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A Dutch paediatric palliative care guideline: a systematic review and evidence-based recommendations for symptom treatment

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Abstract

Background Children with life-threatening and life-limiting conditions can experience high levels of suffering due to multiple distressing symptoms that result in poor quality of life and increase risk of long-term distress in their family members. High quality symptom treatment is needed for all these children and their families, even more so at the end-of-life. In this paper, we provide evidence-based recommendations for symptom treatment in paediatric palliative patients to optimize care.

Methods A multidisciplinary panel of 56 experts in paediatric palliative care and nine (bereaved) parents was established to develop recommendations on symptom treatment in paediatric palliative care including anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition. Recommendations were based on evidence from a systematic literature search, additional literature sources (such as guidelines), clinical expertise, and patient and family values. We used the GRADE methodology for appraisal of evidence. Parents were included in the guideline panel to ensure the representation of patient and family values.

Results We included a total of 18 studies that reported on the effects of specific (non) pharmacological interventions to treat symptoms in paediatric palliative care. A few of these interventions showed significant improvement in symptom relief. This evidence could only (partly) answer eight out of 27 clinical questions. We included 29 guidelines and two textbooks as additional literature to deal with lack of evidence. In total, we formulated 221 recommendations on symptom treatment in paediatric palliative care based on evidence, additional literature, clinical expertise, and patient and family values.

Conclusion Even though available evidence on symptom-related paediatric palliative care interventions has increased, there still is a paucity of evidence in paediatric palliative care. We urge for international multidisciplinary multi-institutional collaboration to perform high-quality research and contribute to the optimization of symptom relief in palliative care for all children worldwide.

Keywords Clinical practice guideline, Evidence-based medicine, Paediatric palliative care, Symptom treatment

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Background

Worldwide, there are approximately 21 million children with conditions that can benefit from a palliative care approach [1]. Of these children, more than eight million need specialized paediatric palliative care [1, 2]. In the Netherlands, it is estimated that 7000 children, adolescents and young adults aged 0 to 20 years are living with life-threatening or life-limiting conditions and need palliative care [3]. Approximately, 23% of these children are diagnosed with oncological conditions and 77% have complex chronic conditions such as neonatal, neurological, or metabolic disorders [4, 5]. Annually, 1000 children die due to the consequences of these conditions [5]. All these children and their families require paediatric palliative care that focuses on improving quality of life and alleviating physical, psychological, social, and spiritual suffering [6].

As all children with life-threatening or life-limiting conditions can experience multiple distressing symptoms, high quality symptom treatment is an essential component of paediatric palliative care [2]. Previous international studies have reported high levels of suffering in children with cancer, complex chronic conditions, and advanced heart disease due to symptoms such as pain, dyspnoea, and fatigue [7–10]. Parents reported that these symptoms, which are often amenable to treatment, are insufficiently controlled [9, 10]. High levels of suffering due to symptoms decrease health-related quality of life in children and adolescents with life-threatening or life-limiting conditions [11, 12]. Poor quality of life affects not only the child but the whole family including parents and siblings [8, 13]. It also increases the risk of long-term distress in surviving family members [14]. Clearly, there is room for improvement in easing distress due to symptoms in these children. This is even more evident at the end of life, when suffering tends to worsen and attempts to control symptoms with traditional symptom-directed interventions are more likely to be unsuccessful [10, 15].

High quality symptom treatment should be ensured for all children with life-threatening or life-limiting conditions and their families. Clinical Practice Guidelines (CPGs) are powerful instruments that can facilitate consistent, efficient, and high-quality care by translating evidence into recommendations for clinical practice [16–18]. As a result, CPGs can contribute to the integration of high-quality palliative care into daily practice.

In 2013, the first Dutch CPG for Paediatric Palliative Care was published and provided the first recommendations on symptom treatment [19, 20]. Almost a decade after the development of the first Dutch CPG for paediatric palliative care, stakeholders expressed the need for an update and expansion of the CPG. Most importantly, health care providers and parents requested guidance on symptom treatment including treatment of refractory symptoms at the end-of life. Additionally, recommendations needed to be updated with evidence from new scientific literature. As a result, the first Dutch CPG for Paediatric Palliative care is revised and updated with recommendations on topics that were not covered in the first CPG [21].

The revised CPG provides recommendations on symptom treatment, advance care planning, shared decision-making, organisation of care, psychosocial care, and loss and bereavement care [21]. In this paper, we present the recommendations on symptom treatment and give an overview of the most recent evidence that was used to base recommendations upon. The recommendations on advance care planning, shared decision-making, and organisation of care; and psychosocial care and loss and bereavement care will be presented in two subsequent papers.

Methods

The full methodology of the Dutch CPG for paediatric palliative care has been published in a separate paper [22].

Scope

This guideline provides guidance on palliative care for all children aged 0 to 18 years with life- threatening or life-limiting conditions, their caregivers, and siblings (hereafter referred to as families) throughout the entire palliative trajectory (from palliative diagnosis till after end-of-life), with the ultimate goal to improve quality of palliative care and thereby quality of life of children and their families [6]. In this paper we provide recommendations for symptom treatment.

Multidisciplinary guideline development panel

The guideline development panel consisted of an expert panel of 56 professionals with expertise in paediatric palliative care and a panel of nine (bereaved) parents (Appendix A). Professionals from multiple disciplines such as psychologists, neurologists, paediatricians, nurse practitioners, dermatologists, anaesthesiologists, intensivists, physical and occupational therapists, and specialists in paediatric rehabilitation and intellectual disabilities were included in the guideline panel. Professionals were selected based on their experience with paediatric palliative care, of whom some had specific certified training in this field. Within the guideline development panel, a core group of 11 experts was established to ensure consistency throughout the guideline. The other 45 experts were appointed to working groups (WGs) that focused on symptom treatment (WG 1) and refractory symptom treatment (WG 2). WGs covered multiple topics for which sub-WGs were established. WG 1 consisted of 11 sub-WGs that focused on non-pharmacological and

pharmacological interventions of anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, and fatigue. WG 2 focused on paediatric palliative sedation and forgoing hydration and nutrition. All topics were selected based on priorities of health care providers and parents [22]. An overview of the working structure and guideline development process is shown in Appendix B and C.

Representation of patients and their families

Different methods were used to include perspectives of children and their families [22]. Two members of the core group were dedicated to ensure representation of child and family and their values during the entire guideline process. Additionally, a diverse panel consisting of nine (bereaved) parents of children with life-threatening or life-limiting conditions reviewed the first drafts of all guideline texts and recommendations and reviewed the complete concept guideline. We ensured that the panel represented a broad spectrum of experiences regarding paediatric palliative care by including parents of children with a variety of palliative conditions, age, and stage of disease (currently receiving palliative care or deceased).

Formulation of clinical questions

The two WGs formulated a total of 27 clinical questions (Appendix D). WG1 formulated 24 clinical questions on the effect non-pharmacological and pharmacological interventions for symptom treatment. WG 2 formulated three clinical questions that focused on the effect of paediatric palliative sedation and the effect of forgoing hydration and nutrition.

Search strategy and selection criteria

For the 27 clinical questions, we updated the literature search that was conducted for the former CPG (2013) [19] identifying randomized controlled trials (RCTs), controlled clinical trials (CCTs), or systematic reviews (SRs) of RCTs and CCTs on paediatric palliative care interventions (last update, January 24, 2020) (Appendix E). Studies were selected according to inclusion criteria related to study design (RCTs, CCTs, SRs of RCTs and CCTs), study population (children aged 0 to 18 with a life-threatening or life-limiting condition, according to the definition of the World Health Organization [6]) and study subject (paediatric palliative care interventions related to symptom treatment). Only studies published in English or Dutch language were included. Studies that described interventions on complementary or alternative medicine were excluded (Appendix F). We also searched for eligible studies in reference lists of included studies and identified SRs, guidelines, and textbooks. Moreover, we asked WG members to provide eligible studies.

Summary and appraisal of evidence

To answer the clinical questions, we summarized included studies in evidence tables. We categorized evidence by outcome measures in summary of findings tables. Then, we formulated conclusions of evidence for each outcome measure. The quality of the total body of evidence was graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [22]. Study selection, summary and appraisal of evidence and formulation of conclusions was performed by one independent reviewer [22]. All processes were checked by members of the core group. In case the systematic literature search would yield little to no evidence, we searched for textbooks on paediatric palliative care and existing evidence-based guidelines on general paediatrics, and paediatric and adult palliative care in several guideline databases (Appendix E). Textbooks and guidelines were included if they were deemed relevant for the topics addressed in the (sub) WGs (Appendix F). We used textbooks and recommendations from guidelines to refine considerations and recommendations for this guideline.

Translating evidence into recommendations

When translating the evidence into recommendations, several factors were taken into account: (1) the quality of the evidence (the higher the quality of evidence, the more likely it is to formulate a strong recommendation), (2) additional literature including textbooks and guidelines, (3) patient and family values and needs, (4) clinical expertise, (5) acceptability (legal and ethical considerations), (6) feasibility (sufficient time, knowledge, and manpower), and (7) benefits versus harms of the interventions. For each clinical question, WG members described the relevant considerations. Decisions regarding the final formulation of the recommendations were made through group consensus.

The strength of each recommendation was graded according to published evidence-based methods (appendix G) [23, 24]. Recommendations were categorised as strong to do (green), moderate to do (yellow) or strong not to do (red).

Results

Identification of evidence and additional literature

The systematic search for RCTs, CCTs and SRs of RCTs and CCTs on paediatric palliative care interventions yielded 5078 studies of which 168 were subjected to full-text screening. A total of 18 studies (three SRs of RCTs and 15 RCTs) on non-pharmacological and pharmacological interventions to treat symptoms were included (Appendix H). Furthermore, we included two textbooks, and 29 CPGs (six paediatric palliative care CPGs, 11 general paediatric CPGs and 12 adult palliative care CPGs) as additional literature to deal with lack of evidence (Appendix I).

Table 1 Conclusions of evidence on symptom treatment in paediatric palliative care [25–41]

Effect of (non) pharmacological interventions for symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions	
Anxiety and depression	**Quality of evidence**
Unknown effect of nonpharmacological and pharmacological treatment	No studies
Delirium	**Quality of evidence**
Unknown effect of nonpharmacological and pharmacological treatment (preventive treatment, antipsychotics, and benzodiazepines)	No studies
Dyspnoea	**Quality of evidence**
Walking with non-invasive ventilation vs. walking without non-invasive ventilation in children with cystic fibrosis No significant effect on *degree of dyspnoea* ↑ *exercise capacity* (walking distance; no significant effect on peripheral oxygen saturation, heart rate, respiratory rate) ↑ *pulmonary function* (forced expiratory volume in the first second, minute volume, tidal volume, and pulmonary ribcage volume; no significant effect on other parameters)	⊕⊖⊖⊖ VERY LOW (1RCT) [25]
High intensity training vs. low intensity training in children with cystic fibrosis No significant effect on *degree of dyspnoea* ↑ *exercise capacity* (inspirational muscle endurance; no significant effect on other parameters) No significant effect on *pulmonary function* (forced expiratory volume in the first second and forced vital capacity)	⊕⊖⊖⊖ VERY LOW (1RCT) [26]
Unknown effect of other nonpharmacological treatment (physical therapy, ventilator use, oxygen, relaxation, and distraction techniques) and pharmacological treatment (opioids, benzodiazepines, corticosteroids, dilators and mucolytics)	No studies
Haematological symptoms	**Quality of evidence**
Erythropoietin (Epoetin Alfa) vs. no treatment or placebo in children with cancer No significant effect on *haemoglobin levels* (in one study, haemoglobin levels did increase in the intervention group; no significant effect) No significant effect on the *number of required blood cell transfusions* Most common *adverse effects* in both intervention and control group were hypertension, fever, infection, and mucositis	⊕⊕⊖⊖ LOW (2 RCTs) [27, 28]
Erythropoietin (Epoetin Alfa) vs. placebo in children with cancer No significant effect on *quality of life*	⊕⊕⊖⊖ LOW (1RCT) [28]
Unknown effect of other pharmacological treatment for anaemia (vitamins, iron, and erythrocyte transfusions), pharmacological treatment for thrombocytopenia (thrombocyte transfusions), pharmacological treatment for bleeding, and pharmacological treatment for thrombosis	No studies
Coughing	**Quality of evidence**
Unknown effect of nonpharmacological (postural advice, physical therapy for sputum mobilization) and pharmacological treatment (non-opioids, opioids, nebulization with saline or cold steam)	No studies
Skin complaints	**Quality of evidence**
Naloxon infusion vs. placebo in children with post-operative opioid-induced side effects ↓ *incidence of pruritus*	⊕⊖⊖⊖ VERY LOW (1RCT) [29]
Unknown effect of nonpharmacological treatment for pruritus and other pharmacological treatment for pruritus and pressure ulcers	No studies
Nausea and vomiting	**Quality of evidence**
Self-hypnosis vs. standard treatment with anti-emetics in children with cancer ↓ *supplemental anti-emetic medication* no significant effect on *nausea and vomiting* ↓ *anticipatory nausea* 1 to 2 months post diagnosis no significant effect on *anticipatory nausea* 4 to 6 months post diagnosis	⊕⊖⊖⊖ VERY LOW (1RCT) [30]
High dose ondansetron or low dose ondansetron vs. placebo in children with cancer ↓ *incidence emetic episodes* within 24h	⊕⊕⊕⊖ MODERATE (1RCT) [31]
High dose ondansetron vs. low dose ondansetron no significant effect on *incidence of emetic episodes* within 24h	⊕⊕⊕⊖ MODERATE (2RCTs) [31, 32]
no significant effect on *nausea severity* within 24h	⊕⊖⊖⊖ VERY LOW (1RCT) [32]
High dose ondansetron + dexamethasone vs. low dose ondansetron + dexamethasone in children with cancer ↓ *incidence of emetic episodes* and *nausea severity* within 24h	⊕⊖⊖⊖ VERY LOW (1RCT) [32]

Table 1 (continued)

Ondansetron vs. metoclopramide ↓ *incidence of emetic episodes* and *nausea severity* within 24h ↓ extrapyramidal symptoms as *adverse effect* after intervention	⊕⊖⊖⊖ VERY LOW (1RCT) [33]
Granisetron vs. ondansetron in children with cancer no significant effect on *incidence of emetic episodes* and *nausea severity* within 24h Most common reported *adverse effects* in both treatment groups was headache (unclear if significant difference).	⊕⊖⊖⊖ VERY LOW (1RCT) [34]
Granisetron vs. tropisetron in children with cancer ↓ *incidence emetic episodes* and *nausea severity* within 24h Most common reported *adverse effects* in both treatment groups were headache and constipation.	⊕⊖⊖⊖ VERY LOW (1RCT) [35]
Aprepipant + dexamethasone + ondansetron vs. dexamethasone + ondansetron in children with cancer ↓ *incidence emetic episodes* within 24h (unclear if significant)	⊕⊖⊖⊖ VERY LOW (1RCT) [36]
Midazolam vs. placebo; dexamethasone vs. placebo; midazolam + dexamethasone vs. placebo in children undergoing surgery ↓ *incidence of emetic episodes* and *incidence of nausea* within 24h	⊕⊖⊖⊖ VERY LOW (1RCT) [37]
Midazolam vs. dexamethasone in children undergoing surgery ↓ *incidence of emetic episodes* within 24h no significant effect on *incidence of nausea* within 24h	⊕⊖⊖⊖ VERY LOW (1RCT) [37]
Neurological symptoms	**Quality of evidence**
Botulinum Toxin-A injections and occupational therapy (OT) vs. OT (and intramuscular sham) in children with cerebral palsy ↑ *parent-reported treatment efficacy* (long-term effect might be dependent on the number of injections)	⊕⊕⊖⊖ LOW (2RCTs) [38, 39]
Botulinum Toxin-A injections and OT vs. OT in children with cerebral palsy ↓ *spasticity levels of upper limbs* (forearm and wrists) No significant effect on *motor performance*	⊕⊖⊖⊖ VERY LOW (1RCT) [38]
Botulinum Toxin-A injections and OT vs. intramuscular sham and OT in children with cerebral palsy No significant effect on *quality of life*	⊕⊖⊖⊖ VERY LOW (1RCT) [39]
Unknown effect of nonpharmacological treatment for spasticity (physical therapy and OT), and other pharmacological treatment for spasticity (baclofen, benzodiazepines)	No studies
Unknown effect of nonpharmacological treatment for epilepsy (ketogenic diet and psychological interventions) and pharmacological treatment for epilepsy (seizure treatment, seizure maintenance treatment, and refractory epilepsy treatment)	No studies
Unknown effect of (non)pharmacological for movement disorders	No studies
Unknown effect of (non)pharmacological treatment for neurological deficits (bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucinations, hearing problems, swallowing difficulties, problems with talking, loss of strength and urinary retention)	No studies
Pain	**Quality of evidence**
Cognitive behavioural therapy vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury) ↓ *child symptoms (post-treatment)*	⊕⊖⊖⊖ VERY LOW (12 RCTs) [40]
No significant effect on *child symptoms (follow-up)*	⊕⊖⊖⊖ VERY LOW (7 RCTs) [40]
Family therapy for parents vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury) No significant effect on *child symptoms (post-treatment)*	⊕⊕⊖⊖ LOW (5 RCTs)(40)
No significant effect on *child symptoms (follow-up)*	⊕⊖⊖⊖ VERY LOW (2 RCTs) [40]
Problem-solving therapy for parents vs. control in children with chronic illness (painful conditions, cancer, diabetes, asthma, traumatic brain injury) No significant effect on *child symptoms (post-treatment)*	⊕⊕⊖⊖ LOW (2 RCTs) [40]
Multi-systemic therapy for parents vs. control No significant effect on *child symptoms (post-treatment)*	⊕⊕⊖⊖ VERY LOW (4 RCTs) [40]
No significant effect on *child symptoms (follow-up)*	⊕⊕⊖⊖ LOW (2 RCTs) [40]
Intrathecal baclofen vs. placebo or therapy as normal in children with cerebral palsy ↓ *pain* Most common *adverse effects* in both intervention and control group were related to Cerebrospinal Fluid Leakage	⊕⊖⊖⊖ VERY LOW (3 RCTs) [41]

[a] In the systematic review of Wiffen et al., no evidence on the effect of opioids on cancer-related pain was identified [42]

Evidence

The evidence tables and summary of findings tables are presented in Appendix J and K and the conclusions of evidence are shown in Table 1.

Studies reported on the effects of the following specific interventions: non-invasive ventilation [25] and high intensity training [26] for dyspnoea; erythropoietin for anaemia (haematological symptoms) [27, 28]; naloxone for pruritus (skin complaints) [29]; self-hypnosis [30] and anti-emetics including ondansetron [31–33], metoclopramide [33], granisetron [34, 35], tropisetron [35], aprepipant [36], midazolam [37] and dexamethasone [37] for nausea and vomiting; botulinum toxin-A injections and occupational therapy [38, 39] for spasticity (neurological symptoms); and psychological interventions for parents including cognitive behavioural therapy, family therapy, problem-solving therapy and multi-systemic therapy [40] and adjuvant medication including intrathecal baclofen, botulinum toxin A injections, oral alendronate, oral risedronate and intravenous pamidronate [41] for pain.

A few interventions showed significant improvement in relief of symptoms or quality of life among children with life-threatening or life-limiting conditions. Non-invasive ventilation and high intensity training significantly improved exercise capacity in children with cystic fibrosis (very low quality evidence) [25, 26]. One study showed that treatment with naloxone significantly decreased incidence of pruritus in children who received opioids postoperatively (very low quality evidence). Regarding nausea and vomiting, self-hypnosis significantly decreased supplemental anti-emetic medication use and anticipatory nausea in children with cancer (very low quality evidence) [30]. In addition, most anti-emetic medication including ondansetron, granisetron, aprepipant, midazolam and dexamethasone significantly decreased the incidence of emetic episodes and/or nausea severity (very low to moderate quality evidence) [31–37]. Concerning interventions for neurological symptoms, botulinum toxin-A injections significantly decreased spasticity levels of upper limbs and significantly increased parent-reported efficacy in children with cerebral palsy (very low to low quality evidence) [38, 39]. Furthermore, cognitive behavioural therapy for parents significantly decreased child symptoms including pain in children with chronic illnesses (very low quality evidence) [40]. Additionally, oral alendronate decreased pain in children with osteogenesis imperfecta (low quality evidence) [41].

For other interventions no significant effects were found. This included treatment with erythropoietin to improve anaemia in children with cancer (low quality evidence) [27, 28]. Regarding pain in children with chronic illnesses, no significant effect was found for family therapy, problem-solving therapy, and multi-systemic therapy for parents which aimed to improve child symptoms (very low to low quality evidence) [40]. Also, botulinum toxin A injections, oral risedronate, and intravenous pamidronate did not significantly decrease pain (very low to low quality evidence) [41]. Furthermore, the effect of opioids on cancer-related pain remains unknown, as the systematic review did not identify any studies on this topic [42].

Additional literature

Because there was limited evidence on paediatric palliative care interventions, we identified additional literature. The relevant recommendations from 29 guidelines on paediatric palliative care, general paediatrics and adult paediatric palliative care [43–71] and the textbooks [72, 73] on paediatric palliative care were used to refine considerations and recommendations.

Translating evidence into recommendations

Recommendations were based upon the evidence, additional literature, clinical expertise, patient and family values, and other considerations such as costs and availability of medication. All members of the guideline development panel agreed that quality of life and values and needs of the child and family should be the main focus of every treatment-related decision. This was the starting point in the process of formulating recommendations.

Clinical experts, patient representatives and parents identified other key aspects that frequently influenced treatment-related recommendations. In addition to the treatment effects, the expected burden of treatment on the child was considered. Physical therapy techniques, for instance, can help to relief suffering due to coughing but are physically challenging and can only be considered if the child is willing and able to perform these techniques. Moreover, the adverse effects of potential interventions were considered. For example, starting antipsychotics to treat delirium carry a high risk of adverse effects [70]. Health care providers should be aware of these adverse effects of antipsychotics and monitor daily. If adverse effects occur, other medication should be considered. Finally, the child's life-expectancy or prognosis is of importance. For example, vitamins and nutritional supplements should not be given to children with anaemia if life expectancy is short.

When formulating recommendations on paediatric palliative sedation and forgoing hydration and nutrition, clinical experts and parent representatives acknowledged the importance of thoughtful communication and careful preparation of all processes related to end-of-life care. Therefore, recommendations on refractory symptom treatment covered the entire process of paediatric palliative sedation and forgoing hydration and nutrition including communication, preparation, execution, and evaluation.

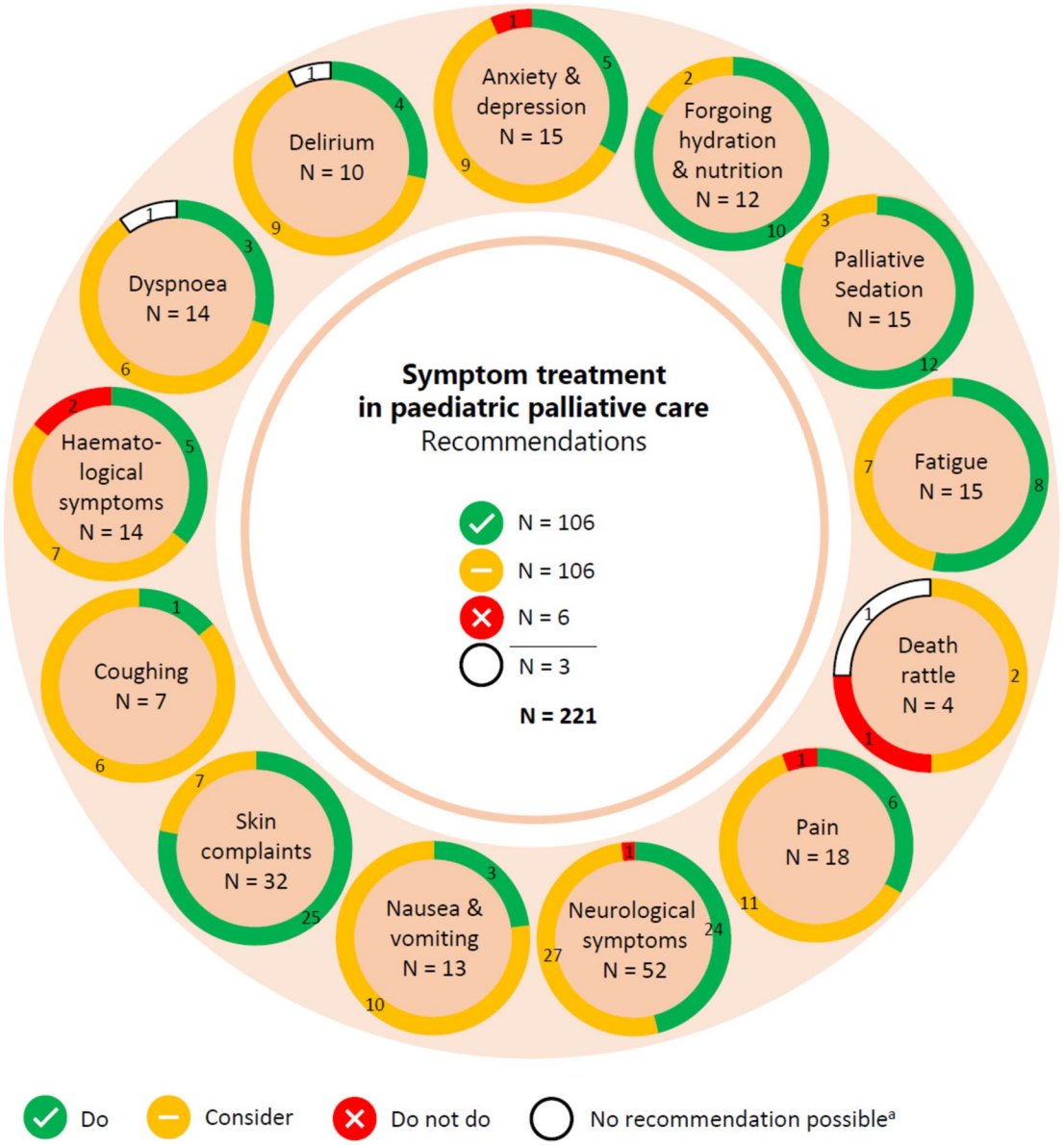

Fig. 1 Number and strength of recommendations on symptom treatment in paediatric palliative care

a It was not possible to formulate a recommendation due to insufficient evidence and lack of consensus among experts

We formulated a total of 221 recommendations on (non-)pharmacological treatment of anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition. Based on the level of evidence and other factors such as patient and family values, clinical expertise, and benefits and harms of the intervention, we formulated 106 strong recommendations to do (green), 106 weak recommendations to consider (yellow) and six strong recommendations not to do (red). In three situations, there was insufficient evidence and lack of consensus among experts to determine whether the benefits of the specific intervention outweigh potential harms. As a result, it was not possible to formulate a recommendation. In Fig. 1 we provide an overview of the number of recommendations on symptom treatment per topic. All recommendations are shown in Tables 2 and 3.

Table 2 Recommendations on symptom treatment in paediatric palliative care

Recommendations on (non)pharmacological symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=194) [a]	
Anxiety and depression	
Nonpharmacological treatment of anxiety and depression	
Do	Provide psychoeducation about the symptoms.
	Organize a day/week structure with attention to rituals, emotion-focused activities and activities that are "as normal as possible" (recovery-oriented).
	Involve a registered psychosocial counsellor with experience in palliative care when deploying counselling or treatment.
Consider	For anxiety, consider engaging experts in self-management in the form of mindfulness, relaxation, self-hypnosis, or guided fantasy.
Pharmacological treatment of anxiety and depression	
Pharmacological treatment for anxiety	
Do	Discuss the use and initiation of medication with a child psychiatrist experienced in palliative care or a paediatrician.
	When initiating medication, consider whether supporting psychotherapy is appropriate and feasible.
Consider	For anxiety reduction in dying children, consider intranasal midazolam.
	For acute anxiety, consider intranasal midazolam or oral lorazepam.
	For acute anxiety in pediatric delirium or psychotic dysregulation, consider antipsychotics (risperidone, haloperidol).
Pharmacological treatment for depression	
Consider	Consider use of medication in consultation with a child psychiatrist experienced in palliative care or a paediatrician.
	When using medication, consider whether supportive psychological therapy is appropriate and feasible.
	For moderate to severe depression in children 8 years and older, consider fluoxetine.
	Consider SSRIs especially for children with cancer.
	Consider methylphenidate.
Do not	Do not administer TCAs because of the potential for serious adverse effects and the need for determinations of blood levels.
Nonpharmacological treatment of delirium	
Do	Deploy, whenever possible, non-medical interventions focused on prevention, orientation, communication, matching stimuli, and safety to treat paediatric delirium.
	Involve parents in the child's care as much as possible.
	Delirium is an intense experience for all involved. Provide adequate (after) care for the child and family, environment, and caregivers (in the form of training).
Pharmacological treatment of delirium	
Pharmacological treatment for prevention of paediatric delirium	
NA[b]	Opinions on the use of drug treatment for prevention of paediatric delirium, for example with antipsychotics, cannot be substantiated due to lack of evidence.
Antipsychotics (haloperidol, risperidone, and quetiapine)	
Consider	In children with delirium, consider treatment with medication if non-drug interventions do not have a sufficiently rapid effect.
	Depending on the adverse effects profile, drug interactions and available routes of administration, a choice may be made between risperidone or haloperidol.
	In case of non-response or adverse reaction to first administered drug (haloperidol or risperidone), consider switching drugs or administering quetiapine.
	When starting antipsychotics, be alert to side effects including extrapyramidal symptoms and prolongation of QT interval.
	For severe acute dystonia as a side effect of medication requiring treatment, consider biperidene.
Benzodiazepines	
Consider	In children in the terminal phase with refractory delirium, consider palliative sedation.
Dyspnoea	
Nonpharmacological treatment of dyspnoea	
High-intensity training	
NA[b]	High-intensity training appears to have no effect on dyspnoea compared with low-intensity training. The application of high-intensity training cannot be substantiated. Therefore, giving a recommendation is not possible. [c]
Physical therapy techniques	
Do	Provide information and advice on breathing exercises and other physical therapy techniques (see also: Coughing - physical therapy techniques for sputum mobilisation).
Consider	Consider employing a physical therapist to apply physical therapy techniques, such as breathing exercises and alternating positions (see also: Coughing - physical therapy techniques for sputum mobilisation).
Non-invasive ventilation	
Consider	In cases of dyspnoea due to Cystic Fibrosis, consider non-invasive ventilation. [c]
Use of a ventilator	

Table 2 (continued)

Consider	Consider the use of a 'hand-held' fan to cool the face
Oxygen	
Consider	Consider administering oxygen as a trial treatment. Stop administering oxygen if it does not work.
Relaxation and distraction techniques	
Do	Create a calm environment.
Consider	Consider bringing in experts for self-hypnosis.
	Consider relaxation and distraction techniques and the use of comfort talk.
Pharmacological treatment of dyspnoea	
Opioids and benzodiazepines	
Do	Give fentanyl nasal spray intranasally for rapid treatment and anxiety reduction.
	Start morphine orally, intravenously, or subcutaneously if the shortness of breath causes discomfort.
Consider	Consider lorazepam or midazolam (in combination with morphine) to reduce perceived discomfort, especially if anxiety is also present.
Corticosteroids, dilators and mucolytics	
Consider	In cases of dyspnoea arising from airway swelling, atelectasis, or broncho-obstruction, consider dexamethasone, other steroids, pulmonary dilators or mucolytics.
Treatment of refractory dyspnoea	
Consider	In In terminally ill children with refractory dyspnoea, consider palliative sedation.
Haematological symptoms	
Pharmacological treatment of anaemia	
Erythropoietin	
Do not	Do not give erythropoietin in chemotherapy-associated anaemia. [c]
Vitamins & iron	
Do not	Do not give vitamins and nutritional supplements to treat anaemia if life expectancy is short.
Erythrocyte transfusions	
Do	In children with long-term anaemia with bone marrow failure (e.g., MDS) in the palliative phase, adopt an individual transfusion policy based on perceived quality of life.
	In hematologic children with anaemia based on bone marrow failure, give erythrocyte transfusion on an individual basis at an Hb between 4.3-5.0 mmol/L or with symptoms of anaemia.
Pharmacological treatment of thrombocytopenia	
Thrombocyte transfusions	
Do	Adhere to the platelet limits from the national transfusion guideline in palliative procedures (such as placement of an epidural catheter).
Consider	In children with thrombocytopenia due to production disorder, consider adhering to the transfusion limits from the national transfusion guideline: • a prophylactic platelet transfusion in case of a platelet count lower than 10 x 10^9/L. in case of a WHO grade 2 haemorrhages, a thrombocyte transfusion in case of platelets lower than 30 x 10^9/L. • with bleeding WHO grade 3 or 4 a platelet transfusion with platelets lower than 100 x 10^9/L.
	Before a particular physical activity with risk of bleeding, consider a platelet transfusion
Pharmacological treatment of bleeding	
Do	Treat nasal bleeding with local adrenaline, xylometazoline, spongostan or possibly local coagulation by ENT physician.
	Consult with a paediatric surgeon when local bleeding cannot be easily stopped.
Consider	In bleeding due to thrombocytopathy, consider desmopressin (DDAVP).
	For persistent or severe bleeding tendency due to coagulation factor deficiency, consider vitamin K, FFP and/or recombinant factor VII.
	In thrombocytopenia and mucosal bleeding (nasal, gum bleeding, menorrhagia) anti-fibrinolytic medication to reduce bleeding tendency. Do not give fibrinolytic drugs in haematuria.
	If bleeding occurs, consider platelet transfusion: see section on platelet transfusion.
Pharmacological treatment of thrombosis	
Consider	Consider giving a direct-acting oral anticoagulants (DOAC) for symptomatic thrombosis.
Coughing	
Nonpharmacological treatment of coughing	
Postural advice	
Consider	If coughing is productive, consider placing the child in a sitting or standing position.
Physical therapy techniques for sputum mobilization	

Table 2 (continued)

Consider	Apply physical therapy techniques for sputum mobilization such as breathing exercises, air stacking, compression, cough machine 'cough assist', postural drainage, PEP, and huffing.
	Discuss with child and parents that physical therapy techniques should be discontinued if the child continues to weaken, and treatment becomes too burdensome.
Pharmacological treatment of coughing	
Non-opioids	
Consider	If coughing is nocturnal, consider administering honey or dextromethorphan.
Opioids	
Do	Start opioids orally or parenteral if coughing causes discomfort. Here, morphine is the first choice.
Consider	Consider noscapine or codeine. Effect has not been demonstrated in cough.
Nebulization with saline or cold steam	
Consider	Consider nebulization with physiological or hypertonic saline or cold steam
Skin complaints	
Pressure ulcers	
Nonpharmacological treatment of pressure ulcers	
Do	Determine whether wound healing or symptom relief is the goal of treatment.
	Assess the wound for infection, pain, fragility, oedema, colour, odour, and deterioration
	Clean the wound (especially for yellow or black wounds and/or odour issues) by flushing with tap water once daily.
	Choose a wound dressing appropriate to the wound. Use the classification model in 'het WCS wondenboek' [e] (also available as an app) for this purpose, if necessary.
	Choose dressing materials that meet a wide range of requirements if more symptoms occur, such as odour, extreme exudate formation and bleeding tendency.
	Indicate rapidly occurring changes in the skin and respond to them promptly.
	Limit the smell of the wound by using: • antiseptic agents • topical metronidazole gel • antimicrobial dressings • charcoal dressings • Use odour neutralizers such as cat litter or activated charcoal
	If necessary, involve a (paediatric) physical therapist, occupational therapist, or medical device manufacturer in using assistive devices or making adjustments so that skin lesions are less stressed.
Nonpharmacological treatment of pressure ulcers	
Consider	Consider treatment of pain due to wounds
	Consider surgical debridement of necrotic tissue to promote wound healing and prevent/heal infections.
Fungating wounds	
(Non)pharmacological treatment of fungating wounds	
Do	Provide clear information to child and family about fungating wounds. Explain that priority is given to the child's comfort and pay attention to the psychosocial consequences of the cancerous ulcer. Provide psychosocial and/or spiritual support if necessary.
	If possible, treat the underlying malignancy
	Clean the wound and care for it using wound dressings and locally or systemically administered medications.
	Treat factors that adversely affect the fungating wound, such as poor nutrition/hydration status, pressure spots, oedema formation.
Radiodermatitis	
(Non)pharmacological treatment of fungating wounds	
Do	Grade the degree of severity of radiodermatitis using the NCI/CTCAE table and tailor treatment accordingly.
Blisters and blister-related disorders	
(Non)pharmacological treatment of blisters and blister-related disorders	
Do	Determine the reason for blistering (exogenous or endogenous or a combination).
	Provide understandable information to child and family about the risks of fragile skin with blisters or skin with a tendency to blister.
	Prevent expansion of blistering by recognising and avoiding external factors as much as possible.
	Inspect the entire skin at least daily and record where the blistering is and where it is about to occur (often red or grey skin abnormalities).
	Make arrangements with any cooperating (multidisciplinary) healthcare provider regarding care for the prevention/treatment of blistering and consult or refer to a dermatologist/specialist in the field of blisters.
Itching	
Nonpharmacological treatment of itching	

Table 2 (continued)

Do	Take good care of the skin.
	Prevent skin irritation.
	Pay attention to mental well-being.
Consider	In children with itching, consider using ointments based on skin condition.
	In children with itching, consider complementary therapy, such as hypnosis.
Pharmacological treatment of itching	
Local treatment	
Do	Treat dry skin.
	In children with itching due to eczematous skin abnormalities, alternate cream with corticosteroids with a neutral cream. Preferably let cream with corticosteroids soak in for 30 min before applying oily ointment over it.
	In children with itching due to fungal infections, use topical antimycotics such as miconazole cream (2dd) or terbinafine cream (1dd).
	Use in children with itching due to bacterial infections, • antibacterial agents such as chlorhexidine 0·5% in 70% alcohol with 1% glycerine 85% (chlorhexidine spirit FNA). • disinfectants such as disinfecting soaps or betadine scrub (dissolved and not applied directly to the skin, supplemented, if necessary, with fusidic acid ointment 2%). • hygienic measures (own towel).
Systemic treatment	
Consider	Consider pharmacological treatment of itching depending on the cause, in accordance with the paediatric formulary.
	For itching due to cholestasis, consider stent placement for (bile) flow obstruction, naloxone (provided the child is not on opioids), colestyramine or ondansetron (be cautious in use). [c]
	For itching due to other causes or itching non-responsive to other agents, consider a sedative antihistamine.
Nausea and vomiting	
Nonpharmacological treatment of nausea and vomiting	
Do	Discuss with child and/or parents the role of nutrition and its possible change in relation to life expectancy.
	Educate about various options when fluids and nutrition are not well tolerated: • Administering smaller portions of oral fluids. • Reduce total amount of nutrition. • Possibly administer tube feeding or parenteral fluids.
	Provide relaxation and distraction, especially in situations involving anxiety.
Consider	Consider providing nutritional counselling. Involve a dietitian, if necessary.
	If the smell of food leads to symptoms, consider offering cold meals
	Consider having the child suck on ice cube, water ice, or frozen piece of fruit.
	In case of decreased gastric motility in children receiving tube feeding, consider, in consultation with an attending physician, a switch to semi-elemental nutrition or blended diet under the guidance of a dietitian.
	Consider self-hypnosis for nausea and vomiting in children with cancer. [c]
Pharmacological treatment of nausea and vomiting	
Nausea and vomiting with identifiable cause	
Consider	The use of medication for nausea and vomiting requires a rational approach. Base the choice of medication on the main (probable) cause and the pharmacological properties of the medication.
Nausea and vomiting with no apparent cause	
Consider	For nausea and vomiting without identifiable cause or with insufficient effect of causative treatment, consider administration of antiemetics according to the step-by-step plan below (and deviate from the order if necessary):
Step 1	
Consider	Consider starting with: 1. A serotonin (5-HT3) antagonist, such as ondansetron [d]; and/or 2. A dopamine (D2)-antagonist, such as domperidone or metoclopramide; and/or 3. An antihistamine such as cyclizine.
Step 2	
Consider	Consider adding or substituting agents from the first step with: 1. Dexamethasone. 2. Granisetron (instead of ondansetron). 3. Haloperidol (instead of domperidone or metoclopramide). 4. Chlorpromazine or levomepromazine (instead of cyclizine)
Step 3	
Consider	Consider adding: 1. Aprepitant. 2. A cannabis preparation containing dronabinol in consultation with an expert

Table 2 (continued)

Neurological symptoms	
Epilepsy	
Nonpharmacological treatment of epilepsy	
Ketogenic diet	
Consider	In children with difficult-to-treat epilepsy, consider a ketogenic diet.
Psychological interventions	
Consider	In children with epilepsy, consider psychological interventions such as relaxation or cognitive behavioural therapy.
Pharmacological treatment of epilepsy	
Seizure treatment	
Do	In children known to have epilepsy, establish a seizure treatment plan and include any treatment restrictions.
	In children with first seizures: most seizures stop spontaneously within 2-3 minutes. After 3 minutes, give seizure treatment according to a step-by-step plan.
	Evaluate the effect after each step.
	If epilepsy cannot be controlled, consult with a pediatric neurologist.
Maintenance treatment	
Do	Initiate maintenance treatment with antiepileptic drugs if there are multiple seizures or if a seizure is highly likely to recur. Always do this in consultation with a pediatric neurologist.
Do not	Do not start preventive maintenance treatment with antiepileptic drugs in children with neurological disorders of the brain who do not have epileptic seizures
Treatment of refractory epilepsy	
Consider	In the case of a refractory form of epilepsy from which the child suffers, consider administration of intravenous anaesthetics
Movement disorders	
Nonpharmacological treatment for movement disorders	
Treatment aimed at reducing impairments due to movement disorders	
Consider	Check for movement disorder luxating factors such as physical discomfort, constipation, bladder retention, inadequate rest, pain, and anxiety.
	Consider low-level consultation with a (pediatric) physical therapist, occupational therapist, or pediatric rehabilitation physician.
	Consider using assistive devices to help the child sit, stand or lie down as optimally as possible.
Pharmacological treatment for movement disorders	
Consider	In acute status dystonicus, consider biperiden. For other acute movement disorders, consult readily with a pediatric neurologist with expertise in movement disorders.
	In dystonia, consider treatment with baclofen, clonazepam, trihexyphenidyl or gabapentin.
	In focal dystonia, consider botulinum toxin A injections in consultation with a pediatric rehabilitation physician.
	In persistent status dystonia, consider a deep-brain stimulator (surgical).
Spasticity	
Nonpharmacological treatment for spasticity	
Physical therapy and/or occupational therapy	
Do	Advise the child on optimal supported posture (in standing, sitting, and lying down) to promote the child's movement and performance of daily activities and prevent complications of spasticity.
Consider	Consider using assistive devices and orthoses/ splints to prevent complications due to spasticity and to support movement.
	Consider referral to a physical therapist, occupational therapist or rehabilitation physician for treatment and advice focused on
	(coping with the limitations due to) spasticity.
Pharmacological treatment for spasticity	
Baclofen (oral/intrathecal)	
Do	Consult with a pediatric neurologist or pediatric rehabilitation physician for drug options for treatment of spasticity.
Consider	Consider treatment with baclofen (oral) or in combination with Tizanidine.
	Consider an intrathecal baclofen pump.
Benzodiazepines	
Do	Consult with pediatric neurologist or pediatric rehabilitation physician for medication options for treatment of spasticity.
Consider	For acute painful muscle spasms, consider diazepam.
	Consider midazolam when there is a need for sedation or treatment of epilepsy.
Botulinum toxin type A injections	
Consider	In cases of localized spasticity, consider botulinum toxin type A injection in consultation with the rehabilitation physician. [c]
Neurological deficits	
Nonpharmacological and pharmacological treatment of neurological deficits	
Bothersome or troublesome double vision	
Do	Pay attention how the child should be approached.

Table 2 (continued)

Consider	Consider an eye patch or taping a lens.
Incomplete closing of the eyes	
Do	Drop methyl cellulose eye drops during the day.
	For sleeping, use oculentum simplex ointment and a watch glass plaster.
Consider	If redness of the eye occurs, consider more frequent drops and/or ointments, both with and without antibiotics.
Visual hallucinations	
Do	Advise children to close their eyes briefly and then open them again.
	Provide good room lighting; this may reduce the likelihood of developing visual hallucinations.
Consider	Consider referral to a vision expertise centre to get targeted advice for how to deal with the visual problems.
Hearing problems	
Do	Make it known that you are present by touching or looking at the child.
	Talk calm and clearly.
	Avoid excessive ambient noise.
	Use visual support through text, pictures, or gestures.
Consider	Consider hearing aids or solo aids depending on the child's condition.
	Consider referral to an expertise centre on hearing problems to obtain practical advice on the management of hearing problems.
Swallowing difficulties	
Do	Provide optimal nutrition in terms of consistency; consider thickening beverages.
	Offer drinking with a straw or from an appropriate drinking cup.
	Provide breaks between sips to prevent choking.
	Monitor administration of medication and adjust the form of administration as needed.
Consider	Consider involving a speech therapist or occupational therapist for swallowing advice.
	To prevent aspiration or for adequate intake, consider a tube.
Problems with talking	
Do	Be alert to changes in communication abilities.
	Make best use of support in communication.
Consider	Consider guidance from a speech therapist (possibly along with an occupational therapist) for advice on supportive communication devices appropriate to the child's abilities.
Loss of strength	
Consider	Consider guidance from a (pediatric) physical therapist, occupational therapist, pediatric neurologist and/or pediatric rehabilitation physician.
Urinary retention	
Do	Be alert for spinal cord injury or other neurological symptoms in cases of urinary retention.
Consider	Consider placement of an indwelling catheter or intermittent catheterization.
Pain	
Nonpharmacological treatment of pain	
Complementary and alternative therapies	
Consider	Consider the use of complementary therapies.
Psychological interventions for children	
Consider	Consider the use of psychological therapies for children. [c]
Psychological interventions for parents	
Consider	Consider cognitive behavioural therapy for parents. [c]
Pharmacological treatment of pain	
Stepwise pain management	
Do	Treat pain according to a set (time) schedule, through the most appropriate route and adapted to the child.
	Follow a stepwise approach to pain management, such as the WHO ladder.
	For complex pain problems, involve a pediatric palliative care team and/or a pain team.
Do not	Do not use codeine in children.
Step 1 - Non-opioids	
Do	Administer in case of mild to moderate pain, paracetamol, ibuprofen or a combination of paracetamol and ibuprofen.
Step 2 - opioids for severe pain	
Do	Administer morphine as first choice in case of severe pain.
Consider	In case of severe pain, consider administering opioids in consultation with a pediatric palliative care team and/or pain team, for example fentanyl, hydromorphone, oxycodone, or methadone.

[a] This table shows the recommendations on (non) pharmacological treatment of symptoms. We also formulated recommendations on diagnosis and evaluation of symptoms for which we did not systematically search in scientific literature. These recommendations are available on request

[b] Not applicable, it was not possible to formulate a recommendation due to insufficient evidence and lack of consensus among experts

[c] For this recommendation, very low to low quality evidence was identified

[d] For this recommendation, moderate quality evidence was identified

[e] Only available in Dutch

Table 3 Recommendations on refractory symptom treatment in paediatric palliative care

Recommendations on refractory symptom treatment in palliative care for children aged 0 to 18 years with life threatening and life-limiting conditions (n=27)	
Palliative sedation	
Education and communication on palliative sedation	
Do	Introduce palliative sedation early during Advance Care Planning conversations in preparation for the last stage of life and at the child's dying stage.
	Check with the multidisciplinary team that all conditions for palliative sedation are met
	Consult experts and/or paediatric palliative care teams about communication about palliative sedation and the implementation of palliative sedation.
	When palliative sedation has been decided upon, discuss the process of palliative sedation with the child, parents and/or loved ones. Pay attention to purpose of palliative sedation, course of the dying process, implementation of palliative sedation, and agreements between child, parents, and caregivers.
Effect of continuous palliative sedation	
Do	Use the step-by-step plan for the recommended agents and corresponding dosage schedule in continuous palliative sedation.
	If symptom-oriented medication (e.g., morphine) is given continuously parenterally, continue the symptom-oriented medication and the medication for the purpose of continuous palliative sedation via a separate pump to prevent unwanted increase in symptom-oriented medication when the dosage of sedatives is increased.
	In children with alcohol abuse, drug use and/or higher doses of psychopharmaceuticals (including chronic use of benzodiazepines with the indication of antiepileptic drugs), consult with paediatric palliative care team prior to palliative sedation.
	If in doubt or questions about necessary dosages, consult with a pediatric palliative care team
Consider	In case of no or little effect of subcutaneous administration of midazolam and/or levomepromazine, consider switching to intravenous administration.
	When administering medication intravenously, consider administering boluses slowly over several minutes because of the risk of apnoea with some agents.
Effect of acute palliative sedation	
Do	Deploy acute palliative sedation when all of the following criteria are present: • an acute life-threatening complication that cannot be treated causally or symptomatically. • the complication leads to unbearable suffering. • the child is expected to die within minutes/hours due to the complication.
	Anticipate if acute complications are expected during the palliative phase by: • discussing the possibility in advance with child, parents and/or loved ones. • creating a plan (available to all involved) for acute sedation if needed.
Evaluation of palliative sedation	
Do	Evaluate the effect of palliative sedation after 30 minutes using comfort score and/or FLACC score and also pain score if pain is among the refractory symptoms. If in doubt whether the effect is sufficient, consider increasing the dose.
	If in doubt about medication/doses used, consult readily with a paediatric palliative care team.
Consider	In case of no or little effect of subcutaneous administration of midazolam and/or levomepromazine, consider switching to intravenous administration.
Forgoing hydration and nutrition	
Do	Include decision-making about not starting or discontinuing (artificial) fluids and/or nutrition in Advance Care Planning conversations.
	In preparation for the last phase of life, communicate with parents on the topic of (artificial) fluid and/or nutrition abstinence.
	Clarify with child (if possible) and parents that not starting, reducing, or discontinuing (artificial) fluids and/or nutrition at the end of life is part of the natural process.
	With refractory symptoms, weigh the pros and cons of not starting or discontinuing (artificial) fluids and/or nutrition.
	Reduce or discontinue (artificial) fluids and/or nutrition if the child experiences discomfort as a result. Continue to confirm that not starting or discontinuing (artificial) fluids and/or nutrition is in the child's best interest and that the child is not suffering extra.
	Discuss the joint assessment of signs of discomfort, whether based on a specific scale or not, and agree how to deal with it.
	In case of discomfort due to thirst/hunger, discuss to initiate additional sedation.
	Continue to give the child good lip and mouth care
	Prepare parents for the changing appearance of the child.
	Document the policy around (artificial) fluids and/or feeding in the medical record and individual care plan.
Consider	Consider comfort feeding if (artificial) fluids and/or nutrition are not started or discontinued.
	Consider organizing training for caregivers on the responsibility and communication around not starting or discontinuing (artificial) fluids and/or nutrition in the terminal phase.

Discussion

Optimal treatment to relieve symptoms in children with life-threatening or life-limiting conditions is intense and challenging. Although progress has been made in improving and integrating paediatric palliative care in the Netherlands [4], health care providers, parents and other stakeholders have urged for more guidance to relieve physical suffering and ease distress in these children and their families. We responded to this need by developing recommendations on symptom treatment, including anxiety and depression, delirium, dyspnoea, haematological symptoms, coughing, skin complaints, nausea and vomiting, neurological symptoms, pain, death rattle, fatigue, paediatric palliative sedation and forgoing hydration and nutrition, as part of the revised Dutch CPG for paediatric palliative care. With these recommendations we aim to optimize symptom treatment in paediatric palliative care in the Netherlands. Furthermore, these recommendations can be used in other countries to optimize symptom treatment on a global scale.

This study has multiple strengths. First of all, the selection of symptoms was based upon priorities of clinical experts and parents [22]. This approach allowed us to provide recommendations on the symptoms that were most relevant to children with life-threatening or life-limiting conditions and their families. Furthermore, in this way, we were able to provide recommendations for a diverse group of children without limiting to a specific diagnosis. It should be noted that the selection of symptoms does not cover the full range of symptoms that may occur in paediatric palliative care. Still, our selection of symptoms is most comprehensive in comparison to other international guidelines on paediatric palliative care [66]. Additionally, we introduce the first evidence-based recommendations on paediatric palliative sedation in Europe.

Second, our recommendations on symptom treatment are based on an evidence-based methodology, meaning that we systematically searched for RCTs, CCTs and SRs of RCTs and CCTs in scientific literature. We identified 18 studies reporting on effectivity of several non-pharmacological and pharmacological interventions to treat symptoms. We found that since the development of the first Dutch guideline in 2013, the number of studies on paediatric palliative care interventions has increased [19, 22]. However, after allocating the studies to the relevant clinical questions, we concluded that the evidence could only (partly) answer eight out of 27 clinical questions. Also, the total body of evidence was rated as low to very low quality, mainly due to imprecision of effects (as a result of small number of participants) and potential risk of bias. For the other 19 clinical questions on effects of symptom treatment, we did not find evidence. Therefore, we developed a strategy to deal with this lack of evidence and included additional literature: 29 guidelines on paediatric palliative care, general paediatrics, and adult palliative care, and two textbooks on paediatric palliative care.

Finally, our recommendations are carefully developed according to a transparent and comprehensive guideline methodology [22]. We closely collaborated with experts in paediatric palliative care from multiple disciplines and parents. The transparency and the interactive relationship between all stakeholders increased validity and trustworthiness of our guideline process and recommendations.

The recommendations within this guideline are based on national clinical expertise, patient perspectives, and international evidence. We believe that these targeted recommendations on symptom treatment will be largely applicable to other contexts and can give guidance for symptom treatment in other countries as well. However, country-specific factors such as availability of non- pharmacological and pharmacological interventions, infrastructure, financial resources, and cultural backgrounds, should always be carefully considered before applying any recommendations in other contexts.

Unfortunately, we identified multiple gaps in knowledge for non-pharmacological and pharmacological interventions to treat symptoms (Table 4). Even though evidence on paediatric palliative care has increased there is still paucity in evidence on non-pharmacological and pharmacological interventions to treat symptoms [19, 74]. However, it should be noted that these knowledge gaps are based on our search that focused on paediatric palliative care only. Extrapolating evidence from general paediatrics might fill some knowledge gaps for treatment of symptoms. On the other hand, it is acknowledged that paediatric palliative care requires expertise that is often lacking in general paediatrics [75]. Extrapolating study results from general paediatrics is not always appropriate, so caution is needed when applying this evidence.

Table 4 Knowledge gaps for symptom treatment in paediatric palliative care

Current knowledge gaps
Effects of non-pharmacological interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions to treat: • Anxiety and depression (e.g., psycho education, mindfulness, relaxation, and self-hypnosis) • Delirium (e.g., interventions focused on prevention, orientation, and communication) • Dyspnoea (e.g., high intensity training, non-invasive ventilation, physical therapy, ventilator use, oxygen, and relaxation and distraction techniques) • Coughing (e.g., postural advice, and physical therapy for sputum mobilisation) • Skin complaints (e.g., psycho-education, and general skincare) • Nausea and vomiting (e.g., relaxation and distraction techniques, nutritional advice, self-hypnosis) • Neurological symptoms: - Epilepsy (e.g., ketogenic diet, and psychological interventions) - Spasticity (e.g., physical therapy, and occupational therapy) - Movement disorders - Neurological deficits (e.g., bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucination, hearing problems, swallowing difficulties, and problems with talking. • Pain (e.g., psychological interventions for children, complementary and alternative therapies, psychological interventions for parents) • Death rattle (e.g., airway suctioning, and postural advice) • Fatigue (e.g., psycho education, lifestyle counselling, physical exercise, nutritional advice, and sleep hygiene)
Effects of pharmacological interventions in palliative care for children aged 0 to 18 years with life-threatening and life-limiting conditions to treat: • Anxiety and depression (e.g., benzodiazepines, antipsychotics, and selective serotonin reuptake inhibitors) • Delirium (e.g., antipsychotics, and benzodiazepines) • Dyspnoea (e.g., opioids, benzodiazepines, corticosteroids, dilators, and mucolytics) • Haematological symptoms - Anaemia (e.g., erythropoietin, vitamins, iron, erythrocyte transfusions) - Thrombocytopenia (e.g., thrombocyte transfusions) - Bleeding (e.g., adrenaline, xylometazoline, and antifibrinolytic medication) - Thrombosis (e.g., direct-acting oral anticoagulants) • Coughing (e.g., non-opioids, opioids, nebulization with saline or cold steam) • Skin complaints: - Pruritus (e.g., naloxone, and antihistamine) - Pressure ulcers (e.g., pain treatment, and surgical debridement of necrotic tissues) • Nausea and vomiting: (e.g., metoclopramide, granisetron, tropisetron, dexamethasone, aprepipant, midazolam) • Neurological symptoms: - Epilepsy: (e.g., seizure treatment, seizure maintenance treatment, refractory epilepsy treatment) - Spasticity: (e.g., botulinum toxin A injections, baclofen, benzodiazepines) - Movement disorders (e.g., biperiden, baclofen) - Neurological deficits such as bothersome or troublesome double vision, incomplete closing of the eyes, visual hallucination, hearing problems, swallowing difficulties, problems with talking. • Pain (e.g., opioids, non-opioids, and adjuvant analgesics) • Death rattle (e.g., anticholinergic agents) • Fatigue: (e.g., methylphenidate)
Effects of paediatric palliative sedation on depth of sedation, quality of life and lifespan in children aged 0 to 18 years with life-threatening and life-limiting conditions or with a (very) severe multiple (intellectual) disability at the end-of-life.
Effects of forgoing hydration and nutrition on quality of life, lifespan, and parental quality of life in children aged 0 to 18 years with life-threatening and life-limiting conditions at the end of life.

It is clear that more research is required to relieve symptom-related suffering and to ease distress in children and family members. Future research should focus on international, multidisciplinary, and multi-institutional collaboration to reach higher numbers of participants, to broaden the scope of study questions and also improve study quality. In this way, we can strengthen the evidence base of our guideline and contribute to the optimization symptom treatment in paediatric palliative care. Additionally, attention should be given to facilitate

implementation of knowledge and guidelines in paediatric palliative care for the purpose of achieving sufficient symptom relief in children with life-threatening and life-limiting conditions [75]. Furthermore, it should be noted that other factors such as access to financial resources and the organizational infrastructure of paediatric palliative care impact the quality of palliative care and differ among countries [2, 76]. These factors should be addressed to achieve optimal symptom treatment in paediatric palliative care on a global scale.

With these recommendations, we aim to limit symptom-related suffering and ease distress in children with life-threatening and life-limiting conditions and their families. Our methodology allowed us to provide evidence-based recommendations on a comprehensive selection of symptoms in close collaboration with experts in paediatric palliative care, and parents. Even though available evidence on symptom-related paediatric palliative care interventions has increased, there still is a paucity in evidence on non-pharmacological and pharmacological interventions to treat symptoms in paediatric palliative care. We urge for international multidisciplinary multi-institutional collaboration to perform high-quality research and to contribute to the optimization of symptom relief for all children with life-threatening or life-limiting conditions worldwide.

Abbreviations

CPG	Clinical Practice Guideline
CCT	Controlled Clinical Trial
GRADE	Grading Recommendation Assessment Development and Evaluation
RCT	Randomized Controlled Trial
SR	Systematic Review
WG	Working Group
WG1	Working group 1: Symptom treatment
WG2	Working group 2: Refractory symptom treatment

Supplementary Information

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Additional file 1: Appendix A. Paediatric palliative care guideline panel. **Appendix B.** Working structure for guideline development. **Appendix C.** Guideline development process. **Appendix D.** Clinical questions. **Appendix E.** Search strategies. **Appendix F.** Inclusion criteria. **Appendix G.** Criteria for grading levels of evidence and strength of recommendations. **Appendix H.** Flowchart of the study selection process. **Appendix I.** Results of the systematic literature search: included studies; **Appendix J.** Evidence tables; **Appendix K.** Summary of findings tables, appraisal of evidence, and conclusions of evidence.

Acknowledgements

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KvT, RM, EM, LK, EV, BB, JV, and HR conceived and designed the study. KvT, RM, and EM performed the search, data extractions, risk of bias assessment, and GRADE assessment. KvT, RM, EM, LK and EV interpreted the data. KvT, RM, IA, KB, CD, AG, MdG, KH, JL, MM, SM, JS, AS, JV, HR, BB, LK, EV, and EM contributed to the formulation of the recommendations. KvT, RM, EM, LK, and EV drafted the manuscript; and all authors critically revised the manuscript. All authors (KvT, RM, IA, KB, CD, AG, MdG, KH, JL, MM, SM, JS, AS, JV, HR, BB, LK, EV, and EM) and the collaborators approved the final version of this paper.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. No institutional or other licensing committee's approval is needed for guideline creation, as participants are not subjected to procedures and are not required to follow rules of behaviour. Therefore, in accordance to the Dutch law (Medical Research Involving Human Subjects Act (WMO), article 1b) ethics approval was deemed unnecessary: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/your-research-is-it-subject-to-the-wmo-or-not.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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