CHARTING THE TERRITORY: END-OF-LIFE TRAJECTORIES FOR CHILDREN WITH COMPLEX NEUROLOGICAL, METABOLIC AND CHROMOSOMAL CONDITIONS

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ABSTRACT

Objectives: For parents, family or clinicians of children with rare, life-threatening conditions there is little information regarding likely symptoms, illness trajectory and end-of-life care. This descriptive analysis of a bereaved cohort recruited in the *Charting the Territory* (CTT) study describes patient characteristics, symptoms, use of medications, discussion of resuscitation orders and care provided preceding and during the end-of-life.

Methods: Of the 275 children enrolled in the CTT study, 54 died between 2009 and 2014. Baseline demographic information, symptoms, interventions and medical information were collected via chart review, interviews and surveys.

Results: 51 of the 54 children had complete medical records. Of the seven symptoms evaluated, children were found to have an increase in median symptoms from baseline (n=2) to time of death (n=3). Opioids were used in the last 48 hours of life in 29 (56.9%) children, whereas only eight (15.7%) were receiving opioids at baseline. Do Not Attempt Resuscitation orders were in place at baseline in 17 (33.3%) children, increasing to 33 (64.7%) at time of death. Death occurred in a hospice setting in 16 (31.4%) children.

Conclusions: While much emphasis on pediatric palliative care has been on supportive treatment and symptom management, when faced with a lack of sound understanding of a rare illness, the mode of care can often be reactive and based on critical needs. By developing greater knowledge of symptoms and illness trajectory, both management and care can be more responsive and anticipatory, thereby helping ease illness burden and suffering.

245/250 Words

Key Message: This cohort study tracked the end-of-life symptom and illness trajectory of 54 children and shows that within this population, children had increased symptoms in their last month of life and were receiving more opioids at death. Importantly, by time of death more children had *Do Not Attempt Resuscitation* orders in place and for most children care was supportive.

Keywords: pediatrics, terminal care, DNAR orders

Running Head: Charting the territory**:** End of life trajectories

INTRODUCTION

There is currently insufficient information about what patients and families can expect when a child is diagnosed with a rare, complex, life-threatening condition. In particular, there is little reported about the symptoms and end-of-life care in the terminal phase of their illness. Literature about the dying child consists of retrospective studies that report various aspects of death in childhood, many of which are focused on cancer[1–20]. A lack of knowledge exists regarding the symptom trajectory, communication and decision-making that occurs at the end of life for children with rare, complex conditions[18–20]. The resulting uncertainty can hamper the patient, family and clinician's ability to manage the experience. Distress arises not only from the physical, cognitive, developmental and social aspects of the affected child, but also because of the limited knowledge pertaining to symptoms or pathways of these rare diagnoses where early mortality is inherent in the disease process and its complications.

The *Charting the Territory* study (CTT) focuses on children with a range of rare and progressive metabolic, neurological or chromosomal conditions[21,22]. These are characteristically progressive illnesses without cure, where treatment is largely palliative - involving symptom management, supportive care and treatment of co-morbid illnesses - and where disease progression and pathophysiological processes continue unabated. Children with these conditions comprise about 50% of those receiving pediatric palliative care and as a group, these conditions are a significant cause of death in childhood[21]. Symptoms in these children are often unstable, unpredictable and add considerably to illness burden. These symptoms occur alongside the multitude of questions and decisions that arise along the journey towards the end of life.

This particular paper provides observational data about the children who died while enrolled in the CTT study. It details the patient characteristics, medications, place of death, and discussions regarding resuscitation, with a focus on the care preceding and during the end of life, as well as a comparison to baseline symptoms and treatments. By analyzing the data collected on children who died within the larger CTT study population, we sought to document at baseline and towards end of life: 1) symptoms present, focusing on a number of symptoms recognized as those with the greatest morbidity to patients; 2) advance care discussions and decisions regarding advance directives; 3) medications required and 4) interventions ordered, and those that were withheld (e.g. fluids or feeds). This report will add to the knowledge base as little has been reported on end-of-life care in this unique population.

METHODS

Children with severe, progressive, life-threatening neurological, metabolic or chromosomal conditions, their parents and siblings were recruited into the CTT study from seven centers in Canada and two in the United States between 2009-2014. The eligibility criteria for the CTT study was 1) child must be between 0-19 years of age; 2) child must have a progressive metabolic, neurological, or chromosomal condition; 3) child must not have been provided potentially curative therapies, such as stem cell transplantation for metabolic conditions; and 4) the caregiver must speak either English or French. The study was approved by the University of British Columbia / Children's and Women's Health Centre of British Columbia Research Ethics Board (Certification #H08-00124) and by the Ethics Boards of all of the participating study sites.

The CTT study utilized data collection using quantitative methods along two parallel streams: 1) the child's clinical symptoms; and 2) bio-psycho-spiritual aspects of

family members' experience throughout illness and, where applicable, after death of the affected child. This design allowed monitoring of illness and symptom trajectory through comprehensive examination of medical records from birth to the end of life as well as parent reports. The complete protocol for the CTT study has been described previously[21]. Baseline data pertain to events that occurred from the child's birth up to their date of enrolment in the study. Data at death pertain to information from within 48 hours of death, however symptoms were also identified in the last 30 days of life through parent report and chart review.

Demographic and family psycho-social information, symptom and medical information were collected by research assistants through the review of hospital charts and by conducting interviews and surveys. The affected children were evaluated prospectively for symptom changes monthly, and parents provided information on their child's functional status annually. If a child died during the study, a chart review was completed in order to collect data relevant to the last 30 days of life.

The presence or absence of seven common symptoms was evaluated at both baseline and within 30 days of death: increased or decreased alertness and interaction(e.g. sedation or hyper-alertness), constipation, dyspnea, feeding difficulties, sleep problems, seizures, and pain. Data pertaining to limits of care orders at the end of life included discussion of resuscitation status, whether a decision regarding Do Not Attempt Resuscitation (DNAR) was reached and the timing of a DNAR order in relation to the child's death. Medications given in the last month of life were recorded along with the timing of their commencement in relation to the child's end of life, and specifically whether the medication was given within 48 hours of death. Medications were placed in eight drug classes (see Supplementary File 1).

Information collected was sent to the main study site where data entry and analysis

occurred. The accuracy of the data compiled was reviewed through a formalised audit process - both of the individual chart reviews and the subsequent data entry.

Statistical analysis was performed using SPSS® Version 20 (IBM, Arkmonk, NY). McNemar's and Student's *t*-tests were used to calculate differences between data at baseline and at death. These differences are reported with *p* values. Missing data was not imputed, but rather is noted in the tables as actual numbers.

RESULTS

During the study recruitment period, 275 pediatric patients from 258 families were enrolled in the CTT study. Of those children, 54 died while participating in the study. Complete medical information was available for 51 children and was used as the sample for analysis in this paper. Of the children who died, 34 (66.7%) were female, the mean age at baseline was 6.0 years (SD 5.32), and at death was 7.1 (SD 5.56) years (see Table 1). Most children lived with both parents (n=46, 90.2%) and the median number of siblings was 1 (SD 1.19, range 0-6). The average number of hours of care provided by a parent in a week was 100.9 (SD 56.33, range 3-168). Palliative care services were involved in 88.2% (n=45) of cases.

The most frequent underlying medical conditions[23] were: multi-organ congenital abnormalities or lysosomal storage/peroxisomal diseases (n=11 for both), and severe neurological impairment with insufficient information for syndrome or disease diagnosis (n=9; see Table 2). There were a number of conditions that primarily occur in females (Aicardi and Rett syndromes) and others that primarily present in males (X-linked adrenoleukodystrophy and Mucopolysaccharidosis type II [Hunter syndrome]).

The majority of children required surgically-inserted feeding support. The most frequently used was a gastrostomy tube, with 29 children having insertion prior to

baseline. Five children had gastro-jejunal tube insertion after the baseline assessment.

Symptoms

The mean time between baseline and death was 1.1 years. Of the seven symptoms evaluated, the children were found to have a median of 2 symptoms at baseline, with an increase to 3 symptoms in the last month of life (see Table 3). Feeding problems and seizures were the most frequently reported symptoms at baseline, with dyspnea, feeding difficulties and seizures the most commonly reported symptoms in the last month (see Figure 1). Nearly one third (n=16) were experiencing dyspnea at baseline and this number more than doubled (n=34) in the last month of life ($p<0.001$). Sleep problems were infrequently reported across both time points, and the frequency of pain was stable with no significant changes from baseline (n=19) to the last month (n=17; $p=1.00$). Alertness and interaction changes increased from baseline (n=12) to the last month of life (n=20), however, the increase was not significant (p=0.115). Constipation also increased slightly from baseline (n=15) to the last month of life (n=17); the increase was not statistically significant (p=0.839).

Medications and interventions

Medication profiles were collected for all patients and allocated into one of seven medication classes (See Table 3). Children at baseline were prescribed agents from a median of three drug classes and this increased to four drug classes within 48 hours of death. This increase in medications prescribed at the time of death was mostly attributable to increased use of opioids, with 29 children prescribed these agents during this terminal phase, yet only eight were prescribed at baseline ($p<0.001$).

Advance directives and medical interventions

At baseline, 26 of these children's families had Advance Care Planning discussions documented, and 16 out of these 26 discussions resulted in a Do Not Attempt

Resuscitation (DNAR) Advance Directive order. At time of death, the number of children with documented DNAR orders had risen significantly to 33 children ($p<0.01$). Median time from DNAR decision to death was 4.5 months. DNAR discussion first took place within 48 hours of death for only four children. There was no documentation recorded or evidence of a DNAR order during the study period in nine patients (see Table 4). For two patients, there was evidence of a DNAR discussion but it did not lead to a documented DNAR order.

In total, 10 children had invasive ventilatory support at some point while enrolled in the study. Seven patients were receiving invasive ventilatory support in the last 48 hours of life. Three of these children had support commenced within 48 hours of death, two between 3-30 days prior to death, and the remaining two children between 31 days prior to death and the baseline assessment. Eight (out of 33) children who were receiving gastro-jejunal supplemental tube feeding had their feeds stopped in the last month of life.

Place of death

Death occurred within a children's inpatient hospice for 16 children, while 12 children died at home. Of the remaining 23 children, 11 died in a major children's hospital intensive care unit, three in a children's hospital general ward, one in a local hospital intensive care unit, one in a children's hospital emergency department, and one in a local hospital emergency department. Two children died elsewhere (not specified), and location of death information was missing for four children (see Table 2).

DISCUSSION

This study provides a description of illness trajectory for children with life-limiting, rare and progressive metabolic, neurological or chromosomal conditions. It

demonstrates that within this cohort a typical patient could be expected to have early problems with seizures and feeding, often in association with multi-organ, and in particular, neurological dysfunction. In general, over the course of their illness, these children typically require increasing numbers of medications (frequently opioids) and medical interventions (frequently gastric or jejunal tube insertion). Over time, it could be expected that overall symptom burden would increase, particularly towards the end-of-life. Encouragingly, advance directives and discussions regarding DNAR often take place early in the course of the child's illness, and while deaths do occur in the context of intensive or emergency care, it is more common that they occur within a hospice or home setting.

Others have previously described outcomes in pediatric palliative care cohorts. Feudtner et al.[16] have reported outcomes from 6 hospital-based pediatric palliative care teams in the US and Canada. They described similarly high rates of gastrostomy use to our cohort (48.5% vs 67%) and a similar symptom burden due to pain (30.9% vs 34.0%). In a cohort of children who died in hospital, mostly commonly from cardiovascular conditions, prematurity and cancer, McCallum et al.[7] reported that opioids were prescribed in 84% of children for pain, dyspnea and/or respiratory distress. In our cohort, opioids were the most commonly prescribed medication at death (in 67% of children with available data). Their deceased populations were quite different to ours, however, with those who died early in their study likely to have had cancer or cardiovascular conditions[7, 16].

Discussions regarding DNAR orders are perhaps some of the most difficult for clinicians. Although emotionally challenging, research in adults has shown that having patients' end-of-life desires and wishes regarding medical care in place allows surviving family members to experience less stress, anxiety and depression[24]. It

may also enhance patient and family satisfaction with end-of-life care[24].Families who are given an opportunity to prepare for the end-of-life period are more likely to feel that their care has been of high quality[25].The majority of the cohort included in this study had an active DNAR order more than 30 days prior to death. This encouraging finding in a cohort of children with life-limiting illnesses contrasts with previous studies where the majority of children did not have DNARs in place at time of terminal hospitalization[7] or the median time to death after DNAR order was less than three days[26It should be noted however that these studies described a population that was frequently cared for in an intensive care setting and involved children who experienced acute events or were receiving potentially curative therapy. It is unsurprising then that in those studies, imminence of death or futility of further treatment were the most common reasons cited for a DNAR order, as opposed to quality of life or excessive burden of treatment.

Our results highlight the role of pediatric palliative care services to support the often complex end-of-life care needs of children with life-limiting diseases. Palliative care services were involved in the majority of cases described in this study and 31.4% of deaths occurred in a hospice setting. The latter statistic reflects the availability of inpatient hospice care for children in several of the sites in Canada. Early referral for hospice care can be advantageous for patients and families, with greater attention to symptoms and quality of life[3]. In a US study, children receiving palliative care were noted to spend fewer days in hospital, have fewer invasive interventions and fewer deaths in ICU compared to children not receiving palliative care[27].The American Association of Pediatrics support the concurrent use of palliative care with curative care from the time of diagnosis for children with life-threatening illnesses[28].

There are limitations to our study. The design of the study resulted in a limited

capacity to obtain clinical information regarding children who died at home, as their medical records revealed fewer details surrounding symptoms and care in the last days of life. While ideally it would be extremely valuable to gain greater insights into the experiences of these families during the terminal phase of their child's illness, a balance between reasonable information gathering and intrusiveness needs to be reached. An additional limitation in this bereaved cohort is that the significant issues of caregiver exhaustion, sibling behavior and family psychosocial variables have not been well described. These are important considerations for clinicians caring for children with life-limiting illnesses and are the subject of further research within the CTT study[22,29]. Clearly, the care of these children needs to extend beyond physical assessment in order to fully support them and their families[30].

This analysis of the bereaved cohort in the CTT study revealed that dyspnea, feeding difficulties and seizures were the main symptoms that affected the majority of children in their last month of life, that DNAR discussions and orders and the use of palliative care are increasingly the norm, and that medications and medical interventions continue to play an essential role. Both the families of children with rare life-limiting illnesses and the clinicians who care for them may benefit from an improved understanding of illness trajectory. For families, increasing awareness of likely symptoms and the circumstances around end-of-life care may provide a greater sense of calm and control. For clinicians, this awareness may allow a more responsive and anticipatory approach to the provision of care and the facilitation of discussions pertaining to symptom management and terminal care.

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Table 1 – Demographic information (n=51)

Age at baseline (mean in years)		6.0 (SD 5.32)
Gender (female/male)		34/17
Number of Siblings (median; range)		1 (SD 1.19); 0-6
Marital status of parent (number (%))	Married or living as married	46 (90.2)
	Divorced/separated	3 (5.9)
	Other	2 (3.9)
Amount of care provided by a parent per week (mean in hours; range)		100.9 (SD 56.33); 3-168

Table 2 – Underlying condition and location of death (n=51)

		n=	%	Average age at death (SD)
Underlying condition	Lysosomal storage/peroxisomal diseases	11	21.6	9.1 (6.46)
	Multi-organ congenital abnormalities	11	21.6	3.3 (2.19)
	SNI-NYD	9	17.6	7.6 (4.60)
	Mitochondrial encephalomyopathies/myopathies	5	9.8	9.7 (6.70)
	Epileptic encephalopathies	4	7.8	5.1 (2.92)
	Neurodegenerative diseases	4	7.8	13.8 (3.88)
	Structural CNS abnormalities	3	5.9	4.7 (6.14)
	Neuromuscular diseases	2	3.9	1.4 (0.77)
	Other conditions NOS	1	2.0	1.4
	Small molecule diseases	1	2.0	13.6
Location of death	Children's Hospice	16	31.4	
	Home	12	23.5	
	Major Children's Hospital ICU	11	21.6	
	Major Children's Hospital General Ward	3	5.9	
	Other	2	3.9	
	Local Hospital ICU	1	2.0	
	Local Hospital ER	1	2.0	
	Major Children's Hospital ER	1	2.0	
	Missing	4	7.8	

CNS – central nervous system, SNI-NYD – severe neurological impairment – not yet diagnosed, NOS – not otherwise specified

Table 3: Chart reviews at Baseline and Death

	Baseline	Death
Age in years (mean; SD)	6.0; 5.32	7.1; 5.56
Number of symptoms (median; range)	2; 0-6	3; 0-6[%] *
	(n=)	(n=)
G/J Tube in place	29	34
Median number of Drug Classes	3	4
Anxiolytics (n=43)[#]	22	23
Anticonvulsants (n=42)[#]	25	25
GI Drugs (n=32)[#]	18	19
Neuroleptics (n=26)[#]	4	2
Opioids (n=43)[#]	8	29**
Non-Opioid Analgesia(n=35)[#]	10	13
Respiratory (n=39)[#]	15	15
Other (n=34)[#]	29	23

*$p<0.05$, McNemar's test

**$p<0.01$, McNemar's test

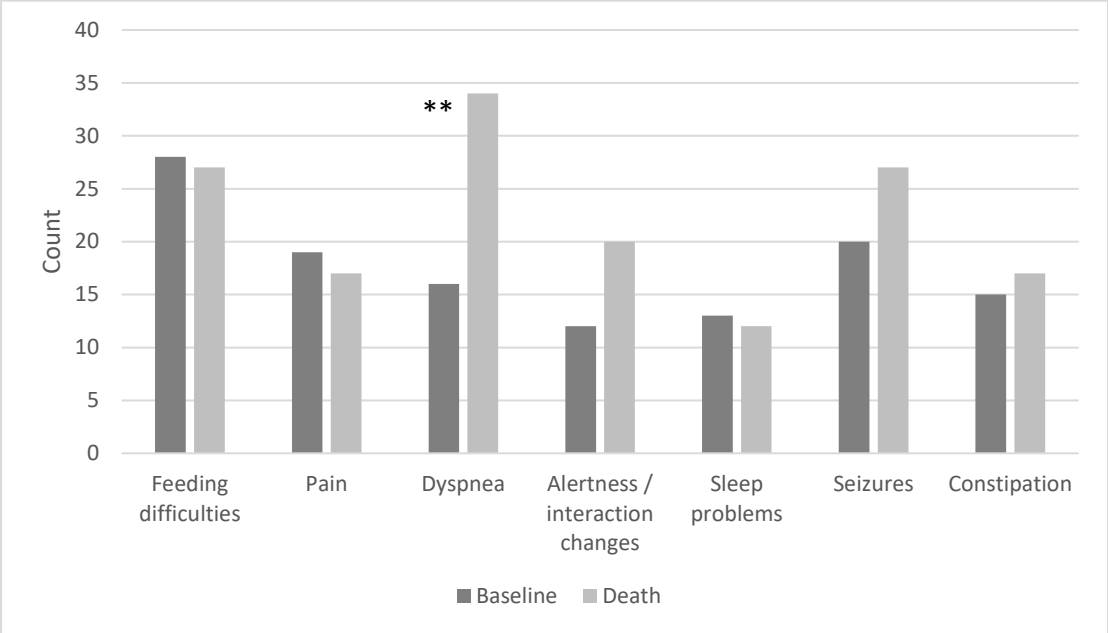
[#]Indicates actual number of children prescribed these medications, where data was available

%pertains to within last 30 days of life

Table 4 – Discussion and orders for limits of care and 'do not attempt resuscitation' orders

		n=	%
First DNAR discussions documented (n=51)	Before Baseline	26	51.0
	Baseline to 31 days before death	11	21.6
	30 to 3 days before death	0	0.0
	≤ 48 hours before death	4	7.8
	Total discussions by time of death	41	80.4
	Not documented	10	19.6
DNAR first ordered (n=51)	Before Baseline	16	31.4
	Baseline to 31 days before death	12	23.5
	30 to 3 days before death	4	7.8
	≤ 48 hours before death	7	13.7
	Total DNARs ordered	39	76.5
	Not ordered	3	5.9
	Not documented	9	17.6
DNAR status 30 to 3 days before death (n=51)	In effect	28	54.9
	Not in effect/not ordered	10	19.6
	Not documented or unknown	13	25.5
DNAR status ≤48 hours before death (n=51)	In effect	33	64.7
	Not in effect/not ordered	3	5.9
	Not documented or unknown	15	29.4
Invasive ventilatory support first introduced (n=51)	Before Baseline	2	3.9
	Baseline to 31 days before death	3	5.9
	30 to 3 days before death	2	3.9
	≤ 48 hours before death	3	5.9
	Total not introduced	38	74.5
	Total not documented or unknown	3	5.9
Stopped g/j tube feeds (n=33 with g/j feeds)	30 to 3 days before death	4	12.1
	≤ 48 hours before death	4	12.1
	Total stopped at death	8	24.2
	Total who continued to be feed	14	42.4
	Total unknown if stopped at death	11	33.3

Figure 1 - Reported symptoms at baseline and death



** $p<0.01$, McNemar's test

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