Like other patients, CF patients often expect that the physician broaches this type of issues.
- The CF team should be helped by palliative care providers in establishing ADs and ACP.

Figure 1: Components of multidimensional assessment



2.1 Advance directives (living will)

- ADs were developed to highlight the role of **active and consent participation of the patient, with the aim of clarifying treatment choices in case of mental incapacity**. They are a national subject because of the new Swiss Adult protection law implemented since 2013. The aims of ADs are:
  - To state the patient's wishes in terms of life-sustaining treatment
  - To list specific treatments that the patient does not want
- An example of ADs helpful for CF patients is available on the website of Dialog Ethik (Interdisciplinary Institute of Ethics in Public Health, Zürich) at the address www.dialog-ethik.ch.
- However, interventions to promote ADs are partially reaching their goals related to a low rate of completion and various ethical and medical controversies. Therefore, experts have suggested a paradigm shift from ADs to a more holistic approach in the form of advance care planning (ACP).

2.2 Advance care planning

- ACP is defined as a **concerted and continuous process between the patient, his/her close relatives and health providers** with the **objective to define a common care orientation** to implement, following the patient's point of view. The aims of ACP are:
  - To take into account the factors that the patient considers as the most important priorities at the end of his/her life in term of needs, values and goals.
  - To involve close relatives and recognize their role as partners.
  - To improve the quality of dialogue between the different partners.
- A change in function resulting from disease progression, new physical and/or psychological symptoms and any other reasons are good opportunities to propose to the patient to start the process of ACP. Of course, such discussion must be deferred if patient is not ready to talk about these issues. For patients unwilling to participate in ACP and/or ADs, identification of a surrogate decision-maker should be encouraged.
- **Listening phase:** Exploratory listening phase with the patient and, if he/she agrees, with close relatives. This first phase often provides essential information on the patient's values and goals on which the therapeutic project can be built.
  - The main objectives of this phase are to understand the patient's:
    - Medical conditions (course of disease, complications, estimated survival) and level of desire for more information
    - Expectations and hopes (lung transplantation, birth of a child, death at home)
    - Fears and concerns
  - The card game called **"Go Wish"** available on the website http://gowish.org/ is a useful tool for this first step.
    - It is composed of 36 cards and it presents statements referring to personal needs, values and beliefs about end of life care.
    - The sentences cover four dimensions: 1) oneself, 2) care (technical, physical, relational and spiritual), 3) family and close relatives, 4) context and organization of the end of life.

- The physician asks the patient to sort the cards into three piles corresponding to high, medium or low importance for him/her. The patient chooses the ideas that are most important and relevant to him and explains why. The role of the physician is to promote discussion, clarify and request personal comments on the selected cards.

- **Continuous building phase:** ACP is a process that takes place over time during reiterated discussions with the physician. It incorporates biomedical, psychosocial, existential issues and treatment goals, and it results in a treatment plan centered on perspectives of the patient.
  - The scope of the discussions should be predicated on the general goals and priorities of care rather than on limiting life-sustaining treatments.
  - It is important for the CF patient to address specific medical issues (cardiopulmonary resuscitation, ventilator support, pulmonary transplantation, antibiotics and comfort care).
  - When the patient has concerns about the possibility of severe end-of-life symptoms, the measures to relieve these should be explained including discussion regarding palliative sedation. Then ACP may be easily supplemented by ADs.
- As the needs of the patient change during the progression of the disease, it is essential to **revisit ACP and/or ADs** annually, or sooner if the patient's medical condition changes.

3. PAIN

- About 50% of CF patients experience pain, often daily **(Table 1)**. The prevalence and the intensity of pain may increase significantly the last months prior to death.
- Pain negatively impacts the ability to participate in disease-related daily care and may lead to decreased mechanical airway clearance, which can worsen infections and promote exacerbations. It reduces the quality of life and it is associated with anxiety, depression, poorer physical functioning, sleeping disorders and restriction on daily and professional activities.

Table 1: Frequency of pain in CF according to location (adapted from[1])

Headache, sinus	25% - 64%
Chest pain	16% - 72%
Back pain	15% - 70%
Gastrointestinal pain	10% - 51%
Musculoskeletal pain	12% - 61%

3.1 Assessment of pain

- Assessment pain is the cornerstone to optimal analgesic management.
- **A systematic and regular evaluation is needed to make the correct diagnosis and to establish the most efficacious etiologic and symptomatic treatment plan.**

- Pain, like other symptoms, must be assessed with a multidimensional approach **(Table S1).**
- Pain is characterized as acute or chronic, and nociceptive, inflammatory and/or neuropathic. The distinction between inflammatory and neuropathic pain is crucial, for the choice of analgesics. The DN4 is a helpful tool to identify neuropathic pain **(Table S2)**.
- A regular self-reporting assessment of pain intensity, with the help of a visual analogue or numerical rating scale **(Figure S1)** is a critical step towards effective and individualized treatments.

3.2 Management of pain

- **Table 2** summarizes the basic principles of pain management**. Individualized pain management should take into account the characteristics and the intensity of pain as well as the comorbidities of the patient**.

Table 2: Basic principles of pain management

Target treatment to the underlying condition. When etiologic treatment is not available or not enough: effective, symptomatic analgesic treatment should be associated
Start the analgesic treatment with drugs indicated by the **WHO analgesic ladder (Table S3)** appropriate for the severity of pain, not the stage of the illness
Choose the oral route of administration of analgesic drugs as a first choice
For continuous daily pain, prescribe analgesic drugs on a regular basis schedule
For breakthrough pain prescribe rescue dose of medications
Anticipate breakthrough pain related to diagnostic or care procedures
Anticipate adverse effects of analgesic drugs **(Table S4)**
Treat neuropathic pain with co-analgesics and/or opioid drugs **(Table S6)**
Combine pharmacological treatment with non pharmacological approaches **(Table S7)**
Consider interventional analgesia in refractory pain
Note: Around-the-clock analgesia is defined as medication given at regularly intervals throughout the day, taking into account the half-life, bioavailability and duration of the analgesic. In contrast to medication given as needed, around-the-clock medication maintains stable analgesic blood and provides better pain control. It should be used when pain is present for 12 or more hours each day.

- **Opioids:**
  - Strong opioids are considered the mainstay of analgesic therapy in treating moderate to severe pain. Their main characteristics are summarized in **Table 3.**
  - There is no evidence that an opioid is superior to another in term of efficacy and tolerability. Morphine is considered the first choice.

- **Titration:**
  - Opioid doses should be titrated to induce satisfactory analgesia as rapidly as possible with acceptable side effects.
  - In this initial phase, opioids with a rapid onset of action and short half-life such as normal-release morphine are preferentially used (indicative starting doses in **Table 4)**. Patients should receive around-the-clock dosing with provision of a rescue dose (up to hourly) to manage breakthrough pain. The rescue dose is usually equivalent to 10% - 15% of the total daily dose.
  - If more than 4 rescue doses per day are necessary, the baseline opioid treatment has to be adapted.
  - When adequate analgesia is achieved, slow-release opioids, including transdermal formulations, can be introduced. Rescue medication has always to be maintained.
- **Adverse effects** of opioids are summarized in **Table S4**. Three different approaches are recommended: a) dose reduction of opioid, if possible, b) symptomatic management of the adverse effect or c) switching or rotation to another opioid.
- **Rotation or switching**: Opioid switching is the term given to the practice of substituting one strong opioid with another when a satisfactory balance between pain relief and adverse effects is not achieved despite an adequate titration of the first opioid. The rationale of opioid substitution is an incomplete cross-tolerance between strong opioids. Relative equianalgesic doses are detailed in **Table 3** and an example of opioid rotation is given in **Table S5**. There are three main indications for opioid rotation: a) Uncontrolled pain with the current opioid, b) intolerable adverse effects with the current opioid, c) convenience or preference of the patient.

- **Co-analgesics (adjuvants):**
  - Co-analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions.
  - They are used in neuropathic, bone (calcitonin, bisphosphonates), musculoskeletal (muscle relaxants) and abdominal pain (spasmolytics, octreotide, anticholinergics), alone or with an opioid. First-line drugs for the management of neuropathic pain are summarized in **Table S6.**
- **Other approaches:**
  - **Interventional analgesia:** Interventional techniques, such as intraspinal delivery of analgesics, reversible blockade with local anesthetics, spinal cord stimulation or ablation with radiofrequency energy or neurolytic agents, must been considered when pain is refractory to the pharmacological management.
  - **Non-pharmacological interventions (Table S7):** lack of knowledge about the effects of such interventions in cancer and non cancer patients but they can be very useful for individualized patients.

4. DYSPNEA

- With cough, dyspnea is the most prevalent symptom in CF patients. About 70% experience dyspnea either during pulmonary exacerbations or due to progression of pulmonary disease.

Table 3: Main characteristics of current strong opioids

Opioid	Relative equianalgesic doses	Route of administration	Formulation	Dosing interval	Pharmacokinetic interactions	Renal failure
Buprenorphine	– Morphine 10 mg PO : 0.2 mg buprenorphine SL – To refer to tables distributed by the manufactures for dose ratios	SL TD		8h 48-72h	– μ opioid antagonist – Inhibitors/ inducers CYP3A4	
Morphine	– 10 mg PO : 7-10 mg PR – 10 mg PO : 3-5 mg SC or IV	PO/PR PO/PR SC/IV	Normal-release Slow-release	4h 12h 4h		– ↓dose – ↑interval dosing
Hydromorphone	– Morphine 10 mg PO : hydromorphone 2 mg PO – Hydromorphone 2 mg PO : hydromorphone 1 mg SC or IV	PO PO SC/IV	Normal-release Slow-release	4h 12h 4h		– ↓dose – ↑interval dosing
Oxycodone	– Morphine 10 mg PO : oxycodone 5 mg PO – Oxycodone 10 mg PO : oxycodone 5 mg SC or IV	PO PO	Normal-release Slow-release	4h 12h	– Inhibitors/ inducers CYP3A4 (2D6)	– ↓dose – ↑interval dosing
Fentanyl	– Morphine 10 mg PO : 50 μg fentanyl SC – To refer to tables distributed by the manufactures for dose ratios	SC/IV TM TD		30 min 30 min 72h	– Inhibitors/ inducers CYP3A4	– ↓dose

PO: oral route; SC: subcutaneous route; SL: sublingual; IV: intravenous route; TD: transdermal route; PR: rectal route; TM: transmucosal route

Table 4: Indicative starting dosage in opioid-naïve adult patients (adapted from[2])

Opioid	PO	SC/IV
Morphine	5 -10 mg	2.5 - 5 mg
Hydromorphone	1 - 2 mg	0.5 -1 mg
Oxycodone	2.5 - 5 mg	1.25 - 2.5 mg
Fentanyl	N/A	25 μg/h

PO: oral route; SC: subcutaneous route; IV: intravenous route

- Dyspnea reduces quality of life and is associated with anxiety, sadness, poorer physical functioning, restriction on daily activities and sleeping difficulties. Acute attacks and terminal dyspnea are devastating for patients as they are associated with feelings of anxiety, fear and sensation of impending death.

4.1 Assessment of dyspnea

- Dyspnea is a subjective experience that includes physical elements and affective components. Its assessment and management requires a multidimensional approach:
  - **Qualitative assessment:** explores the duration, temporal patterns, and number of acute exacerbations to determine the best pharmacological symptomatic treatment (as need or/and around-the-clock prescriptions).
  - **Quantitative assessment:** evaluates the intensity of dyspnea with the help of a visual analogue or numerical rating scale to specify the type of symptomatic drugs and their doses.
  - **Multidimensional evaluation:** explores the psychosocial impact of dyspnea and the combined effects of other symptoms, especially anxiety, to establish the most efficient pharmacological and non-pharmacological individualized treatment plan.

4.2 Management of dyspnea

- It is essential to reverse what is reversible depending on the patient's physical and psychological conditions. Relatively small improvement on different components may give significant relief.
- The cornerstone of symptomatic pharmacological treatment is morphine, prescribed a) as need during transient acute episodes or b) around-the-clock for continuous dyspnea at rest. Anticipate adverse effects of opioid drugs **(Table S4).**
- Combine psychotropic drugs, such as phenothiazines or benzodiazepines, if anxiety persists despite the opioid treatment.
- Combine early non-pharmacological approaches with pharmacological treatment.
- Intensify communication with the patient and close relatives.
- Consider palliative sedation in terminal refractory dyspnea

4.3 Treament of dyspnea

- When etiologic treatment is unavailable or insufficiently effective, non-pharmacological and pharmacological symptomatic interventions should be associated **(Tables 6 and 7).**
- **Morphine and other strong opioids**
  - Morphine is considered the first line symptomatic treatment for dyspnea but other strong opioids may be tested, if morphine is contraindicated because of adverse effects.
  - Current data do not specify the initial dose of morphine. The titration of morphine and other strong opioids is similar to their analgesic use **(Section 4 of this chapter, Tables 3 and 4)**.
  - They can be administered via diverse routes suitable to patients' needs. For patients with terminal severe dyspnea, parenteral administration (subcutaneous intermittent or continuous injection, or intravenous infusion) is recommended. There is insufficient data to conclude whether nebulizer opioids are effective.
  - The side effects of opioids are presented in **Table S4**. When adequate opioid titration is performed, there is no evidence of deleterious effect on respiratory function.
- **Anxiolytic drugs:**
  - Dyspnea is frequently linked to anxiety in a vicious circle. Anxiolytics are often administered with the objective to break this link. However their effectiveness for the treatment of dyspnea is controversial.
  - Phenothiazines, such as levomepromazine, are often preferred to benzodiazepines when anxiolysis is needed in severe dyspnea. Levomepromazine can be administered orally or subcutaneously. Its anticholinergic effects are especially useful in dying patients with death rattle.
  - Regarding benzodiazepines, although there are no strong data in cancer patients and data are controversial in COPD patients, they are widely used in dyspneic patients with anxiety. It is recommended to choose an intermediate-acting substance, which should be without active metabolites and metabolized by conjugation, such as lorazepam and oxazepam.
  - Midazolam, a short-acting benzodiazepine, is only used in continuous subcutaneous or intravenous infusion for palliative sedation in terminally ill patients with unendurable and refractory dyspnea.
- **Anticholinergic drugs**
  - Anticholinergic drugs are used for the treatment of the death rattle in terminally ill patients (loss of effective reflexes for swallowing and coughing leading to accumulation of secretions in the pharynx and/or airways).
  - Anticholinergic drugs are equally effective but scopolamine (hyoscine hydrobromide) and atropine, which pass the blood-brain barrier, can cause central effects such as delirium or deep sedation. Hyoscine butylbromide and glycopyrrolate are better tolerated.
- **Non-pharmacological interventions**
  - They can be categorized according to two main mechanisms of action: a) interventions to improve breathing efficiency and b) approaches targeting the affective component of dyspnea (reduction of anxiety and distress). They are summarized in **Table 7.**
  - As symptomatic drugs for dyspnea are only partially successful, it is crucial to combine them early with approaches such as behavioral, psychosocial and environmental modification.
  - Physical therapy, inhalation therapy and invasive/non invasive ventilation are discussed in the corresponding chapters.

Table 6: Pharmacological symptomatic interventions for dyspnea and associated symptoms in adult CF patients

Symptom	Drug treatment	
Dyspnea		
– Opioid-naïve patient	– Morphine PO NR 2.5 - 5 mg/4h or – Morphine PO SR 10 mg/12h	– Morphine SC 2.5 mg/4h or – Morphine CSCII 15 mg/24h
	– And morphine PO NR 2.5 mg as needed (rescue dose)	– And morphine SC 2.5 mg as needed (rescue dose)
– Opioid-tolerant patient	Increase the daily dosage of 25%	
Anxiety		
	– Levomepromazine PO/SC 3 - 5 mg as needed or every 8 - 12h	
	– Lorazepam SL 1 mg as needed or every 6 -8h	
Secretions/ death rattle		
– Patient able to participate to airway clearance techniques	– Carbocisteine PO 750 mg/8h	
– Patient to weak to participate to airway clearance techniques	– Hyoscine butylbromide SC/IV 20 mg as needed or every 4h or in CSCII or – Glycopyrrolate SC/IV 200 µg as needed or every 4h or in CSCII or – (Atropine SC/IV 0.25 - 0.75 mg as needed or every 4h) – (Hyoscine hydrobromide: N/A)	

NR: normal release; SR: slow release; PO: orally; SC: subcutaneously; IV: intravenous; CSCII: continuous subcutaneous or intravenous infusion; SL: sublingually; N/A: not available in Switzerland

Table 7: Non pharmacological interventions for dyspnea and associated symptoms

Symptom	Non-pharmacological interventions
Dyspnea	– Oxygen if patient is hypoxic – Breathing training (pursed lip breathing, slowed pattern of breathing, prolonged exhalation, posture modification) – Walking aids – Neuro-electrical muscle stimulation – Chest wall vibration – Cool air fan – Relaxation techniques and cognitive behavioral therapy

Anxiety	– Reassurance, communication – Distraction – Relaxation techniques and cognitive behavioral therapy
Secretions/ death rattle	
– Patient able to perform airway clearance techniques	– Nebulized 0.9 - 7% saline/6h – Sputum clearance physiotherapy
– Patient too weak perform airway clearance techniques	– Reduction or withdrawal of parenteral fluids – Gentle suction in the nasopharynx and trachea – Postural drainage

5. SEDATION IN PALLIATIVE OR TERMINAL CARE

- Sedation in palliative or terminal care is the **monitored use of a sedative drug to relieve refractory and unendurable symptoms in a patient by inducing varied degrees of unconsciousness**.
  - A symptom is considerate refractory, when "it cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy, within an acceptable time frame and without unacceptable adverse effects".
  - This approach varies in terms of level of sedation (mild, intermediate or deep) and duration (intermittent or continuous).
  - The aim of sedation is to relieve suffering, not to hasten death. If modalities of its use are rigorously applied, it does rarely shorten life.
- **Table 8** summarizes the main indications, contraindications and preconditions of terminal care.
- **Table 9** provides details on information and consent.

5.1 Titration, maintenance and monitoring of sedation

- **Choice of the sedative drug**
  - **Table S9** presents the main drugs used for sedation.
  - Midazolam is the most commonly used drug because of its short half-life, rapid onset of action and relatively easy use.
  - Other sedative drugs have a long half-life with difficult reversal of sedation (levomepromazine, phenobarbital) or require the presence of an experienced physician (propofol). Their advantages, disadvantages and adverse effects are summarized in **Table S9.**
  - Opioids are contraindicated because they have weak sedative effects. Sedation will occur only at high toxic doses (risk of neurotoxicity, such as delirium, and respiratory depression). They should be given or continued only to relieve pain and/or dyspnea.
- **Table 10** summarizes the phases of midazolam titration and maintenance.
- **Table 11** summarizes sedation monitoring.

Table 8: Main indications and contraindications of sedation in palliative care

Indications

– Refractory symptoms: terminal dyspnea, delirium, pain, seizures
– Catastrophic events: hemorrhage, asphyxiation
– Respite sedation of psychological or existential suffering

Contraindications

– Unconscious and peaceful patient
– Unconscious but uncomfortable patient: investigate the causes of discomfort to target the symptomatic treatment

Preconditions

– Discuss early with the CF patient at risk of refractory symptoms or catastrophic events the goals and modalities of sedation
– Reserve this approach only for palliative or terminally ill patients with symptoms or overall level of suffering that may be considered refractory
– Verify the refractory nature symptoms or suffering by a multidisciplinary team with sufficient experience and expertise in palliative care
– Explain to the participating staff members the rationale for sedation and goals of care
– Select the level of sedation (lowest necessary to provide adequate relief from suffering).
  • Mild and intermittent sedation is generally used to provide temporary relief whilst waiting for benefic effects from other therapeutic attempts.
  • Continuous deep sedation is used for terminal patients with severe and irreversible refractory symptoms or catastrophic events.
– Record in the patient's medical file: the rationale for sedation, the decision-making process, the aims of sedation and the planned depth and duration of sedation.

Table 9: Information and consent regarding sedation in palliative care

In a patient with decisional capacity, the aims, benefits and risks of the sedation should be discussed before obtaining his consent. The main issues to address are:

– Cause of the distress, treatments attempted, limitations of current options of care
– Rationale for the decision of the sedation
– Aims and method of planned sedation (mild or deep, intermittent or continuous, type of monitoring)
– Anticipated effects on consciousness levels and communication
– Potential risks (paradoxical agitation, inadequate relief, hastened death)
– Continuation of medical treatments and nursing care to maximize comfort
– Other treatment options if sedation is not performed
– With the patient's consent, it is recommended to conduct this discussion with the participation of the close relatives.

If the patient lacks decisional capacity and had not supplemented ADs, consent needs to be obtained from a surrogate decision-maker or family member in accordance with the new Swiss Adult protection law.

Table 10: Midazolam titration, maintenance and dose adaptation during sedation in palliative care

Titration phase	BIGORIO best practice recommendations propose to induce sedation with intravenous or subcutaneous bolus of midazolam. The starting dose is: – SC midazolam 1 - 2.5 mg every 10 - 15 minutes or – IV midazolam 0.5 - 1 mg every 5 minutes until adequate relief of suffering with a minimum suppression of the consciousness level and undesirable effects.
Maintenance phase	When appropriate relief of suffering is achieved, start immediately a continuous subcutaneous or intravenous infusion of midazolam. The dosage per hour is the 50% of the total dose given during the titration phase.
When and how to increase the dose	In an acute, catastrophic event: combine bolus given repetitively with the continuous infusion of midazolam. In a stable situation with unsatisactory relief, increase dose of continuous infusion of midazolam of 1 mg every hour until adequate relief.
When and how to decrease the dose	If the patient experiences heavy snoring and abrupt onset of apnea. At the patient's request related to a event such as family visit: stop the perfusion or decrease the dosage of 50% six hours before the event.

Table 11: Monitoring of palliative sedation

Patient	– Level of consciousness (depth of sedation) – Relief of suffering – Potential adverse effects of sedation Monitoring modalities: – In the first 15 minutes of the sedation, a constant presence of a health care provider is needed. – In the first hour, assess every 15 minutes: • Heart and respiratory rate • Blood pressure • Oxygen saturation • Depth of sedation with a scale (for example Rudkin, **Figure S8**) • Relief of suffering (verbal comments of the patient, facial expressions, body movements or posture) – Then, assess these items every two hours or less often, according to the location of care, the goals of sedation (intermittent or deep sedation) and the level of relief from suffering. Various guidelines propose an assessment at least 3x/d.
Family and professionals	– Psychological and spiritual distress

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S19. Palliative and end-of-life care

Table S1: Multidimensional components of pain assessment

1. Qualitative evaluation		
– Characteristics	– Words to describe pain: DN4 **(Table S2)**	Distinguish between inflammatory and neuropathic pain
– Duration, temporal patterns of the pain	– Occasionally – Continuous – Induced by daily activity or procedure	Constant pain requires around-the-clock analgesia
– Localization(s)	– Often more than one localization	
– Number of break-through pains		Transitory episodes of pain that occur on a background of pain, moderate to severe intensity, rapid onset and relatively short duration
– Irradiation(s)	– Absence/presence of radiating pain	Distribution of pain on nerve pathway suggests neuropathic pain
– Aggravating/alleviating factors	– Aggravating factors such as movement, physical therapy, difficulty sleeping – Alleviating factors such as analgesics, massage, relaxation, biofeedback, heat or cold	Determine benefits of pharmacological and non pharmacological approaches
2. Quantitative evaluation (Figure S1)		
– Intensity of pain	– Visual analogue scale – Numerical rating scale	Determine the type of analgesics according to WHO pain ladders
3. Multidimensional evaluation (Figure 1)		
– Interference of pain – Impact of pain, disease and psychological and social conditions – Presence and intensity of other physical and/or psychological symptoms associated with CF	– Daily activities – Work – Social life – Sleep patterns – Appetite – Sexual functioning – Mood and well-being – Coping	

(continued)

4. Continuous evaluation		
	– Regular self reporting assessment of pain intensity with the help of a visual analogue or a numerical rating scale	Adapt analgesic treatment according to response to drugs, adverse effects, and disease progression

Table S2: DN4 tool to identify neuropathic pain [Adapted from Bouhassira D et al. Pain 2005;114(1-2):29-36]

1) Interview of the patient			
	Question 1: Does the pain have one or more of the following characteristics?	yes	no
	1. Burning	☐	☐
	2. Painful cold	☐	☐
	3. Electric shocks	☐	☐
	Question 2: Is the pain associated with one or more of the following symptoms in the same area?	yes	no
	4. Tingling	☐	☐
	5. Pins and Needles	☐	☐
	6. Numbness	☐	☐
	7. Itching	☐	☐
2) Examination of the patient			
	Question 3: Is the pain located in an area where the physical examination reveals one or more of the following characteristics?	yes	no
	8. Touch hypoesthesia	☐	☐
	9. Pricking hypoesthesia	☐	☐
	Question 4: In the painful area, can the pain be caused or increased by:	yes	no
	10. Brushing	☐	☐
Total score		☐/10	

Interpretation: If the patient's score is ≥ 4, the test is positive for neuropathic pain (sensitivity: 82.9%; specificity: 89.9%)

Figure S1 : Current tools of intensity pain assessment

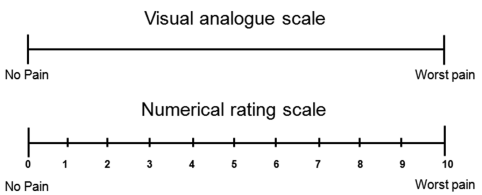
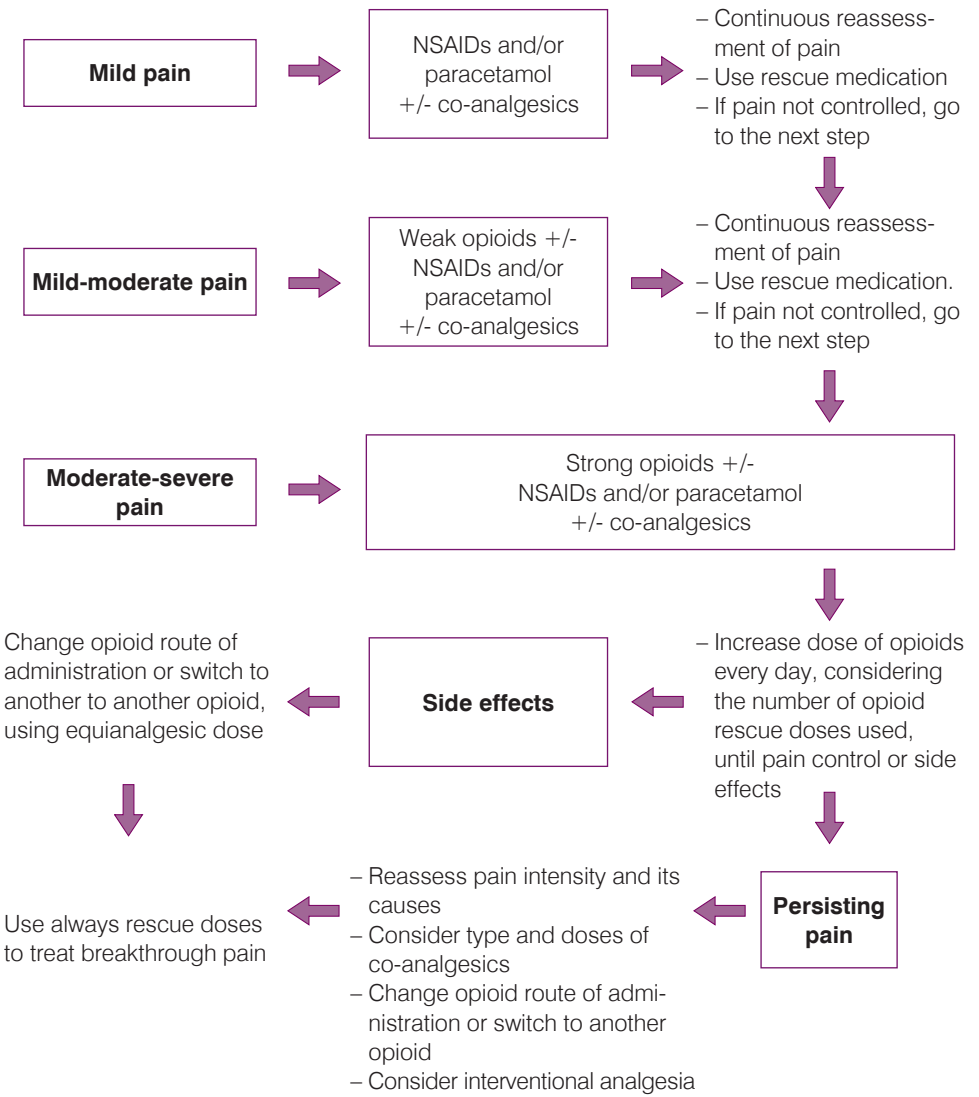


Table S3: The WHO analgesic ladder [adapted from Ripamonti CI et al. Ann Oncol 2012;23(Suppl 7): vii139-54]. The WHO 3-step pain ladder is widely accepted and adopted for selecting analgesics among patients with cancer and non-cancer pain



Co-analgesics such as anticonvulsivants, antidepressants should be considered at any step, if necessary

Table S4: Common opioid-induced adverse effects

Adverse effect	Prevalence	Tolerance	Management
Constipation	40% - 100%	No	– Patient education – Systematic daily prophylaxis – Osmotic laxatives (polyethylene glycols as first line) and stimulants laxatives (picosulfate sodique, bisacodyl)
Nausea, vomiting	15% - 30%	Yes	– Slow titration – Symptomatic treatment: Metoclopramide or haloperidol as first line – Opioid rotation
Drowsiness	20% - 60%	Yes	– Slow titration – Opioid rotation – Psychostimulant (methylphenidate)
Neurotoxicity – Delirium – Hallucinations – Myoclonus – Deep sedation	?	No	– Speedy opioid rotation – Hydration – Haloperidol if delirium
Pruritus	2% - 10%	?	– Antihistamines – Opioid rotation (fentanyl) – Serotonin 5-HT3 antagonist (ondansetron)
Respiratory depression	Exceptional	Yes	– Naloxone

Table S5: Recommendations for switching opioids [adapted from Fine PG et al. J Pain Symptom Manage 2009;38(3):418-91]

Step 1	
– Calculate the equianalgesic dose of the new opioid based on the equianalgesic table **(Table 6)**	For example, switching from morphine 100 mg/24h to oxycodone: – Morphine to oxycodone ratio 2:1 – Morphine 100 mg/24h = oxycodone 50 mg/24h
Step 2	
– If switching to any opioid other than methadone or fentanyl, identify a dose reduction window of 0% to 50% lower than the calculated equianalgesic dose	1) No reduction of the dosage: – Presence of persistent pain 2) 25% reduction of the dosage: – Young patient, caucasian patient – Low dose of the current opioid

3) 50% reduction of the dosage:
   – Older patient
   – Renal failure, comorbidities
   – High dose of the current opioid

Step 3

– Assess pain intensity frequently and titrate the dose of the new opioid to optimize analgesia.
– If a rescue dose is used for titration, calculate this at 10%–15% of the total daily opioid dose and administer at an appropriate interval.

Table S6: First-line drugs for neuropathic pain [adapted from Dworkin RH et al. Arch Neurol 2003; 60(11):1524-34, Finnerup NB et al. Lancet Neurol 2015;14(2):162-73)]

Drug class	Starting dose	Titration	Maximum dose	Titration duration	Cautions
Anticonvulsants					– Renal failure
– Gabapentine	100 - 300 mg/8h	↑ by 100-300 mg/24h every 1 to 7 days as tolerated	3600 mg/24h	3 - 8 wk	
– Pregabaline	25 - 50 mg/12h	↑ by 50-100 mg/24h every 1 to 7 days as tolerated	600 mg/24h	3 - 8 wk	
Antidepressants					
– Tricyclic antidepressants					– Cardio-toxicity – Drug interactions
– Nortriptyline	10 - 25 mg/24h	↑ by 25mg/24h every 3 to 7 days as tolerated	75 - 150 mg/24h	6 - 8 wk	
– SNRIs*					– Hepatic failure
– Duloxetine	30 mg/24h	↑ by 30 mg/24h every 7 days as tolerated	120 mg/24h	3 wk	

(continued)

Strong opioids					
– Morphine	5 - 10 mg/4h	↑ by steps of 20% every 1 to 7 days as tolerated	No maximal dosage	2 - 4 wk	– Renal failure
5% Lidocaïne patch	one patch once a day for up to 12h	None needed	3 patches once a day for up to 12h	2 wk	

* SNRIs: Serotonin/norepinephrine reuptake inhibitors

Table S7: Non-pharmacological interventions for pain [adapted from Hokka M et al. J Adv Nurs 2014;70(9):1954-69]

Physical modalities	Cognitive modalities
– Bed, bath and walking supports	– Imagery / Hypnosis
– Position instruction, physical therapy	– Distraction training
– Energy conservation, pacing of activities	– Relaxation training
– Massage	– Active coping training
– Heat and/or ice	– Cognitive behavioral training
– Transcutaneous electrical nerve stimulation(TENS)	– Spiritual care
	– Creating outlets, such as music

Table S8: Rudkin scale to monitor the patient's level of consciousness

Level of consciousness	
1	Fully awake
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation
5	Eyes closed and unrousable to mild physical stimulation

Table S9: Main drugs used in sedation

Drug class		Advantages	Adverse effects Precautions	Disadvantages
Midazolam	– Drug of first choice	– Rapid onset – Short half-life – Therapeutic safety margin – Anxiolytic – Anticonvulsant and muscle relaxant – Easy titration – Easy use by continuous subcutaneous or intravenous infusion	– Paradoxical agitation → change of drug class – Respiratory depression – Withdrawal if rapid reduction of dose after extended infusion	– Tolerance
Levopromazine	– Refractory delirium	– Rapid onset – Antipsychotic effect in delirium – Analgesic effect?	– Orthostatic hypotension – Paradoxical agitation – Extrapyramidal symptoms – Anticholinergic effects – Skin irritation	– Long half-life with difficult reversal of sedation
Propofol	– Severe agitation – Drug of last resort	– Rapid onset – Short half-life – Rapid titration – Rapid washout	– Hypotension – Respiratory depression	– Only by continuous intravenous infusion – Frequent dose adjustments – Presence of an experienced physician
Phenobarbital	– Severe agitation – Drug of last resort	– In case of tolerance to other medications – Rapid onset – Anticonvulsant	– Paradoxical excitation in high doses – Respiratory depression – Hypotension – Skin irritation	– Long half-life with difficult reversal of sedation