

# CLiPPs

## FALL 2018

**CLiPPs** (Current Literature in Pediatric Psychosomatics) is a pertinent article review from a range of medical science journals and literature from the AACAP Physically Ill Child Committee for consultation/liaison psychiatrists.

We are excited to present our 7th edition this Fall, and we look forward to our 8th edition coming out this 2018-2019 winter.

This issue represents a diverse array of inpatient and outpatient C-L concerns including a robust adherence study in transplant youth, two neuropsychiatric presentations in an emerging new medical treatment modality, implications of parent religiosity in child suicidality, and data on ACE associations for pre-school aged children.

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### **Self-Management Measurement and Prediction of Clinical Outcomes in Pediatric Transplant**

**Background:** It is well established that the period of transition from pediatric to adult healthcare is a time of vulnerability associated with declines in adherence and morbidity. It has been theorized that enhancing patient self-management skills may improve compliance and facilitate healthcare transition thus leading to improved clinical outcomes. *The Responsibility and Familiarity with Illness Survey* (REFILS) is a checklist of skills that has been used to quantify and track self-management levels over time. It demonstrated reliability and validity in single site studies but has lacked correlation with medical outcomes. The authors of this multi-site, prospective cohort study sought to further develop the REFILS through correlation with biological and clinical measures to evaluate association with non-adherence and rejection in pediatric liver transplant recipients.

**Methods:** Participants were 400 children ages 1-17 years and their families from 5 pediatric liver transplant centers enrolled in The Medication Adherence in Children Who Had a Liver Transplant (MALT) cohort. They were followed for 2 years, and the REFILS was administered to dyads at baseline in patients 9 years of age or older and their parents. A total score as well as a “discrepancy” score (the difference between patient and parent reports of patient’s self-management) were calculated. The REFILS examines two self-management domains in patients and parents’ perceptions about their children: perceived knowledge about illness, and responsibility for medical management. Higher scores equal greater reported self-management. Medical outcomes were measured using the

Medication Level Variability Index (MLVI) which is the degree of variation in blood levels of the patients' primary immunosuppressive agent, Tacrolimus. A higher MLVI denotes more fluctuation in levels and more erratic adherence. The main clinical outcome was biopsy-defined rejection as determined by 2 independent pathologists.

**Results:** 213 parent-patient dyads completed the REFILS. There were no significant associations between any demographic variables and scores except for parent level of education. REFILS scores increased with patient age as expected. Patients who reported greater self-management had lower adherence ( $r=0.26$ ,  $P<.01$ ). Greater discrepancy between patient and parent report was associated with lower adherence; when patients endorsed higher levels of self-management than their parent reported for them, it was associated with higher MLVI poorer adherence ( $r=0.20$ ,  $P<.01$ ). Patient REFILS scores predicted non-adherence and future rejection (26.1 (SD 4.2) vs 23.7 (SD 4.8)). Discrepancies between patient and parent report were larger for those who experienced rejection (1.6 (SD 4.2) vs 0.01 (SD 4.2)).

**Conclusion/Commentary:** Patients who reported a higher degree of self-management had worse clinical outcomes. This study echoes other pediatric transplant literature cautioning the transition of responsibility from the parent/caregiver to the patient may be ill-advised if poorly timed, and that a gradual and thoughtful transfer of accountability is essential and must be individualized.

Greater discrepancy between child/adolescent and parent self-management scores was also associated with poor adherence and rejection and is a novel approach to evaluating transition readiness. This discrepancy may reflect a basic level of communication discord in the home which is known to negatively impact adherence. This measure may be a useful tool to facilitate and inform conversations about adherence and allocation of caregiver and patient responsibility. This paper highlights why adolescent self-report must not be taken as the sole indicator of adherence and readiness for transition.

**Take-away:** The REFILS may be a useful tool to aid in recognizing patients at risk for poor adherence and transplant rejection, and to prompt conversations between providers and parent-child dyads about the importance of continued parent involvement and thoughtful transition of responsibility. Patient reports of high self-management and parent and child discrepancies between the child's self-management may be helpful warnings about the need for intervention in adherence and prevention of transplant rejection.

#### **References:**

1. Gutierrez-Colina, AM, et al. Transition readiness, adolescent responsibility, and executive functioning among pediatric transplant recipients: Caregivers' perspectives. *Pediatr Transplant* 2017 May; 21(3), epub.

**Reviewer:** Alison Manning, MD, Duke University Medical Center

**Source:** Annunziato, RA, et al. Self-Management Measurement and Prediction of Clinical Outcomes in Pediatric Transplant. *J Pediatrics* 2018 Feb;193:128-133. [Link here](#)

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## Chimeric antigen receptor T-cell neuropsychiatric toxicity in acute lymphoblastic leukemia

**Background and Objective:** Chimeric Antigen Receptor T-cells (CAR-T) is a novel treatment option for ALL patients who fail standard chemotherapy and stem cell transplant options. CAR T-cell therapy targets B-cell specific antigens universally expressed on tumor cells, causing T-cell proliferation and tumor lysis, providing disease control and potentially cytokine release syndrome (CRS). It has potential for 90% remission rate, but can be associated with neuropsychiatric toxicity with symptoms ranging from mild confusion to aphasia, seizures, psychosis, obtundation, and possible death. This treatment is increasingly being provided for refractory and relapsed B-cell leukemias in pediatric hospitals. This article reviews two cases of young adults with neurotoxic symptoms associated with CAR-T. It then reviews CAR-T cell neuropsychiatric toxicity.

**Methods:** Two cases of neurotoxicity following CAR-T cell treatment were described in detail. Progression of symptoms was reviewed, including the point at which psychiatry was consulted, the differential considered, recommendations made, and response to interventions and outcome. Specific tests used to differentiate cytokine release syndrome from other etiologies were highlighted.

25 yo M w/refractory ALL	33 yo F w/refractory ALL
Bifrontal headache w/photophobia 6 days post-tx, phonophobia, N/V, word finding difficulties, REM, confusion, irritability 8 days post-tx	Patient endorsed hallucinations and was diagnosed with mild delirium, and started on olanzapine. Factors contributing to mentation: steroid and opiate tx, hyponatremia, possible infection
When seen by psychiatry, had intermittent confusion, delayed response to questions	
Head CT: Negative	Head CT: no acute changes
EEG: diffuse slowing	EEG: mild diffuse cerebral dysfunction, no epileptiform discharges
Pancytopenia, increased LFTs, elevated ferritin and CRP	Elevated ferritin and CRP associated with CRS

Recommended low dose neuroleptic and lowering levetiracetam dose, but was not done; returned to baseline w/in 5 days of initial confusion episode	Within 4 days of starting CAR-T, patient was transferred to ICU for worsening mentation. She was minimally responsive, nonverbal, could not recognize loved ones or follow commands. Tocilizumab (anticytokine antibody) given 5 days post CAR-T infusion with minimal improvement. She developed seizures, developed septic shock requiring pressors, intubated twice, and received dexamethasone for cytokine storm. Final ICU diagnosis: CRS with catastrophic multiorgan deterioration, including possible CAR T-cell neurotoxicity with seizures. Indications of CAR-T neurotoxicity and CRS: timing of worsening mentation, elevated ferritin and CRP, seizures, response to steroids. She eventually recovered.
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**Conclusions/Commentary:** The two cases detailed timing of neurologic changes and delirium in relation to CAR-T cell infusion (first 7-10 days post treatment). After the case reports, there is a review of CAR T-cell treatment, a description of CRS and neuropsychiatric toxicity, CRS diagnostic criteria along with treatment and prognosis of neuropsychiatric (NP) toxicity. C/L psychiatrists need to be familiar with diagnosis and treatment of CAR T-cell related CRS due to potential of developing progressive NP toxicity. Use of CAR T-cell therapy is likely to expand to cover other cancer types and therefore rates of associated CRS are likely to increase. It is appropriate that psychiatrists be enlisted to help with management of associated delirium and behavior.

**Take-away:** Familiarity with CAR-T cell therapy and potential NP toxicities is necessary in C/L psychiatry. Pediatric C/L psychiatrists should be aware of the range of presentation of NP symptoms, be able to identify CRS using related lab findings (specifically elevated CRP and ferritin), have familiarity with potential treatments and outcomes.

## References:

1. Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. *Molecular Therapy – Oncolytics* 2016;3:16011.2.
2. Brudno JN, Kochenderfer. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016; doi:10.1182/blood-2016-04-703751.
3. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy – assessment and management of toxicities. *Nat Rev Clin Oncol* 2017;doi:10.1038/nrclinonc.2017.148

**Reviewers:** Janet Charoensook, MD, CHLA+USC Child Psychiatry Fellow; Julianne Jacobson, MD  
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**Source:** Prudent,V and Breitbart,WS. Chimeric antigen receptor T-cell neuropsychiatric toxicity in acute lymphoblastic leukemia. *Palliative Support Care* Aug. 2017; 15(4): 499-503. [Link here](#)

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## Parent Religiosity and Children's Suicidality

**Background:** Suicide rates among adolescents are climbing. This recently published study by Connie Svob, PhD, et al. adds additional factors to consider in a child's risk assessment for suicide. Although prior studies have examined religiosity in adults, finding lower rates of suicide associated with religious beliefs and practices, little is known about how the parent's religious beliefs and practices can shape the child's risk for suicide ideation and attempts (e.g., Dervic et al 2004).

**Methods:** The research objective was to examine the associations of parent and offspring religiosity with suicide ideation and attempts in offspring. The study followed 3 biologically related generations (grandparents, parents, and children) for 30 years (spouses were excluded). The first generation was categorized as either high risk or low risk based on history of diagnosed Major Depressive Disorder. Participants in the study's analysis included 214 individuals in generation 3 who were assessed between age 6 and 18. Religiosity was assessed by examining religious service attendance and religious importance to participants and their parents (generations 2 and 3).

**Results:** Parent and child religiosity was assessed for relationships with child suicidal ideation or attempt. The child's own religiosity was inversely associated with suicidal behavior in girls but not in boys. Parental religious importance and religious service attendance of a parent was inversely associated to daughter's suicidal behavior, but only parental religious importance was inversely associated with sons' suicidal behavior.

**Conclusion/Commentary:** Parental belief in the importance of religion may be a more robust factor than religious attendance. Although the study does not examine the mechanism, religious importance seems to play a role in lowering suicidal behavior. Additionally, the fact that religious importance of parents may mitigate the risk of suicidal behavior in both males and females may add important information to a child and family's assessment. In certain children and families, involving spiritual or pastoral care as a part of a multidisciplinary treatment team may bolster both engagement in treatment and protective factors.

**Take-Away:** Parental religious importance was associated with decreases in child's suicidal behavior, whereas the child's own religiosity was only associated with decreases in girls' suicidal behavior. Asking about both parent and child's beliefs can add another protective factor to safety planning for suicidal adolescents.

## References/Further Reading:

1. Dervic K, Oquendo MA, Grunebaum MF, Ellis S, Burke AK, Mann J.. Religious Affiliation and suicide attempt. *Am J Psychiatry*. 2004; 161(12): 2303-2308
2. Landor A, et al. The Role of Religiosity in the Relationship Between Parents, Peers, and Adolescent Risky Sexual Behavior. *Journal of Youth and Adolescence*, vol. 40, no. 3, 2010, pp. 296-309., doi:10.1007/s10964-010-9598-2.

**Reviewers:** Rebecca Ba'Gah, MD, PGY3, Triple Board Resident, University of Kentucky College of Medicine; Amy L Meadows, MD, MHS, Departments of Psychiatry and Pediatrics, University of Kentucky College of Medicine

**Source:** Svob C, et al. Association of Parent and Offspring Religiosity with Offspring Suicide Ideation and Attempts. *JAMA Psychiatry*, vol. 75, no. 10, 2018, p. 1062., doi:10.1001/jamapsychiatry.2018.2060.

[Link here](#)

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## Association of Adverse Childhood Experiences with Co-occurring Health Conditions in Early Childhood

**Background:** Adverse Childhood Experiences (ACEs) have been repeatedly studied since originally described by Felitti et al (1998), demonstrating strong associations between increasing childhood adversity and a wide array of medical and mental health conditions. Recent review articles have demonstrated associations between 4+ adverse childhood events and 23 different health conditions in adults with particularly strong associations for sexual risk-taking, mental illness, alcohol misuse (ORs 3-6), substance misuse and interpersonal and self-directed violence (ORs > 7) (Hughes et al., 2017). A systematic review of pediatric physical health outcomes found associations between ACEs and developmental delay, asthma, somatic complaints, recurrent infections requiring hospitalization, and sleep disruption (Oh et al., 2018). Another study demonstrated associations between parents' own ACE scores and their children's mental health outcomes (Schickedanz et al, 2018). In the context of these associations, many clinicians, academics and health administrators have argued for increased efforts to prevent, detect and mitigate ACEs.

The article reviewed is the first using this methodology in children ages birth to five.

**Methods:** The study used a subset of subjects (age 2-5yrs, n=19,957) from the 2011-12 National Survey of Children's Health (NSCH), a retrospective parent-report phone survey representative of all noninstitutionalized children in the US, with response rate estimates between 23% and 54% (CDC, 2013). The authors used univariate, bivariate and multivariable logistic regression models. Predictors were the sum number of ACEs reported since birth: divorce/separation of parents; household member

with substance abuse; household member with mental illness; parent spent time in jail; witness or victim to neighborhood violence; exposure to domestic violence; parent death; discrimination because of race or ethnic group. Outcomes included if parents were ever told by a health care practitioner that their child had any of 18 health conditions, which were grouped into 3 domains of developmental, physical or mental health. Covariates analyzed included demographic factors, access and utilization of health care.

**Results:** Notably, only 11% of parents reported 1 ACE, 3.8% reported 2 ACEs, and 3.5% reported 3 or more ACEs. In multivariate regression, compared to those with no ACEs, having 1 ACE was associated with 1.42 increased odds of having at least one condition; this increased to OR of 1.57 with 2 ACEs and OR 3.19 with 3+ ACEs. Having 3+ ACEs was associated with 7.19 times the odds of having comorbid physical, mental and developmental conditions. Unadjusted relationship in Figure 1 of the article demonstrates the growing comorbidity of developmental, physical, and mental health conditions associated with increasing number of ACEs reported. Of children who were diagnosed with both a physical and mental condition, 71% had experienced at least one ACE and 32% had experienced 3+ ACEs.

**Conclusion/Commentary:** This study identified a lower prevalence of ACEs in children ages 2-5 than previously documented for children ages birth to 18, potentially reflecting less cumulative time for children to have experienced ACEs, selection bias in the sample, or parents' response bias. Most importantly, the study extends the observation that children age 2-5yrs have increased odds of physical, mental, and developmental conditions with increasing number of adverse experiences. Experiencing 3+ ACEs compared to 0 ACEs in the first 5 yrs of life is associated with an approximate 3.19 times adjusted odds of having any medical condition. Importantly, these are associations and do not necessarily reflect causal relationships given there may be confounders that were not adjusted for in this analysis and there may be elements of reverse causality, such as children with increased medical needs leading to increased parental distress or poverty and maladaptive coping, such as substance use or intimate partner violence. High quality, prospective studies and randomized clinical trials of interventions to reduce ACEs could support evidence of causality.

**Take-Away:** CL psychiatrists serve populations with comorbid physical, developmental, and/or mental health conditions and thus are likely to have many of their patients under age 5 experiencing multiple ACEs. This prevalence highlights the need for detailed assessment and interventions to address ACEs for young patients on medical psychiatry services.

## References:

1. Centers for Disease Control and Prevention. National Center for Health Statistics, State and Local Area Integrated Telephone Survey. 2011-2012 National Survey of Children's Health Frequently Asked Questions. April 2013. Available from URL: <http://www.cdc.gov/nchs/slaits/nsch.htm>
2. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine, May 1998;14(4), 245-258.

3. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet Public Health*, Aug 2017;2(8), E356-E366.
4. Schickendantz, A., Halfon, N., Sastry, N., & Chung, P. Parents' Adverse Childhood Experiences and Their Children's Behavioral Health Problems. *Pediatrics*, Aug 2018;142(2), epub July 8.
5. Oh D, Jerman P, Silvério Marques S, Koita K, Purewal Boparai S, Burke Harris N, & Bucci M. Systematic review of pediatric health outcomes associated with childhood adversity. *BMC Pediatrics*, Feb 2018;18(1), 83.

**Reviewer:** Jake Crookall, MD, MPH

**Source:** Bright MA, Thompson LA. Association of Adverse Childhood Experiences with Co-occurring Health Conditions in Early Childhood. *J Dev Behav Pediatr* 2018 Jan;39(1):37-45. [Link here](#)

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#### **CLiPPs Feedback**

We appreciate any feedback for our young, developing review series.

CLiPPs is edited by Chase Samsel, MD, Boston Childrens Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115. All critical summaries are written by the designated reviewers.

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