

Improving Developmental Outcomes for Infants with Cancer

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POGO Multidisciplinary Symposium on Childhood Cancer
Cancer in Infancy – Tiny Patients, Huge Challenges
November 10, 2017, Toronto

Introduction and Goals

- Most children with cancer are diagnosed and treated in early childhood
- The cancers and treatments of early childhood often exert adverse effects on brain structure and function impacting development
- Goals:
 - Briefly review early childhood development and milestones
 - Review the impact of diagnosis and treatment for cancer in early childhood on development
 - Discuss ways to improve developmental outcomes for these children



Development of Infants and Young Children



Early Child Development

- The first few years of life are a crucial developmental period
- The brain grows quickly in size and capacity
- The young child rapidly acquires new skills and abilities in key areas:
 - Physical (movement and motor skills)
 - Social emotional (relationships)
 - Communication and language (non-verbal and verbal)
 - Cognition and learning (problem solving)



Early Child Development

- Birth to 6 Months
 - Responding to touch - most important sensory input
 - Recognizing faces, voices, smells; responds to smiles and touch with pleasure
 - Communicating feelings, needs and desires through sounds, facial expressions and body movements
 - Learning balance, control of body; begin to use body to make things happen (grips fingers, reaches for toys) and explore the world
 - Developing routines
 - Building attachments and trust



Early Child Development

- 6 to 12 Months
 - Controlling body/muscles:
 - Fine motor: picking up small objects with thumb and fingers
 - Gross motor: sitting, crawling, standing, walking
 - Communicating progresses from babbling to syllables to words; express feelings, desire with voice; understanding words
 - Learning to think and solve problems; “experiments” with replication (repetition)
 - Developing strong attachment to caregivers (and object permanence); some fear of strangers
 - Displaying personality (preferences, patterns)



Early Child Development

- 12 to 18 Months
 - Walking and exploring the world; need a safe/secure “base”
 - Understanding more words
 - Using intonation and gestures to communicate as ability to form and use words continues to develop
 - Developing memory, displaying ability to learn from others through observation (repeat behaviors at a later time)
 - Controlling impulses and behaviors arising from emotions such as frustration are a challenge



Early Child Development

- 18 to 24 Months
 - On the move; Lively and energetic; become irritable when movement is limited
 - Growing sense of mastery, confidence
 - Improving fine motor skills: scribbling, coloring
 - Speaking about 50 words; putting words together in short phrases, sentences
 - Pretending in play (symbolic representation is emerging)
 - Growing awareness of self (me, mine), independence and autonomy
 - Emerging self-control; still difficulty stopping and transitioning



Early Child Development

- 24 to 36 Months
 - Controlling motor skills
 - Fastening and unfastening buttons, zippers; using spoon and fork
 - Jumping, climbing, skipping, hopping, throwing
 - Learning 2-3 words per day
 - Building problem solving skills through play
 - Learning how behaviors reflect emotions and that words can be used to express emotions



Factors Underlying Early Child Development

- Physical maturation of the brain (neuronal connections; myelination)
- Touch, sights, smells, sounds (“sensory nourishment”)
- Exploring objects and the world through movement and play
- Interacting with attentive and responsive caregivers who provide a sense of safety and security and scaffold development



Cancer in Early Childhood

- May impact structure and functioning of the brain (brain tumors, surgery, intrathecal chemotherapies)
- May impact sensory systems (enucleation, neurotoxic chemotherapies)
- May limit touch, movement, exploration and interaction (pain, fatigue, infection control, hospitalization)



Cancer in Early Childhood

- May overwhelm caregivers reducing ability to meet child's developmental needs
 - 48% of mothers (N=41) and 38% of fathers (N=25) of infants (< 2 years) with cancer, at least 3 months from diagnosis and on active treatment, report moderate to severe cancer-related traumatic stress symptoms (Vernon et al., 2017)
 - 20% of mothers and fathers reported elevated depressive symptoms (Vernon et al., 2017)
 - Higher levels of parenting stress within 3 months of diagnosis of retinoblastoma predicted greater declines in child functioning at 5 years of age (Willard et al., 2017)



Some Early Childhood Specific Findings

- Children 4-42 months old (N=61), newly diagnosed with non-CNS cancer (56% ALL, 10% AML, 20% NB, 5% RB) (Bornstein et al., 2012)
 - Deficits in motor and mental development compared to age- and gender-matched comparisons; within the normal range as a group
 - Deficits in language skills per standardized assessment, but not mother report
 - Greater anxiety among mothers (controlled in above analyses)
 - Frequency and duration of symbolic play by the child and the quality of emotional exchanges between mother and child during play were no different from healthy controls
 - Mothers of children with cancer engaged in more demonstrations of play than comparison mothers



Developmental Outcomes after Cancer in Early Childhood



General Conclusions

- Survivors of brain tumors are at risk for deficits in neurocognitive, academic, adaptive and social functioning (Willard et al, 2017)
 - Caused by mass itself and forms of treatment used (surgery, cranial radiation, intrathecal chemotherapy)
 - Early age at diagnosis and treatment significantly increases risk of deficits
- Survivors of leukemia are at risk for difficulties with attention, processing speed and academic problems (Jacola et al., 2016)
 - Attributed to intrathecal chemotherapies used in treatment
 - Some evidence that younger age at diagnosis and treatment confers greater risk though this is inconsistently found (e.g., Campbell et al., 2007)

General Conclusions

- Neurotoxic chemotherapies (cisplatin) and other treatments (enucleation) that result in sensory impairments contribute to poorer developmental outcomes in specific domains
 - Hearing loss is associated with declines in IQ and academic achievement (Schreiber et al., 2014); younger ages more sensitive to ototoxic drugs
 - Bi-lateral retinoblastoma is associated with greater motor and visuomotor deficits (Ross et al., 2001)
- Across types of cancer, declines in functioning across time are most pronounced for those diagnosed and treated at young ages (Schreiber et al., 2014; Willard et al., 2014)
- Effects emerge over time; typically not a loss of skills but failure to achieve skills at an age appropriate rate

Some Limitations of the Research

- Few studies focus specifically on those diagnosed during infancy
 - May examine effects of age at diagnosis (continuous variable) for a broad sample
 - When groups are formed, different age cut-offs are used
 - Age at diagnosis is confounded with time since diagnosis
- Cancers (and their treatment) of infants/young children are different from one another and within diagnoses severity/treatment may be confounded with age
- Measurement issues: assessment devices change across ages
- Comparison group issues: norms vs. controls
- Age at follow-up needs to be considered; services received are rarely considered



Improving Developmental Outcomes: General Guidelines and Specific Interventions



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General Recommendations

- Continue to refine treatment protocols to deliver the least amount of neurotoxic treatment while preserving life (More precise radiological techniques; intrathecal chemotherapies instead of cranial radiation; lowering dosages)
- Explore the role of neuroprotective drugs
 - Pioglitazone – anti-inflammatory peroxisome proliferator-activated agonist (Green-Schloesser et al., 2012)
 - Donepezil – acetylcholinesterase inhibitor (Castellino et al., 2012)
- Identify physiological correlates/mechanisms of neurocognitive impairment
 - Example: Folate depletion and homocysteine elevation following methotrexate; folate pathway polymorphism genotype (Kamdar et al., 2011)

General Recommendations

- Attend to child development and environmental factors during treatment
 - Screen functioning with standardized measures throughout treatment – provide specialized services as needed if milestones are significantly delayed
 - Evaluate psychosocial risk factors and resources of the family – intervene as needed to provide support
 - Provide Child Life services to the patient and family – opportunities for play and information/reassurance for parents regarding engaging with their children
 - Assist in arranging appropriate educational placements/early intervention services
- Continue to monitor development and psychosocial needs of the child and family after treatment and throughout the child's life

SEE: Wiener, Kazak, Noll, Patenaude, & Kupst (2015) Standards for the Psychosocial Care of Children With Cancer and Their Families. *Pediatric Blood & Cancer*, 62, S419-424.

Screening and Assessment

Child Screening and Assessment

- Ages and Stages Questionnaires-3 ® (Squire, Bricker, & Twombly, 2009)
 - A 30-item parent-completed developmental screening tool for children 2 to 60 months of age
 - Evaluates communication, gross and fine motor, problem-solving and personal-social skills. “At-risk” and “Refer” cut-scores are provided
 - Use evaluated with 30 children (4 to 48 months) newly diagnosed with cancer within 1 month of diagnosis, then at 6 and 12 months (Quiss, Mahajerin, Sullivan, Pradhan & Bauer, 2013)
 - 7 newly detected delays (4 known) at baseline; 4 new (5 known) at 6 months; and, 3 new (5 known) at 12 months
 - Sensitivity and specificity data not provided

Child Screening and Assessment

- Pediatric Quality of Life Inventories (PedsQL™; Varni, 1998)
 - Parent-report inventories for ages 1-12 months (36 items), 13-24 months (45 items), 2-4 years (21 items), etc.; Self-report inventories start at age 5
 - Assesses physical, emotional, social, cognitive (under 2) and school functioning (2 and older); A separate cognitive functioning scale (6 items) is available for ages 2 and older
 - Scores can be compared to norms to identify those with problems
- Vineland Adaptive Behavior Scales – III (Sparrow, Cicchetti & Sauliner, 2016)
 - Interview and parent report versions, ages birth through adulthood
 - Assesses communication, daily living skills, socialization, motor skills
 - Provides standardized scores; requires training for administration/interpretation

Child Screening and Assessment

- Adaptive Behavior Assessment System (ABAS®-3; Harrison & Oakland, 2015)
 - Parent-report inventories for ages 0-5 years and 5-21; Teacher-report (≥ 2 years)
 - Assesses conceptual, social and practical skills
 - Scores can be compared to norms to identify those with problems; requires training
- Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 2013)
 - Parent-report inventories for ages 2-5 years (BRIEF-P, 2013); 5-18 years (BRIEF-II, 2015); Self-report version (BRIEF-SR,) for age 11 and older; Teacher-report
 - Assesses ability to inhibit responses, shift attention, control emotions, plan/organize and manipulate information while holding it in memory
 - Scores can be compared to norms to identify those with problems; requires training

Child Assessment – Abbreviated Neurocognitive Batteries

- COG protocol ALTE07C1 (Embry et al., 2012)
 - Under 2: parent-report ABAS
 - 2 and older: parent-report measures (ABAS, BASC, BRIEF, PedsQL) plus standardized testing of the child: Wechsler IQ subscales (Vocabulary, Block Design, Symbol Search, Coding) and memory and learning subscales (CMS, CVLT)
- Trackwell Screen (Pejnovic et al., 2012)
 - Under 3: Vineland interview with parent
 - 3 and older: Wechsler IQ subscales (Symbol Search, Coding, Digit Span); NEPSY subscales (Sentence Repetition, Visual Attention, Statue, Category Fluency, Phonological Processing), and subscales from TEA-CH and brief achievement tests
 - Could be completed within 5 weeks of diagnosis, for most within an hour

Child Assessment – Abbreviated Neurocognitive Batteries

- DIVERGT (Krull et al., 2008)
 - Ages 6 and older (long-term survivors)
 - Parent-report Child Symptom Inventory (screens for behavioral, emotional, academic and cognitive symptoms)
 - Child administered: Digit Span, Verbal Fluency, Grooved Pegboard, Trail Making
 - 240 survivors screened; 48 screened twice; 52 had comprehensive follow-up testing
 - Strong association between DIVERGT score and IQ ($r=0.66$); 94% of those with IQs below 85, scored in the impaired range on DIVERGT; 63% of those with IQs above 85 were not in the impaired range on DIVERGT
 - Better predictor than parent-report measure

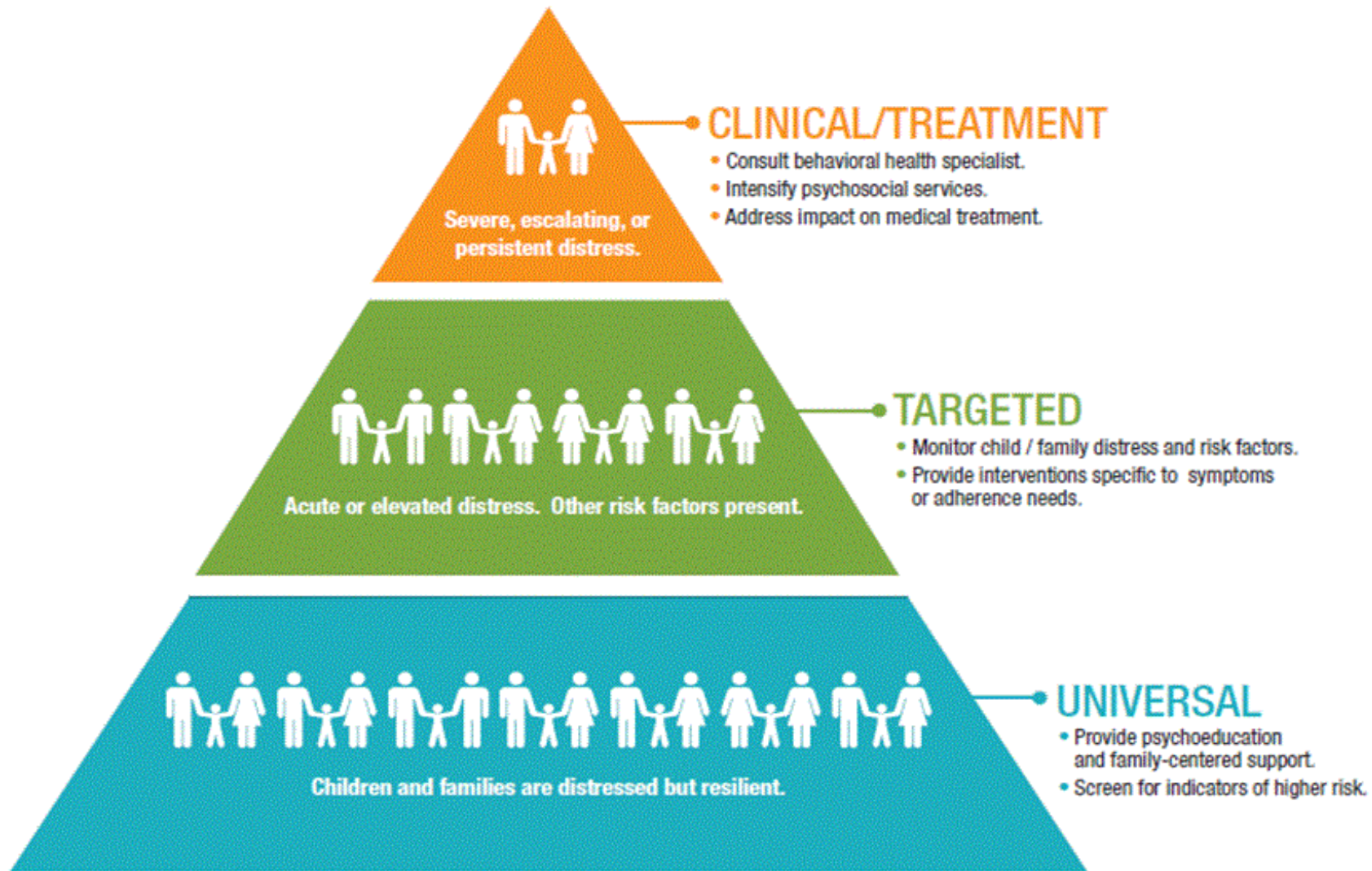
Family Screening

- Family Symptom Inventory (Karlson et al., 2015)
 - Caregiver-report measure screens for patient and sibling emotional, physical and behavioral problems and caregiver and spouse emotional problems during the past month. Also collects information on family demographics and medical history.
 - Patient (10 items), Caregiver (7 items), Sibling (10 items,if applicable) and Spouse (7 items, if applicable); subscales are calculated and averaged to create a total score
 - Good internal consistency of scales and preliminary evidence of concurrent validity
 - Empirically-derived cut-scores are available that suggest when further evaluation is needed

Family Screening

- The Psychosocial Assessment Tool (Kazak et al., 2011)
 - Widely used brief parent report screener of risk and resources across multiple domains (e.g., family structure and resources, family problems, social support, child problems, acute/post-traumatic stress, sibling problems)
 - Evidence of good internal consistency, concurrently validity and predictive utility (Alderfer et al., 2009; Kazak et al., under review; Pai et al., 2008)
 - Scores map onto the Pediatric Psychosocial Preventative Health Model (PPPHM; Kazak, 2006) which provides a tri-level determination of family risk (Universal, Targeted, Clinical)
 - Level of risk has implications for treatment recommendations to support family adaptation and address problems

The Pediatric Psychosocial Preventative Health Model



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Interventions

Interventions

- Developmental Support Nursing Intervention (Yu et al., 2014)
 - Tested the impact of a 12-week family-centered nursing intervention involving age-tailored group-based sessions for parents centered on establishing developmentally supportive behaviors and environments for their children, and practicing play and activities of daily living with their children
 - Enrolled families of children aged 3-7 diagnosed with malignant tumors
 - Randomized to “Family-Centered” (n=120) or Standard Care (n=120)
 - Those in the intervention group showed greater improvements in adaptive behavior skills than those in the control group
 - Exp: 27.5% Above Average 55% Average 17.5% Below Average
SC: 2.5% Above Average 32.5% Average 65% Below Average

Interventions

- Educational-based interventions
 - Individualized Education Plans (IEP) and classroom accommodations (504 plans) developed by school, parent, and (ideally) a member of the treatment team
 - Based upon results of neurocognitive testing, tailored to assess known cancer-related deficits
 - May involve early intervention services including occupational, physical and other therapies in the community
 - Typically not evaluated through research
- Pharmacological interventions
 - Use of methylphenidate to improve attention – demonstrated efficacy in clinical trials

Psychostimulant Medications

- Thompson et al. (2001)
 - Double-blind placebo-controlled clinical trial of 32 pediatric cancer survivors (6 to 18 years of age) with sustained attention and academic achievement deficits; 6 months to 14 years of age at diagnosis
 - Significantly improved sustained attention by standardized test and caregiver report; no effects on processing speed or learning skills
- Mulhern & Butler (2004)
 - Similar design involving 83 pediatric cancer survivors; one improvement – crossover trial with administration of MPH at two dosages and placebo in home environment
 - Significant improvements in parent and teacher rated inattention/cognitive problems; teacher-rated academic competence and teacher (not parent)-reported social skills

Interventions

- Social Skills interventions
 - Specific programs developed to improve social difficulties of children with cancer
 - Two common models of care:
 - Individual one-on-one training of problem-solving skills and cognitive-behavioral skills in the context of social difficulties, delivered over many sessions, often with parent training (e.g., Patel et al., 2009; Poggi et al., 2009)
 - Group-based training of social skills with modeling, practice, activities and parent training delivered over 6-8 sessions (e.g., Barakat et al., 2003; Maurice-Stam et al., 2009; Shulte et al, 2014a; 2014b)
 - Most focus on school-age children age 8 and older
 - Most published studies are uncontrolled pre-post designs

Social Skills Interventions

- Poggi et al. (2009)
 - One-on-one sessions with children on treatment aged 4 to 8
 - Based on cognitive-behavioral principles (changing dysfunctional beliefs, reinforcement, relaxation, modeling, shaping) tailored to participant age
 - Compared those accepting the intervention (n=17) to those refusing it (n=23)
 - Intervention group demonstrated greater improvements on social skills and social problems per parent report

Social Skills Interventions

- Shulte, Bartels & Barrera (2014)
 - Eight 2-hour group sessions with children off treatment aged 7-12 and 13-18
 - Based on cognitive-behavioral principles focused on friendship making, cooperation, managing bullying, resolving conflicts, being assertive and empathic
 - Those able to take part in the intervention (n=15) were compared to those interested but unable to attend (n=12)
 - Intervention group improved more on parent (not child or teacher) reported social skills; stayed stable on parent-reported social problems while control group declined
- Barrera et al. (2017)
 - Same intervention as above; children off treatment aged 8-12 and 13-16, groups formed then randomized to intervention (n=43) or attention placebo (n=48)
 - The intervention group showed significantly greater improvements in social competence by self-report; not parent or teacher report

Interventions

- Cognitive-remediation interventions
 - Specific programs to improve executive functioning skills of children with cancer
 - Two common models of care:
 - Individual one-on-one sessions based on cognitive-behavioral techniques, massed practice, and meta-cognitive strategies (e.g., Butler et al., 2008; Patel et al., 2009)
 - Computer-based cognitive “brain training” focused on specific executive functioning skills (e.g., Conklin et al., 2017; Hardy et al., 2011; Hardy et al., 2013; Kesler et al., 2011)
 - Focus on survivors of school-age with identified deficits

Cognitive Rehabilitation Interventions

- Butler et al., (2008)
 - Twenty 2-hour individual sessions for children aged 6-17, off treatment for cancer, with attention problems based upon standardized assessment
 - Randomized to intervention (n=109) or waitlist control (n=54)
 - Intervention combined hierarchically graded mass practice, meta-cognitive strategy acquisition and cognitive-behavioral interventions (self-talk)
 - Intervention produced significantly greater improvements in academic achievement, but not attention, vigilance, memory or working memory; parent-reports indicated improvements in attention and cognitive abilities

Cognitive Rehabilitation Interventions

- Hardy et al. (2013)
 - Enrolled 8 to 16 year olds, off treatment, with assessed working memory deficits
 - *Cogmed*® computerized cognitive training program (www.cogmed.com):
Twenty five 30-45 minute training sessions, completed at home, targeting working memory through games; Weekly coaching telephone call
 - Intervention increased in difficulty with progress (n=13); control did not (n=7)
 - Demonstrated improvements in visual working memory and parent-rated learning problems but not verbal working memory; no differences at 3 month follow-up
- Conklin et al. (2015; 2017)
 - Same sampling scheme, randomized to *Cogmed*® (n=34) or waitlist control (n=34)
 - Intervention produced significantly greater improvements in examiner assessed working memory and processing speed and parent reported attention and executive function at the end of training and maintained at 6-month follow-up



In Summary



In Summary

- Early childhood is a period of great developmental advances
- Cancer and treatment during early childhood can impact development with implications across the lifespan
- To improve developmental outcomes for these children attention needs to be paid to development during and after treatment
 - Screen development, adaptive behavior, neurocognitive functioning and social functioning of patient to identify deficits
 - Screen family for psychosocial risk and resources – address family needs and help them provide developmental support for their children
 - Refer for or provide empirically-validated interventions when needed

Thank you for your attention!

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