Chapter 9
Symptom Assessment and Management Across the Cancer Trajectory

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I want to go out because I feel ok, but my body isn't ok. I don't quite understand that. It is frustrating and I get mad. I am used to being outside all of the time.

After we get his chemo we don't really go out. We just stay home and make as pleasant a weekend there. The smells of everything bothers him. Even if I were to do the housekeeping I can't use certain things. I just have to wait until he is better. It is just the way it is.

Introduction

Children undergoing cancer treatment experience substantial symptom burden related to the disease, treatment, and alterations in family life [1–4]. Not surprisingly, children receiving cancer-directed therapy as well as survivors of childhood cancers have reported poorer psychological, social, and physical health-related quality of life as compared to siblings, same-age peers, and children with other chronic conditions [2–5]. Too often, symptoms are seen by patients, families, and providers as part of the treatment process leading to a complex interaction of under-reporting of symptoms by children and parents and under-recognition of the extent of symptom burden by providers [6, 7]. The obligation to relieve pain and suffering related to disease is inherent in both medical and nursing codes of ethics related to principles of beneficence, patient autonomy, and veracity [8–11]. It is incumbent on health-care providers to attend to the known symptom burden of children and their family members by engaging in open and honest conversations aimed at establishing the expectation that symptoms will be managed to the best of their ability to maximize quality of life and minimize unnecessary suffering.

Much of the research in symptoms in childhood cancer focuses on multi-item assessment tools that rate individual symptoms experienced [12–15]. However,

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qualitative interviews with children about their symptom experience demonstrate that rather than discrete, quantifiable experiences, children and adolescents experience symptoms as a state of being in the context of multiple, overlapping symptoms [16–18]. Assessing individual symptoms common to particular cancer treatments or diseases limits opportunities for children who are experiencing a global level of discomfort to report more complex symptom experiences [6, 17]. Additionally, the complex nature of cancer and treatment-related symptoms creates challenges in management, risking increased symptom distress and poor quality of life [12, 17].

Childhood cancer providers have a moral and ethical responsibility to act intentionally to mitigate the harms of cancer treatment with the goal of maximizing not only quality of life but also overall treatment outcomes. As such, oncology providers should be familiar with the available evidence regarding the symptom experience of patients and families, genetic and immune-related mediators of cancer-related symptoms, and multimodal approaches to managing symptoms across the cancer trajectory. This chapter will explore current research and practice in symptom assessment and management in childhood cancer. The growing body of evidence provides both challenges and opportunities for researchers and clinicians to advance effective, evidence-based childhood cancer pain and symptom management for all children to achieve our ethical obligations to address suffering in all forms over the course of childhood cancer care.

Symptom Assessment in Childhood Cancer

Symptoms, Symptom Distress, and Symptom Experience

Cancer treatment is inexorably linked to several common symptoms as well as numerous toxicities and treatment complications; however, patient and family suffering as a result of treatment-related symptoms can and should be minimized. A growing body of literature has demonstrated that unpleasant symptoms are an expected and often accepted part of cancer treatment [6, 18]. Children who experience overwhelming symptoms risk delays or alterations in therapy that can compromise treatment outcome [7, 19].

To better discuss current knowledge in symptom assessment and management as it relates to children with cancer, it is important to have a clear understanding of the terms used by cancer symptom researchers and clinical experts. In its most basic and objective definition, a symptom is the presence of a physical or mental feature that indicates disease [20, 21]. Beyond this primarily biomedical definition, symptoms are also subjectively defined as a phenomenon recognized by a person as a change in normal function, sensation, or appearance [22–26]. *Symptom distress* reflects the amount of physical and mental suffering experienced from specific symptoms on the part of the person experiencing the symptom, which results in an overall sense of distress related to a perceived threat of illness [24, 25]. *Amplification*

of symptom distress occurs through the amount of attention given to the symptom as well as the context of the symptom occurrence and coping mechanisms of the person experiencing the symptom [25]. Lastly, an individual's *symptom experience* represents the perception and cognitive/emotional appraisal of the symptoms – to include frequency, intensity, distress, and the associated meaning given to symptoms as they occur and are expressed to a health-care provider [24]. As such, symptoms are a subjective experience that requires both a biologic and meaning-centered approach to adequately address the totality of the patient's discomfort. Patient/caregiver report of the symptom experience is also influenced by cultural, individual, and disease-specific characteristics as well as the consequences of the symptom on functional status, mood, and quality of life. [20, 24]

Multidimensional/Interrelated Symptom Experience

Symptoms experienced as the result of a diagnosis of cancer and accompanying treatment have both multidimensional and interrelated qualities [27, 28] that affect the symptom experience and add challenge and complexity to adequate symptom management. Multidimensional aspects of symptoms include the physical nature of symptom, frequency of symptom occurrence, and the severity and associated level of distress, in addition to the effect of the symptom on the emotional, social, and spiritual well-being of the child (Fig. 9.1). An adolescent with osteosarcoma receiving chemotherapy may experience moderately severe and distressing pain related to tumor size and location, leading to emotions of frustration/anxiety about the pain.

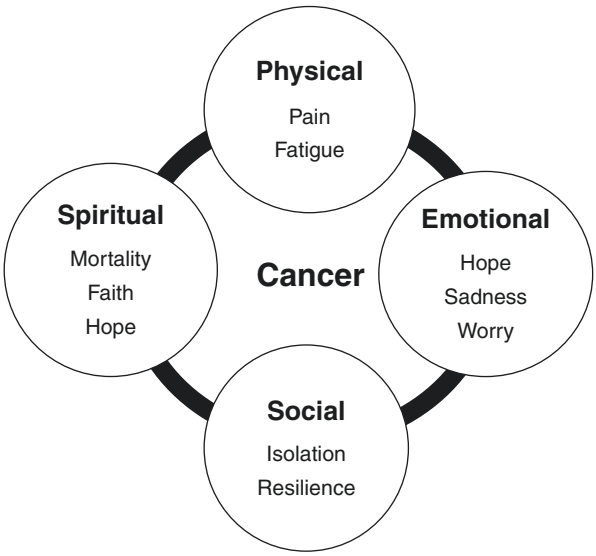

Fig. 9.1 Multidimensional symptom experience

Consequent limitations in their social interactions with friends can lead to irritability, creating tension with parents and siblings. The reality of having cancer may also lead the adolescent to question why they got cancer, engendering feelings of guilt or weakness, perhaps questioning their faith in God or a greater power. Lastly, sadness over the perceived loss of long held plans for their future and fears of their own mortality [7, 29] further add to symptom distress. The interplay of these factors related to the symptom experience can, in turn, amplify the symptom distress experienced by both the child and family as they grapple with the altered family dynamics brought about by the cancer diagnosis.

Another layer of complexity with regard to the symptom experience is the interrelatedness of symptoms with the underlying disease, side effects, comorbidities, and adverse events (Fig. 9.2). A child with leukemia in delayed intensification may experience physical symptoms of fatigue and weight loss from the side effects of persistent or uncontrolled nausea and vomiting in the setting of chemotherapy and underlying comorbid hepatic complications. This scenario may further complicate symptom distress as invasive interventions to address comorbidities are performed and additional medications with additive side effects are prescribed over time possibly increasing symptoms and distress. Studies examining polypharmacy at 42 children's hospitals found that nearly half of all children were exposed to a potentially dangerous drug interaction (PDDI), with the risk of exposure increasing for older children, those with prolonged hospitalization, or those who had complex medical conditions. By far, the greatest risk of PDDI was respiratory depression (20%) [30]. Children in intensive care settings had even greater exposure to PDDI (81%) with the cumulative number of distinct medications increasing from 7 to 45 by PICU day 30 [31].

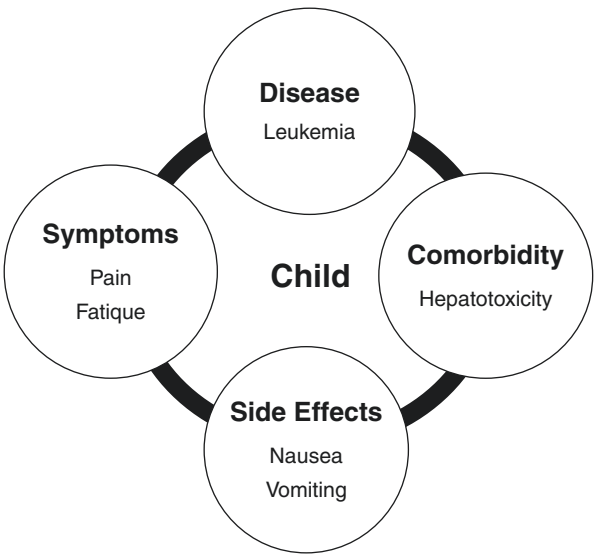

Fig. 9.2 Interrelated symptom experience

Symptoms and Suffering

Suffering is often used by researchers and clinicians to describe the experience of cancer treatment and symptoms in children. Cassell [32] defines suffering as "a state of severe distress associated with events that threaten the intactness of the person." Suffering as it applies to an individual is a phenomenological experience arising from a perception of threat to their personal integrity or limitations to significant aspects of their life [32]. This broad definition encompasses multidimensional sources of suffering that include physical, emotional, spiritual, and existential factors. Suffering is a deeply subjective personal experience and cannot be objectively assessed by an outside observer; therefore much like pain, one must believe the person's experience of suffering is as they describe it [32, 33].

Early symptom research in childhood cancer focused on understanding how children and families experienced the diagnosis of cancer, its treatment, and resulting symptoms. Parents recalling the symptoms experienced by their child in the last week of life were asked to assess the degree of suffering as a result of each individual symptom, with nearly 90% of parents sharing that their child suffered a lot or a great deal from at least one symptom and 50% of children suffered from 3 or more symptoms [34, 35].

Interviews with parents of children with cancer-related pain [18] offered visceral descriptions of seeing their child in pain as "unendurable," and feeling "helpless"; as if "watching your child dangle from a rope off a cliff." Pain was also impactful to the family as a whole, causing disruption in marriage and family life, sleep deprivation, feelings of guilt and failure as a parent, and a constant struggle for normalcy [36].

Interviews of children with cancer, their parents, and siblings have also explored broader symptom experiences and have similarly characterized reported symptom distress as suffering [6, 37]. Woodgate's seminal work on symptom experiences [9], based on 230 longitudinal interviews with 39 children with cancer and their families, provided insights into children, their parents, and sibling's beliefs and expectations about cancer. Findings centered on the family's belief that uncomfortable symptoms were a necessary and expected part of cancer care that were to be endured in order to survive. In fact, if symptoms were minimal or not present, there was concern that the chemotherapy was not working. Families also believed that suffering from symptoms was directly related to treatment not the disease. Similarly, there were no "getting used to" symptoms, as suffering would always be present while the disease was being treated. Children and families found it difficult to distinguish which symptoms were most difficult to bear, as they often could not be separated from one another, but rather existed as a gestalt. Lastly, symptom management was seen as "sort of helpful"; however children and families did not expect symptom relief, which leads to symptoms' being unrelieved, ignored, or uncontrolled [9].

Contemporary exploration of the experiences of children with cancer and their family have reported presence of physical and emotional suffering as a result of: lack of preparation for the complex care needs of their child; the strain of prolonged or repeated hospitalizations; job-related and financial stress; and taking on the role

of parent to a seriously ill child [38]. Lastly, greater symptom burden, severity of the child's condition, and intensity of treatment has been associated with increased parental distress [39–41].

Resilience

Although childhood cancer treatment often leads to periods of disease and symptom-related stress and suffering, most children and their families are able to effectively cope with the demands of cancer treatment and return to reasonable levels of functioning after the diagnosis [40, 42, 43]. Key aspects of family functioning that promote resilience include family cohesion, conflict management, adaptability, communication, family support, spiritual coping, and overall family functioning [43].

The diagnosis of cancer and the illness burden associated with treatment is often seen as a traumatic life event; however studies evaluating post-traumatic stress in children and families suggest that the unique nature of being diagnosed with cancer can facilitate positive coping and growth [40]. Post-traumatic growth theory regards exposure to serious life events as an opportunity for individuals to restructure their assumptions about themselves and the world to make sense of or find meaning in the traumatic experience [40, 44, 45]. Studies on post-traumatic growth suggest that children and families who had had fewer life stressors and were functioning well prior to diagnosis tended to have more post-traumatic growth related to their cancer experience. The stress of the cancer experience was viewed as drawing the family closer to each other, increasing parent/child bonds, and in essence looking for the "silver lining." There remains a small group of families, however, that have more substantial struggles during cancer treatment, particularly families with a younger child with cancer, those in active phase of treatment, and those with higher cumulative life stressors or a less cohesive and supportive family structure [40–42, 46]. This high-risk patient/family group requires further research and clinical attention to better understand factors that affect coping and symptom distress as well as developing management strategies to address coping and symptom distress.

Symptom Assessment in Childhood Cancer

Thorough assessment of symptoms is a necessary precursor to effective symptom management. It is commonly accepted in pain and symptom assessment research and clinical care that the best source of information regarding symptoms is the patient. Unfortunately, most clinical encounters have been shown to consist of providers and parents exchanging the majority of the information regarding the patient, while children and adolescents participate substantially less in the discussion [47–50]. Patient-reported outcome measures of cancer symptoms have been advanced by numerous federal agencies and professional societies as essential in pediatric cancer research and clinical care [51–53] as a means to improve patient outcomes and overall survival [54] as well as reduce costs associated with poorly managed symptoms [55].

While there is increased interest and inherent benefit in clinical implementation of patient-reported symptom screening, there are numerous challenges that need to be overcome [50, 51]. Studies of patient-reported symptom burden that included feedback to providers regarding symptoms that exceed pre-determined levels of severity did not significantly improve symptoms [56, 57]; however patients and parents reported some improvement in emotional health-related quality of life (HRQOL) and improved scores on total sickness measures [52]. Such studies highlight challenges to clinical implementation of standardized symptom assessment tools. Variability and level of distress from symptoms across diseases and patients requires careful consideration of measures to be introduced over the course of care and how to respond to endorsed symptoms and associated frequency, severity, and distress reported. Practical challenges to the use of standardized symptom assessment include providers' lack of familiarity with patient-reported symptom screening tools as well as how to interpret the data in an actionable way in real time that does not impede workflow.

There are a number of valid and reliable pain and symptom assessment scales for children and adolescents with cancer that allow both direct patient and parent proxy report to screen for the occurrence of common cancer treatment symptoms [58]. With or without patient-reported symptom measures, multidimensional assessment of the child's symptom experience should be a discussion between the child and/or parent and the oncology clinician. Open and encouraging exploration by the provider should include not only the presence of symptoms but also a thorough discussion of the perceived severity and distress and the effect of symptoms on the child's function and quality of life, as well as what medications and home management strategies help to alleviate symptoms. Challenges in clinicians consistently eliciting such a thorough exploration of the symptoms include the child's age and ability to recall and describe their symptoms; underreporting due to child and parent expectations and beliefs about symptoms; under-assessment by clinicians, patient, family, and provider communication style; and clinician time constraints [55, 59].

Symptom Burden in Childhood Cancer

The availability of valid and reliable pain and symptom assessment scales has led to an expanding body of literature reporting on the prevalence of symptom burden experienced by children over the course of treatment and into survivorship. The majority of studies using a multi-symptom assessment instrument involve the child or adolescent providing direct report of the symptoms they experience and included multiple oncologic disease groups, across various stages of treatment, in both inpatient and outpatient settings [1, 12, 16, 60]. Child participation and response rates are high across studies, and researchers report that patients as young as 7 years old are able to complete symptom assessment tools, in English or translated versions, although adolescents (≥10 years of age) represent by far the largest group of patients in symptom assessment studies [1, 61–75].

Symptom Prevalence, Severity, and Distress

There are limited studies on the incidence and prevalence of pain in children with cancer, and even fewer exploring the type and characteristics of the cancer pain experience [76–80]. Cancer pain can present as episodic, persistent, or chronic, and some children experience complex cancer pain syndromes requiring multimodal treatment. Across various studies, about 50–60% of children with cancer and their parents report clinically significant pain over the course of treatment [79–82].

Common sources of pain include needle procedures, mucositis, procedural/surgical pain, phantom limb pain, and neuropathic pain from tumor or chemotherapy agents [83, 84]. Pain is often the most commonly reported symptom at diagnosis and, depending on the underlying disease, has been reported as being present from one to three or more months prior to diagnosis [81]. Additionally, pain is problematic for many children throughout treatment, at end of life, and well into survivorship [34, 76, 79, 80, 85–88].

In addition to pain, children with cancer report multiple concurrent symptoms in all diseases and phases of treatment. Across all studies, children and/or their parents report between 3 and 11 concurrent symptoms during active treatment and at end of life (EOL) [14, 34, 64, 65, 71, 72, 76, 85, 86, 89–91]. The most frequently occurring symptoms in both younger children and adolescents across all symptom reports in order of prevalence were lack of energy, pain, lack of appetite, nausea, drowsiness, worry, and sadness. Older children and adolescents undergoing treatment have been shown to experience higher symptom burden than younger children [14, 75, 92, 93]. Similarly, children receiving chemotherapy report higher symptom burden and distress than children not receiving chemotherapy [65, 66, 94, 95]. Both solid and CNS tumors have been associated with higher symptom prevalence and severity than leukemia and lymphoma [65, 76, 96].

Race and gender differences in symptoms were generally not significant across studies; however, in many of the US and European studies, white/caucasion participants constitued the largest groups. Further research is needed in other ethnic populations to better understand possible differences between various populations. In a large multisite randomized controlled trial, female gender was associated with higher symptom burden [76]. Interestingly, across studies, the most frequent or severe symptoms endorsed by both children and parents were often not the most distressing. Less evident symptoms, such as sadness, lack of appetite, and pain when present, were often rated as more severe and distressing [64, 65, 67, 71, 72, 76].

Studies that assessed parent/child concordance found that symptoms reported by children tended to also be the most frequent symptoms reported by parents [61, 64, 65, 97–100]. Baggott [99] noted that parents rarely underestimated their child's symptoms; however parents did overestimate psychological symptoms compared to their child's report. Studies using parent ratings of symptoms by both parents [93, 101] demonstrated concordance between mothers' and fathers' ratings of symptoms; however mother's ratings were more likely to be higher than fathers.

In repeated measured studies, children and adolescents receiving initial treatment experienced a wide range of symptoms that were generally more frequent and distressing in the early stages of treatment and subsequently diminished in frequency and

level of distress over the course of treatment [1, 19, 61, 71, 73, 93, 101]. This pattern was reported in both inpatient and outpatient settings, with hospitalized children reporting greater numbers of symptoms and greater distress than outpatients [15, 64, 65, 70]. Children with advanced cancer experience pain and other highly distressing symptoms that persist over the course of their terminal illness [34, 76, 85, 86, 102].

Symptom distress has been linked to changes in several other dimensions of children's and parents' experience with cancer treatment. Higher levels of symptom frequency, intensity, and distress have been found to lead to decreases in health-related quality of life and functional status [66, 70, 74]. In particular, children who reported higher total number of symptoms had significantly lower measures of physical and emotional health-related quality of life and poorer functional status [66, 70]. Arslan [42] found that children who endorsed lack of energy, constipation, and sweating had significantly lower physical HRQOL scores. Nervousness, sadness, pain, worry, drowsiness, irritability, and changes in appearance were significantly related to lower emotional HRQOL. Lastly, the combination of sadness, worry, and irritability resulted in lower overall HRQOL.

Symptom burden has also been found to persist well into survivorship. Lack of energy, difficulty sleeping, headaches, pain, and lack of concentration were the most frequent, severe, and distressing symptoms reported and are often associated with functional difficulties [103–107]. Increased symptom burden and physical changes such as persistent hair loss, scars, and disfigurement have all been associated with decreased quality of life [2, 104, 108, 109]. Female cancer survivors of acute lymphoblastic leukemia (ALL) with greater levels of sleep dysfunction reported greater inattention, hyperactivity, and aggression as well as worse executive function, processing speed, and behavioral symptoms than male ALL survivors [110]. Psychosocial and mental health symptoms such as anxiety, depression, social withdrawal, peer conflict, and attention deficits have been found to co-occur and have been linked to treatment exposure and physical symptoms in survivors [111–113].

Symptom Clusters

Growing evidence of multidimensional and interrelated co-occurring symptoms reported by children with cancer has led researchers to explore the relationships among symptoms reported by patients [16, 28, 114–118]. Symptom clusters have been reported in a variety of adult [28] and childhood illnesses [115] and are generally considered as 2 or more co-occurring symptoms that are predictable and related to one another (i.e., pain and anxiety, sleep disturbance, fatigue, and irritability) [28, 118, 119].

Across studies, symptom clusters varied with regard to the specific symptoms included in the cluster; however symptoms generally clustered in logical groups. For example, a commonly occurring cluster that includes nausea/vomiting/sleep disturbance [1, 66, 68, 118, 120] varies across studies with regard to associated symptoms, such as pain [1, 68, 96] and loss of appetite [66, 68]. The cluster of fatigue, sleep disturbance, and nausea/vomiting was shown to increase depressive symptoms and behavioral changes in adolescents, while in younger children, fatigue

alone increased depression and behavior changes [96]. Yeh [68] described five symptom clusters and found that the presence of pain led to reports of significantly higher symptom distress in all clusters.

Symptom clusters have also been described based on the class of chemotherapy patients receive and their effect on quality of life [74]. Children receiving antimetabolites reported significantly more worry and irritability, whereas those receiving anthracyclines reported significantly more lack of energy and skin changes, leading to decreased quality of life. Lastly, Hockenberry [96] found that adolescents with solid tumors receiving chemotherapy who experienced the cluster of fatigue and sleep disturbance had higher levels of depression. Adolescents with solid tumors also experienced the cluster of nausea and vomiting and had greater sleep disruption and significantly less daytime activity compared to other children with cancer.

Two studies evaluated changes in symptom clusters over time. Atay [116] reported shifts in symptom clusters over the first 3 months, with emotional symptom clusters reported more frequently in the first and third month of treatment, while symptoms related to chemotherapy were more frequent in the second month of treatment. Hockenberry [19] evaluated symptoms in 236 children with leukemia over four time periods and identified three distinct symptom groups: mild symptoms (46%), moderate symptoms (52%), and severe symptoms (11%). Analysis of symptom change over time demonstrated that sleep disturbance and nausea changed little over time; however fatigue, pain, and depression decreased over the four time periods.

Lastly, Finnegan [103] described a cluster of eight symptoms in adult survivors of childhood cancer (ACC) and explored factors likely to predict subgroup membership according to presence of chronic health conditions (CHC), health-promoting lifestyle, and quality of life. Similar to Hockenberry, three distinct groups were identified as high symptom (21%), moderate symptom (45%), and low symptom (34%). ACC with at least one CHC were six times more likely to be in the high symptom group. Mean health-promoting lifestyle scores were lower in the high symptom group and highest in the low symptom group. Quality of life differences across subgroups were statistically significant with the high symptom group having the lowest quality of life. Quality of life in the moderate symptom group and low symptom group matched or exceeded quality of life scores of healthy young adults.

Symptom cluster research, while still in the early stages, is providing important insight into symptom interrelatedness and the consequent effect on function and quality of life. Evolving statistical modeling has expanded cluster research beyond describing symptoms that coexist, toward a better understanding of patients with similar symptom experiences. Understanding both the interrelatedness of symptoms within a cluster and the child's symptom experience with regard to their everyday life is important to creating an optimal symptom management plan to maximize comfort and quality of life over the course of treatment. Ongoing research into symptom clusters will advance our understanding of the global symptom experiences of children with cancer and provide opportunities for developing and evaluating symptom management interventions.

Immunomodulation and Sickness Behavior in Cancer-Related Symptoms

The interrelated symptom experience frequently reported by children receiving cancer treatment results from a complex physiologic and pathophysiologic milieu. There have been great gains in both pre-clinical and clinical research in the past 30 years leading to a deeper understanding of the relationship between the physical symptom experience and the cognitive and emotional responses to cancer symptoms [121–126].

There is an increasing body of evidence that cancer-related pain and symptoms are initiated and in some cases amplified by key mediators within the peripheral immune system inflammatory cascade that interact with cytokines and glial cells in the central nervous system, prompting a process of neuroinflammation [123, 124, 126, 127]. Circulating cytokines act on receptors via neurotransmitters in the CNS to stimulate the release of pro-inflammatory cytokines that affect the brain creating symptoms such as fatigue, fever, anorexia, and cognitive dysfunction. These symptoms are consistent with infectious illnesses and serve to motivate energy conservation to facilitate healing [123, 125, 128].

Cytokine-induced "sickness behavior" is a cluster of symptoms that includes lethargy, anorexia, depression, anxiety, fatigue, and hyperalgesia and is promoted by changes in cytokines that are abnormally produced by cancer cells as well as various phagocytic cells [122–124]. Neuroinflammatory symptoms can become pathologic if there are high levels or prolonged duration of pro-inflammatory cytokine production, if there are defective down-regulation of molecules and cellular components, or if neuronal circuits become sensitized [123, 129]. Lastly, subtle genetic variations of cytokines have been associated with depression in adult cancer patients [121, 124, 130], pain sensitization [124, 131, 132], and higher levels of fatigue, sleep disturbance, and cognitive impairment [122, 124, 132, 133] .

Relationships between symptom clusters in adults and children at risk for higher symptom burden have been linked to cytokine-mediated inflammatory processes that promote the development and perpetuation of sickness behavior. Hockenberry [118] identified two symptom clusters in children receiving chemotherapy and noted that they corresponded to the symptoms commonly associated with sickness behavior. The symptom cluster of fatigue/depression is related to emotional sickness behavior symptoms, while the nausea-vomiting/performance status/sleep disturbance cluster is related to physical sickness behavior symptoms. In a similar study, Cheung [110] evaluated the role of sleep, fatigue, and systemic inflammation and found that female survivors of acute lymphoblastic leukemia (ALL) had greater levels of sleep dysfunction and experienced more inattention, hyperactivity, and aggression. Fatigue, in combination with higher levels of IL6, IL1B, and C-reactive protein, was also associated with worse executive function, processing speed, and behavioral symptoms in female survivors of childhood cancer.

Genetic polymorphisms have also been linked to cytokine-induced sickness behavior in cancer as well as other chronic illnesses [124]. In a study of adult cancer patients, Illi [121] compared cytokine genes with patient-reported measures of pain, fatigue, sleep disturbance, and depressive symptoms in adult patients with breast,

prostate, lung, or brain cancer. Three distinct classes of patients were identified based on similar symptom experiences. Findings indicated significant differences between the classes, with the high depression/high pain group (12%) being significantly younger and female, having higher co-morbid conditions and lower functional status. Additionally, having a minor allele for IL4 was associated with membership in the all high group.

These studies provide further areas of exploration as to the role of inflammatory cytokines and genetic alterations in patients exhibiting high symptom burden during cancer treatment. Identifying clear biochemical and genetic markers of risk for high symptom burden would provide opportunities to more closely monitor and manage symptoms and increase the likelihood of improved quality of life and treatment outcomes.

Symptom Management in Childhood Cancer

Research in symptom management is limited, with very few outcomes studied to provide evidence-based guidance in childhood cancer symptom management. Following is a discussion of the most commonly experienced symptoms and research-based non-pharmacologic and pharmacologic interventions.

Sleep Disturbance and Fatigue

Sleep disturbance underlies several frequently reported symptoms, such as lack of energy, fatigue, and difficulty concentrating. Fatigue in children has been defined as a "profound state of being physically tired or having difficulty with bodily movements," while adolescents experience fatigue as a "changing state of exhaustion that can include physical, mental, and emotional tiredness [134]." Sleep is a biologically necessary process of disengagement from external stimuli, and disturbance of restful sleep is detrimental to a child's mood, cognitive and physical functioning, and behavior [135–137]. There are numerous types of sleep disturbance experienced by children being treated for cancer that exert substantial effect on overall quality of life [107, 136, 137], with excessive daytime sleepiness (EDS) being the most frequently reported [135, 136].

Non-pharmacologic Interventions Increased physical activity is the most frequently studied intervention aimed at improving sleep and fatigue in children receiving chemotherapy [138–141]. Studies of physical activity monitored either by wrist fitness tracker or by actigraph suggest that patients with increased physical activity have significantly lower fatigue [140, 141], improved sleep [139], and improved physical endurance [142]. Similarly, nursing educational interventions with patients and parents that focus on cancer-related sleep disturbance and fatigue

found that instruction on sleep hygiene, nutrition, and scheduled walking activities decreased fatigue [143], while use of relaxation techniques increased sleep time and decreased sleep disruption [144]. Home-based exercise, healing touch, and yoga interventions have also been associated with lower fatigue and/or improved sleep [141, 145, 146]. However, these findings are tempered by a stationary bicycle exercise [147], massage therapy [148], and yoga interventions [149] that did not demonstrate improvement in fatigue symptoms. Numerous other self-help strategies aimed at managing sleep disturbance and fatigue such as engaging in relaxing activities, warm baths, availability of comfort items, and sleeping with parent/friend have also been reported [137, 150].

Pharmacological/Interventional There are no published clinical outcome trials on the efficacy and safety of pharmacologic agents to manage sleep disturbance or fatigue in children with cancer. Stimulant medications, growth hormone, and scheduled naps have been prescribed to manage fatigue in children experiencing EDS [135–137, 150]. Pharmacologic management of underlying pain and sedatives and melatonin have been used to address insomnia, and anticonvulsants prescribed for parasomnias [137, 150]. Lastly, for children with cancer who were diagnosed with either central or obstructive sleep apnea in a pediatric sleep center, use of noninvasive ventilation (continuous or biphasic positive airway pressure) and supplemental oxygen have provided relief [136, 151].

Pain

Pain is one of the most frequent symptoms reported by children with cancer and their parents [80, 82, 152]. Studies of parents' experiences of pain provide a conflictual attitude toward pain management, as they prefer to limit strong analgesics such as morphine and other opioids due to concerns about side effects and addiction, while also advocating for appropriate pain management for their child [36, 80, 82, 153].

Parents report managing their child's pain primarily with physical and psychological strategies rather than pharmacological agents [80]. In general, there is evidence that parents believe that their child's comfort is their responsibility and that they would benefit from pain education and clear pain management instructions from their health-care team to help them achieve those goals [6, 18, 82]. While a comprehensive discussion of cancer pain management in children is beyond the scope of this chapter, following are summaries of research related to non-pharmacologic and pharmacologic pain management strategies.

Non-pharmacologic Interventions Several randomized trials have demonstrated that distraction is an effective form of non-pharmacologic management for procedural pain [154]. Distraction with and without medications is also the most common intervention used by parents to manage their child's pain at home [80, 82]. In

addition to distraction techniques, several complementary/alternative and integrative medicine techniques such as hypnosis, guided imagery, healing touch, and cognitive-behavioral therapy have been shown to improve pain and quality of life in children with cancer [155–158]. Lastly, recent studies evaluating animal-assisted activities (pet therapy) reported pain and other distressing symptoms improved significantly in patients who had animal visits [159, 160].

Pharmacologic/Interventional Although nearly all children with cancer will report some level of pain during their treatment, with 60% reporting clinically significant pain [80, 161] there are no controlled trials of pharmacological approaches to cancer pain management [162–164]. This lack of evidence-based management contributes to substantial variability across health-care settings and providers, increasing the risk of inadequate pain relief and complications related to opioid therapy. In busy oncology clinics where multiple providers see patients, there is an increased risk that patients may receive multiple prescriptions of various pain medications. Persistent myths regarding the safety of opioids and other analgesic and adjuvant medications, the wide variety of pharmacologic options, and the risk of opioid overuse and abuse [165–167] further complicate effective pain management.

Opioids are the mainstay of pediatric cancer pain management [168] although little is known about the prevalence, indication, and duration of opioid use in this population of children. Getz [169] reviewed data from the national health service in Ireland and found that over 75% of children with acute myeloid leukemia (AML) were exposed to opioids over the course of their treatment, while children with cancer represented nearly 40% of patients receiving opioid infusions for more than 28 days in a US children's hospital [170]. A retrospective chart review of approximately 400 children treated at a US pediatric cancer center found that approximately 25% of children were prescribed outpatient opioid therapy for 7 or more days [166]. Additionally, there is evidence that chronic pain syndromes in childhood cancer survivors result in increased risk of receiving opioids up to 3 years post therapy [88].

Mu receptor agonists such as hydrocodone, morphine, and hydromorphone are the most frequently used opioids and are effective analgesics for moderate to severe acute and episodic cancer-related pain. Opioids are generally considered safe for use in children with cancer over the course of their care [171]; however there are undesirable effects that must be managed, such as constipation, development of tolerance, physiologic dependence, and, with chronic use, a risk of increased pain sensitivity (hyperalgesia) [168].

In recent years, methadone has played a role in chronic, neuropathic, and end-of-life cancer pain management. While methadone has utility in managing complicated cancer pain syndromes, it should be used with caution and in consultation with pain and/or palliative care professionals. Methadone has unique pharmacodynamics that include QTc prolongation, prolonged time to steady state (3–5 days), as well as a prolonged and variable half-life requiring caution in initiation, monitoring, and titration [172, 173].

Recent recommendations on methadone management [173] in adult chronic pain and addiction settings include routine electrocardiogram (ECG) prior to initiation and routinely while on therapy. The recommendation was extended to children as there were no available studies on methadone in children at the time. However, recent reviews of methadone use in two pediatric cancer centers found no correlation between methadone dose, duration of therapy, or concomitant QT prolonging medications and QT prolongation in children with cancer [174, 175], suggesting that methadone, when prescribed and monitored appropriately, is safe for use in children.

In addition to methadone, there are a number of adjuvant medications that have demonstrated utility in neuropathic and other complex pain syndromes [176–180]. Gabapentinoids are generally first-line agents for chemotherapy-related neuropathic pain, with agents such as tricyclic antidepressants, lidocaine, and alpha agonists also having utility in refractory neuropathy [84, 181, 182]. Complex, refractory pain interventional management includes peripheral nerve blocks and epidural infusions [176–178, 183].

In the face of the national crisis of opioid-related deaths, there is increasing concern regarding the widespread use of opioids as the primary remedy for cancer pain, and there are increased calls to develop policies and procedures related to opioid risk evaluation and mitigation strategies (REMS) [165–167]. Reports from two large US pediatric cancer centers using risk evaluation in adolescents with cancer reported high opioid risk in 34% [167] and 39% [166] of screened patients. While there are efforts to increase safe prescribing through standardized risk screening at initiation of opioid therapy in adolescent and young adult (AYA) cancer patients, the counter concern is that gains made in addressing pain in children and AYA may be lost out of fear of prescribing opioids despite a sound clinical indication. Healthcare provider's obligation to address suffering while minimizing exposure to opioids can be actualized by engaging in efforts to advocate for effective pain assessment and management policies and practice standards as well as expanding the availability of integrative health providers to provide a balanced approach to pharmacologic and patient-centered approaches to care.

Nausea/Vomiting

Anticipatory, acute, and delayed chemotherapy-induced nausea and vomiting (CINV) is a challenge in childhood cancer, particularly with regard to nausea management [184]. Nausea is generally reported by children with cancer and their parents as more distressing than vomiting [12, 15, 96, 185]. Parents, nurses, and children who were asked to score the child's nausea and vomiting before, during, and after chemotherapy found that parent, patient, and nurse reports of vomiting were similar at all time points; however nurses and parents underreported nausea in both the anticipatory and delayed phase of nausea/vomiting [186].

Non-pharmacologic Children have reported various active and passive coping strategies related to managing nausea and vomiting (CINV), with the most fre-

quent being distraction, wishful thinking, and emotional regulation [187–190]; however there was no assessment of the success of these strategies in reducing nausea and vomiting. Distraction with video games has been shown to reduce nausea in children with cancer as well as other cognitive-behavioral interventions such as guided imagery, story-telling, systematic desensitization, and hypnosis [191, 192]. Chan [193] reported on a psychoeducational intervention that evaluated the use of progressive muscle relaxation and guided imagery versus an educational program focused on risk assessment, antiemetic use, and meal planning with patients and parents. Patients in the intervention groups tended to use less antiemetics than controls and reported significantly less vomiting on day 3. Parents in both the relaxation and educational groups had significant decrease in anxiety levels, although children's anxiety did not change significantly.

A number of integrative medicine techniques aimed at managing CINV have been reported in both adult and pediatric cancer research. Acupuncture is the most frequently studied integrative technique and successful in controlling nausea and vomiting, with the most common side effect being localized redness at the site [192, 194]. Reindl [195] reported on a multicenter crossover trial of antiemetics with and without acupuncture. Recruitment was a challenge as nearly half of eligible patients declined, and another 11 could not receive acupuncture at the appropriate start time. However, data from the 11 patients who did consent and participated in the acupuncture sessions suggested that acupuncture is feasible, particularly in adolescents, and that although there was not sufficient power to detect significant changes in antiemetic use, there was a decrease in use of sedative as-needed (PRN) antiemetics and increased alertness in the acupuncture group. Interestingly, there was no significant difference in subjective nausea reports despite the decrease in PRN antiemetics.

Acupressure has also been evaluated as an integrative approach to CINV in adults and children and has been found most useful in combination with antiemetics in decreasing acute nausea severity, but less effective in reducing vomiting or controlling delayed nausea and vomiting [192]. Yeh [194] utilized auricular acupressure on a group of Taiwanese children and adolescents with cancer and reported a significant decrease in both the frequency and severity of nausea and vomiting when compared to a control group. However, a study on the use of acupressure bands versus placebo bands in 21 patients in a US cancer center found no significant effect on nausea or vomiting between the groups, although surveys of patient's expectations of acupressure to improve their nausea and vomiting demonstrated only a moderate expectation of benefit [196].

Sensory interventions using essential oils and popsicles/lollipops have also been reported in adult stem cell transplant patients, with orange popsicles, as well as orange scent and taste demonstrating significant reduction in nausea intensity and retching over deep breathing and aromatherapy massage interventions [192].

However, in a double-blind placebo-controlled study, Ndao [197] found that children exposed to bergamot aroma therapy during stem cell transplant had greater anxiety after cell infusion, while parent anxiety declined in both treatment and control groups.

Although the research on integrative management of nausea and vomiting is limited, there is increasing interest in the use of integrative techniques in clinical settings, particularly in persistent or refractory symptoms. Clinicians should carefully assess patients and consult with integrative medicine and palliative care colleagues to determine the appropriate techniques and tailor an integrative symptom management plan to the individual child.

Pharmacologic Control of chemotherapy-induced nausea and vomiting has improved substantially in the past two decades with the development of several agents that specifically target key emetic receptor pathways in the brain. Agents such as ondansetron, granisetron, and palonosetron target 5-hydroxytryptamine 3 (5-HT3) receptors [198], while aprepitant targets substance P and neurokinin 1 receptors [199]. The emetic potential of a given chemotherapeutic agent can range from low (10–30% frequency of emesis) for common agents such as etoposide, doxorubicin, low-dose methotrexate, and topotecan to high (> 90% frequency of emesis) for agents such as cisplatin, high-dose cyclophosphamide, and high-dose methotrexate [186].

There are a number of evidence-based guidelines by the Pediatric Oncology Group of Ontario (POGO) Guideline Development Committee on the pharmacologic management of anticipatory, acute, and delayed nausea and vomiting that have been published in recent years [200–204]. Pharmacologic control of anticipatory nausea and vomiting (ANV) is based on the need to prevent acute and breakthrough NV, and guidelines recommend lorazepam at bedtime the night before and morning of chemotherapy for children with persistent ANV [200]. Acute CINV prophylaxis recommendations provide suggestions for various agents, based on detailed and well-supported evidence that considers the patient's age, potential contraindications, and emetogenicity of the chemotherapy received [202]. Breakthrough NV recommendations include escalating acute CINV prophylaxis and addition of olanzapine for highly emetic chemotherapy [202]. For children with refractory CINV, the guidelines provide several suggestions for antiemetic rotation as well as additions to aggressively manage refractory NV [202].

In addition to 5-HT3 and NK 1 receptor antagonists, there are a number of adjuvant medications that can be incorporated into a patient's CINV regimen to maximize control. Dexamethasone is the most frequently used adjuvant to manage CINV; however it is contraindicated in some children, particularly those with leukemia. Benzodiazepines such as lorazepam are useful in anticipatory NV based on adult studies [200], and in a retrospective review of 60 children receiving chemotherapy, the atypical antipsychotic olanzapine was found to be effective for acute phase chemotherapy-induced vomiting [205].

Psychosocial Symptoms

Anxiety, worry, and depression are reported less frequently than physical symptoms, which is consistent with a number of studies that report children with cancer generally function as well as or at times better than healthy peers [206–208]. A longitudinal study of children in the first year of treatment for leukemia found that overall experience of anxiety and depression were similar to same-age peers; however approximately 25% of children experienced higher levels of anxiety and depression, with anxiety levels returning to normal while depression persisted throughout the first year [209].

Anxiety in childhood cancer is generally related to treatment and procedures, particularly those that entail some level of pain, as well as anticipatory nausea and vomiting [185, 208]. Depression has been linked with higher levels of cancer symptom frequency and severity, severe medical complications from treatment, and neurologic sequelae from disease and treatment [96, 208, 210, 211].

There are a number of risk factors that contribute to poorer psychosocial functioning for children that require ongoing assessment and management [207–209, 212]. Family functioning and individual dispositional traits of children have been consistently identified as primary risk factors for anxiety and depression during childhood cancer therapy [206, 208, 209, 211, 213]. Families with unhealthy patterns of functioning and poor social support have significantly increased risk for children to experience anxiety and depression [206, 209, 211, 214]. Children who demonstrate higher levels of worry and difficulties distracting themselves during stressful treatment and procedures experience higher levels of treatment-related anxiety and distress [209, 213].

Risk factors for development of anxiety and depressive disorders in survivors of childhood cancers include being female, unmarried, lower economic and educational status, presence of physical late effects and chronic health conditions, and lack of health insurance [207]. There is also emerging evidence that there is a small subset of survivors with chronic complications such as poor physical health, chronic pain, and emotional difficulties that are at risk for suicidal ideation [5, 207].

Supportive Management Interventions aimed at managing treatment-related anxiety and depression should begin at diagnosis with a thorough assessment of known risk factors followed by tailored educational and psychosocial interventions (psychoeducation) based on individual patient and family needs [215, 216]. Psychoeducational interventions focus on guidance around a variety of topics such as developmentally based disease education, family coping, treatment management, procedures and symptoms, fertility, medical decision making, and numerous other topics unique to each family. Children and families who receive psychoeducational interventions have been found to have increased health locus of control and improved symptom management outcomes [217, 218]. Psychological support through individual, marital, and family therapy can assist children and families with adjusting to the life-altering experience of childhood cancer. Cognitive behavioral therapy and problem-solving skills training are effective psychological interventions for

reducing stress in parents and children with cancer [219]. Creative arts and expressive therapies [220–222] have also demonstrated a role in relieving anxiety and depression in children and adolescents.

Pharmacologic Management Studies of oncologists prescribing habits have found that prescriptions for antidepressants and anxiolytics in children with cancer exceed that of general population of children [223, 224]. Similarly, survivors of childhood cancers had nearly 5 times the risk for antidepressant use and up to 7 times that risk for anxiolytic use up to 3 years post-treatment compared to non-cancer controls [88]. Many of the symptoms of anxiety and depression in particular overlap with common treatment-related symptoms and clusters such as sleep disruption, fatigue, difficulty concentrating, and irritability, suggesting that it may be difficult for clinicians and parents to distinguish depressive symptomatology from known cancer-related symptoms, leading to overprescribing [224].

Supportive interventions discussed above should be the first line of management of depression and anxiety; however there may be a role for adding pharmacologic management in certain circumstances, particularly in children and adolescents with pre-diagnosis history of depression, anxiety, or other mental health disorders [208, 225]. The most common class of antidepressant prescribed by oncologists is selective serotonin re-uptake inhibitors (SSRI) [208]. However in a survey of pediatric oncologists in nine US cancer centers [224], consultation with psychology or psychiatry colleagues was low, with less than 20% always consulting mental health professionals, while three-quarters of oncologists reported not adhering to black box guidelines for monitoring of SSRIs and just 9% assessed for suicide risk.

Symptom Management in Advanced Disease and at End of Life

While most symptoms experienced during cancer care are generally related to treatment, symptoms in advanced disease and at the end of life (EOL) are related to both the cumulative effects of disease treatment and progression of the disease itself [76, 226–228]. Symptoms in advanced cancer are similar to those experienced throughout treatment, with pain, fatigue/drowsiness, dyspnea, nausea and lack of appetite, loss of mobility, communication, and breathing changes being the most prevalent EOL symptoms [229]. Symptom burden increases over time from progression to death, with prevalence and distress levels increasing in the weeks before death, leading to substantial decrease in quality of life [3, 76, 86, 228].

Interviews with bereaved parents suggest that as disease progresses, symptoms of most concern to parents are those which were unexpected or they were not prepared for, occur suddenly, or caused fear to the child or parent [85]. In particular, unrelieved pain and other symptoms, as well as difficulties at the time of death, have been shown to affect parents for several years after their child's death [34, 230, 231].

Parents of children with advanced, incurable cancer find themselves faced with witnessing the toll that the disease and treatment is taking on their child. The utmost attention should be given to addressing symptoms as disease progresses. Symptoms should be routinely assessed and managed across all care settings (home, clinic, and hospital) to maximize comfort.

Symptom management interventions should be balanced with the overall condition of the child to assure that the benefit outweighs any burden of the intervention. Parents should be provided with a point person to call if there is any worsening of pain or other symptoms so they can be addressed quickly to avoid intractable discomfort. Specialty community-based hospice and palliative care experts [232–237] can assist by providing home visits to assess pain and symptoms and coordinate with the primary oncology team to adjust medications as needed.

Symptom Management at End of Life

Unfortunately, there is a significant dearth of clinical outcome research on pain and symptom management interventions in advanced and terminal care of children with cancer [162, 163, 238]. Generally, symptom management at end of life is a continuation and at times escalation of previously discussed symptom management strategies to address global symptoms at end of life.

In addition to the global symptoms that most parents report across all diseases, there may also be disease-specific management needs. Children with central nervous system (CNS) tumors experience substantial symptom burden related to focal neurological deficits [239, 240] such as impaired mobility, altered levels of consciousness, and dysarthria/dysphagia in the months prior to death. The most prevalent medications aimed at management include analgesics, laxatives/steroids, sedatives, antiepileptic agents, and antisecretory medications as well as low-dose chemotherapy and palliative radiation therapy [239, 240].

Children with hematologic cancers may have symptoms such as pallor, petechiae, and fatigue [235]that are related to pancytopenia in advanced disease. Blood and platelet transfusions may be helpful over the course of disease progression [241]; however these may be less effective as disease worsens. Consideration should be given to the child's overall clinical condition and history of major bleeding complications when considering the risks and benefits of transfusions at the end of life.

Lastly, children with solid tumors may experience wound care issues and intractable pain related to tumor growth. Consultation with wound care specialists for open and/or fungating tumors can be extremely helpful and mitigate parent/child distress related to odor and appearance concerns. Targeted palliative radiation [242–245] has been shown to provide pain relief with minimal toxicity in children with advanced tumors. Children with intractable pain may require rapid escalation of opioids and the addition of adjuvant agents such as ketamine [246–248] and methadone [249, 250] to maximize analgesia.

Managing symptoms in children at end of life is challenging for all members of the treatment team as they bear witness to the physical, emotional, and spiritual suf-

fering of the child and family. In the rare cases where significant pain or other symptoms such as severe anxiety, profound restlessness, or delirium persist despite ongoing attempts to manage the symptoms, palliative sedation may be considered as an intervention of last resort [251–254].

In the setting of intractable symptoms, physicians and nurses often worry that escalation of opioids and other sedating medications aimed at optimizing comfort will lead to the patient's death. Families and the treatment team are left with no "good" options and therefore may feel culpable in hastening the child's death [255]. It is imperative that the team pauses with the family to review the care provided over time and the level of perceived suffering of the child and acknowledge that death is now the expected outcome and the intention of care is to minimize suffering.

Palliative sedation has an ethical basis in the principle of beneficence, where the intent of sedation is to alleviate suffering and should not be conflated with euthanasia or assisted suicide. The principle of double effect has been used to address this dilemma by focusing on the intent of the actions taken, such that those interventions purely intended to provide comfort are considered ethically sound, even if there is a risk that they may have known but unintended consequences that may be perceived to hasten death [256–258]. While this principle is well established in palliative care, concerns regarding clinicians interpretation of intent and foresight as well as a clear understanding of the moral basis of the actions being contemplated are best reasoned out with the assistance of an experienced clinical ethicist [256–258].

Palliative sedation therapy should be managed by experienced pain and palliative care professionals after consensus by family and interdisciplinary team members that the child is imminently dying and all available attempts to manage suffering have been exhausted [251–253, 259]. Implementation of palliative sedation should include having a do not resuscitate order in place, reviewing goals for comfort care (hydration, antibiotics, transfusions) during the period of sedation, and define outcome measures for assessing comfort and when to titrate or discontinue sedation [254].

The explicit goal of palliative sedation therapy is to achieve a satisfactory level of unconsciousness that minimizes suffering. The choice of sedative agents should be determined based on the goals. Midazolam is a common agent for moderate to deep sedation due to its short half-life, allowing for easy reversal in situations where sedation may be time limited to allow rest or re-evaluation of symptom control. Other agents that provide deeper sedation are commonly used include barbiturates, ketamine, and propofol [260].

Psychosocial/Spiritual Support

Even in terminal stages of disease, children and adolescents can have periods of reasonably good quality of life and functional ability if symptoms are managed and treatment-related side effects are minimized to the extent possible. The strategies to manage symptom distress using supportive, complementary, and integrative interventions discussed earlier can be equally effective during advancing disease and at end of life.

Supportive activities that are particularly important during EOL care involve helping children and families maximize family and peer interactions and engage in legacy building and meaning making [261–264]. Studies focused on legacy building have demonstrated that children as young as 2 years old have an awareness of their impending death and intentionally leave items for special people or share their wishes for remembrance. These intimate activities between children and families provide a sense of the sacred and bring comfort to parents, siblings, and others who were touched by the child long after the child's death [261–264].

Spiritual support and exploration is important across the cancer trajectory, but is increasingly important in advanced disease and end-of-life care [265–269]. Consultation with a hospital chaplain who is experienced with caring for children with cancer and their families can provide a through spiritual assessment and coordinate care with community spiritual providers to maximize coping and bereavement outcomes after the child's death. Spiritual well-being in parents has been associated with positive outcomes such as feelings of comfort and hope, acceptance of limits within disease, and emotional support and guidance in contending with their child's illness and the difficult decisions they faced [265]. Spiritual development in children evolves as they move through the cognitive stages of development first from their connection to their parents' beliefs as a child, through experiences of spiritual questioning and disappointments in the school age years, to adolescence searching for understanding and answers in various religious frameworks [270, 271]. Children's spiritual beliefs can provide comfort, strengthen bonds to family and friends, elicit desires to be remembered and leave a legacy, and provide opportunities for expression of feelings, finding meaning and transition of hope from a focus on cure to acceptance and hope for comfort, desired activities, and anticipation of an afterlife [266]. While spiritual connection is generally reported to be protective and supportive, for some parents and children, cultural experiences of spirituality can also be a source of distress from a sense of punishment through illness and suffering as a requirement for entrance to heaven [267, 268].

Health-care providers can optimize spiritual well-being by assessing parent and child beliefs [266, 272]. Providing opportunities for children to express feelings and concerns through empathic listening and exploring their spiritual experiences and journey using interventions such as creative and expressive arts, story-telling, and prayer can help the child manage strong emotions related to dying [273].

Ethical Imperatives in Symptom Assessment and Management

Resolving the Ethical Dilemma in Pain and Symptom Management

While the impressive gains in overall survival in childhood cancer should be celebrated and advanced in the coming decades, it is clear from the growing body of symptom research that there is a substantial treatment-related symptom burden over the course of therapy that has substantial effects for roughly half of children and

adolescents with cancer. Symptom researchers have poignantly captured what children and parents have elucidated through interviews and surveys, the outward face of strength and coping that many families put forward as they fight for survival, while within they harbor the belief that symptoms are an accepted, tolerated, and even necessary part of surviving the disease [6, 29, 267], contributing to underreporting, inadequate assessment, and suboptimal management of symptom distress [17, 18, 55]. To achieve ethically sound symptom assessment and management, there is a need for further research and clinical efforts toward understanding child and family symptom experiences as well as increasing provider knowledge in symptom assessment and management.

Standardized Symptom Assessment

To maximize well-being across the childhood cancer continuum, the starting point is systematic assessment of symptoms across the trajectory of care using patient-reported outcome measures (PROM). Symptom research to date has been focused on using symptom PROM to describe the prevalence, severity, and distress of cancer symptom experience as it relates to quality of life and functional and emotional outcomes of cancer treatment. Attention now should shift to the clinical application of symptom assessment PROM instruments. Wolfe [53] reported on the results of a randomized, controlled trial evaluating the use of a symptom screening tool in children with advanced cancer that included feedback of symptom reports to oncologists. Children and parents completed a standardized symptom assessment scale as frequently as once a week, and results were emailed to the provider when predetermined symptom scores were exceeded; however feedback did not significantly affect symptom trends. There are a number of questions to explore when moving a research measure into a clinical setting. How will the instrument be distributed? How frequently should it be given? Who reviews the instrument with the family? What do symptom scores mean clinically? Further research and quality initiatives focused on the implementation of symptom assessment instruments in clinical care and their effect on symptom management will go a long way toward improving child and family quality of life.

Symptom Management

As with assessment, efforts to improve symptom management should be a priority area in pediatric oncology research. Pain is the most commonly managed symptom in children, with opioids being the most frequently prescribed. Despite this fact, there are no randomized trials of opioid pain management outcomes in children with cancer [162]. Similarly, the incidence of opioid misuse in children and adolescents with cancer is currently unknown [274]. The current regulatory climate regarding opioids in pain management requires substantial assessment and monitoring of pain and a desire to reduce opioid exposure by increasing availability of integrative medicine and other non-pharmacological interventions [275, 276]. Pediatric cancer research institutions should take the lead in supporting comparative

effectiveness trials of opioid management strategies in children with cancer to assure pain is managed effectively, safely, and consistently across institutions.

Another area of improvement with regard to symptom management is the creation of multimodal management plans. Symptoms are often intertwined and it is difficult to determine what symptom is inciting other symptoms. Including non-pharmacologic (i.e., distraction or guided meditation) and pharmacologic interventions in symptom management plans may lead to lower overall doses of analgesics and adjuvant medications. Again, studies on the use of multimodal and integrative medicine interventions and their effect on symptom burden would provide valuable evidence for symptom management planning.

The Ethical Imperative in Symptom Management

The continued strive for cure in childhood cancer certainly meets the ethical requirement of beneficence, to do the right thing by children with cancer through systematic clinical research aimed at improved survival and ultimately cure rates for the leading disease-related cause of death in childhood [277–280].

However, if the scale is tipped solely to the beneficence of cure, there is a breach of the ethical requirement of non-maleficence, to do no harm, if we do not simultaneously seek to develop and integrate symptom and quality of life outcomes in treatment protocols and clinical practice across the cancer trajectory. The current body of symptom research has clearly demonstrated the presence of a complex symptom experience over the course of cancer treatment and into survivorship and end-of-life care. Increasing symptom management outcomes research and implementing standardized symptom assessment and management within cancer treatment protocols address both high-quality cancer care and minimization of harm to patients and families.

Lastly, the principle of justice in childhood cancer requires equal access to care that is appropriate to the child's health-care needs. The relative lack of symptom and psychosocial outcomes research as well as evidence-based guidelines in cancer symptom management leads to wide variability in symptom management across care providers and settings, quite possibly affecting overall survival outcomes [281].

An ethical dilemma exists in the reality that childhood cancer cannot be cured without incurring suffering related to risks of symptoms [53, 282], which patients and parents accept as the price to pay for cure. Few standardized symptom management processes exist for children receiving treatment to maximize quality of life across the trajectory of care regardless of disease or location of care [162]. Recent findings from an expert panel on pediatric oncology care recognized this dilemma and proposed that in addition to efforts aimed at new therapeutic options for cancer treatment, there should be an equal focus on integration of psychosocial and palliative care with disease-directed therapy to ensure patient and family well-being across the continuum of care [53]. The remedy then, for the dilemma of children and families suffering as a reality of cancer care, is to hold both disease treatment and symptom management equally important in cancer research and clinical manage-

ment by advancing comprehensive cancer care as the gold standard [53, 283]. Parent and provider engagement in shaping symptom reporting, and improving management of the child and family's symptom experience and quality of life over the course of care is an important first step toward achieving comprehensive, high-quality patient- and family-centered symptom assessment and management [51] that will minimize suffering and potentially avoidable harms.

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