BIOBEHAVIORAL INFLUENCES OF CHEMOTHERAPY-INDUCED MUCOSITIS IN ADOLESCENTS AND YOUNG ADULTS WITH CANCER

by
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Abstract

Cancer-directed therapies are inherently toxic and their use requires a fine balance between administering chemotherapy that is aggressive and potent enough to kill the neoplastic tissues, but not to cause undue permanent harm to the patient. Mucositis is one of these toxicities, and one of the most burdensome and distressing adverse effects of therapy. The condition is acutely painful, introduces risk for life-threatening infections, and significantly contributes to the financial burden of cancer therapy. Importantly, it is a dose-limiting toxicity, so when it presents to severe degrees, therapy intensity must be de-escalated to allow for healing and to prevent subsequent development; a solitary incidence can change the trajectory of therapy for a patient, compromising the ability to deliver intensive therapy and reducing the chance of survival. The pathobiology of mucositis is not well-understood, but cross-sectional and in-vitro studies suggest that the patient's inflammatory response perpetuates and exacerbates development and animal models suggest that stress predicts development via stress-induced inflammation, but this has not been well explored in humans. Adolescents and young adults with cancer have the highest rates of dose-limiting mucositis and the highest reported stress while undergoing therapy, suggesting that findings from animal models hold true in humans. These relationships have not yet been explored in the clinical setting, but an improved understanding would identify if stress and inflammation are risk factors for mucositis and warrant intervention to prevent toxicity development.

This study employs a prospective design to assess if stress and inflammation at the time of chemotherapy administration in adolescent and young adults predicts mucositis development. Thirty adolescents and young adults receiving chemotherapy with a significant chance of inducing mucositis completed baseline stress questionnaire and had inflammatory markers evaluated via blood the morning they received chemotherapy. For the following fourteen days, participants reported intensity of

mucositis symptoms. Regression analyses evaluated if baseline stress or inflammation predicted mucositis and tests of mediation assessed if inflammation mediated the relationship between stress and mucositis. When controlling for relevant confounding variables, stress emerged as a significant predictor for peak mucositis intensity (β=0.052, p=0.018) and predicted total mucositis score (β=0.281, p=0.023), but did not reliably predict mucositis incidence (OR = 1.13, p=0.125). Multiple inflammatory biomarkers were analyzed and IL-1a was predictive of mucositis incidence (OR = 2.66, p=0.084), but this was only significant at the α=0.1 level. Epidermal growth factor predicted peak severity (β=-0.004, p=0.025) and total score (β=-0.024, p=0.030). Mediation analysis suggests that epidermal growth factor, IL8, and vascular endothelial growth factor mediate 1.4-8.1% of the effect that stress has on mucositis. While these effect sizes are small, these data suggest that baseline stress and inflammatory profiles influence mucositis development. Additional research is needed to better elucidate and quantify these relationships in larger, more robustly powered studies that can control for additional clinical factors. However, since stress and inflammation are modifiable factors, they hold promise as targets for interventions to prevent mucositis development.

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Dedication

It is with genuine gratitude that I dedicate this dissertation to the patients in which it intends to serve and to those who graciously took time to participate in this study. This work has always been for you. You inspired it, informed it, and participated in it knowing that it would not benefit you, but potentially others down the road. Your unselfish desire to help make a difference for others while going through therapy yourself will always astonish me and I have learned more about myself from working with you than anybody else. Never let anyone tell you that you cannot change the world; you have already changed mine, and I am eternally grateful for it.

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Table of Contents

List of Tables

List of Figures

Dissertation Organization

This dissertation is organized into five chapters. The first chapter provides background and conceptual grounding for the study, identifying and defining key concepts and providing the conceptual framework used to guide analyses along with identifying the significance and innovation of this work.

Chapter two is presented in three parts. Manuscripts one and two systematically review psychosocial interventions for adolescents and young adults with cancer as well as the role of self-efficacy in symptom development in this population. Manuscript three provides a meta-analysis evaluating the use of anti-inflammatory mouthwashes in preventing mucositis development. Cumulatively, these publications set the foundation for the design of this study and justify inclusion of stress, self-efficacy, and inflammatory markers in evaluating mucositis development.

Chapter three (manuscript four) describes the prospective design of this study including the quantitative methods that were employed when conducting this research necessary to meet the dissertation's overall study aims. Chapter four (manuscript five) presents the quantitative study results and shares findings from regression models that predict mucositis development from stress and inflammation. Mediation analyses are employed to explore the role of inflammation in the relationship between stress and mucositis and the findings provide effect size estimates for this work as a pilot study. This chapter shares all findings related to the three principal aims of this dissertation.

Chapter Five provides a summary of results and discusses integration of findings across the five manuscripts and within other existing literature. The chapter discusses implications of these results for future research, interventions, and policies relevant to nursing research and practice while considering the relevant limitations and strengths of this design.

CHAPTER 1: INTRODUCTION

Background and Rationale

Cancer-directed therapies are inherently toxic and while they are lifesaving, they are also associated with a number of toxicities that significantly threaten quality of life in persons who receive them. Chemotherapy, radiation therapy, surgical intervention, immunotherapy, and bone marrow/stem cell transplant are all frequently employed as means to control cancer and each holds its own unique toxicity profile. In clinical practice, these therapies are used in combination, exposing persons with cancer to a multitude of adverse effects that may present nearly immediately or not until several years have passed. In doing so, patients frequently endure a myriad of adverse toxicities of which nausea, pain, fatigue, gastrointestinal distress, weight change, and dermatologic conditions prevail alongside the neurocognitive, financial, and logistical challenges of treatment.[1-4]

During the treatment period, these adverse effects serve as limiting factors for therapy delivery, meaning that therapy is delivered intermittently so patients have time to recover between doses or cycles of treatment. They also serve as dose-limiting toxicities; when present at high intensities or for long durations, treatment regimens are altered and therapy must be de-escalated, delayed, or discontinued entirely to prevent subsequent toxicity development. This reduced intensity of therapy allows for healing but also reduces chance of cancer survival. In this sense, acute dose-limiting toxicities become life-threatening because they preclude patients from receiving optimal cancer-directed therapy.[5, 6]

Mucositis, a condition involving ulcer development in the gastrointestinal tract, is a frequent dose-limiting toxicity ubiquitous to many chemotherapy and radiation therapy regimens. The development of severe mucositis at *any* point after chemotherapy requires that future doses be reduced, delayed, or withheld completely. About half of

people treated for cancer will report development of mucositis[7, 8] but risk varies by chemotherapy regimen and dose; up to 80% of patients undergoing stem cell transplant report mucositis.[7, 8] Nearly 43% of patients treated on pediatric protocols develop mucositis to a degree that necessitates de-escalation of therapy[9] with higher incidence in the adolescent and young adult (AYA) age group.[10-12]

Patients frequently cite mucositis as one of the most distressing adverse effects of cancer-directed therapy.[13, 14] When present to a severe degree, the condition necessitates that treatment intensity is reduced to limit future development. Mucositis is a challenging side effect of treatment because it is acutely painful and interferes with the ability to speak, eat, and drink normally – significantly impacting quality of life. Furthermore, there is no treatment to spur resolution once it develops and evidence-based preventative strategies are limited, making mucositis a frequent, burdensome, life-threatening side effects of cancer therapy.[13, 14]

Impact of Mucositis During Therapy

Mucositis is acutely painful, and ulcerations are most prominent in the oral cavity and throat[7, 15, 16] which limits the ability for patients to speak, eat, and drink normally, further contributing to poor quality of life. Challenges with intake and dysphagia that result from mucositis lead to malnutrition, weight loss, and caloric deficits that further delay healing and recovery from other effects of chemotherapy.[14, 17, 18] Mucositis typically develops within 10 days after chemotherapy administration and lasts for several days before beginning to resolve,[19] presenting concurrently with therapy-induced immunosuppression. Because mucositis interrupts the protective function of the oral mucosa, its presence significantly increases risk of infections,[14, 20, 21] which are also life-threatening for persons receiving chemotherapy.

Evidence-based therapies for mucositis and for mucositis prevention are currently lacking[16, 22-24] so once it develops, patients are provided only supportive care until the condition resolves. Treatment in this regard may include intravenous fluids, parenteral nutrition, and aggressive pain control. Patients with severe mucositis typically require inpatient hospital care, adding to the financial cost of mucositis. Mucositis prevention is an unmet clinical need for all persons undergoing chemotherapy; because there are no interventions that reliably accelerate recovery once mucositis develops, prevention has become a desirable clinical goal. Preventing mucositis is imperative to reduce the burden and cost of cancer care, improve the cancer experience, and provide patients with the greatest chance of disease survival.

Mucositis Pathophysiology

Effective prevention of mucositis requires a thorough understanding of the development of the condition. Unfortunately, the pathobiology of mucositis is not yet well understood, but research suggests that development results from a combination of the direct toxic effects of therapy and the patient's physiological response; making mucositis development multi-factorial in nature. Chemotherapy, by design, reduces or arrests cell growth and differentiation, but is not specific to cancerous cells and tissues. The cytotoxic effects of chemotherapy are frequently seen in other tissues, especially those with high proliferation and turnover, like the gastrointestinal mucosa. Chemotherapy damages cellular structures, repair mechanisms, and DNA strands leading the alterations in the cell's ability to grow and differentiate. Resultant cell death results in tissue friability, compromise of mucosal tissue integrity, and eventual cell death and necrosis.[15, 16, 25]

Cell death increases oxidative stress on the tissues leading to the generation of reactive oxygen species[26-28] and damage-associated pattern molecules that recruit an

inflammatory response. At the same time, cells in damaged mucosal tissues begin to promote transcription of genes that are associated with mucositis development, primarily, nuclear factor kappa-B which modulates over 200 pro-inflammatory genes associated with pro-inflammatory cytokine production and recruitment.[16, 25, 27] This high inflammatory profile and increased pro-inflammatory cytokines leads to worsening tissue damage through dissolution of connective tissues, damage to the endothelial layer of the mucosa, and inhibition of tissue oxygenation and repair mechanisms.[15, 16, 27, 28] Together, the damage to the tissues caused by chemotherapy and the inflammatory response perpetuate further increases in the inflammatory profile. Chemotherapy alone is not likely sufficient to cause mucositis, but the resultant damage it imparts and the stimulation of the inflammatory response are what likely exacerbate mucositis development.[29]

This cascade of events occurs concurrently with damage that chemotherapy produces in other cells that normally function in the repair and recovery of tissues including fibroblasts, macrophages, and lymphocytes. The end result is a mucosal tissue that is composed of damaged cells incapable of self-repair, an inflammatory response that worsens tissue necrosis, and an immune system that is not robust enough to rapidly repair and protect the mucosa. Microorganism invasion of mucosal tissues and mechanics of the mouth from eating and talking can also exacerbate the development of oral lesions.[16, 27] The high bacterial flora of the oral cavity also contributes to mucositis and invasion of microbes into the mucosal layer further exacerbates mucosal lesion development.

Adolescents and Young Adults (AYAs)

Mucositis disproportionally affects AYAs with cancer,[30-36] they experience more frequent and worse severity of mucositis than other age groups.[10-12, 37] In fact, AYAs have overall worse toxicity profiles compared to other age groups treated on the same

chemotherapy regimens[10] leading to more therapy interruptions from other dose-limiting toxicities as well. Because mucositis is frequent within this age demographic, it is an important symptom of cancer therapy that warrants investigation so that age-appropriate preventative measures can be developed. Reducing dose-limiting toxicities is especially important, since AYAs have experienced the slowest improvements in cancer survival over the past 20 years compared to all other age groups in the United States.[38] Limiting the development of dose-limiting toxicities may be an avenue to improve AYA cancer survival.

Reasons driving frequent and severe mucositis among this population are not well understood,[10-12, 37] but the inflammatory component of mucositis development may provide some explanation. In addition to mucositis, AYAs with cancer report some of the highest rates of psychological stress when compared other age groups[39] and these stress profiles have been correlated to worse therapy-related toxicity profiles.[40-43] Psychological stress, the response an individual has to ongoing challenges, like a cancer diagnosis, lead to inflammation by altering immune function and inflammatory cytokines.[44-47] Stress increases interferon gamma (IFNγ), tumor necrosis factor alpha (TNFα), and interleukins IL-1, IL6, and IL-12 which have all been suggested as contributors of mucositis.[29, 48, 49] It stands to reason, then, that the high stress profile in AYAs with cancer may be contributing to an elevated inflammatory profile that is contributing to and exacerbating mucositis development with chemotherapy. Animal models have suggested that stress-induced inflammation is a driving force behind mucositis development,[49] but these relationships have not been explored in humans or in the clinical setting.

Purpose and Study Aims

This dissertation study explores relationships between stress, inflammation, and mucositis in AYAs receiving chemotherapy. The purpose is to describe these relationships, to evaluate if stress at the time of chemotherapy administration reliably predicts mucositis development, and to determine if the inflammatory response mediates the relationship between stress and mucositis.

Specific Aims and Hypotheses

Aim 1: Determine the associations between self-reported psychological stress and inflammatory biomarkers (IFNγ, IL-1, IL-6, IL-12, and TNFα) in AYAs receiving chemotherapy. With this aim, there is a hypothesized positive correlation between reported stress and inflammatory biomarkers

Aim 2: Determine the association between inflammatory biomarkers (IFNγ, IL-1, IL-6, IL-12, TNFα) at the time of chemotherapy administration with the development and intensity of post-chemotherapy mucositis in AYAs. With this aim, there will be a hypothesized positive relationship between inflammatory biomarkers at the time patients receive chemotherapy and the presence and intensity of oral mucositis following chemotherapy.

Aim 3: Explore a) the direct relationship between stress and post-chemotherapy oral mucositis and b) the indirect effect through inflammatory biomarkers as mediators of this relationship in AYAs receiving chemotherapy. In this aim, there is a hypothesized positive correlation between perceived stress at the time patients receive chemotherapy and the presence/intensity of mucositis following chemotherapy (direct effect). There is also a hypothesized mediating relationship of inflammatory biomarkers at the time of chemotherapy administration that will explain the relationship between stress and subsequent mucositis development (indirect effect)

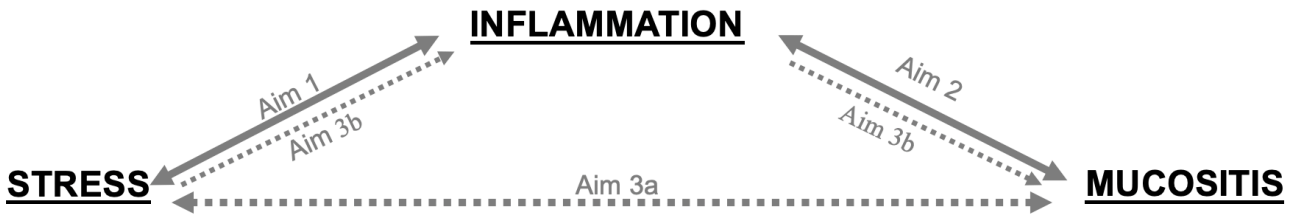

Figure 1: Specific Aims

Conceptual/Theoretical Framework

This research is grounded in the conceptual basis outlined by the NIH Symptom Science Model[50] and Theory of Unpleasant Symptoms.[51] The symptom science model guides research through identifying a symptom, phenotyping the symptom, and describing biomarkers for clinical intervention (figure 1).[50-52] This project specifically serves to fulfill the latter portion of this model, identifying important biomarkers to explain symptom development. In recognizing that symptom development is complex and influenced by a multitude of factors, the Theory of Unpleasant Symptoms was used to scaffold relationships for investigation. The theory is a recursive and bi-directional model that identifies physiological, psychologic, and situational factors that all influence symptom development as well as each other and should be considered when investigating symptom etiology.[51] This study therefore considers influences from inflammation (physiological), stress (psychological), and treatment-related (situational) factors in the development of mucositis (figure 2).

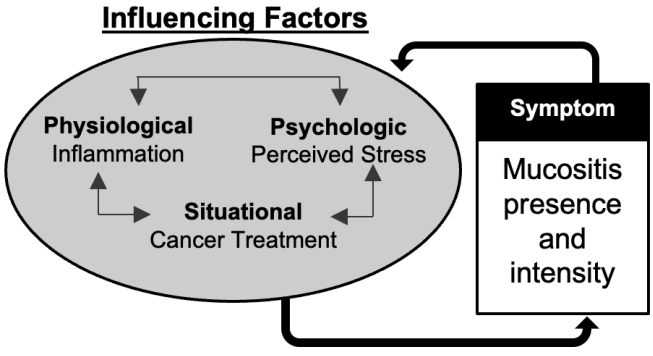

Figure 2: Adapted Framework of Theory of Unpleasant Symptoms

Significance

The need to focus more attention on the research and clinical care of AYAs with cancer cannot be understated. Cancer is currently the leading medical cause of death in this age group and in 2022 alone, an estimated 88,260 AYAs will be diagnosed with cancer leading to nearly 10,000 deaths.[38] The incidence of cancer in the US population as a whole has been decreasing over the past 20 years but the incidence in AYAs has been climbing; they are presently the only age group that continues to see annual increases in the incidence of cancer.[38] Fortunately, survival rates have been improving across the United States but the slowest rate of improvement is seen among AYAs.[38] Meaning, that AYAs are the only age group facing a rising incidence of cancer but have not yet experienced the benefit of improved therapies that their younger and older counterparts have seen. Because of the high prevalence of mucositis in this age group and the grave impact it has on quality of life and therapy delivery, addressing causes of mucositis for AYAs is an important component of improving treatment and outcomes for these individuals.

Nursing, as a science and clinical practice, tends to the patient's response to disease, illness, and therapy and seeks to provide equitable care to all persons, ensuring that they can live life to their highest potential. In this regard, nursing is the field of science best suited to investigate symptoms of cancer therapy since they are the clinicians charged with managing these symptoms once they present. Approaching mucositis development through a holistic nursing lens allows consideration of both biologic and psychosocial factors that contribute to the symptom experience. High stress profiles and high toxicity profiles are well-documented in AYAs being treated for cancer, but few studies have been conducted to explore relationships between these unique factors in this age group. Examining mucositis development through biobehavioral

modalities will inform models of nursing science that better explain symptom development, especially those detailing mucositis in AYAs.

The main focus of this work is to establish effect sizes and direction of relationships between stress, inflammation, and mucositis with intention to use these data to inform larger, more robustly-powered studies. Articulating and elucidating these relationships may identify potential modifiable factors that contribute to mucositis that may become targets for interventions. Therefore, results from this work will have important policy implications with regard to the provision of psychosocial care for AYAs with cancer. Despite knowledge that these persons have unique psychosocial needs, delivery of psychosocial care is lacking.[2, 53-55] Access is challenging; less than 20% of pediatric oncology divisions have a psychologist available and insurance coverage is often denied citing that psychosocial care is not medically necessary.[53, 55] By demonstrating that psychosocial metrics/stress have a direct influence of toxicity, clinicians can have data for which to justify insurance coverage for these services and being to explore psychosocial interventions as a means to prevent toxicity. The incorporation of a biologic marker in this study will explore a physiologic risk factor of mucositis. This may identify a biomedical target for intervention and will inform future inquiry as to how clinicians may approach mucositis prevention through the use of anti-inflammatory agents.

Innovation

There currently exists a gap in the literature addressing the understanding of mucositis development in AYAs. This project will be one of the first studies to investigate the complex relationships between stress and its inflammatory response and how these may contribute to chemotherapy-related mucositis in AYAs with cancer. Thus far, predictive relationships have only been explored in animal studies and human models

remain correlative in nature. The longitudinal design of this study introduces a temporality factor that assists in the determination of causal relationships and is an important step in the translational science pathway from in-vitro/animal models to clinical studies. The use of daily patient-reported symptoms also introduces the opportunity to explore feasibility of this work within the AYA oncology population. The contributions of this proposed research are significant because they will (1) inform a better understanding of the biobehavioral influences of mucositis, (2) provide initial estimates for relationships between relevant treatment-related factors, (3) have important policy implications (e.g. support funding of mental health and stress reduction aspects of cancer therapy), and (4) set the groundwork for future research in therapy-related toxicities.

Chapter 1 References

1. Carlotto A, Hogsett VL, Maiorini EM, Razulis JG, Sonis ST. The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. *Pharmacoeconomics*. 2013;31(9):753-66. doi:10.1007/s40273-013-0081-2
2. Doherty M, Miller-Sonet E, Gardner D, Epstein I. Exploring the role of psychosocial care in value-based oncology: Results from a survey of 3000 cancer patients and survivors. *Journal of Psychosocial Oncology*. 2019;37(4):441-455. doi:10.1080/07347332.2018.1504851
3. Gupta A, Jensen EH, Virnig BA, Beg MS. Time-Related Burdens of Cancer Care. *Journal of Clinical Oncology - Oncology Practice*. 2021;0(0):OP.21.00662. doi:10.1200/op.21.00662
4. Jairam V, Lee V, Park HS, et al. Treatment-Related Complications of Systemic Therapy and Radiotherapy. *JAMA Oncology*. 2019;5(7):1028-1035. doi:10.1001/jamaoncol.2019.0086
5. Cairo MS. Dose reductions and delays: limitations of myelosuppressive chemotherapy. *Oncology*. 2000;14(9)(8):21-31.
6. Rosenthal DI. Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes. *Journal of Supportive Care in Oncology*. 2007;5(9 Suppl 4):23-31.
7. Çakmak S, Nural N. Incidence of and risk factors for development of oral mucositis in outpatients undergoing cancer chemotherapy. *International Journal of Nursing Practice*. 2019;25(1):e12710. doi:10.1111/ijn.12710
8. Curra M, Soares Junior LAV, Martins MD, Santos P. Chemotherapy protocols and incidence of oral mucositis. An integrative review. *Einstein (Sao Paulo)*. 2018;16(1):eRW4007. doi:10.1590/s1679-45082018rw4007

9. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2006;109(7):2773-2780. doi:10.1182/blood-2006-07-036673
10. Bukowinski AJ, Burns KC, Parsons K, Perentesis JP, O'Brien MM. Toxicity of cancer therapy in adolescents and young adults (AYAs). *Seminars in Oncology Nursing*. Aug 2015;31(3):216-226. doi:10.1016/j.soncn.2015.05.003
11. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology*. Jul 2016;34(20):2380-U129. doi:10.1200/jco.2015.62.4544
12. Relling MV, Fairclough D, Ayers D, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *Journal of Clinical Oncology*. Aug 1994;12(8):1667-1672. doi:10.1200/jco.1994.12.8.1667
13. Kanagalingam J, Wahid M, Lin J-C, et al. Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT) study. *Supportive Care in Cancer*. 2018;26(7):2191-2200. doi:10.1007/s00520-018-4050-3
14. Otmani N, Hattad S. Clinical Outcome in Children with Chemotherapy-Induced Mucositis. *Seminars in Oncology Nursing*. 2021;37(3):151160. doi:10.1016/j.soncn.2021.151160
15. Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation

Therapy. *Journal of the National Cancer Institutes Monographs*. 2019;2019(53) doi:10.1093/jncimonographs/lgz011

16. Pulito C, Cristaudo A, Porta CL, et al. Oral mucositis: the hidden side of cancer therapy. *Journal of Experimental & Clinical Cancer Research*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7
17. McCullough RW. US oncology-wide incidence, duration, costs and deaths from chemoradiation mucositis and antimucositis therapy benefits. *Future Oncology*. 2017;13(30):2823-2852. doi:10.2217/fon-2017-0418
18. Shu Z, Zeng Z, Yu B, et al. Nutritional Status and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study. *Frontiers in Oncology*. 2020 doi:10.3389/fonc.2020.594687
19. Bachour PC, Sonis ST. Predicting mucositis risk associated with cytotoxic cancer treatment regimens: rationale, complexity, and challenges. *Current Opinion in Supportive and Palliative Care*. 2018;12(2):198–210. doi:10.1097/SPC.0000000000000339
20. Kishimoto M, Akashi M, Tsuji K, et al. Intensity and duration of neutropenia relates to the development of oral mucositis but not odontogenic infection during chemotherapy for hematological malignancy. *PLOS ONE*. 2017;12(7):e0182021. doi:10.1371/journal.pone.0182021
21. Sobue T, Bertolini M, Thompson A, Peterson DE, Diaz PI, Dongari-Bagtzoglou A. Chemotherapy-induced oral mucositis and associated infections in a novel organotypic model. *Molecular Oral Microbiology*. 2018;33(3):212-223. doi:10.1111/omi.12214

22. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and Treatment of Chemotherapy and Radiotherapy Induced Oral Mucositis. *Medicina*. 2019;55(2):25.
23. Sonis ST, Villa A. Phase II investigational oral drugs for the treatment of radio/chemotherapy induced oral mucositis. *Expert Opinion on Investigational Drugs*. 2018;27(2):147-154. doi:10.1080/13543784.2018.1427732
24. Thomsen M, Vitetta L. Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. *Integrative Cancer Therapies*. 2018;17(4):1027-1047. doi:10.1177/1534735418794885
25. Hamouda N, Sano T, Oikawa Y, et al. Apoptosis, Dysbiosis and Expression of Inflammatory Cytokines are Sequential Events in the Development of 5-Fluorouracil-Induced Intestinal Mucositis in Mice. *Basic & Clinical Pharmacology & Toxicology*. 2017;121(3):159-168. doi:10.1111/bcpt.12793
26. Basile D, Di Nardo P, Corvaja C, et al. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. *Cancers*. 06/20 2019;11(6):857. doi:10.3390/cancers11060857
27. Sonis ST. The pathobiology of mucositis. *Nature Reviews Cancer*. 2004;4(4):277-284. doi:10.1038/nrc1318
28. Wong HM. Oral Complications and Management Strategies for Patients Undergoing Cancer Therapy. *The Scientific World Journal*. 01/08 2014;2014:581795. doi:10.1155/2014/581795
29. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 Suppl):1995-2025. doi:10.1002/cncr.20162
30. Advani AS, Sanford B, Luger S, et al. Frontline-Treatment Of Acute Lymphoblastic Leukemia (ALL) In Older Adolescents and Young Adults (AYA) Using a Pediatric

Regimen Is Feasible: Toxicity Results of the Prospective US Intergroup Trial C10403 (Alliance). *Blood*. 2013;122(21):3903-3903. doi:10.1182/blood.V122.21.3903.3903

31. Canner JA, Alonzo TA, Franklin J, et al. Treatment outcomes in older adolescent and young adult (AYA) patients with newly diagnosed AML. *Journal of Clinical Oncology*. 2011;29(15) doi:10.1200/jco.2011.29.15_suppl.9506
32. Franklin ARK, Alonzo TA, Gerbing RB, et al. Outcome of Adolescents and Young Adults (AYAs) with Non-M3 Acute Myeloid Leukemia (AML) Treated on Children's Oncology Group (COG) Trials Compared to Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) Trials. *Blood*. 2010;116(21):84-84. doi:10.1182/blood.V116.21.183.183
33. Freyer DR, Felgenhauer J, Perentesis J, Adult COGAY. Children's Oncology Group's 2013 blueprint for research: Adolescent and young adult oncology. *Pediatric Blood & Cancer*. 2013;60(6):1055-1058. doi:10.1002/pbc.24431
34. Gupta A, Damania RC, Talati R, O'Riordan MA, HMatloub YH, Ahuja SP. Increased Toxicity Among Adolescents and Young Adults Compared with Children Hospitalized with Acute Lymphoblastic Leukemia at Children's Hospitals in the United States. *Journal of Adolescent and Young Adult Oncology*. 2021;10(6):645-653. doi:10.1089/jayao.2020.0154
35. Gupta AA, Anderson JR, Pappo AS, et al. Patterns of chemotherapy-induced toxicities in younger children and adolescents with rhabdomyosarcoma. *Cancer*. 2012;118(4):1130-1137. doi:10.1002/cncr.26358
36. Gupta AA, Chi Y-Y, Anderson JR, et al. Patterns of chemotherapy-induced toxicities and outcome in children and adolescents with metastatic rhabdomyosarcoma: A report from the Children's Oncology Group. *Pediatric Blood & Cancer*. 2017;64(9):e26479. doi:10.1002/pbc.26479

37. Burke MJ, Devidas M, Chen Z, et al. Outcomes in adolescent and young adult patients (16 to 30 years) compared to younger patients treated for high-risk B-lymphoblastic leukemia: report from Children's Oncology Group Study AALL0232. *Leukemia*. 2021;doi:10.1038/s41375-021-01460-6
38. Institutes NC. Surveillance, Epidemiology, and End Results Program. Accessed January 20, 2022. Retrieved from https://seer.cancer.gov/
39. McCarthy MC, McNeil R, Drew S, et al. Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents. *Journal of Adolesccent and Young Adult Oncology*. 2016;5(4):322-329. doi:10.1089/jayao.2016.0015
40. Geue K, Brähler E, Faller H, et al. Prevalence of mental disorders and psychosocial distress in German adolescent and young adult cancer patients (AYA). *Psycho-Oncology*. 2018;27(7):1802-1809. doi:10.1002/pon.4730
41. Harlan LC, Lynch CF, Keegan TH, et al. Recruitment and follow-up of adolescent and young adult cancer survivors: the AYA HOPE Study. *Journal of Cancer Survivorship*. 2011;5(3):305-314. doi:10.1007/s11764-011-0173-y
42. Quinn GP, Gonçalves V, Sehovic I, Bowman ML, Reed DR. Quality of life in adolescent and young adult cancer patients: a systematic review of the literature. *Patient Relat Outcome Meas*. 2015;6:19-51. doi:10.2147/PROM.S51658
43. Zebrack BJ, Corbett V, Embry L, et al. Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*. 2014;23(11):1267-1275. doi:10.1002/pon.3533
44. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunology Research*. 2014;58(2-3):193-210. doi:10.1007/s12026-014-8517-0

45. Perwez Hussain S, Harris CC. Inflammation and cancer: An ancient link with novel potentials. *International Journal of Cancer*. 2007;121(11):2373-2380. doi:10.1002/ijc.23173

46. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain, Behavior, and Immunity*. 2013;30 doi:10.1016/j.bbi.2012.06.015

47. Wu W, Chaudhuri S, Brickley DR, Pang D, Karrison T, Conzen SD. Microarray analysis reveals glucocorticoid-regulated survival genes that are associated with inhibition of apoptosis in breast epithelial cells. *Cancer Research*. Mar 1 2004;64(5):1757-64. doi:10.1158/0008-5472.can-03-2546

48. Hall PD, Benko H, Hogan KR, Stuart RK. The influence of serum tumor necrosis factor-alpha and interleukin-6 concentrations on nonhematologic toxicity and hematologic recovery in patients with acute myelogenous leukemia. *Experimental Hematology*. 1995;23(12):1256-60.

49. Sonis ST, Peterson RL, Edwards LJ, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncology*. 2000;36(4):373-81. doi:10.1016/s1368-8375(00)00012-9

50. Cashion AK, Gill J, Hawes R, Henderson WA, Saligan L. National Institutes of Health Symptom Science Model sheds light on patient symptoms. *Nursing Outlook*. 2016;64(5):499-506. doi:10.1016/j.outlook.2016.05.008

51. Lenz ER, Pugh LC, Milligan RA, Gift A, Suppe F. The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*. 1997;19(3):14-27. doi:10.1097/00012272-199703000-00003

52. Cashion AK, Grady PA. The National Institutes of Health/National Institutes of Nursing Research intramural research program and the development of the National Institutes of Health Symptom Science Model. *Nursing Outlook*. 2015;63(4):484-7. doi:10.1016/j.outlook.2015.03.001

53. Cuviello A, Boss R, Shah N, Battles H, Beri A, Wiener L. Utilization of palliative care consultations in pediatric oncology phase I clinical trials. *Pediatric Blood & Cancer*. Aug 2019;66(8)e27771. doi:10.1002/pbc.27771

54. Kusch M, Labouvie H, Ladisch V, Fleischhack G, Bode U. Structuring psychosocial care in pediatric oncology. *Patient Education & Counseling*. 2000;40(3):231-45. doi:10.1016/s0738-3991(99)00109-3

55. McGrady ME, Peugh JL, Brown GA, Pai ALH. Spending on Hospital Care and Pediatric Psychology Service Use Among Adolescents and Young Adults With Cancer. *Journal of Pediatric Psychology*. 2017;42(9):1065-1074. doi:10.1093/jpepsy/jsx001

CHAPTER 2: LITERATURE REVIEW

This review of the literature is presented in three parts. The first manuscript (Thornton, Ruble, & Kozachik; Journal of Pediatric Oncology Nursing, 2020) presents a review of the literature that identifies current approaches to psychosocial care of adolescents and young adults undergoing cancer-directed therapy. Manuscript two (Thornton, Li, Yeh, & Ruble; Supportive Care in Cancer, 2021) explores the role that self-efficacy plays in symptom management for adolescents and young adults with cancer and provides guidance for the use of self-efficacy in symptom research within this population. The final manuscript (Thornton, Li, Budhathoki, Yeh, & Ruble; Supportive Care in Cancer, 2022) presents an integrative review and meta-analysis evaluating the role that local anti-inflammatory control has on mucositis development in persons undergoing therapy for cancer. An addendum to this chapter follows these manuscripts and provides a brief summary of findings and discusses how these results are integrated into the design of this dissertation study.

Manuscript One: Psychosocial interventions for adolescents and young adults with cancer: An integrative review

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Abstract

Background: Adolescents and young adults with cancer sit in a precarious position facing an increasing cancer incidence while incidence in other age groups has been declining. A cancer diagnosis at this age imposes undue distress in a demographic with limited coping resources creating psychosocial needs that differ from children and older adults. Addressing psychosocial needs early in the cancer trajectory is postulated as an approach to address distress, improve quality of life, and promote optimal outcomes from therapy. The purpose of this review is to identify current successful approaches to psychosocial care in adolescents and young adults receiving therapy for cancer.

Methods: An integrative review of publications identified through six relevant databases was conducted. Thematic analysis was performed to identify types of interventions followed by assessment of publication level of evidence, quality, and a critique of the effectiveness of interventions.

Findings: A total of 6,292 articles were identified and 17 met inclusion criteria for this review. Thematic analysis and critique identified six themes for intervention approaches with mixed outcomes: creative expression, promoting peer interactions, individual coaching, employing technology, promoting physical activity, and clinical interactions.

Discussion: Adolescent and young adult psychosocial needs while receiving treatment are complex and best addressed with the involvement of an interdisciplinary team. Effective interventions include those that have been tailored to the patient and consider the individual's developmental stage. Interventions that promote autonomy and decision making, provide privacy, are executed in individual sessions, and facilitate social/peer interactions have been more successful in improving psychosocial outcomes.

Introduction

Over the past 20 years, annual cancer incidence has been decreasing for the United States population as a whole, but has been increasing for persons 15 to 39 years of age.[1] While survivorship rates have been improving over this same time period, these adolescents and young adults (AYAs) have not experienced the same degree of improvement in cancer survivorship as other age groups.[1] This presents a concerning trend as AYAs are expected to have ongoing increased incidence of cancer with some of the slowest improvements in mortality rates. Cancer is currently the leading medical cause of death in AYAs[2] necessitating investigations into the multifaceted contributions to survivorship. Addressing the psychosocial needs of AYAs is not only a cornerstone in providing holistic nursing care and improving quality of life but holds potential to improve the side effect profile of treatment[3] allowing for improved cancer mortality rates.

A cancer diagnosis for an AYA rapidly interrupts important typical development during essential formative years and imposes significant amounts of stress, creating psychosocial needs distinct from younger children and older adults.[4] AYAs have difficulties adjusting to the diagnosis, are limited in self-care and management, have higher intolerance to therapy, and experience lower adherence to treatment compared with other ages.[5] Addressing the psychosocial needs of AYAs with cancer facilitates typical development and acts as a means to promote lifelong health and well-being.[6] Providing psychosocial support for AYAs with cancer is postulated as a novel means to continue the momentum in improving treatment outcomes[4] and holds potential to help close the gap in survivorship between AYAs and other age groups. Furthermore, AYAs with cancer endorse an ongoing need to improve the delivery of psychosocial care during cancer treatment.[7]

Despite being recognized as an important component of care, there currently exists a lack of evidence on best interventions for the psychosocial needs of AYAs who

are currently undergoing treatment. Previous literature reviews have been conducted on psychosocial interventions for AYAs who are on active treatment or have completed therapy for cancer.[8-11] Taken together, these reviews suggest that AYAs with cancer continue to have psychosocial needs distinct from other age groups and that some interventions are successful, but there is no consensus on the means to best address these needs.[8-11] Furthermore, many studies and reviews include patients who have completed therapy for cancer but it has been noted that the psychosocial needs of patients on therapy differ from those who have completed therapy.[11]

Research specific to survivors of AYA cancers, while important, does not necessarily translate to the AYA population as a whole or to those AYAs who are early in the cancer trajectory. The psychosocial needs of AYAs who have completed cancer therapy are not the same as the needs of those who are still receiving treatment. The cost of cure in AYAs is high – treatment itself causes burdensome acute, chronic, and lifelong toxicities;[12] providing appropriate psychosocial support interventions early in therapy may address short and long-term quality of life by equipping patients with skills and tools required to endure the stressors of treatment. Early integration of psychosocial care may allow patients to carry these skills forward through their cancer journey so that they may overcome hurdles of care and gain full benefit from therapy.[13] In recognition of the importance and potential impacts of psychosocial interventions delivered early in the cancer journey, this review purports to report on the types and efficacy of psychosocial interventions for AYAs undergoing treatment for cancer. Findings from this review will be an important first step in understanding what types of interventions or approaches have been successful for psychosocial support for AYAs receiving cancer therapy and can be used to guide the development of future interventions and programs.

Methods

A comprehensive search of the literature was conducted with the aid of a medical research librarian at the Johns Hopkins University. The search was executed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach.[14] A search strategy was constructed with terms relating adolescents, young adults, cancer, psychosocial metrics, and outcome measures to identify all published works relating to the topic. All search terms, truncated terms, and medical subject heading terms are outlined in Table 1. Six databases were searched for publications; PubMed, CINAHL Plus, the Cochrane database, Embase, PsychoINFO, and Web of Science; and all search terms were included in the database searches combined with Boolean terms as applicable and possible per database. Medical subject heading and index terms were employed with appropriate truncation and combination as guided by the research librarian to ensure comprehensive searching of the peer-reviewed literature. Hand searching was undertaken by identifying similar literature reviews and reviewing included publications in these reviews; no additional publications were noted through hand searching, suggesting that the executed search strategy was appropriate for this review.

Table 1: Search Terminology, Inclusion Criteria, and Exclusion Criteria

Concept	**Search Terms**	
Adolescent and Young Adults	Adolescen*	Teen*
	Young adult [MeSH]	Young adult*
	Adolescent [MeSH]	
Cancer	Neoplasms [MeSH]	Cancer*
	Neoplasm*	Tumor*
Psychosocial metrics	Stress [MeSH]	Social isolation [MeSH]
	Self-efficacy [MeSH]	Coping [MeSH]
	Social support [MeSH]	
Outcome measures	Intervention	Impact*
	Outcome	Therapy
	Effect*	
Inclusion Criteria		**Exclusion Criteria**
Peer reviewed		Dissertations or conference abstracts
Adolescent or young adult population (≤40yrs)		
Participants on active therapy		Sibling or parent studies
Report any psychosocial outcomes		Participants in survivorship/post therapy
Discuss intervention or modifiable care approach		

*indicates truncated search terms
Note: MeSH = Medical subject heading

To be included in this review, articles were required to be an original peer-reviewed publication that reported on interventions to impact psychosocial outcomes of AYAs undergoing treatment for cancer (see Table 1). Psychosocial outcomes were defined as psychological or mental health related impacts from therapy with potential to impact quality of life, stress, coping, and mental health. There were no exclusions based on cancer diagnosis, date of publication, country of origin, or language of publication. Publications that did not present any data on AYAs, included survivors (defined as those who were no longer receiving therapy), or focused on parents or siblings were excluded. The number of participants, ages of participants, intervention, study method, measures, and outcomes were extracted and are summarized in Table 2. The level of evidence (LOE) and quality grade for each publication was determined following the Johns Hopkins Nursing Evidence-Based Practice Guidelines grading tool.[15] In this model, evidence levels for original research are defined as Level I: experimental or randomized control studies; Level II: quasi-experimental study or explanatory mixed-method study; Level III: nonexperimental study, exploratory/convergent mixed method studies; Level IV: opinion of respected authorities; and Level V: literature reviews of non-research evidence. Grading recommendations specific to each LOE are provided by the tool.[15]

Publications were coded based on type of intervention and then grouped together for discussion based on these codes. To code the publications, the articles were first read in full to familiarize the reviewer with the subject matter and material being described. The approach to psychosocial care was then evaluated, critiqued, and coded with a single descriptor (e.g., art therapy, group therapy, video game, etc.) as applicable. Publications were grouped together based on assigned codes and revisited after all publications were grouped to ensure appropriateness of coding. The groups were analyzed and labeled based on the underlying themes of the included publications six approaches to address the psychosocial health of AYAs with cancer emerged;

Table 2: Overview and summary of included studies

N	Ages	Study Design	Measures (Assessment tools)	Findings and Outcomes		LOE	Quality
Agnese et al. (2011) – Art therapy intervention							
74	19-37	Mixed methods	Self-report of perceived usefulness	100% of respondents reported the intervention was helpful	+	III	B
			Comments about the experience and thoughts on helpfulness	Feeling more peaceful, relaxed, improved expression, share feelings, connect with family	+		
Burns, Robb, & Haase (2009) – Therapeutic music video intervention							
12	11-24	Experimental randomized study	Symptom Distress (Medical Outcomes Study: Short-Form, McCorkle Symptom Distress Scale)	No change		I	C
			Defensive and Courageous Coping (Jalowiec Coping Scale)	Unable to statistically compare to control due to sample size	–		
			Resilience (Nowotny Confidence Subscale)				
			Quality of Life (Index of Well-being) (LASA Uniscale)				
Clark et al. (1992) – Peer support group with local high school students							
8	13-21	Nonexperimental cohort study	Coping skills (Likert scale)	Strongly agree: 63.5% Agree: 16.6% Neutral:20.8%	+	III	C
			Social skills (Likert scale)	Strongly agree: 37.5% Agree: 37.5% Neutral 25%	–		
			Personal insight (Likert scale)	Strongly agree: 50% Agree: 37.5% Neutral: 12.5%	+		
			Quality of life (Likert scale)	Strongly agree: 25% Agree: 50% Neutral: 25%	–		
			Friendship (Likert scale)	Yes: 75% No: 25%	+		
Fasciano et al. (2015) – Directed informational website for adolescents/young adults with cancer							
30	18-39	Descriptive study	Connectedness (Likert scale)	82% moderately or extremely connected	+	III	C
			Worry (Likert scale)	Improved: 29% No impact: 53% Worsened: 18%	–		
			Sadness (Likert scale)	Improved: 29% No impact: 56% Worsened: 15%	–		

			Fear (Likert scale)	Improved: 29% No impact: 62% Worsened: 9%	_		
Heiney et al. (1988) – Support group intervention for adolescents/young adults with cancer							
7	15-19	Quasi-experimental	Anxiety (Spielberger State Anxiety Scale) Depression (Zung Depression Scale) Self-esteem (Rosenberg Self-Esteem Scale) Locus of control (Wallston Health Locus of Control Scale)	No statistically significant difference between pre-test and post-test for each category was detected	_	I	A
Hinds et al. (2000) – Three part educational intervention for adolescents/young adults with cancer							
75	12-21	Longitudinal Experimental two-group design	Hopefulness (Hopefulness Scale for Adolescents) Hopelessness (The Hopeless Scale) Self-esteem (Rosenberg Self-Esteem Scale) Symptom distress (Symptom Distress Scale) Treatment toxicity (Toxicity: The NCI Common Toxicity Criteria Scale) Locus of control (Nowicki-Strickland Locus of Control Scale) Self-Efficacy (Self-Efficacy Scale)	No statistically significant differences between experimental or control groups	_	I	A
Kato et al. (2008) – Video game intervention							
37 1	13-29	Randomized controlled trial	Self-efficacy (Self-Efficacy Scale) Knowledge about cancer (Cancer Knowledge Scale) Health locus of control (Multidimensional Health Locus of Control Scale C) Stress (Perceived Stress Scale 10) Quality of life (Pediatric Quality of Life Generic Core Scale V4)	Statistically significant improvement No statistically significant change	+ _	I	A
Keats et al. (1999) – Leisure time physical activity							
53	12-18	Retrospective cohort study	Depression (Center for Epidemiological Studies Depression Scale) Self-Concept (Self-Description Questionnaire II)	No statistically significant differences overall	_	III	B
Lyon et al. (2014) – Advance care planning for newly diagnosed adolescents with cancer							
30	14-20	Two-arm randomized controlled trial	Anxiety (Beck Anxiety Inventory) Depression(Beck Depression Inventory) Quality of Life (Pediatric Quality of Life Inventory V.4) Spiritual Well-Being (Spiritual Well-Being Scale)	No statistically significant improvement over time Depression worsened compared to baseline	 _	I	B
Rosenberg et al. (2019) – Teaching stress management, goal setting, cognitive restructuring, and benefit finding							
92	12-25		Hopeful thinking (Hope Scale)			I	A

		Randomized controlled trial	Benefit Finding (Benefit Finding Scale for Children)	Greater magnitude and direction of hopeful and benefit-finding scores in intervention group compared to control group, statistically significant	+		
			Goal Setting (Open-ended question)	No change from baseline or difference between groups	_		
Rosenberg et al. (2018) – Skills-based psychosocial intervention for adolescents/young adults with cancer							
92	12-25	Randomized controlled trial	Resilience (Connor-Davidson Resilience Scale-10)	Statistically significant increases from baseline in intervention group	+	I	A
			Anxiety and Depression (Hospital Anxiety and Depression Scale)	Scores not significantly different between groups			
			Psychological Distress (Kessler-6 Psychological Distress Scale)				
			Quality of Life (Pediatric Quality of Life)	No change	_		
Skaczkowski et al. (2018) – Impact of fertility-related discussions at diagnosis with adolescents/young adults with cancer							
20 9	15-24	Cross-sectional survey	Quality of Life (Functional Assessment of Cancer Therapy – General FACT-G)	Sensitive, supportive discussion and fertility preservation had positive impact on social well-being only		III	B
			Measures domains of physical, social, functional, and emotional well being	Having discussion regarding fertility and referral to specialist had no correlation with QOL domains			
				Sensitive, supportive discussion and preservation had no impact on physical, functional, or emotional wellbeing			
Stegenga (2014) – Teen cancer camp with adolescents							
9	14-17	Qualitative descriptive study	Semi-structured interviews to explore experiences and impact of the weekend	Themes of improved social support emerged to include support of patient autonomy, peer support, and building hope		III	B
Torabi et al. (2018) – Spiritual care intervention for adolescents with cancer							
32	12-18	Single group quasi-experimental pre-test post-test study	Coping (Coping Strategies Questionnaire)	Statistically significant increases in mean coping scores over time	+	II	A
				No impact on confronting, seeking social support, escape-avoidance, emotion-oriented coping, and accepting responsibility			
Trevino et al. (2014) – Patient-oncologist therapeutic alliance as a correlate with quality of life in young adults with cancer							
95	20-40	Descriptive cross-sectional study	Suicidal ideation (Yale Evaluation of Suicidality)	Lower suicidal ideations were associated with better Karnofsky scores, higher physical quality of life, fewer physical symptoms, and lack of depression or PTSD		III	A
			Therapeutic Alliance (Human Connection Scale)				
			Performance Status (Karnofsky Performance Scale)				
			Physical Quality of Life (McGill Quality of Life Questionnaire)				
			Social Support (Social Support Subscale of McGill)	Strong therapeutic alliance is associated with lower suicidal ideation when patients feel their oncologist:			

			Physical Symptoms (Patient report) Use of Mental Health Services (Yes/No Question)	- Takes time to listen to concerns - Explanations and suggestions are understood - Offers hope - Asks about coping - Concerned with quality of life - Is open-minded			
Woodside et al. (2018) – DVD-based yoga program for young adults with cancer							
4	35-38	Single arm, pre-test/post-test	Quality of life (Functional Assessment of Cancer Therapy – General) (Functional Assessment of Chronic Illness Therapy – Palliative Care and Spiritual Well-Being)	Improved scores in functional well-being, physical well-being, spirituality, palliative-specific scores, and quality of life	+	II	C
			Phone interview to ask about program satisfaction (Motivation, benefits, if they would recommend the program)	Opportunity to improve health outside of biomedical interventions, promoted self-care, personal time	_		
Yurkiewicz et al. (2018) – Wearable technology (Fitbit) and synced iPad for adolescents/young adults with cancer							
33	15-29	Prospective cohort study	Health-Related Quality of Life (Short Form Health Survey RAND-36)	Significant improvements across all domains (physical, role/physical, role/emotional, energy/fatigue, emotional well-being, social function, pain, general health)	+	II	A
			Experiences of the study (Qualitative survey designed by study authors)	79% felt it increased activity 58% used meditation app on the iPad 27% played cancer-associated game 27% participated in online cancer support community			

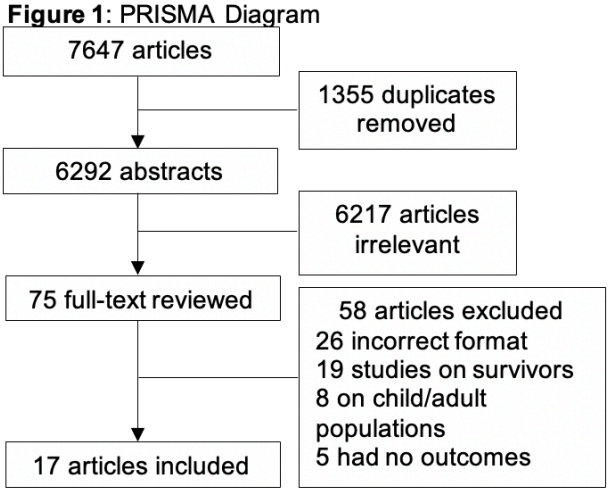
LOE: Level of evidence
+: Indicates improvement or protective relationship
X: Indicates age group
+ or – has not been assigned to qualitative or correlative studies
– : Indicates no improvement or protective relationship

creative expression, promoting peer interactions, individual coaching, engaging technology, promoting physical activity, and clinical interactions.

Results

The initial search yielded 7,647 publications, 6,292 remained after duplicates were removed and were reviewed for eligibility to be included in this review. After review, 6,217 were excluded and 75 were retained for full review. The remaining 75 articles were reviewed in full; 26 were not peer-reviewed (conference abstracts, dissertations, etc.), 19 included survivors, 8 included young children or older adults, and 5 did not report psychosocial outcomes leaving 17 articles that met inclusion criteria for this review (see Figure 1). Of note, one publication[16] included older adults but the article was retained because there was unanimous (100%) agreement on the intervention's usefulness; only the case report responses from AYAs were included for discussion in this review. The majority of included articles (14, 82.4%) addressed specific psychosocial interventions, and three (17.6%) explored how clinical interactions or practice relationships that may impact psychosocial health. The articles that discussed clinical interactions were retained because, while they are not interventions, they address modifiable practice styles and approaches that can be used to impact the psychosocial care of AYAs with cancer.

Figure 1: PRISMA Diagram



The 17 articles that comprise this review include an aggregate 1,226 patients aged 11 to 40 years. Traditionally, the AYA population is defined as those 15 to 39 years of age.[17] Because adolescence is a developmental time point, setting strict age cutoffs is difficult. Recent literature suggests that the transition from childhood to adulthood spans 10 to 24 years of age.[18] This review included publications for adolescents as defined by the original author instead of limiting to those 15+ years of age. This allowed for the inclusion of 11 (58%) of the publications and reflects current trends in definitions of adolescent medicine and research.

Fifteen publications (88.2%) measured outcomes of patient self-reported assessments, the remaining two (11.8%) were qualitative studies that discussed patient experiences with interventions or care relationships. Of the 15 studies that employed psychometric analysis, 13 (86.7%) used validated tools to assess constructs; the remaining 2 (13.3%) assessed participant response solely on a tools or surveys developed by the author for the purpose of the publication.

Discussion

Thematic analysis of the included studies revealed six approaches to addressing psychosocial needs of AYAs with cancer: creative expression, promoting peer interactions, individual coaching, engaging technology, promoting physical activity, and clinical interactions. Thematic analysis and main findings for included publications are summarized by theme in Table 3.

Creative Expression

Two of the included studies evaluated the impact of interventions involving creative expression on psychosocial measures with favorable outcomes. Agnese et al. (2012) conducted a mixed-method study to explore the impact of art therapy on quality

Table 3: Summary of Main Findings

Author(s)	Intervention	Findings
Creative Expression		
Agnese et al. (2011)	Three component art therapy intervention provided to patients admitted for stem cell transplant to 1) create art, provide empathic silence, verbal interaction to establish rapport with the patient 2) provide direction to externalize feelings to visual images, and 3) help patients get in touch with positive memories and resources	Qualitative evaluation of feedback from participants 100% report the intervention was helpful Increased feelings of peace, relaxation, expression, share feelings, and improved family connectedness
Burns, Robb, & Haase (2009)	Patients undergoing stem cell transplant were randomized to creation of a music video (select music, write lyrics, discuss meaning, record video, discuss production, and viewing the video) and control group (listening and discussing audiobooks with child life) over 6 sessions	Small sample size limited comparison between groups Symptom distress, coping, resilience, and quality of life were unchanged across the treatment timeline (did not worsen during intense treatment)
Promoting Peer Interactions		
Author(s)	Intervention	Findings
Clark et al. (1992)	Assessed the effects of peer support group for adolescents with cancer; patients had monthly social activities with a group of students from a local high school; participants were provided a set of questions graded on Likert scale assessing perceived benefits from the intervention	Most participants agreed or strongly agreed that peer groups improved coping skills quality of life and agreed it improved coping skills and developed new friendships
Heiney, Ruffin, Ettinger, Ettinger (1988)	Quasi-experimental pre-test/post-test design of a peer support groups facilitated by therapists and focused on diagnosis, treatment, school/peer relationships, parents, and the future (including death)	There was no statistically significant change in mean score from baseline for anxiety, depression, self-esteem, or health locus of control
Stegenga (2014)	Assessment of the impact on a teen weekend event for adolescents with cancer via qualitative exploration of experiences; the weekend getaway had structured activities promoting autonomy, adjustment to illness, and emotional support (swimming, bowling, manicures, massages, arcade time, sports, scavenger hunts, and murder mystery lunch)	Qualitative evaluation revealed themes of social support provided by peers, support for autonomy, and building hope Peer support was tied to the opportunity spend time with others in similar situations Autonomy support was built through staff and family encouraging attendance and by being offered choices of activities at camp
Individual Coaching		
Author(s)	Intervention	Findings
Hinds et al. (2010)	Experimental study of a three part educational intervention for self-care coping including 1) information on self-care coping delivered by nurses, 2) 25 minute video of adolescents showing coping skills, and 3) rehearsal of strategies the participant found most useful; the control group spent equal time with research staff discussing topics of interest (of their choice)	There was no statistically significant differences between the intervention and control group at any time point (shortly after chemo started, 5-7 weeks, 3 months, and 6 months after diagnosis) in scales of hopefulness, hopelessness, self-esteem, symptom distress, treatment toxicity, locus of control, or self-efficacy
Rosenberg et al. (2019)	Randomized controlled trial of the Promoting Resilience in Stress Management (PRISM) intervention; an individualized intervention to promote	Improvements in benefit-finding and hope with moderate to large effect sizes with greater magnitude in the intervention group than control group

	stress management, goal setting, cognitive restructuring, and benefit finding skills delivered in four sessions (30-50 minutes) every other week	
Rosenberg et al. (2018)	Randomized controlled trial of the Promoting Resilience in Stress Management (PRISM) intervention; an individualized intervention to promote stress management, goal setting, cognitive restructuring, and benefit finding skills delivered in four sessions (30-50 minutes) every other week	Intervention was associated with higher resilience, cancer-specific quality of life, and lower psychological distress No change seen to general quality of life There were improvements in resilience, distress, anxiety, and depression but were not statistically significantly different from the control group
Torabi et al. (2018)	Quasi-experimental pre-test/post-test intervention examining the effects of spiritual care delivered in individual meetings over six 45 minute sessions that involved building relationships, empathetic listening, spiritual assessments, and learning about the patient's spiritual needs and roles	Statistically significant improvement in total coping scores over time but they down-trend after the intervention stopped No impact on confronting, seeking social support, escape-avoidance, emotional-oriented coping, and accepting responsibility

Engaging Technology

Author(s)	Intervention	Findings
Fasciano, Souza, Braun, & Trevino (2015)	Preliminary report on the perceived helpfulness and emotional impact of a website developed to provide information, facilitate social networking, and address underlying emotional needs to reduce worry, sadness, and fear	Overall, 87% of users reported that the website was useful 28% reported decreased worry, sadness, and fear regarding their cancer 53% reported no impact on worry, 56% no impact on sadness, and 62% no impact on fear
Kato, Cole, Bradlyn, Pollock (2008)	Randomized intervention/control trial of a video game where players navigate a robot to destroy cancer cells and manage infections, nausea, and constipation to assess impact on adherence, self-efficacy, knowledge, control, stress, and quality of life	Cancer-related knowledge score and cancer-specific self-efficacy scores increased from baseline in the intervention group There was no difference in adherence, quality of life, stress, or locus of control scores between groups or after intervention
Yurkiewicz et al. (2018)	Prospective cohort study of the association between wearable activity tracking technology (Fitbit) and educational material (synced iPad) and quality of life over the course of 6 months	Statistically significant improvements in physical functioning, role function/physical reports, role function/emotional reports, energy and fatigue, emotional well-being, social functioning, pain, and general health 85% enjoyed using the technology, 79% felt it helped them be more active, 58% used a meditation app, 27% played a cancer-related video game, and 27% participated in online social communities

Promoting Physical Activity

Author(s)	Intervention	Findings
Keats, Courneya, Danielsen, & Whitsett (1999)	Examination of the relationship between leisure time physical activity and self-reported depression and self-concept	No statistically significant differences in activity patterns before or during treatment and psychosocial outcomes; patients with more activity had higher mean scores Patients who had participated on organized sports before and during treatment had better depression and self-concept scores (areas of physical abilities, peer relations, and parent relations)
Woodside et al. (2018)	Single arm pre-test/post-test of the feasibility and usefulness of a DVD-based at-home, 75 minute, weekly yoga program	Use was associated with improvements in self-reported physical well-being, spirituality, palliative quality of life and general quality of life

		Described the program as an opportunity to improve health and provide self-care
Yurkiewicz et al. (2018)	Prospective cohort study of the association between wearable activity tracking technology (Fitbit) and educational material (synced iPad) and quality of life over the course of 6 months	Statistically significant improvements in physical functioning, role function/physical reports, role function/emotional reports, energy and fatigue, emotional well-being, social functioning, pain, and general health 85% enjoyed using the technology, 79% felt it helped them be more active, 58% used a meditation app, 27% played a cancer-related video game, and 27% participated in online social communities
Clinical Interactions		
Author(s)	Intervention	Findings
Lyon et al. (2014)	Randomized controlled trial testing the impact of pediatric advanced care planning interventions; intervention consisted of five visits for 1) baseline assessment, 2) Family-care planning survey, 3) respecting choices advanced care planning survey, 4) five wishes, and 5) 3-month follow-up	Anxiety scores decreased in the intervention and control group, depression was lower for the intervention group There was no differences in quality of life between groups over time
Skaczkowski et al. (2018)	Cross-sectional survey to assess the relationship between fertility-related discussions and quality of life	Discussing fertility in a sensitive, supportive way and offering fertility preservation was correlated with improved social well-being but not physical, functional, or emotional well-being
Trevino et al. (2014)	Mixed methods evaluation of the relationship between patient-oncologist alliance and suicidal ideation in young adults	Lower suicidal risk was associated with higher performance status, higher quality of life scores, fewer physical symptoms, and less depression Stronger therapeutic alliance was associated with lower suicidal ideation; taking time to listen, clear explanations, offering hope, inquiring about coping, addressing quality of life, and remaining open-minded were protective factors

of life for 19- to 37-year-old patients admitted for stem cell transplant.[16] In this intervention, an art therapist met weekly with patients over the course of their admission and focused on discussions through image creation, assisting with externalization of feelings, and exploring positive memories and resources. At the time of discharge after transplant, all participants reported that art therapy was subjectively helpful.[16] Qualitative analysis revealed that participants felt more peaceful and relaxed and felt that art was a way to express themselves and aid others in understanding their situation.[16]

Burns et al. (2009) conducted an experimental study in which participants were randomized to create a music video or spend an equivalent amount of time listening to

and discussing audiobooks with a child life specialist. The music video intervention included active (music selection, lyric writing, discussion, and recording) and passive (video design, discussion, and video viewing) components.[19] Measures of distress, coping, resilience, and quality of life were taken at baseline, completion, and 100 days after the intervention. The authors note that mean scores for participants were stable over the course of transplant which may suggest some benefit in protecting patients from distress, especially given the intensity and difficulty of transplant[19] but small sample size prohibited identifying statistically significant changes in domains from baseline.

Promoting Peer Interactions

Three of the included publications investigated the role that peer interactions had on psychosocial outcomes. Two involved peer groups with other AYAs who were receiving treatment and showed mixed impacts on psychosocial health.[20, 21] Heiney et al. (1988) conducted a quasi-experimental study of a peer support group of 15- to 19-year-old patients facilitated by therapists focusing on disease and treatment elated topics. After the intervention, anxiety, depression, self-esteem, and locus of control scores were unchanged from baseline.[20] All adolescent participants reported that they met their personal goals for the group sessions regardless of scores on the abovementioned scales[20] suggesting that the group therapy had some personal benefit for participants without impacting anxiety, depression, self-esteem, or locus of control measures.

Stegenga (2014) found that semi-structured social weekends had positive outcomes on psychosocial measures in adolescents. In this study, the impact of an existing teen weekend intervention, designed as a respite camp for adolescents with cancer, was assessed through qualitative interviews with campers after their trip. Participants endorsed support from peers, increased autonomy from providers and parents, and the ability to build hope as strengths of the camp.[21] Participants shared

value in the ability to spend time with other patients who had similar health experiences outside of the hospital or clinical setting. Being offered the choice to attend camp, participate in activities at camp, and getting encouragement from peers and families were cited as valued interactions surrounding the weekend.[21]

Adolescents with cancer reported that regularly scheduled activities with a group of similarly aged teens without cancer provided psychosocial benefits.[22] In this case report, several high school students without cancer joined an adolescent cancer support group for an assignment. They built relationships with the patients and continued to participate in monthly social meetings together. After 8 months, researchers asked participants to report their perceived changes in coping skills, social skills, personal insight, quality of life, and friendships due to the program.[22] The majority of participants agreed or strongly agreed that peer interactions were beneficial in the aforementioned domains. Up to 25% of the participants were neutral when asked if the peer groups were helpful in developing coping skills, social skills, insight, or improving quality of life; none of the participants rated the interactions as unhelpful.[22]

Individual Coaching

Individualized coaching in one-on-one sessions with a health care professional delivered through a variety of formats exhibited success in improving psychosocial measures. Two publications from the same study evaluated the Promoting Resilience in Stress Management (PRISM) intervention; a randomized controlled trial involving interventions focusing on stress management, goal setting, cognitive restructuring, and benefit finding skills.[23, 24] In this intervention, skills were delivered to participants in four 30- to 50-minute sessions every other week. There were statistically significant improvements in both benefit finding and hope from baseline (benefit finding: 0.6, hope: 0.4; $p = 0.05$)[23] in addition to an association of higher resilience (+3.0 points, 95%

confidence interval [CI: 0.5, 5.4], p = 0.02), higher cancer-specific quality of life (+9.6 points, 95% CI [2.6, 16.7], p = .01), and lower psychological distress (−2.1 points, 95% CI [−4.1, −0.2], p = 0.03).[24] The PRISM intervention was also associated with improvements in depression (p = .06); but these were not different from the control group and there were no changes in overall quality of life after the intervention (p = 0.08).[24]

In a quasi-experimental pretest/posttest intervention, spiritual care was delivered in six individual 45-minute sessions and were associated with improvements in coping.[25] The sessions focused on building relationships, empathetic listening, conducting spiritual assessments, and learning about the patient's spiritual needs while providing guidance.[25] After completion, participants had improvement in coping but scores decreased overtime suggesting an ongoing need for spiritual care.[25] Aspects of coping that improved after the intervention included confronting, distancing, self-control, seeking social support, planful problem-solving, and accepting responsibility (p < 0.05).[25] There was no noted change in the patients' responsibility acceptance as a result of spiritual care (p = 0.425).[25]

Individual coaching was also studied in a randomized control group study of a self-care/coping intervention in which 78 adolescents with cancer were randomized to an intervention for self-care and coping or control group. The intervention group underwent 40-minute sessions consisting of (a) teaching self-care coping, (b) watching a video describing or demonstrating coping strategies, and (c) practicing coping skills the participant selected as most likely to be beneficial.[26] In the control group, participants spent an equal amount of time discussing chosen topics of interest with research staff. Hopelessness, hopefulness, locus of control, self-esteem, symptom distress, and self-efficacy measures were completed throughout a 6-month period. There were no differences in measures between the experimental and control groups at any measurement point.[26] There were surprisingly high ratings of hopefulness at the

beginning of the intervention suggesting a ceiling effect of measurement or perhaps as a marker of resilience in this population.

Engaging Technology

Articles in this section discuss the potential role of technology in AYAs including video games, social media use, wearable technology, and digital education sources. In a randomized controlled trial, Kato et al. (2008) evaluated the impact that a cancer-specific video game had on knowledge, self-efficacy, quality of life, stress, and locus of control. The game ("Remission 2™") involves a nanobot that destroys cancer cells and manages infections, nausea, and constipation.[27] Patients in the intervention group had significant increases in cancer-specific self-efficacy ($p = .011$) and cancer-related knowledge ($p = .035$), whereas those in the control group demonstrated no improvement in these outcomes.[27] There were no noted effects on medication adherence, quality of life, stress, or locus of control scores after the intervention within or between groups.[27]

Interventions utilizing technology as a means to provide education for AYAs and as a medium for information dissemination had limited impact on mental health related outcomes. A study evaluated the impact of a website with AYA cancer-specific information on psychoeducation material, self-help resources, young adult programming, and disease-related information. The majority of users (87%) rated the website as helpful.[28] However, a majority of the users also reported that it had no perceived impact on their worry (53%), sadness (56%) or fear (62%), and only a minority (29%) reported that it did have any improvement in these symptoms.[28]

In a study focusing on the association between wearable technology, physical activity, and the use of a synced tablet, similar results were noted. The intervention was aimed at improving physical activity, but also provided participants with a tablet preloaded with a meditation app, cancer-related video game ("Remission 2™"), and AYA

cancer-specific information. Participants in this study were encouraged to make an online profile (that could be anonymous) to interact in a virtual cancer-specific peer community. The majority (58%) of participants used the mediation app, but only 27% played Remission 2™ or participated in the online social community.[29] When compared with baseline scores, use of the technology was associated with improvements in self-reported physical functioning ($p < .00$), role function ($p < .00$), energy/fatigue ($p < .00$), emotional well-being ($p = .01$), social functioning ($p < .00$) pain ($p < .00$), and overall general health ($p = .01$); but was not reported as being readily accepted by AYAs.[29]

Promoting Physical Activity

All three publications discussing means to promote physical activity during treatment showed beneficial relationships between physical activity and mental health-related quality of life. A retrospective cohort study conducted with adolescents with cancer found no statistically significant differences between level of physical activity and self-reported depression or self-concept.[30] However, authors did find that patients with higher activity levels consistently had better depression and self-concept scores, similar to those who participated in organized sports prior to and during treatment.[30] Specifically, adolescents who participated in organized sports had improved scores in the areas of self-reported physical abilities, peer relations, and parent relations.[30] It is difficult to discern whether the involvement in organized sports led to better depression and self-concept scores or if the qualities necessary for participation in organized sports (communication, teamwork, and social skills) were correlated with improvements.

Two articles shared the results of interventions to improve physical activity in AYAs with cancer. The first was a single arm pretest/posttest quasi-experiment that provided young adults with a DVD-based yoga program to use at home.[31] Participants were asked to complete the 75-minute yoga session weekly. Self-reported quality of life

evaluations were administered at the beginning of the intervention and repeated at the completion of the yoga program along with open-ended questions to assess impact of the program. The yoga intervention was associated with statistically significant improvements in self-reported well-being, spirituality, addressing palliative care needs, and general quality of life.[31] Use of yoga as a means to improve health outside of the medical model and as an opportunity to provide self-care emerged as common beneficial themes from the qualitative component of the study.[31]

The second intervention aimed to improve physical activity provided activity tracking technology (Fitbit™) that was synced to a tablet (iPad™).[29] Participants were encouraged to use both items of technology frequently. The wearable technology had the capability to track steps, sleep, and calories and was synced to the tablet to provide easy viewing of the data it collected. Overall, 85% of participants reported that they enjoyed using the technology (both wearable technology and the tablet) and 79% reported that they thought it helped them be more active.[29] There were statistically significant improvements in physical function, physical role function, emotional role function, energy, fatigue, emotional well-being, social function, pain, and general health at the end of the study.[29]

Clinical Interactions

Three studies examined clinician roles, relationships, or approaches to care and how they were associated with psychosocial outcomes. One publication reported on the results of a randomized controlled trial testing the impact that pediatric-focused advanced care planning had on anxiety and quality of life of AYAs with cancer.[32] The care planning intervention consisted of five interactions. The first was to complete enrollment and a baseline assessment followed by three weekly 60-minute sessions reviewing (a) the Lyon Family-Centered Advanced Care Planning survey, (b) Respecting

Choices Disease-Specific Advanced Care Planning Interview, and (c) the Five Wishes. Participants were then visited 3 months later for postintervention assessment. The control group received an advanced care planning brochure, the practice's current standard of care.[32] Anxiety scores at follow-up were significantly lower than that at baseline for both groups ($\beta = -5.6$, $p = .0212$). Depression scores had a statistically significant decrease for the intervention group ($\beta = -5.4$, $p = .0268$) but were not statistically significantly different from baseline in the control group.[32] There were no noted differences in quality of life scores for either group over time or comparisons between groups.[32]

The remaining articles discussing clinician roles and interactions involve investigations of provider–patient relationships and fertility content discussed during clinical interactions. When providers discussed fertility concerns, patients reported improvement in social well-being, but not physical, functional, or emotional well-being.[33] Even though having a discussion about infertility or fertility difficulties after treatment did not have a direct correlation with well-being, patients reported that having the discussion in a sensitive and supportive manner, or even just being told about the options of fertility preservation, was associated with improved social well-being.[33]

In a study examining physician–patient alliance on suicidal ideations, Trevino et al (2014) found that strong physician–patient alliance relationships built on clear communication and a caring foundation have been associated with decreased suicidal ideations in patients. In a mixed-method evaluation of patient–oncologist relationships, Trevino et al. (2014) found that patients had lower suicidal ideations when their treatment team took time to listen, provided clear explanations, offered hope, asked about how they were coping, addressed quality of life during visits, and remained open-minded when speaking with patients.[34]

Summary

The purpose of this integrative review was to identify and summarize current interventions to address the psychosocial needs of AYAs receiving therapy for cancer. The identified body of literature suggests that effective interventions exist, but there continues to be an incomplete understanding of the psychosocial needs and best methods for them to be addressed in AYAs with cancer.

Clinical Implications

The findings from the literature included in this review reinforces the idea that effective psychosocial interventions for AYAs with cancer utilize an interdisciplinary team to provide interventions tailored to the developmental needs of AYAs. Successful interventions were those that were delivered in a format that recognized and respected AYAs' values of privacy, autonomy, decision making, and social interactions during treatment.

Interventions involving art therapists,[16] nurses, social workers, spiritual care workers,[25] psychologists, counselors, psychiatry teams, and palliative care providers[32] have shown success. Building interdisciplinary teams to address the complexity of medical and psychosocial needs of AYAs with cancer is necessary to improve quality of life for this population. By doing so, specialists can offer strengths that complement the unique components of care delivered by other members of the team. Unfortunately, specialists are not always available or regularly used. In a survey of 142 pediatric oncology practices, 68% had a social worker, but only 19% included an art therapist, and only 9% included a psychologist.[35] Recent literature suggests that referrals for interdisciplinary holistic support remain low.

The psychosocial needs of AYAs with cancer are complex.[36] Care is more effective when it is customized to the needs of the patient, recently coined as precision

medicine; this approach to care has been adopted and is encouraged by the National Cancer Institute.[37] All patients do not respond the same to psychosocial care[38] and designing programs for the age and developmental stage of the patients for which it is intended can lead to better outcomes.[39] By considering AYAs' values of autonomy, privacy, and peer interactions, clinicians can develop approaches to address a plethora of needs for patients, as seen with findings in this review. As developing adults, AYAs prefer to remain involved in their care and value the ability to exercise autonomy. A diagnosis of cancer and its treatment invokes a sense of powerlessness and imposes strict schedules, routines, and tasks that remove a significant amount of decision making from life. Approaches to provide autonomy provide psychological relief for patients. The chance to make even small decisions, like which activities to participate in while at a weekend camp, was strongly endorsed by participants described by publications in this review.[21] In creating a music video, patients were heavily involved in the direction of their intervention by choosing music, writing lyrics, and controlling production which sustained coping, resilience, and quality of life during a distressing hospital admission.[19] Choosing how to express feelings through art created a sense of peace, relaxation, and improved family relationships.[16] Interventions provided in an individual format allow the patient to hold some decision-making roles within their care. Psychosocial measures are improved when AYAs are provided avenues to set their own goals,[24, 40] can share and direct their needs,[25] and are provided an intervention they can conduct on their own schedule.[31] Facilitating and protecting the power of decision making is important in maintaining autonomy and may have a beneficial impact on quality of life.

Adolescence, more so than young adulthood, is a developmental stage where there is a general value of privacy and feelings of discomfort when speaking about their bodies or health issues. Discussion of personal or sensitive material in a private setting is generally preferred by AYAs. Interventions from this review that involved one-on-one

interactions had success in addressing psychosocial needs of patients,[23-25, 41] while group therapy sessions did not.[20] The use of technology as a medium for education and providing support has been investigated without significant impact on psychosocial health. A majority of users of a cancer-specific website reported that it had no impact on worry (53%), sadness (56%), or fear (62%).[23-25, 41] This could be due to the lack of discussion involved or inability to tailor the information to the patient. Similar findings were seen when using a cancer-specific video game as a means of intervention.[27] An individual, tailored format is important because it allows the patient to remain involved in care and communicate their needs in a setting that addresses the need for privacy. This approach is also supported by other literature in the field. In a survey of 111 AYAs with cancer, participants were asked about means to address psychosocial support and reported a preference for one-on-one or in-person discussions.[42] Providing interventions on sensitive or personal topics is more readily received and utilized by AYAs when clinicians deliver information in a professional and interactive format.[39] Findings from this review reflect this idea; having a clinician who approached needs from a holistic and caring platform was associated with better psychosocial outcomes.[33, 34]

Despite the values of personal privacy, peer and social interactions remain an important component of typical development. The ability to function in social groups described by several articles in this review (including peers with and without cancer) led to improvements in some psychosocial measures[33, 34] along with involvement in organized sports.[30] Findings suggest that face-to-face interactions with peers are preferred by AYAs. When provided with access to an online cancer support community, only 27% of participants engaged with the community.[29] By promoting involvement in group activities outside of the clinical environment, clinicians may be able to assist with mitigating the psychosocial impacts of cancer. Facilitating social interactions with peers provides an environment that promotes typical development and allows patients to focus

on the nonclinical aspects of their lives. Peer activities may also promote physical activity, which has been associated with improvements in both physical and mental function while on cancer therapy. Opportunities for social interactions with peers provide a necessary distraction from diagnosis and treatment and facilitates the construction of their own social support system.

Limitations

As with any literature review, this review is limited by the quality of included publications. By nature of the topic, this review included both qualitative and quantitative publications reflective of evidence Levels I through III. The majority of articles were of high quality. Included articles evaluated 27 separate constructs measured using 48 associated tools which impedes direct comparison of outcomes between studies, even if the same construct was measured in some cases. Ten studies utilized author-developed outcome measures, open-ended questions, or a combination of the two to assess psychosocial outcomes. This raises the issue of validity in an accurate measure of the construct under question.

The definition of the AYA population varies by organization and/or individual researchers and the included articles reflect a broad age range (11-40 years). Developmental milestones, psychosocial needs, and ability to articulate needs within this age range have drastic variations. A 16-year-old female in high school will undoubtedly have differing needs than a 34-year-old male with a full-time career and children, for example. The inclusion of a large age range and diverse definition of psychosocial care introduces challenges to meaningful summary and application of findings from individual studies.

Directions for Future Research

There remain multiple deficits in understanding the best approaches to address psychosocial needs of AYAs with cancer. Future research is needed to determine whether there are specific differences in needs within this population and if the 15- to 39-year-old definition of age is meaningful in this realm. Research addressing how the experiences of therapy differ between AYAs is necessary. There is also a great need to further define the topic of psychosocial support and needs within this population. The development of a singular tool or metric to assess this concept, as well as its universal adoption, would greatly benefit the field as a whole.

In general, there is a lack of literature focusing on AYAs who are currently receiving therapy. During the initial phases of this review, hundreds of publications were excluded because they included or focused on survivors of childhood cancer or on addressing the psychosocial needs of siblings and/or caregivers. Childhood, adolescent, and young adult cancer is often an acute diagnosis that is associated with chronic and lifelong complications from the disease or treatment. While there is a significant need to work with survivors of cancer or their siblings and caregivers, there is scant literature that address the potential for improving the psychosocial needs of those who are receiving therapy. Understanding how to address the holistic needs of AYAs early in the treatment trajectory may prove to be an effective means to mitigate the acute and longstanding effects of diagnosis and therapy and subsequently improve the quality of life for the duration of the cancer trajectory, including transitioning to survivorship. We need a better understanding of how adjustment to diagnosis and treatment impacts the clinical outcomes of treatment and quality of life in survivorship.

Conclusions

AYAs with cancer remain an underserved, overlooked, and at-risk population. They have developmental and psychosocial needs that are unique from other age groups and a diagnosis of cancer poses significant challenges to typical development. Addressing the psychosocial needs of AYAs with cancer is an important component of holistic care and is paramount in promoting optimal function and quality of life in these patients. AYAs undergoing treatment for cancer have complex psychosocial needs that require the use of an interdisciplinary team to appropriately meet these needs. Interventions for psychosocial support should be designed to (a) offer choice as a means to respect AYAs' values of autonomy; (b) be direct, professional, and individualized to match their need for privacy and professionalism; and (c) facilitate typical social interactions and physical activities in order to develop peer support and typical development. Addressing the psychosocial impacts of cancer therapy and improving the quality of life of AYAs with cancer are important components of continuing the progress of cancer therapy for AYAs.

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Manuscript Two: Self-efficacy in symptom management for adolescents and young adults with cancer: A systematic review.

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Abstract

Background: Adolescents and young adults (AYAs) have more frequent and intense adverse effects from cancer therapy than other age groups. Self-efficacy, the ability for persons to maintain health-related behavior change, may assist with symptom management but the role it plays in AYAs with cancer has not been thoroughly investigated. This review explores the role that self-efficacy has in symptom management for AYAs with cancer and provides guidance for clinicians to utilize self-efficacy as a means to reduce side effects of therapy.

Methods: A systematic review of peer-reviewed literature was conducted to identify works discussing self-efficacy and symptom management for AYAs with cancer. Five databases were searched with key terms and articles that discussed relationships between self-efficacy and cancer therapy symptoms were retained for analysis.

Findings: Twelve manuscripts representing 1,180 individuals age12 to 43 years were identified. Self-efficacy was found to be related to 1) health management behaviors, 2) psychosocial health, 3) sexual & reproductive health, and 4) physical symptoms. Self-efficacy had direct correlations with physical activity, nutritional intake, symptom regulation, mental health, sexual health, and fertility preservation. The included studies did not find significant relationships with medication adherence or pain management.

Discussion: Self-efficacy is an attribute that impacts behavior change, health maintenance, and overall wellness and can be changed over time and through interventions to improve symptoms of cancer therapy. Self-efficacy should be evaluated as a construct in relevant studies aimed to improve side effects of cancer therapy to better understand outcomes from interventions. Symptoms, toxicities, and adverse effects of cancer therapy may be improved by increasing self-efficacy of patients.

Introduction

Chemotherapy, surgery, radiation, and immunotherapy approaches to treat cancers are necessary and life-saving interventions but are also inherently toxic and induce a myriad of adverse effects and symptoms that threaten quality of life and life itself for patients. Therapy-related adverse effects are more frequent and severe for adolescents and young adults (AYAs) when compared to other age groups.[43-48] This sub-population of individuals, generally defined as those 15 to 39 years of age, also experience unique psychosocial challenges and lower abilities to cope and manage their diagnosis and therapy than young children or older adults.[13, 49] This is concerning because cancer is currently the leading medical cause of death for AYAs in the United States.[17]

Effective symptom management reduces treatment morbidity, improves quality of life, and improves cancer survivorship[50] but symptom management requires significant behavior changes, or the development of entirely new behaviors, on behalf of patients[51]. The ability for persons to initiate and maintain a health-related behavior change requires high self-efficacy, a concept that refers to an individual's belief in their capacity to successfully execute behaviors in order to achieve specific goals.[52, 53] Persons with cancer are often expected to self-manage their symptoms, but may not have the self-efficacy to do so.[51] Self-efficacy is built through experiences, and living with a chronic illness can facilitate developing this set of skills to better manage health and disease.[54] However, most AYAs with cancer do not have a history of chronic illness, so they lack the experience needed to develop these skills prior to a cancer diagnosis.

Without the ability to manage the symptoms and toxicities that result from cancer therapy, AYAs experience additional morbidity and undue distress during treatment.[55] Research suggests that patients are willing, and often prefer, to be involved in symptom management and can effectively self-manage adverse effects from therapy[56-59] yet many

still experience distressing symptoms of cancer treatment. An exploration into the ability for patients to adhere to clinical recommendations and execute these health-related behavior changes may assist with further improving symptom management.

Because AYAs with cancer have unique psychosocial challenges during therapy, have limited coping and self-management abilities, and experience high degrees of symptoms from therapy;[13, 49, 60] it is important to understand the role that self-efficacy may play in management of side effects specific to this age group. Accordingly, the purpose of this review is to determine the role that self-efficacy has in symptom management for AYAs with cancer. Findings from this review will be significant for understanding how psychological constructs may aid in effective interventions for symptoms and guide future approaches to symptom management and alleviation of the burden of therapy for patients.

Methods

A systematic review of the literature was conducted to determine the role of self-efficacy in symptom management in AYAs receiving therapy for cancer. A comprehensive literature search was conducted with the assistance of a medical informationist and the search strategy was constructed with terms relating to adolescents, young adults, cancer therapy, and self-efficacy (table 1). Five databases were searched for publications; PubMed, CINAHL Plus, EMBase, PsychINFO, and Web of Science to capture nursing, allied health, psychology, and biomedical publications. Boolean terms, truncation, and index terms were used as appropriate per database as guided by the medical informationist. Table 2 depicts the search strategy and number of identified articles. The search was conducted in June 2020 and had no date restrictions. Hand searching was undertaken by reviewing the references in the included publications as well as similar

literature reviews[61, 62] and no additional publications were identified, suggesting a comprehensive search strategy had been used.

Table 1: Search Terminology, Inclusion Criteria, and Exclusion Criteria

Concept	Search Terms	
Adolescent and young adults	Adolescent [index term] Young adult [index term] Adolescen*	Teen* Young adult*
Cancer and therapy	Neoplasms [index term] Cancer patients [index term] Transplant [index term] Bone marrow [index term] Cancer* Tumor*	Chemo* Radiation Transplant Stem cell* Bone marrow
Self-efficacy	Self-efficacy [index term] Self-concept [index term]	Self-efficacy

Inclusion Criteria	Exclusion Criteria
Peer reviewed	Inclusion of cancer survivors (off therapy)
Adolescent or young adult (≤39 years)	Findings also include children (<10 years) or older adults (>39years)
Participants on cancer therapy	Self-efficacy only measured as an outcome of intervention, not related to symptoms
Measure self-efficacy	
Relate self-efficacy to symptoms of cancer or therapy	

Note: *indicates truncated search terms, index terms were specific to database searched

Table 2: Search Strategy

	Terms	PubMed	CINAHL Plus	EMBase	PsychINFO	Web of Science
A	Adolescent and young adult	2,643,796	721,535	2,069,664	581,371	558,520
B	Cancer and therapy	6,328,082	685,877	8,013,845	113,727	5,140,925
C	**[A + B]**	513,379	55,843	357,439	14,718	39,500
D	Self-efficacy	35,504	32,157	104,704	48,445	62,499
E	**[A + B + D]**	716	323	1,180	389	275

To be included in this review, articles must be an original peer-reviewed publication that discusses a relationship between self-efficacy and any symptom of cancer therapy for adolescents and young adults receiving treatment for cancer (table 1). Self-efficacy was defined by the manuscript author and must have been discussed in relation to therapy or cancer-related symptoms. Symptoms of cancer and/or therapy maintained a broad definition for this review and encompassed any toxicity or adverse

effect from treatment including physical, mental, or psychological impacts. Adolescents and young adults are traditionally defined as persons aged 15-39 years of age,[17] but for this review, the age range was expanded to include publications on adolescents as defined by the manuscript's author. Because adolescence is a developmental stage, setting a strict age cutoff is difficult and recent literature suggests that the transition from childhood to adulthood spans 10 to 24 years of age.[18] Notably, one study that had participants up to age 43 and was included because the mean age for the 97 participants was 29 (SD=5.7 years, range 18-43) and the study findings were unanimous.[63] Participants were considered to be "on therapy" if they were currently or actively receiving any cancer-directed therapy. There were no exclusions based on cancer diagnosis, date of publication, country of origin, or language of publication.

Once identified, two reviewers screened all articles for relevance based on the title and abstract and if relevant, were reviewed in full. Articles were included for review if they met the above inclusion criteria. Data were extracted from each article by one author and verified by a second for accuracy. The level of evidence (LOE) and quality grade for each publication was determined following the Johns Hopkins Nursing Evidence-Based Practice Guidelines grading tool.[15] In this tool, evidence for original research are defined as Level I: experimental or randomized controlled studies; Level II: quasi-experimental or explanatory mixed methods study; Level III: nonexperimental study, exploratory or convergent mixed methods study; Level IV: opinion of respected authority; and Level V: literature review of non-research evidence. Quality of evidence was also evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) System[64-66] which includes evaluation for methodologic issues, effect size, publication bias, inconsistencies, and indirectness yielding a quality score of high, moderate, low, or very low. LOE and quality grades were assigned independently by two authors and compared, discrepancies were addressed through consensus

between the authors. Manuscripts were then read in full and relationships between self-efficacy and symptom management were extracted, evaluated, and synthesized together to provide a comprehensive description of the phenomenon under investigation.

Results

The executed search strategy identified 2,883 studies, 1,043 of which were duplicates. After duplicates were removed, 1,840 studies underwent title and abstract screening and at that point, 1,708 were removed. The remaining 132 articles underwent full text review and 120 were eliminated at this stage leaving 12 manuscripts that met inclusion criteria for this review (figure 1). The included studies represent an aggregate 1,180 participants ranging in age from 12 to 43 years. Included studies used different measures of self-efficacy but all were patient/participant self-report and did not measure self-efficacy through surrogate (e.g. parent or provider) report. Two studies[27, 67] utilized measures of self-efficacy that were designed for the purpose of the study at hand, and had not previously undergone validity and reliability testing. The remaining publications measured self-efficacy through a variety of dedicated scales or sub-scales of other measurement tools (table 3). Interestingly, each study included in this review utilized a different measure of self-efficacy. Outcomes measured by each study varied greatly and are listed in full in table 3. Many studies evaluated multiple primary outcomes or symptoms, but only examined self-efficacy's relationship with a sub-set or limited number of these outcomes.

Figure 1: PRISMA Diagram

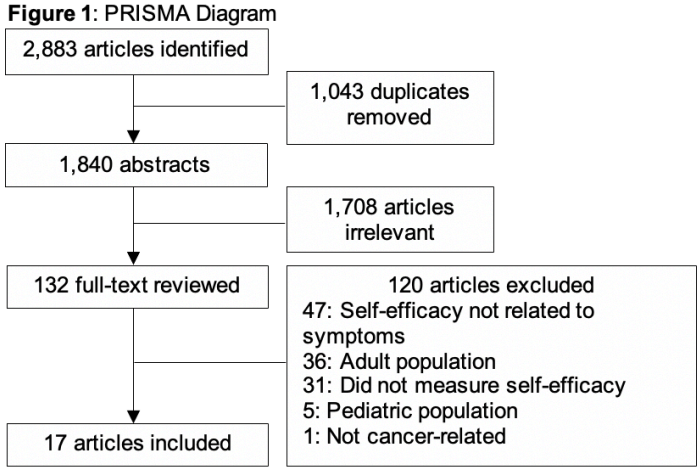

Table 3: Included studies' purpose, design, measured outcomes, and quality assessment

N	Ages	Study Design	Measured Self-Efficacy	Symptoms Measured	LOE	Q	GRADE
Aubin et al. (2019) – Evaluation of impact of a cognitive behavioral intervention							
113	18-39	Quantitative Repeated measures experimental design	Chronic Disease Self-Efficacy Scale	Depression and anxiety Health-related quality of life Sexual well-being Sexual self-esteem	I	B	Moderate
Diorio, Lin, Ginn, & Ladas (2018) – Evaluate psychosocial variables, stages of change, and self-efficacy with physical activity and nutritional intake							
118	12-25	Quantitative Exploratory cross-sectional study	Component of PACE + survey as "capacity to change"	Patient-centered assessment and counseling for exercise (PACE+) Physical activity and diet survey Change strategies Family support Friend/social support	III	A	High
Erickson et al. (2019) – Examine effects of symptom assessment tool on self-efficacy for symptom management and communication with providers							
79	15-29	Mixed methods Single-group longitudinal	PROMIS self-efficacy for managing symptom scale	Patient-provider communication Self-monitoring of symptoms Reflective thinking Decision-making and communication with providers	III	B	Moderate
Hinds et al. (2000) – Determine effects of educational intervention to facilitate coping on psychological and clinical outcomes and toxicity							
78	12-21	Quantitative Longitudinal experimental two-group design	Self-efficacy scale	Hopefulness Hopelessness Locus of control Symptom distress and toxicity	I	A	Moderate
Hullman, Brumley, & Schwartz (2015) – Examine patient-reported rates and responses for therapy nonadherence							
103	13-19	Quantitative Secondary data analysis of cross-sectional study	Cowen Self-Efficacy scale	Health-related hindrance inventory Positive and negative affect Perceived social and family support Parental bonding Medical adherence	III	A	Moderate
Jibb et al. (2017) – Evaluate implementation of app to assist with pain management							
40	12-18	Quantitative Pre-test/post-test	General Self-Efficacy Scherer Scale	Pain intensity and interference	III	B	Moderate

				Pediatric quality of life (physical, emotional, school, and social function)			
Kato, Cole, Bradlyn, & Pollock (2008) – Determine effectiveness of a video game intervention to improve adherence and behavioral outcomes							
129	13-29	Quantitative Randomized trial	Author-devised self-efficacy scale	Medication adherence Cancer-related knowledge Quality of life Stress Control	I	C	Low
Klosky et al. (2018) – Investigate contribution of developmental, communication, and psychological factors in sperm banking decisions							
146	13-21	Quantitative Cross-sectional study	Author-devised scale with self-efficacy subset	Sperm banking attempt and/or success Fertility health belief Perceived barriers Perceived benefits to fertility preservation Anxiety	III	C	Low
Pugh et al. (2020) – Evaluate the impact of a series of physical activity and nutrition support groups							
97	18-43	Quantitative Single-group longitudinal correlation study	Self-efficacy for exercise scale	Physical activity Mood Motivation to attend more sessions	III	B	Moderate
Rosenberg et al. (2017) – Determine if early psychological distress, resilience, or self-efficacy were predictive of later distress							
21	14-22	Quantitative Longitudinal descriptive study	Snyder Hope Scale (agency and pathway subscales)	Psychological distress Resilience	III	B	Moderate
Wu, Yu, Jou, & Hung (2018) – Examine physical activity self-efficacy as a mediator of the relationship between symptom distress and exercise							
97	13-20	Quantitative Cross-sectional mediation analysis	Self-efficacy scale for physical activity and calcium intake	Symptom distress Exercise involvement (frequency, intensity, and duration)	III	A	Moderate
Zebrack, Kwak, & Sundstrom (2017) – Examine participation in one-week adventure program's effect on psychological distress, self-efficacy, and support							
159	18-40	Quantitative Longitudinal correlational study	Subscale of Cancer Behavior Inventory – Brief	Psychosocial distress Social support	II	A	Moderate
LOE: level of evidence. Q: quality							

Self-Efficacy in Symptom Management

Four main types of symptom management approaches or types of therapy-related symptoms emerged as explored concepts with relation to self-efficacy from the literature included in this review. These include health management behaviors, psychosocial health, sexual/reproductive health, and physical symptoms. A synthesis of findings discussed with relation to each study are included below and outlined in table 4.

Table 4: Self-efficacy related study findings by types of outcomes

Health Management Behaviors	
Diorio, Lin, Ginn, & Ladas (2018)	Moderately strong, positive correlations were found between stages of change (phases of initiating and executing a health behavior) and self-efficacy (r = 0.251-0.354, p<0.01) for physical activity, dietary fat intake, and fruits & vegetables intake When controlling for other variables related to stages of change, patients who reported higher degrees of self-efficacy reported higher stages of change (β = 0.19, p=0.045) which was, in turn, related to higher likelihood of meeting dietary recommendations for fruits and vegetables intake Path analysis shows that higher degrees of self-efficacy may lead to improved behavior changes related to nutritional intake during cancer therapy
Erickson et al. (2019)	Self-efficacy increased with the number of clinical visits, but was not impacted by age, gender, or months since diagnosis Exploring symptom profiles with an app increased self-efficacy over multiple visits which had positive relationships with enhancement of multiple self-regulation abilities related to symptom management (awareness, identification, and recall)
Hullmann, Brumley, & Schwartz (2015)	There were no differences in self-efficacy noted between participants who reported perfect adherence and non-perfect adherence to medication regimens
Kato, Cole, Bradlyn, & Pollock (2008)	There were significant increases in self-efficacy for participants who used a video game intervention aimed at improving adherence and other behavioral outcomes Changes in self-efficacy alone did not account for intervention effects on prophylactic antibiotic regimen adherence, but self-efficacy and cancer knowledge together partially account for increased prophylactic antibiotic regimen adherence Self-efficacy and cancer-related knowledge did not have an association with adherence to oral chemotherapy regimens
Pugh et al. (2020)	There were no improvements in self-efficacy or exercise after completion of the physical activity support group; relationships may have remained constant throughout the program
Wu, Yu, Jou, & Hung (2018)	Physical activity self-efficacy partially mediated the relationship between symptom distress and physical activity in adolescents and with cancer; even after adjusting for age, gender, and diagnosis Physical activity self-efficacy accounted for 24.7% of variation in physical activity
Psychosocial Health	
Aubin et al. (2019)	Illness-related self-efficacy was significantly improved after the intervention in the intervention group, but the intervention was not conductive to greater illness-related self-efficacy when compared to the control group Depression, anxiety, social well-being, and family well-being all improved along with self-efficacy
Hinds et al. (2000)	Self-efficacy was significantly associated with hopefulness at all time points for participants in the intervention (r-0.40 – 0.49, p<0.03) and control (r=0.50-0.75, p<0.01) group in an educational intervention program

	Self-efficacy was negatively correlated with hopelessness at all time points, again for both intervention (r = 0.53-0.61, p = 0.001) and control (r = 0.40-0.50, p<0.03) groups Hopefulness was associated with symptom distress, which indicates that self-efficacy is a strong component in self-care behaviors Self-efficacy varied over time for adolescents of all ages and in both experimental and control groups
Rosenberg et al. (2017)	Higher self-efficacy (along with higher resilience and lower distress) measured at the time of diagnosis was correlated with lower distress three months later in therapy Self-efficacy measures were correlated with distress later in cancer treatment; distressed decreased by 0.3 points (95% CI -0.1, -0.5) for every 1 point increase in self-efficacy at diagnosis
Zebrack, Kwak, & Sundstrom (2017)	Self-efficacy and distress scores had significant improvements immediately and 1 month after a week-long adventure program; social support scores did not change significantly Participants who were distressed reported significantly lower self-efficacy scores prior to the experience (β = -5.12, p<0.001) when compared to non-distressed participants Participants who were not distressed had significant increases in self-efficacy over time (β = 2.30, p<0.001) and the interaction term in the model indicates improvement in self-efficacy over time for distressed participants was greater than non-distressed participants (β = 4.31, p<0.001) Self-efficacy improvements were associated with reductions in psychological distress in all participants
Sexual and Reproductive Health	
Aubin et al. (2019)	Self-efficacy improvements were associated with improvements in sexual well-being and sexual esteem
Klosky et al. (2018)	Adolescents who reported higher levels of self-efficacy were more likely to be successful in fertility preservation via sperm collection (OR 1.16, 95% CI 1.01-1.33, p = 0.034)
Physical Symptoms	
Jibb et al. (2017)	Self-efficacy did not change during the course of the study involving an app to assist in pain management, but use of the app did improve pain severity, pain scores, current pain, and interference of pain on daily life

Health Management Behaviors

Publications in this category are those that have outcomes addressing behaviors aimed at maintaining health during cancer therapy.

Physical Activity and Nutrition

Diorio and colleagues (2018)[68] conducted an exploratory cross-sectional study with 188 participants 12 to 25 years of age. In this study, they examined the relationships between self-efficacy and stages of change (phases of initiating and executing a health behavior) as it relates to physical activity along with dietary fat, fruit, and vegetable intake.[68] They found moderately strong correlations between self-efficacy

and stages of change behaviors (r = 0.251 - 0.354, p<0.01) for participants. When other variables related to stages of change were controlled, it was found that participants who had higher degrees of self-efficacy continued to show higher stages of change (β = 0.19, p=0.045) which was related to a higher likelihood of meeting dietary recommendations for healthy nutritional intake.[68] Path analysis showed that self-efficacy is linked with improved behavior changes related to nutritional intake during cancer therapy. Similar findings were identified in a study of 97 adolescents in a cross-sectional study aimed to examine if self-efficacy mediates the relationship between treatment-related distress and physical activity.[69] In this study, self-efficacy accounted for a significant proportion (24.7%) of the variance in physical activity behaviors. The authors concluded that physical activity self-efficacy significantly mediates this relationship such that higher levels of self-efficacy were associated with higher levels of physical activity.[69] A final study examining the relationship between physical activity and self-efficacy was a single-group longitudinal study designed to evaluate the impact that a physical activity and nutritional support group had on 97 AYAs.[63] In this study, self-efficacy and physical activity were measured before, during, and after enrollment and it was found that there were no changes in self-efficacy or exercise after the program but relationships between self-efficacy and physical activity remained relatively constant.[63]

Medication Adherence

Two studies examined the relationship between self-efficacy and medication adherence in AYAs with cancer. The first was a secondary data analysis conducted with 103 participants aged 13 to 19 years.[70] In this cross-sectional analysis, self-efficacy was compared between participants who reported perfect vs. nonperfect adherence to therapy-related medications and it was found that there was no difference in self-efficacy between these groups.[70] Another publication shared results of a video game intervention

for 129 participants aged 13 to 29 years.[27] The intervention was intended to improve cancer-related knowledge and self-efficacy as a means to improve medication adherence with secondary outcomes of improved quality of life, stress, and control.[27] Self-efficacy did increase significantly for the experimental group in this study, but self-efficacy alone did not account for intervention effects on medication adherence.[27] Interestingly however, self-efficacy and cancer knowledge together did partially account for increased medication adherence even though knowledge alone, similar to self-efficacy alone, did not have an impact on adherence.[27]

Symptom Self-Regulation

Lastly, one publication examined self-efficacy's relationship with symptom regulation and provider communication.[71] This single-group longitudinal study with 79 participants aged 15-29 years aimed to examine the effects that a heuristic application had on self-efficacy for symptom management with regard to self-regulation activities and communication with providers about their symptoms.[71] The study found that exploring symptom profiles increased self-efficacy with participants and self-efficacy had positive correlations with behaviors related to self-regulation of symptoms including awareness, identification, and recall of symptom experiences.[71]

Psychosocial Health

Publications were included in this section if any outcome was related to psychosocial health, mental well-being, or the psychological impacts of cancer therapy. Impacts of therapy explored in these publications were varied and include depression, anxiety, hopefulness, hopelessness, social wellbeing, social support, family well-being, and distress.

In a study evaluating the impact of a cognitive behavioral intervention with 113 AYAs, illness-related self-efficacy was found to be correlated with both depression and anxiety throughout the intervention such that higher self-efficacy was associated with lower depression and anxiety.[72] The same study also found that higher self-efficacy was associated with higher family wellbeing and social wellbeing.[72] Conversely, a study examining psychological distress, self-efficacy, and support with 159 AYAs with cancer who attended a week-long outdoor adventure camp found that changes in self-efficacy scores were not accompanied with changes in perceived social support.[73]

The same study, however, did find that self-efficacy had significant inverse relationships with distress in participants.[73] Additionally, participants who were distressed reported lower self-efficacy scores at baseline (prior to the experience) when compared to non-distressed participants (β=-5.12, $p<0.001$)[73]These relationships are also reflected in another study designed to determine if early psychological distress, resilience, or self-efficacy were predictive of distress later in cancer therapy.[40] In this longitudinal study with 21 participants, it was found that higher self-efficacy (along with higher resilience and lower distress) at the time of diagnosis were predictive of lower distress three months into therapy.[40] Distress decreased by 0.3 points (95% CI -0.1, -0.5) for every 1 point increase in self-efficacy at diagnosis, indicating that self-efficacy at the start of cancer therapy may have significant impacts on improving psychosocial status during cancer therapy.[40]

Symptom distress has also been found to correlate with factors associated with self-efficacy. In an educational intervention, it was found that hopefulness had significant association with symptom distress and self-efficacy.[26] In this study, self-efficacy had a significant positive correlation with hopefulness for both the intervention ($r = 0.40$-0.49, $p<0.03$) and control ($r = 0.50$-0.75, $p<0.01$) groups in the study.[26] Self-efficacy was also

negatively correlated with hopelessness at all time points, again for both the intervention ($r = 0.53\text{-}0.61$, $p = 0.001$) and control ($r = 0.40\text{-}0.50$, $p<0.03$) groups involved.[26]

Sexual and Reproductive Health

Two publications explored relationships between self-efficacy and sexual/reproductive health. In an evaluation of cognitive behavior therapy, improvements in self-efficacy were associated with improvements in ratings of sexual wellbeing and sexual self-esteem.[72] In a second study, Klosky and colleagues investigated the contributions that developmental, communication, and psychosocial factors had on the willingness to have fertility preservation and the success of sperm collection for this purpose.[67] Findings reveal that adolescents who reported higher levels of self-efficacy were more likely to be successful in fertility preservation (OR 1.16, 95% CI 1.01-1.33, $p = 0.034$).

Physical Symptoms

Only one study evaluated self-efficacy's role in impacting specific symptoms of pain. In this study, an app was used to assist with pain management with the effect was measured in 40 adolescents aged 12-18 years who used the application.[74] It was found that use of the app did not change self-efficacy but there were significant improvements in pain severity, pain scores, current pain, and interference of pain on daily activities.[74]

Discussion

The purpose of this review is to determine if self-efficacy has an impact in symptom management for AYAs with cancer and to explore the extent to which that role exists. The identified body of literature suggests that self-efficacy does impact symptom

management, but the domains in which this holds true and the means through which these relationships work are not yet completely understood.

Clinical Implications

Self-efficacy had positive, strong, and beneficial relationships in interventions or studies that explored physical activity and nutrition.[27, 63, 68-71] These findings are clinically significant because increasing physical activity is an important component of promoting health, increasing psychological outcomes, minimizing treatment toxicity, improving quality of life, and assisting with typical development.[75-78] A cancer diagnosis and the treatment that follows often induce fatigue, pain, and symptoms that prevent typical physical activity that leads to worsening symptom clusters during therapy.[78-80] Limitations in the ability to perform typical physical activities or participate in athletics is one of the most frequently discussed reasons adolescents with cancer experience reduced quality of life.[81] Physical activity in persons with cancer can ameliorate or attenuate therapy-induced side effects[79, 82] but this is challenging during the treatment phase because of the burdens of therapy and aforementioned side effects from treatment. Nonetheless, many interventions have led to increased physical activity in participants, but low rates of physical activity remain an issue for AYAs with cancer.[82] Despite the fact that there are many publications and interventions to increase physical activity in AYAs with cancer, only a small number include addressing or evaluation of self-efficacy. Findings from this review suggest that self-efficacy has a significant relationship with the improvement or change in physical activity in AYAs with cancer. Because self-efficacy involves beliefs regarding behavior changes, it should be strongly considered as a construct to measure or address in interventions or educational programs intended to increase physical activity in AYAs with cancer. Clinicians caring for AYAs with cancer who wish to improve

their levels of physical activity may want to consider assessing and aiding in improving self-efficacy in these patients as a means to increase their physical activity.

Self-efficacy also had beneficial relationships with nearly all psychosocial effects of therapy with the exception of social support. Higher self-efficacy is related to lower depression, anxiety, hopelessness, and distress at multiple timepoints and later in cancer treatment.[40, 72, 73, 83] Higher self-efficacy was also correlated with increased family and social wellbeing[72] but there was no relationship between self-efficacy and social support.[73] These findings are not surprising, because self-efficacy and the aforementioned outcomes are all psychosocial constructs, so it is expected that they will have close relationships with each other and social support is not an internal attribute, but an attribute of one's environment. What is important to note here, is that cancer therapy for AYAs is incredibly distressing, and is often accompanied by significant threats to psychosocial health.[6, 84] Tending to the psychosocial needs of AYAs with cancer facilitates development, promotes health, improves treatment outcomes, and is postulated as a means to increase survivorship.[6, 85]

Self-efficacy has also been associated with improvements in sexual health and fertility preservation[67, 72] which are significant findings because effects on sexual and reproductive health are frequently cited as major sources of distress for AYAs with cancer.[86-88] Successful completion of fertility preservation improves quality of life for young adults with cancer[89] yet less than 30% of patients successfully bank sperm prior to therapy.[90] Findings of this review suggest that self-efficacy is associated with improvements in fertility preservation among males. Increasing self-efficacy may improve fertility preservation rates and, in turn, reduce the distress and impacts on quality of life that a cancer diagnosis imposes on AYAs.

This review found that self-efficacy alone did not have a significant impact on medication adherence[27, 70] which remains a significant issue for management of AYA

cancers. Studies indicate that more than 40% of AYAs with cancer have challenges adhering to medication regimens.[5, 91] The ongoing issues with medication adherence suggest that the problem is more complex than originally thought, or that medication non-adherence is the result of more than just behaviors on the part of the patient. There was also no link between self-efficacy and pain management in one intervention study,[74] as with medication adherence, this may be due, in part, to the fact that the pain experience is incredibly complex, and that pain management is not achieved through behavior alone. Self-efficacy is an attribute that is involved in behavior changes, and may not be as relevant to management of symptoms effects of therapy that are not amenable to management with behavior interventions alone but further investigation into these relationships is needed to better understand the phenomenon.

Addressing Self-Efficacy

Self-efficacy has long been discussed as an attribute required for health behavior changes and is a component in many theories and frameworks that guide behavior changes for improving and maintaining health and wellness.[53, 91] Self-efficacy can evolve and changes may lead to subsequent health behavior changes[53] Studies included in this review show that self-efficacy may change over time with or without interventions for AYAs with cancer.[26] However, the construct of self-efficacy has not been explored in depth or measured frequently in interventions or programs intending to improve symptoms of cancer therapy in AYAs. Cancer therapy is inherently toxic and presents a myriad of adverse effects, side effects, and toxicities that span the continuum of the treatment period and last into survivorship.

Management of toxicities in part requires performing specific behavior and investment by patients. Because many of the studies in this review suggest that higher self-efficacy leads to improvements in health management behaviors, psychosocial

health status, quality of life, and sexual functioning; it is important that self-efficacy be continuously addressed in approaches to symptom management. Means by which patients can improve self-efficacy should be addressed when discussing behavior changes and clinicians should be aware that varying levels of self-efficacy will impact the ability of AYAs to successfully manage symptoms and effects of cancer therapy. Future research should focus on continuing to understand the ways in which self-efficacy impact cancer therapy and future interventions for behavior change and symptom management in AYAs may benefit from evaluation of self-efficacy as a potential confounder and/or mediator for the intended outcome.

Limitations

As with any literature review, this review is limited by the quality of included publications. By nature of this topic, the majority of publications were quantitative and reflective of a level of evidence I through III and most were of moderate quality. Low quality articles were deemed as such because self-efficacy was not measured with a validated tool. Each publication also measured self-efficacy with a different tool and had varying definitions of self-efficacy. For example, some studies examined general self-efficacy and some examined self-efficacy specific to the outcome of interest (such as physical activity self-efficacy or behavior-change self-efficacy). The varying definitions and measurements of self-efficacy in each publication makes direct comparison between publications challenging. Similarly, each publication addressed a different outcome with regard to symptom management or approaches to symptom management, making synthesis of findings together difficult to compare directly. Additionally, many studies were correlative in nature, and did not always offer a control group which makes determination of directionality of the relationship between self-efficacy and the outcome difficult.

Conclusions

Improvements in managing symptoms of cancer therapy may increase quality of life, reduce morbidity from therapy, and increase survivorship of cancer. Because AYAs with cancer have higher therapy-related toxicities and lower survivorship than other age groups, understanding how self-efficacy may impact management of therapy-related toxicities is important. Findings from this review suggest that increased self-efficacy is associated with better physical, mental, and sexual health outcomes during cancer therapy in AYAs. Improving the symptom profile created by cancer therapy increases quality of life, reduces therapy-related morbidity, and may increase survival by increasing tolerability of therapy and limiting interruptions in treatment. Intervention studies aimed at addressing symptoms of cancer therapy in AYAs should consider exploring the role of self-efficacy in impacting outcomes. Studies focused on increasing self-efficacy in AYAs with cancer should investigate the means by which this construct impacts health management and symptom profiles. Importantly, knowing that self-efficacy may correlate with multiple positive aspects of health, clinicians can incorporate ways in which they can increase their patients' self-efficacy in routine care as a means to address challenges and symptoms of cancer therapy.

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<u>Manuscript Three</u>: Anti-inflammatory mouthwashes for the prevention of oral mucositis in cancer therapy: An integrative review & meta-analysis

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Abstract

Purpose: Mucositis is severely painful and often reported as one of the most distressing adverse effects of cancer therapy; it is a significant threat to quality of life as well as life itself. Anti-inflammatory agents may modulate physiologic mechanisms that perpetuate mucositis and be useful in prevention efforts. Because systemic anti-inflammatory agents are not appropriate for many patients, locally-acting agents (mouthwashes) may be more feasible for use. This review and meta-analysis evaluates the role that anti-inflammatory mouthwashes have in preventing or reducing oral mucositis associated with chemotherapy and radiation therapy.

Methods: A systematic literature review was conducted to identify studies evaluating the efficacy of anti-inflammatory mouthwashes to prevent therapy-associated mucositis. Meta-analysis was conducted to determine efficacy in preventing any mucositis and dose-limiting mucositis.

Results: Eight peer-reviewed publications were identified; corticosteroid and non-steroidal anti-inflammatory mouthwashes are effective in reducing overall incidence of mucositis and are associated with lower severity of mucositis. Meta-analysis reveals significant reduction in symptomatic mucositis (OR 6.00, 95% CI 4.39-8.20, $p<0.0001$) and in reduction of dose-limiting mucositis (OR 2.12, 95% CI 1.07-4.28, $p=0.032$).

Conclusion: Mouthwashes containing anti-inflammatory agents are a potential effective means to prevent or reduce mucositis associated with cancer therapy. There are limited adverse effects from these agents and adherence is high, indicating safety and feasibility of use. Anti-inflammatory mouthwashes should be considered for supportive care in persons at risk for mucositis and must be further evaluated to investigate efficacy across multiple chemotherapy agents, adverse effects, and impacts on symptoms, pain, and quality of life.

Introduction

Therapy-associated mucositis is a frequent burden and health risk for individuals undergoing treatment for cancer.[92-95] The condition presents as painful gastrointestinal ulcerations that are most frequent in the oral cavity[92, 96, 97] and is associated with pain, dysphagia, malnutrition, weight loss, and caloric deficits that delay healing and recovery from chemotherapy.[95, 98, 99] Mucositis development is acute and concurrent with immunosuppression that results from therapy, which presents a significant risk for life-threatening infections.[98, 100, 101] Additionally, the cluster of symptoms associated with mucositis have a substantial impact on quality of life and patients cite mucositis as one of the most distressing adverse effects of treatment.[98, 102] Because of the severity and gravity of effects caused by mucositis, cancer-directed treatment must be interrupted, reduced, or withheld entirely to allow for healing and to prevent repeat mucositis development. In the acute phases, mucositis introduces immediate threats to life by way of malnutrition and infection but also limits therapy delivery which may impact overall survival. Preventing mucositis is imperative to reduce suffering of patients, to reduce the burden of cancer care, and allow patients to receive therapy that provides them the greatest chance of disease survival.

The development of oral mucositis is the result of exposure to antineoplastic therapy and the physiologic response of the patient. Mucositis pathobiology is, therefore, multi-factorial in nature. Many types of cancer-directed therapy are inherently cytotoxic and unfortunately, not specific to malignant cells, so effects of chemotherapy and radiation therapy are also seen in other rapidly diving and growing cells which includes mucosal basal epithelial cells. Exposure to radiation or chemotherapy damages DNA structure which leads to alterations in the cell's ability to grow and differentiate.[96, 97] The DNA damage also leads to DNA strand breaks and causes direct cell death in mucosal tissues that results in necrosis and compromise of mucosal tissue integrity.[96, 97, 103] This

cell damage initiates a cascade of inflammatory signaling, eliciting a response that further worsens cell and tissue damage and exacerbates mucosal lesions.[96, 97, 103] Cell death and necrosis increases oxidative stress on the tissues leading to the generation of reactive oxygen species[104-106] along with endogenous damage-associated pattern molecules. Cells in the damaged mucosal tissues then begin to promote transcription of genes associated with mucositis development; namely nuclear factor kappaB which modulates over 200 pro-inflammatory genes that are associated with pro-inflammatory cytokines.[97, 103, 105] The increase in pro-inflammatory cytokines is associated with worsening tissue damage due to dissolution of connective tissue, damage to the endothelium, and inhibition of tissue oxygenation and cellular repair mechanisms[96, 97, 105, 106] that further signal for an increasing inflammatory response. This cascade of events occurs concurrently with damage to other cells that normally function in the repair and resolution of tissue damage including fibroblasts, macrophages, and lymphocytes. The end result of this biological response to therapy is a friable mucosal tissue damaged directly by cancer-directed therapy and a biological microenvironment that worsens tissue integrity and limits inherent cellular repair mechanisms leading to the formation of ulcers. Unfortunately, mucosal ulcerations can be self-perpetuating; if the ulcer allows microorganisms to invade the tissues directly, they may stimulate an additional inflammatory response that further worsens mucositis development.[97, 105]

There is great heterogeneity in the development of mucositis; varying chemotherapy agents have differing levels of risk for mucositis development, depending on their mechanism of action. Furthermore, there is a dose-response relationship with chemotherapy and radiation therapy such that higher doses of each modality are associated with more frequent and more severe mucositis.[96, 97, 106] Use of chemotherapy and radiation therapy together, especially if the radiation field involves the mouth or throat, greatly increases the incidence of mucositis. Targeted therapies that interfere with

specific molecular targets of the tumor to prevent tumor growth have been introduced to the treatment of many types of cancers with the hopes that their specific area of action yields lower systemic side effect profiles.[107] While their overall side effect profile is lower, many are unfortunately still associated with mucositis development which continues to have a strong inflammatory component to its pathogenesis.

Because an elevated inflammatory response is a common factor leading to mucositis development among multiple types of therapies, reducing the inflammatory response may assist with preventing mucositis development or progression. Systemic anti-inflammatory agents have been evaluated in this capacity with mixed results[108-111] and unfortunately, systemic anti-inflammatory agents have an extensive side-effect profile, which limits use in the oncology population due to compound adverse effects and existent polypharmacy. Topical (oral) anti-inflammatory mouthwashes, however, hold promise as a means to prevent mucositis development[112] because they act locally on mucosal tissues, have limited systemic absorption, and may be an easy-to-implement patient-directed intervention. The use of anti-inflammatory mouthwashes as mucositis prophylaxis has not yet been extensively studied and no standard of care currently exists for their use.

The purpose of this review and meta-analysis is to evaluate the efficacy of anti-inflammatory mouthwash for the prevention of mucositis and summarize the state of the science on these agents with this regard. Findings from this work are relevant to plan mucositis prevention interventions and to guide future clinical trials to prevent mucositis development.

Methods

A systematic literature search was conducted to identify studies evaluating the use of anti-inflammatory mouthwashes for the prevention of therapy-induced mucositis

following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses approach.[113] The search strategy was designed with the assistance of a medical librarian.

A series of three progressive searches were employed within four relevant databases (PubMed, CINAHL Plus, EMBase, and Web of Science) run in May 2021 with no date restrictions. Search terms included those relating to mucositis, mouthwashes, and cancer (table 1); appropriate index terms, truncation, and Boolean phrasing were used when applicable. Anti-inflammatory search terms were omitted from the search strategy because indexing terms for this medication class were not consistent.

Table 1: Search Terminology, Inclusion Criteria, and Exclusion Criteria

Concept	Search Terms	
Mucositis	Mucositis [index term]	Mucositis
	Stomatitis [index term]	Stomatitis
	Mouth sore*	
Mouthwash	Mouthwashes [index term]	Mouth bath*
	Mouthwas*	Mouthrins*
	Mouth rins*	
Cancer	Cancer [index term]	Antineoplastic protocols [index term]
	Neoplasm [index term]	Chemotherapy [index term]
	Cancer*	Tumor
	Therapy	Tumour

Inclusion Criteria	**Exclusion Criteria**
Original study	Inadequate control group
Investigated anti-inflammatory mouthwash	No systematic grading of mucositis
	Non-pharmacologic anti-inflammatory agent
Intervention intended for mucositis prevention	

Note: *indicates truncated search terms, index terms were specific to database searched

Identified articles were compiled and duplicates removed, two authors independently reviewed abstracts for relevance to the research question, then read articles in full to ensure they met the inclusion criteria for this review. To be included, articles must have been an original study investigating an anti-inflammatory mouthwash for mucositis prophylaxis in persons receiving cancer-directed therapy. Articles that did

not have an adequate control group, did not use a standardized evaluation of mucositis, or used non-pharmacologic anti-inflammatory agents were excluded (table 1). Standardized evaluation of mucositis was determined to be present if there was an explicit and intentional assessment of mucositis severity at pre-determined time points during the study in a manner that adequately compared intervention to control groups. Level of evidence and quality grades for each publication were determined using the Johns Hopkins Nursing Evidence-Based Practice Guidelines.[15] In this tool, evidence for original research is defined as Level I: experimental or randomized controlled studies; Level II: quasi-experimental; Level III: nonexperimental; Level IV: opinion of respected authority; and Level V: literature review. The same tool was used to assess quality by evaluating consistency, generalizability, sampling, control, conclusions, and validity of the work. Additional quality of evidence was also evaluated using the Grading of Recommendations Assessment, Development and Evaluation system[66, 114] which yields a quality score of high, moderate, low, or very low based upon methodologic issues, effect size, bias, inconsistencies, and indirectness. Two authors independently reviewed all included articles to assess level of evidence and quality of the work. Scores were then compared and any differences were discussed among the group. Final scores were determined through consensus adjudication.

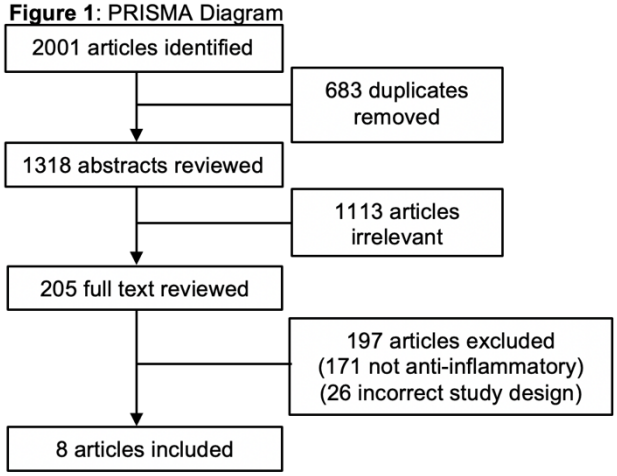
A meta-analysis was performed to determine the role of anti-inflammatory mouthwashes in the prevention of two clinically relevant outcomes: 1) any mucositis and 2) dose-limiting mucositis. Using count of success and failure (dichotomous data) in each study group, meta-analyses for a fixed-effects model were executed as there were not many studies. Comprehensive Meta-Analysis, V2 software was used for analyses[115] and publication bias was assessed via funnel plot. Forest plots for each outcome were generated and include odds ratio, 95% confidence interval, and p-value for each included study and for the meta-analysis overall. Higher odds ratio reflects higher odds

of success (better mucositis prevention) in the intervention group compared to control group.

Findings

The search strategy identified 1318 articles which underwent abstract review, 1113 were removed at this point and 205 underwent full-text review (figure 1). Of those, only 8 met the inclusion criteria for this review. The included manuscripts were published between 2001 and 2019 and represent 8 novel experimental studies and a cumulative 1,137 participants, all aged 18 and older.

Figure 1: PRISMA Diagram



Literature Review

The included studies investigated anti-inflammatory agents that fell into two categories: corticosteroids (hydrocortisone, prednisolone, and dexamethasone) and non-steroidal anti-inflammatory medications (benzydamine). Notably, all studies that involved steroid mouthwashes were conducted in patient populations taking kinase inhibitors (everolimus) and all that investigated benzydamine recruited participants receiving radiation therapy. Therefore, they are discussed and analyzed within these groupings below. Study design, outcome, and quality assessment for each of the included articles are summarized in table 2.

Table 2: Included studies' design, outcomes, and quality assessment

Intervention	Study Design	Comparison Group	Mucositis Measurement*	Outcomes	LOE	Q	GRADE
Chitapanarux et al. (2018) Randomized control trial of benzydamine HCL versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis							
Benzydamine 0.15% rinse x 2 min QID (n=30)	RCT	Sodium Bicarbonate (n=30)	OMAS	Total mucositis score was 25 in experimental group and 37 in control group (p<0.001) Mucositis score was lower in the experimental than control group in every week from week 2 through 8 (p<0.04)	I	High	High
Epstein et al. (2001) Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial							
Benzydamine 0.15% rinse x 2 min 4-8 times daily (n=62)	RCT	Placebo (n=66)	4-point scale	For all doses of therapy, intervention produced a 26.3% reduction in mean mucositis for area under the curve for radiation dose At higher doses of radiation therapy, the intervention group had a more pronounced decrease in mucositis scores measured as area under the curve	I	Good	Moderate
Hattori et al. (2019) A single-arm, phase 2 study of steroid-containing mouthwash for the prevention of Everolimus-associated stomatitis in multiple tumor types							
Hydrocortisone 10mL 4 times daily (n=29)	Quasi-experimental	Historical Control (n=482)	CTCAE	Control: 20% had grade 2 stomatitis Intervention: Incidence of grade >2 mucositis at 8 weeks was 28.1% (90%CI = 26.2-46.1%)	II	Good	Moderate
Jones et al. (2019) Evaluation of Miracle Mouthwash plus Hydrocortisone Versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis: A Randomized Phase II Study							
Hydrocortisone or Prednisolone (n=100)	Quasi-experimental	Historical Control (n=482)	CTCAE	Historical controls: 67% developed mucositis (24% grade 2, 8% grade 3) MMW: 18% developed grade >2 mucositis, (4% developed grade 3) Prednisolone: 12% developed grade >2 mucositis, (0% developed grade 3)	II	Good	Moderate
Kazemian et al. (2009) Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: a double-blind placebo-controlled randomized clinical trial							
Benzydamine 0.15% rinse x 2 min QID (n=39)	RCT	Placebo (n=42)	RTOG	Benzydamine produced a statistically significant reduction in mucositis during radiation Grade 3 mucositis was 43.6% in intervention group, 78.6% in control	I	High	High

				Grade 3 or higher mucositis was 2.6 times more frequent in placebo group (RR = 2.6, 95% CI=1.38-5) Both groups experienced similar onset of mucositis within first three weeks, but it plateaued in the intervention group and increased in control group Multivariate logit analysis for intervention affecting grade 3+ mucositis found that intervention mouthwash had significant impact (odds ratio of 0.2; 95%CI = 0.07-0.58; P=.0003)			
Rastogi et al. (2017) Role of Benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients treated with radiotherapy (>50 Gy) with or without chemotherapy							
Benzydamine 0.15% rinse x 1 min 4-6 times daily (n = 57)	RCT	Saline placebo (n=63)	WHO and CTCAE	For those who received radiation, intervention group had less grade 3 mucositis per WHO criteria than control group (62.1 vs. 36.4%, p=0.038) as well as less grade 3 mucositis by CTCAE criteria (51.7 vs. 27.3%, p=0.043) For those receiving chemotherapy and radiation therapy together, persons in the intervention group had less grade 3+ mucositis per WHO criteria (64.3 vs 43.4%, p=0.091) and per CTCAE criteria (53.6 vs. 43.3%, p=0.30) but these differences in proportion were not statistically significant	I	Good	Moderate
Rugo et al. (2017) Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial							
Dexamethasone (n=86)	Quasi-experimental	Historical Control (n=482)	CTCAE	Control at 8 weeks: 39% had no symptoms, 34% had grade 1, 20% had grade 2, and 7% had grade 3 Intervention at 8 weeks: 79% had no symptoms, 19% had grade 1, 2% had grade 2, and 0% had grade 3	II	High	Moderate
Sheibani et al. (2015) Efficacy of Benzydamine oral rinse in prevention and management of radiation-induced oral mucositis: A double-blind placebo-controlled randomized clinical trial							
Benzydamine 0.15% 15mL rinse x 2 min 4-8 times daily	RCT	Placebo (n=25)	4-point scale	There were no differences in mean mucositis score for the first three weeks of therapy Week 4, intervention group mean mucositis score was 1.27, control 1.81 (p=0.01)	I	Good	Moderate

(n=26)	Week 5, intervention group mean mucositis score was 1.58, control 2.10 (p=0.01) Week 6, intervention group mean mucositis score was 1.60, control 2.12 (p=0.01) Week 7, intervention group mean mucositis score was 1.43, control 1.98 (p=0.01)	

LOE: level of evidence. Q: quality. RCT: Randomized Control Trial. WHO: World Health Organization. CTCAE: Common Terminology and Criteria for Adverse Events. OMAS: Oral Mucositis Assessment Scale, RTOG: Radiation Therapy Oncology Group
*For measurement scale details see Table 4.

Approaches to Mucositis Assessment

The included studies evaluated mucositis using five different scoring scales displayed in table 3 to show how each correlates with the others. A score of 2 on the OMAS scale or 3 on all other scales identifies a dose-limiting degree of mucositis. Each scale can be used to describe a single lesion or area of the mouth (e.g. grade 1 to oropharynx, grade 3 to buccal mucosa) or used to summarize the overall severity of mucositis (e.g. CTCAE or WHO grade 3 if there is any interference with oral intake) and were used in both ways in the studies included in this review.

Table 3: Oral mucositis assessment scales

	Oral Mucositis Assessment Scale (OMAS)	0-3 Scale (4-point scale)	Common Terminology Criteria for Adverse Event (CTCAE)	Radiation Therapy Oncology Group (RTOG)	World Health Organization (WHO)
Non-Dose-Limiting	0 = no lesions	0 = normal	0 = no lesions	0 = none, no change	0 = none
		1 = erythema	1 = asymptomatic or mild	1 = mild irritation, slight pain	1 = oral soreness, erythema
	1 = lesions less than 1 cm^2	2 = single ulcer, <1cm	2 = moderate pain, do interference with intake	2 = patchy mucositis, moderate pain	2 = oral erythema with ulcers
Dose-Limiting	2 = lesions 1-3cm^2	3 = multiple ulcers or single ulcer >1cm	3 = severe pain, interferes with intake	3 = confluent mucositis, painful, requires narcotic	3 = ulcers interfering with solid oral intake
	3 = lesion more than 3cm		4 = life-threatening consequences	4 = life-threatening hemorrhage or necrosis	4 = ulcers making oral intake impossible

Steroid Mouthwashes with Kinase Inhibitors

A quasi-experimental non-randomized trial evaluated a combination mouthwash consisting of hydrocortisone, itraconazole, tetracycline, and chlorpheniramine in persons receiving everolimus 10mg daily for the treatment of breast, neuroendocrine, and renal cell carcinoma.[116] Participants were instructed to swish and expectorate with 10mL of the mouthwash four times daily while taking chemotherapy. Oral health was assessed by an oral surgeon utilizing the CTCAE criteria at enrollment then every 2 weeks until week 8. The incidence of grade $\geq$2 mucositis at week 8 was 28.1% (90% CI: 16.2-46.1%) and since the confidence interval overlapped with the historic control of 30% incidence, it was concluded that this anti-inflammatory-containing cocktail was not effective in reducing the development of chemotherapy-associated mucositis.[116] The use of a

consistent examiner improved this study's measurement consistency, but the historical control group was not well described and the comparison of mucositis incidence at a single timepoint limits the study's external validity.

Historic control was also utilized in a randomized two-arm study that evaluated mucositis after prophylaxis with prednisolone (15mg/5mL) or miracle mouthwash (320mL diphenhydramine, 2 grams tetracycline, 80mg hydrocortisone, and 40mL nystatin).[117] In this study, 100 participants with breast cancer treated with 10mg everolimus daily plus standard dose of aromatase inhibitors (letrozole, exemestane, or anastrozole) were instructed to swish and expectorate with 10mL of either agent four times daily while receiving a 12-week course of chemotherapy. Mucositis was evaluated via CTCAE criteria. The incidence of grade $\geq$2 mucositis was 18% for the miracle mouthwash group and 12% for the prednisolone arm. Both investigational agents yielded lower grade $\geq$2 mucositis than historic control (30% incidence). The authors concluded that both mouthwashes substantially reduced the development of oral mucositis associated with aromatase inhibitors.[117] Similar to the above, this study also utilizes a historic control group for comparison which limits the external validity of these findings, even though the incidence of mucositis with this chemotherapy regimen is well documented. Furthermore, this study also used patient-reported symptoms of mucositis, which may not correlate well with the clinician-assessed mucositis incidence and severity in the control group, making comparison more difficult.

Dexamethasone was evaluated in a third study using historic control.[118] In this non-randomized study, participants with breast cancer taking 10mg everolimus and 25mg exemestane daily were asked to use 10mL of dexamethasone mouthwash four times daily for the eight-week chemotherapy cycle.[118] When compared to historic control, dexamethasone mouthwash improved all grades of mucositis assessed via CTCAE criteria; 21% of participants developed any grade of mucositis, which was lower than

historic control of 61%.[118] All other grades of mucositis were lower in the intervention when compared to control group; Grade 1: 19% vs 34%, grade 2: 2% vs 20%, and grade 3: 0% vs 7%.[118] Dexamethasone mouthwash reduced total incidence by 61% and grade 2 or worse by 91%.[118]Chemotherapy dose reductions and interruptions were lower in the intervention group (30%) than control (62%), attributed to the lower incidence of dose-limiting mucositis seen with dexamethasone use.[118] This historic control group was more directly comparable for this study, which allowed for a larger intervention sample to be obtained. However, the timing of mucositis assessment was not well described, and may not be directly comparable to the control group. The participants in this intervention have received slightly less intensive therapy than the control group which would theoretically reduce their risk of mucositis at baseline, although this difference was presumed to be negligible.

NSAID Mouthwashes with Radiation and Chemoradiation

All of the included studies evaluating non-steroidal anti-inflammatory agents utilized benzydamine 0.15% and also recruited participants receiving a radiation therapy with cumulative dose of at least 50Gy. One study intentionally recruited participants receiving chemoradiation for separate analysis;[119] but three others performed subgroup analyses on participants who were receiving concurrent chemotherapy with radiation (discussed below).

One randomized study recruited 128 participants from 16 clinical sites and stratified them based first on clinical site and then on radiation dose, participants were then randomized to use benzydamine or placebo mouthwash.[120] Oral exams were performed at baseline and every clinic visit, mucositis score was assigned with the 4-point scale to 14 pre-identified oral sites in the radiation field; mean score was determined by dividing the cumulative score by number of lesions sites.[120] Benzydamine

was associated with a 26.3% reduction in mean score compared to placebo ($p=0.009$).[120] Furthermore, benzydamine was associated with a reduced rate of mucositis in multiple strata of radiation doses including a single dose of 180-220cGy (32.2% mucositis reduction) and twice daily dose of 110-150cGy (33.8% reduction of mucositis).[120] Stratification of patients based upon clinical site and radiation dose was helpful in minimizing effects of potential confounders, but there were no measures employed to standardize additional supportive care or other mucositis preventing interventions. The study also did not specify who was conducting the oral examinations or if this was a consistent clinician across all participants at each site. A similar double-blind placebo-controlled trial in 51 participants receiving radiation therapy evaluated benzydamine used 4-8 times daily compared to placebo.[121] Mean mucositis score was evaluated via the same process as above and were similar between intervention and control groups for the first 3 weeks of treatment ($p>0.05$). Starting at week 4, however, the control group experienced worse mucositis for the remainder of the 8-week treatment period ($p<0.01$ for each week).[121] The double-blind approach to this study is methodologically strong and yields a robust study, but the participants within this trial could dilute the interventional agent if desired. The frequency of dilution was not shared and not specified if it was accounted for in the analysis.

A randomized non-blinded study recruited 120 participants to use 10mL of benzydamine for 1 minute 4-6 times daily or saline placebo during radiation.[119] Participants were evaluated weekly and mucositis was scored following CTCAE criteria. It was found that benzydamine was associated with reduced rates of grade $\geq$3 mucositis (27.3%) compared to placebo (51.7%) ($p=0.043$).[119] In this study, the authors did not describe who was performing the mucositis assessment and if this was consistent among all participants or done at one clinical site. Additionally, a power analysis determined a sample size of 200 was required to identify an effect size of $\geq$20% between

groups but resources limited the sample to only 120, which may limit internal validity of this study. The randomized approach, however, does offer strengths to the study design. A similar study evaluated benzydamine used for 2 minutes four times daily compared to placebo throughout the duration of radiation therapy in 81 participants with a double-blind, randomized, placebo-controlled design.[122] Mucositis was assessed weekly following the RTOG criteria and it was found that benzydamine produced a 30% reduction in the development of any mucositis during treatment (p=0.002); 66% of participants in the benzydamine arm developed mucositis compared to 72% in the control group (p=0.037) and there was a significant reduction in overall mucositis for the intervention group compared to control (p=0.049).[122] When examining dose-limiting mucositis, the intervention group had a much lower (43.6%) rate than control (78.6%, p=0.001) and control group members were 2.6 times more likely (95% CI: 1.38-5.0) to develop dose-limiting mucositis overall.[122] The double-blind, randomized, placebo design of this study strongly improves the statistical conclusions of this work and is a robust approach to this research question. However, the authors do disclose that time limitations necessitated early analysis of data with only 81 of the 100 participants.

Four of the included studies evaluated benzydamine prophylaxis in participants receiving chemoradiation. The first was a multicenter blinded randomized study that purposively recruited 60 participants with head and neck cancers that were receiving platinum-based chemotherapy with a cumulative radiation dose of at least 50Gy.[123] Participants were randomized to benzydamine or control arm and instructed to use 15mL of benzydamine or sodium bicarbonate placebo for 2 minutes four times daily. Mucositis was assessed for 8 weeks following OMAS evaluation of 9 pre-determined oral sites and the total aggregate score was recorded. All participants developed mucositis by week 2 but mean scores were lower in the intervention group from weeks 2 through 8 (week 2 $p<0.002$; weeks 3-7 $p<0.001$; week 8 $p<0.04$).[123] This study was well-designed, the

multi-site approach with clear and consistent inclusion criteria increased sample size and the randomization of participants minimizes the potential effect of several important confounding variables. However, the authors did not incorporate evaluation of oral hygiene interventions into analysis, which may influence mucositis development and scores assessed by clinicians at multiple sites may differ and introduce potential for measurement error.

The remaining publications on chemoradiation recruited participants receiving radiation and performed subgroup analyses for those who were also receiving concurrent chemotherapy. In the first, grade $\geq$3 mucositis (via CTCAE) was lower in the intervention group than control group (43.3% vs 53.6%), but this difference was not significant (p=0.30).[119] The next study found that benzydamine use was associated with a 57.7% reduction in mean mucositis scores when compared to placebo.[120] The last study found that the control group members were 2.4 times as likely to have dose-limiting degrees of mucositis (95% CI: 1.14-5.28) compared to intervention.[122] Because each of these studies had relatively small sample sizes and were performed as subgroup analysis within larger studies, the ability to identify meaningful effect sizes is reduced.

Meta-Analysis

Meta-analysis was conducted to determine cumulative effect sizes for 1) the prevention of any mucositis and 2) prevention of dose-limiting degrees of mucositis. Three publications[120, 121, 123] determined mean or total mucositis scores and unfortunately, these data were not amenable to inclusion in the meta-analysis because dichotomous data for mucositis development were not available. One study had two study groups of steroid agents, both were included in analysis as separate entries.[117] One study with Benzydamine recruited participants receiving radiation or

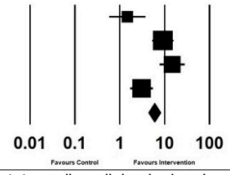
chemoradiation, but the radiation arm was not included in this study because total radiation dose differed between intervention and control which threated validity of outcomes by means of confounding.[119] The chemoradiation arm, however, was included in the meta-analysis since these individuals had equivalent exposure to both chemotherapy and radiation.[119] Funnel plots did not show publication bias was present in any study.

Prevention of Any Mucositis

All studies included in the analysis to evaluate prevention of any mucositis happened to be powered to detect grade 2+ mucositis via CTCAE criteria, so this was used as the outcome variable to maintain statistical validity. All studies also happened to utilize corticosteroids in the intervention groups and were conducted with patient samples receiving chemotherapy with kinase inhibitors. The meta-analysis suggests that the odds of developing symptomatic (CTCAE grade 2 or higher) mucositis are nearly 6 times higher for individuals who do not use steroid mouthwashes with chemotherapy compared to those who do (OR 6.00, 95% CI 4.39-8.20, p<0.0001) (table 4).

Table 4: Prevention of CTCAE 2+ mucositis

Study	Control		Mouthwash		Statistics for each Study		
	Success (n)	Failure (n)	Success (n)	Failure (n)	OR	95% CI	p
Combination^[116]	347	135	23	6	1.491	0.594 - 3.743	0.395
Combination#[117]	159	323	82	18	9.254	5.370 - 15.950	0.000
Prednisolone [117]	159	323	88	12	14.897	7.961 - 28.036	0.000
Dexamethasone[118]	188	154	68	18	3.095	1.765 - 5.426	0.000
Total	853	935	261	54	5.996	4.386 - 8.197	0.000



^Hydrocortisone, Itraconazole, tetracycline, chlorpheniramine, #Hydrocortisone, tetracycline, diphenhydramine
OR: odds ratio, CI: confidence interval, success indicates no mucositis development, failure indicates mucositis development noted

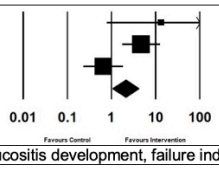
Prevention of Dose-Limiting Mucositis

Studies evaluating the prevention of dose-limiting mucositis include those that evaluated Dexamethasone in persons taking kinase inhibitors and Benzydamine during

radiation therapy. Mucositis was evaluated by CTCAE or RTOG evaluation scales for these studies. The meta-analysis showed that the odds of developing dose-limiting mucositis is over two times higher in individuals who do not use anti-inflammatory mouthwash while receiving chemoradiation (OR 2.12, 95% CI 1.07-4.28, p=0.032) (table 5).

Table 5: Prevention of dose-limiting mucositis

Study	Control		Mouthwash			Statistics for each Study		
	Success (n)	Failure (n)	Success (n)	Failure (n)		OR	95% CI	p
Dexamethasone[118]	448	34	86	0		13.308	0.808 - 219.123	0.070
Benzydamine[122]	9	33	22	17		4.745	1.796 - 12.536	0.002
Benzydamine [119]	16	12	14	16		0.656	0.233 - 1.851	0.426
Total	473	79	122	33		2.117	1.065 - 4.208	0.032



OR: odds ratio, CI: confidence interval, success indicates non-dose limiting mucositis development, failure indicates dose-limiting mucositis development

Discussion

The identified body of literature and this meta-analysis suggests that mouthwashes containing anti-inflammatory agents significantly reduce the incidence of mucositis development as well as reducing dose-limiting degrees of mucositis. While the use of some anti-inflammatory mouthwashes have been recommended for mucositis prophylaxis in low-dose (<50Gy) radiation therapy,[108, 112] this review and meta-analysis provides evidence to suggest that efficacy may be seen in higher doses of radiation therapy and chemoradiation and provides more concrete effect sizes in describing their benefits.

Anti-Inflammatory Mouthwash Mechanism of Action

Topical anti-inflammatory agents have been employed for the treatment of inflammatory-related oral conditions for quite some time and have proven efficacy in this regard. The oral mucosa is an area amenable to topical therapy by use of direct

application (e.g. ointments) or through use of swish-and-expectorate mouthwashes. Steroid-containing mouthwashes employ their anti-inflammatory action by suppressing inflammation through inhibition of white blood cell function, stabilization of lysozyme membranes, inhibition of plasminogen activators, and reduction in the synthesis of inflammatory mediators.[124] Topical steroids and mouthwashes, therefore, have been used for the treatment of many mucosal-related disorders and conditions that have an underlying inflammatory cause such as aphthous stomatitis, oral lichen planus, submucous fibrosis, erythema multiforme, pemphigoid, lupus, and localized graft versus host disease that involves the mucosa.[124-126]

Similarly, benzydamine is a locally-acting anti-inflammatory medication with limited systemic physiological mechanisms that produces its anti-inflammatory effect through reductions in proinflammatory cytokine and prostaglandin production.[127] It has been used for the treatment of a number of inflammatory-related oral conditions including stomatitis, pharyngitis, gingivitis, and tonsillitis.[128-130] In animal models, use of benzydamine has been associated with reductions in inflammatory mediators associated with mucositis development following radiation exposure[130] and it has been employed for the treatment of therapy-induced mucositis. In both cases, the presumed effect of preventing mucositis lie within the anti-inflammatory properties of these medications. Since there is a demonstrated inflammatory component to the development of mucositis, anti-inflammatory mouthwashes may be used to blunt the inflammatory pathway between therapy-induced cell death and tissue erosion and ulceration.

Clinical Implications

Because mucositis is a common adverse effect associated with chemotherapy[92,94] and introduces risk for multiple sequelae,[95 98,99] prevention is a desirable clinical goal. Anti-inflammatory mouthwashes may be utilized to reduce the

incidence of one of the most distressing toxicities from cancer therapy.[98, 102] Reduction may lead to reduced burden of cancer therapy, lower side effect profiles of treatment, and interruption or reduction of therapy due to toxicities.

Mucositis is associated with intense pain that sometimes requires hospital admission for management, and interrupts communication and oral intake.[95, 98, 99] Several studies in this review evaluated pain and nutrition as secondary outcomes and found that prevention of mucositis was associated with reduced pain.[116,120,121] The use of miracle mouthwash and prednisolone both reduced pain scores from 5 out of 10, to 2 out of 10.[117] Benzydamine use was associated with a longer time interval before participants required non-opioid (p=0.031), mild/moderate opioid (p=0.003), and strong opioid (p=0.018) pain medications.[120] Benzydamine was also associated with 25.8% reduction in reported mouth pain and 22.5% reduction in throat pain.[120] Another study found no difference in pain medication use or pain scores with anti-inflammatory mouthwashes, but scores were wide-ranging (2-9 on a 10-point scale)[123] which suggests that ceiling and floor effects were present in the study. It should also be noted that pain outcomes were not the primary aim of these studies and therefore they were not necessarily powered to detect significant effect sizes for this domain. Irrespective, mucositis is consistently reported as a painful condition, so reduction in incidence or severity is a primary step in preventing pain.

Reduction in oral intake is also a concern with mucositis because it may lead to caloric deficits that delay wound healing, slow count recovery, and lead to delays in subsequent chemotherapy cycles.[98, 131, 132] Proxies of nutritional status were evaluated in some studies included in this review. Benzydamine use was not associated with differing rates of feeding tube placement (24% in study group, 22% in control) in one study[123] and was related to lower rates of nasogastric or intravenous nutrition support in another but this was not significant (p=0.06).[119] Tending to the nutritional status of persons receiving

cancer-directed therapy is important since nutritional status, weight loss during therapy, and being underweight while receiving treatment has been associated with worse clinical outcomes, delays in therapy delivery, and lower survival.[133-137] The literature in this review suggests that anti-inflammatory mouthwashes may prevent mucositis to a degree that also prevents subsequent malnutrition and weight loss, contributing to improved therapy tolerability and disease survivorship but these data are not consistent and require further investigation.

Adherence and Implementation

Evaluation of the efficacy of an intervention extends beyond clinical outcomes and must also consider implementation measures; evaluating tolerability and feasibility helps to determine if the recommendation for a new intervention is reasonable for patients. Two studies in this review evaluated implementation domains by evaluating medication adherence and found that 94.6-98.8% of mouthwash doses were used during the study periods.[116, 118] In another study, no participants withdrew or experienced adverse effects that precluded use of mouthwashes.[117] These findings suggest that the use of mouthwashes are easily implementable for patients and non-burdensome interventions for mucositis prevention. It is important to also consider the role of polypharmacy in persons with cancer. Individuals undergoing cancer therapy utilize many prescription and non-prescription medications and polypharmacy has been associated with lower overall medication adherence and higher medication misadministration.[138-140] Findings from this review, however, suggest that prophylactic anti-inflammatory mouthwashes did not pose challenges to adherence and were overall well tolerated. Furthermore, there were no findings within the included studies that the use of these medications had interactions with the cancer-directed therapies or interactions with other components of the mouthwashes. However, in clinical practice,

consideration of potential medication interactions should be maintained if electing to use additional supportive care medications, even though systemic absorption of oral mouthwash agents is low.

Potential Adverse Effects

Systemic absorption of topical oral corticosteroids is negligible, but is possible with high-dose, high-potency medications or very frequent use.[126, 141] Therefore, systemic and localized adverse effects of topical anti-inflammatory agents warrants investigation when evaluating their use in new populations. Articles included in this review evaluated adverse effects related to anti-inflammatory mouthwash including hyperglycemia, oral candidiasis, and reported on localized oral symptoms which are all discussed below.

A known side effect of systemic corticosteroid use is hyperglycemia and accordingly, two studies in this review evaluated hyperglycemia associated with steroid mouthwashes. A combination of diphenhydramine, tetracycline, and hydrocortisone was associated with a 4% incidence rate of hyperglycemia; the other treatment arm in this study used prednisone, and was associated with a 6% incidence rate of hyperglycemia.[117] Both rates were lower than the historic control which used no steroid mouthwash and13% of participants developed hyperglycemia ($p<0.05$).[117] Hyperglycemia was noted in a group using Dexamethasone mouthwash (14%) but was also comparable to the rate noted in historic control (15%).[118]

Risk for opportunistic infections remains another ongoing concern with cancer therapy and chronic corticosteroid use is a known risk for fungal infections. Oral candidiasis was identified in 8% of participants using prednisone and 2% of those using a combination of hydrocortisone, diphenhydramine, tetracycline, and nystatin mouthwashes.[117] The lower incidence in the second group was attributed to the

antifungal agents included in that mouthwash cocktail. In a benzydamine study utilizing sodium bicarbonate for placebo, no participants in the intervention group required antifungal medications compared to 19% in the placebo group[123] which is similar to overall incidence of thrush with chemotherapy (20%).[142] The literature in this review suggests that oral anti-inflammatory mouthwashes do not significantly increase the risk of thrush but mouthwashes containing antifungal agents significantly reduce thrush, but more thorough investigations will be required to more confidently determine this risk.

Participants in one study using dexamethasone mouthwash reported hyperpigmentation of the tongue (41%) which resolved with discontinuation of the medication.[116] Benzydamine has reported adverse effects to include potential tingling and numbness with use. In one study included in this review, 6% of participants in the intervention group reported tingling, numbness, and taste alterations with benzydamine use, but this was also present in 5% of the control group[120] suggesting that this may have also been due to radiation and chemotherapy. Similarly, 12% of participants in another benzydamine study stopped the study due to oropharyngeal discomfort and nausea.[122] These findings are in contrast to other studies in which the authors state that participants had no reported adverse effects with the same strength of benzydamine mouthwashes.[121]

Limitations

As with any literature review, the work is limited by the quality and number of included publications. Most publications in this study were level of evidence I (experimental) or II (quasi-experimental) design which does offer strength to the conclusions drawn herein. Unfortunately, there were not many studies available to make for a robust meta-analysis which is why a thorough literature review was included in this review to discuss studies which did not have data amenable to meta-analysis.

Additionally, the meta-analysis that investigates prevention of dose-limiting mucositis includes studies investigating steroids with kinase inhibitors as well as NSAID mouthwashes with radiation therapy. The pathology of mucositis with these therapies are different as is the mechanism of action of the investigational agents. However, despite these differences, they share many similarities which makes comparison of these studies clinically relevant. As more data become available from additional studies, these analyses should be conducted separately to provide better clarity. Until that time, meta-analysis with the limited studies available is warranted to provide initial evaluation of currently-available data and this is the first meta-analysis to quantify the combined estimate of success of the intervention over multiple studies.

The differing approaches to measurement of mucositis in the included studies makes comparing severity of the condition challenging. Additionally, mucositis was not measured at consistent times, by the same clinicians, or at regular intervals in all studies which further introduces some risk of measurement error. Three publications utilized a historic control of the comparable sample and chemotherapy regimen.[116-118] while this allowed for a larger intervention group, it does introduce some risk of confounding and mildly threatens the validity of these studies. There was not a standardized approach to the allowance of additional supportive care measures participants could use in studies; some disallowed any supportive care interventions while others recommended regular oral hygiene and allowed for other non-pharmacologic supportive care measures which also introduces potential for confounding. Finally, this review included participants receiving radiation therapy, chemotherapy, and chemoradiation which all confer differing levels of risk for mucositis and makes comparison between studies challenging. Studies were only included if the control arms were comparable to intervention, including modality of cancer therapy, which offsets these differences but did limit the sample size for an already small review.

Conclusions

Delivery of cancer therapy requires a balance of providing aggressive, anti-neoplastic treatments while also preventing and treating the adverse effects that accompany these therapies. Prevention or reduction of mucositis is a means to improve quality of life during therapy and allows for the continued, uninterrupted delivery of full-dose therapy therefore, improving chance of cancer survival. The use of corticosteroids or benzydamine mouthwash during therapy has been identified as a potential effective prophylaxis of mucositis and has been associated with a lower rate of dose-limiting degrees of mucositis. Use is readily feasible for participants and seems to introduce no significant additional adverse effects from mouthwash agents. These findings are based on a small number of studies that were designed with enough rigor to make these conclusions. Future research should include large-scale randomized designed studies that evaluate anti-inflammatory mouthwashes across a number of cancer diagnoses and types of therapy. Secondary outcomes that are important to investigate include impact on pain, discomfort, and distress and should also consider relevant clinical and therapy-related outcomes such as secondary infections, treatment reductions/delays, and overall survivorship. It is also important to evaluate implementation measures of adding frequent mouthwashes to treatment regimens to ensure the intervention is feasible and not burdensome within this population. Preventing or reducing therapy-related toxicities is a cornerstone in oncology care; anti-inflammatory mouthwashes may be a means to reduce one of the most frequent and burdensome toxicities of therapy.

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Chapter 2 References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Accessed January 20, 2022. https://seer.cancer.gov/
2. Institutes NC. Adolescents and Young Adults with Cancer. Accessed January 20, 2021. https://www.cancer.gov/types/aya
3. Kazak AE, Noll RB. The Integration of Psychology in Pediatric Oncology Research and Practice Collaboration to Improve Care and Outcomes for Children and Families. *American Psychologist*. Feb-Mar 2015;70(2):146-158. doi:10.1037/a0035695
4. Coccia PF, Pappo AS, Beaupin L, et al. Adolescent and Young Adult Oncology, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 01 Jan. 2018 2018;16(1):66-97. doi:10.6004/jnccn.2018.0001
5. Bleyer A. Young adult oncology: The patients and their survival challenges. *Cancer Journal for Clinicians*. Jul-Aug 2007;57(4):242-255. doi:10.3322/canjclin.57.4.242
6. Warner EL, Kent EE, Trevino KM, Parsons HM, Zebrack BJ, Kirchhoff AC. Social well-being among adolescents and young adults with cancer: A systematic review. *Cancer*. Apr 2016;122(7):1029-1037. doi:10.1002/cncr.29866
7. Cheung CK, Zebrack B. What do adolescents and young adults want from cancer resources? Insights from a Delphi panel of AYA patients. *Supportive Care in Cancer*. Jan 2017;25(1):119-126. doi:10.1007/s00520-016-3396-7
8. Barnett M, McDonnell G, DeRosa A, et al. Psychosocial outcomes and interventions among cancer survivors diagnosed during adolescence and young adulthood (AYA): a systematic review. *Journal of Cancer Survivorship*. Oct 2016;10(5):814-831. doi:10.1007/s11764-016-0527-6

9. Richter D, Koehler M, Friedrich M, Hilgendorf I, Mehnert A, Weissflog G. Psychosocial interventions for adolescents and young adult cancer patients: A systematic review and meta-analysis. *Critical Reviews in Oncology Hematology*. Sep 2015;95(3):370-386. doi:10.1016/j.critrevonc.2015.04.003
10. Seitz DCM, Besier T, Goldbeck L. Psychosocial interventions for adolescent cancer patients: a systematic review of the literature. *Psycho-Oncology*. Jul 2009;18(7):683-690. doi:10.1002/pon.1473
11. Walker E, Martins A, Aldiss S, Gibson F, Taylor RM. Psychosocial Interventions for Adolescents and Young Adults Diagnosed with Cancer During Adolescence: A Critical Review. *Journal of Adolescent and Young Adult Oncology*. Dec 2016;5(4):310-321. doi:10.1089/jayao.2016.0025
12. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in Adolescents and Young Adults A Narrative Review of the Current Status and a View of the Future. *Jama Pediatrics*. May 2016;170(5):495-501. doi:10.1001/jamapediatrics.2015.4689
13. Zebrack B, Kent EE, Keegan THM, Kato I, Smith AW, Grp AHSC. "Cancer Sucks," and Other Ponderings by Adolescent and Young Adult Cancer Survivors. *Journal of Psychosocial Oncology*. Jan 2014;32(1):1-+. doi:10.1080/07347332.2013.855959
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. Jul 21 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
15. Dang D, Dearholt SL, Bissett K, Ascenzi J, Whalen M. *Johns Hopkins Evidence-based Practice for Nurses and Healthcare Professionals, 4th Edition*. Sigma Theta Tau International Honor Society of Nursing; 2022.
16. Agnese A, Lamparelli T, Bacigalupo A, Luzzatto P. Supportive care with art therapy, for patients in isolation during stem cell transplant. *Palliative & Supportive Care*. Jun 2012;10(2):91-98. doi:10.1017/s147895151100071x

17. American Cancer Society. When adolescents and young adults get cancer. Accessed January 20, 2021. https://www.cancer.org/latest-news/when-adolescents-and-young-adults-get-cancer.html
18. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. *Lancet Child & Adolescent Health*. Mar 2018;2(3):223-228. doi:10.1016/s2352-4642(18)30022-1
19. Burns DS, Robb SL, Haase JE. Exploring the Feasibility of a Therapeutic Music Video Intervention in Adolescents and Young Adults During Stem-Cell Transplantation. *Cancer Nursing*. Sep-Oct 2009;32(5):E8-E16. doi:10.1097/NCC.0b013e3181a4802c
20. Heiney SP, Ruffin J, Ettinger RS, Ettinger S. The effects of group therapy on adolescents with cancer. *Journal of Pediatric Oncology Nursing*. 1988;5(3):20-4. doi:10.1177/104345428800500305
21. Stegenga K. Impact of a Teen Weekend on the Social Support Needs of Adolescents With Cancer. *Journal of Pediatric Oncology Nursing*. Sep-Oct 2014;31(5):293-297. doi:10.1177/1043454214531858
22. Clark HB, Ichinose CK, Meseck-Bushey S, et al. Peer support group for adolescents with chronic illness. *Children's Health Care*. 1992;21(4):233-8. doi:10.1207/s15326888chc2104_6
23. Rosenberg AR, Bradford MC, Barton KS, et al. Hope and benefit finding: Results from the PRISM randomized controlled trial. *Pediatric Blood & Cancer*. Jan 2019;66(1)e27485. doi:10.1002/pbc.27485
24. Rosenberg AR, Bradford MC, McCauley E, et al. Promoting Resilience in Adolescents and Young Adults With Cancer: Results From the PRISM Randomized Controlled Trial. *Cancer*. Oct 2018;124(19):3909-3917. doi:10.1002/cncr.31666

25. Torabi F, Rassouli M, Nourian M, Borumandnia N, Farahani AS, Nikseresht F. The Effect of Spiritual Care on Adolescents Coping With Cancer. *Holistic Nursing Practice*. May-Jun 2018;32(3):149-159. doi:10.1097/hnp.0000000000000263
26. Hinds PS, Quargnenti A, Bush AJ, et al. An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *European Journal of Oncology Nursing*. Mar 2000;4(1):6. doi:10.1054/ejon.1999.0051
27. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: A randomized trial. *Pediatrics*. Aug 2008;122(2):E305-E317. doi:10.1542/peds.2007-3134
28. Fasciano KM, Souza PM, Braun I, Trevino K. An Innovative Website in the United States for Meeting the Emotional and Supportive Care Needs of Young Adults with Cancer. *Journal of Adolescent and Young Adult Oncology*. Mar 2015;4(1):44-49. doi:10.1089/jayao.2014.0035
29. Yurkiewicz IR, Simon P, Liedtke M, Dahl G, Dunn T. Effect of Fitbit and iPad Wearable Technology in Health-Related Quality of Life in Adolescent and Young Adult Cancer Patients. *Journal of Adolescent and Young Adult Oncology*. Oct 2018;7(5):579-583. doi:10.1089/jayao.2018.0022
30. Keats MR, Courneya KS, Danielsen S, Whitsett SF. Leisure-time physical activity and psychosocial well-being in adolescents after cancer diagnosis. *Journal of Pediatric Oncology Nursing*. Oct 1999;16(4):180-8. doi:10.1177/104345429901600402
31. Woodside H, Culos-Reed SN, Gregoire M-C, Rutledge R, Keats MR. Yoga for Young Adults With Noncurative Cancer: A Brief Report. *Global Advances in Health and Medicine*. 2018;7:2164956118763523. doi:10.1177/2164956118763523

32. Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang JC. A Longitudinal, Randomized, Controlled Trial of Advance Care Planning for Teens With Cancer: Anxiety, Depression, Quality of Life, Advance Directives, Spirituality. *Journal of Adolescent Health*. Jun 2014;54(6):710-717. doi:10.1016/j.jadohealth.2013.10.206
33. Skaczkowski G, White V, Thompson K, et al. Factors influencing the provision of fertility counseling and impact on quality of life in adolescents and young adults with cancer. *Journal of Psychosocial Oncology*. 2018;36(4):484-502. doi:10.1080/07347332.2018.1443986
34. Trevino KM, Abbott CH, Fisch MJ, Friedlander RJ, Duberstein PR, Prigerson HG. Patient-Oncologist Alliance as Protection Against Suicidal Ideation in Young Adults With Advanced Cancer. *Cancer*. Aug 2014;120(15):2272-2281. doi:10.1002/cncr.28740
35. Weaver MS, Rosenberg AR, Tager J, Wichman CS, Wiener L. A Summary of Pediatric Palliative Care Team Structure and Services as Reported by Centers Caring for Children with Cancer. *Journal of Palliative Medicine*. Apr 2018;21(4):452-462. doi:10.1089/jpm.2017.0405
36. Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and Addressing theNeeds of Adolescents and Young Adults With Cancer: Summary of an Institute of Medicine Workshop. *Oncologist*. Feb 2015;20(2):186-195. doi:10.1634/theoncologist.2014-0265
37. National Cancer Institute. NCI and the Precision Medicine Initiative Accessed January 21, 2022. https://www.cancer.gov/research/areas/treatment/pmi-oncology
38. Fraguas D, Diaz-Caneja CM, State MW, O'Donovan MC, Gur RE, Arango C. Mental disorders of known aetiology and precision medicine in psychiatry: a promising but neglected alliance. *Psychological Medicine*. Jan 2017;47(2):193-197. doi:10.1017/s0033291716001355

39. Thornton CP. Best Practice in Teaching Male Adolescents and Young Men to Perform Testicular Self-Examinations: A Review. *Journal of Pediatric Health Care*. Nov-Dec 2016;30(6):518-527. doi:10.1016/j.pedhc.2015.11.009
40. Rosenberg AR, Bradford M, Bona KO, et al. Screening for self-efficacy and distress: A report from the "Resilience in Adolescents and Young Adults with Cancer" study. *Journal of Clinical Oncology*. May 2015;33(15)
41. Racine NM, Lafay-Cousin L, Schulte F. Patient-Reported Outcomes in Psychological Treatment for an Adolescent Oncology Patient: A Case Report. *Journal of Adolescent and Young Adult Oncology*. Jun 2018;7(3):395-399. doi:10.1089/jayao.2017.0090
42. Barakat LP, Galtieri LR, Szalda D, Schwartz LA. Assessing the psychosocial needs and program preferences of adolescents and young adults with cancer. *Supportive Care in Cancer*. Feb 2016;24(2):823-832. doi:10.1007/s00520-015-2849-8
43. Bukowinski AJ, Burns KC, Parsons K, Perentesis JP, O'Brien MM. Toxicity of cancer therhapy in adolescents and young adults (AYAs). *Seminars in Oncology Nursing*. Aug 2015;31(3):216-226. doi:10.1016/j.soncn.2015.05.003
44. Canner JA, Alonzo TA, Franklin J, et al. Treatment outcomes in older adolescent and young adult (AYA) patients with newly diagnosed AML. *Journal of Clinical Oncology*. May 2011;29(15)doi:10.1200/jco.2011.29.15_suppl.9506
45. Franklin ARK, Alonzo TA, Gerbing RB, et al. Outcome of Adolescents and Young Adults (AYAs) with Non-M3 Acute Myeloid Leukemia (AML) Treated on Children's Oncology Group (COG) Trials Compared to Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) Trials. *Blood*. Nov 2010;116(21):84-84. doi:10.1182/blood.V116.21.183.183

46. Freyer DR, Felgenhauer J, Perentesis J, Adult COGAY. Children's Oncology Group's 2013 blueprint for research: Adolescent and young adult oncology. *Pediatric Blood & Cancer*. Jun 2013;60(6):1055-1058. doi:10.1002/pbc.24431
47. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology*. Jul 2016;34(20):2380-U129. doi:10.1200/jco.2015.62.4544
48. Relling MV, Fairclough D, Ayers D, et al. PATIENT CHARACTERISTICS ASSOCIATED WITH HIGH-RISK METHOTREXATE CONCENTRATIONS AND TOXICITY. *Journal of Clinical Oncology*. Aug 1994;12(8):1667-1672. doi:10.1200/jco.1994.12.8.1667
49. Patterson P, McDonald FEJ, Zebrack B, Medlow S. Emerging issues among adolescent and young adult cancer survivors. *Seminars in Oncology Nursing*. Feb 2015;31(1):53-59. doi:10.1016/j.soncn.2014.11.006
50. Dalal S, Bruera E. End-of-Life Care Matters: Palliative Cancer Care Results in Better Care and Lower Costs. *Oncologist*. 2017;22(4):361-368. doi:10.1634/theoncologist.2016-0277
51. White LL, Cohen MZ, Berger AM, Kupzyk KA, Swore-Fletcher BA, Bierman PJ. Perceived Self-Efficacy A concept analysis for symptom management in patients with cancer. *Clinical Journal of Oncology Nursing*. Dec 2017;21(6):E272-E279. doi:10.1188/17.Cjon.E272-e279
52. Bandura A. Self-efficacy mechanism in human agency. *American Psychologist*. 1982;37(2):122-147. doi:10.1037/0003-066x.37.2.122

53. Strecher VJ, McEvoy DeVellis B, Becker MH, Rosenstock IM. The Role of Self-Efficacy in Achieving Health Behavior Change. *Health Education Quarterly*. 1986/03/01 1986;13(1):73-92. doi:10.1177/109019818601300108
54. Belil FE, Alhani F, Ebadi A, Kazemnejad A. Self-Efficacy of People with Chronic Conditions: A Qualitative Directed Content Analysis. *Journal of Clinical Medicine*. Nov 2018;7(11)411. doi:10.3390/jcm7110411
55. Sodergren SC, Husson O, Robinson J, et al. Systematic review of the health-related quality of life issues facing adolescents and young adults with cancer. *Quality of Life Research*. Jul 2017;26(7):1659-1672. doi:10.1007/s11136-017-1520-x
56. Howell D, Harth T, Brown J, Bennett C, Boyko S. Self-management education interventions for patients with cancer: a systematic review. *Supportive Care in Cancer*. Apr 2017;25(4):1323-1355. doi:10.1007/s00520-016-3500-z
57. Leahy AB, Feudtner C, Basch E. Symptom Monitoring in Pediatric Oncology Using Patient-Reported Outcomes: Why, How, and Where Next. *Patient-Patient Centered Outcomes Research*. Apr 2018;11(2):147-153. doi:10.1007/s40271-017-0279-z
58. Levine DR, Liederbach E, Johnson LM, et al. Are we meeting the informational needs of cancer patients and families? Perception of physician communication in pediatric oncology. *Cancer*. May 2019;125(9):1518-1526. doi:10.1002/cncr.31937
59. McLaughlin CA, Gordon K, Hoag J, et al. Factors Affecting Adolescents' Willingness to Communicate Symptoms During Cancer Treatment: A Systematic Review from the Children's Oncology Group. *Journal of Adolescent and Young Adult Oncology*. Apr 2019;8(2):105-113. doi:10.1089/jayao.2018.0111
60. Zebrack BJ, Corbett V, Embry L, et al. Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*. Nov 2014;23(11):1267-1275. doi:10.1002/pon.3533

61. Chirico A, Lucidi F, Merluzzi T, et al. A meta-analytic review of the relationship of cancer coping self-efficacy with distress and quality of life. *Oncotarget*. May 2017;8(22):36800-36811. doi:10.18632/oncotarget.15758
62. White LL, Cohen MZ, Berger AM, Kupzyk KA, Bierman PJ. Self-Efficacy for Management of Symptoms and Symptom Distress in Adults With Cancer: An Integrative Review. *Oncology Nursing Forum*. Jan 2019;46(1):113-128. doi:10.1188/19.Onf.113-128
63. Pugh G, Petrella A, Fisher A, Reynolds J, Epstone S. Trekstock Meet & Move: The Impact of One-Day Health and Well-Being Events for Young Adults with Cancer. *Journal of Adolescent and Young Adult Oncology*. Apr 2020;9(2):278-285. doi:10.1089/jayao.2019.0108
64. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011/04/01/ 2011;64(4):383-394. doi:https://doi.org/10.1016/j.jclinepi.2010.04.026
65. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Rating Quality of Evidence and Strength of Recommendations*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
66. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal*. Apr 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD
67. Klosky JL, Lehmann V, Flynn JS, et al. Patient factors associated with sperm cryopreservation among at-risk adolescents newly diagnosed with cancer. *Cancer*. Sep 2018;124(17):3567-3575. doi:10.1002/cncr.31596

68. Diorio C, Lin MK, Ginn E, Ladas EJ. Psychosocial determinants of physical activity and dietary behaviors in adolescents and young adults with cancer and survivors. *Pediatric Blood & Cancer*. Sep 2018;65(9)e27243. doi:10.1002/pbc.27243
69. Wu WW, Yu TH, Jou ST, Hung GY. Physical activity self-efficacy mediates the effect of symptom distress on exercise involvement among adolescents undergoing cancer treatment. *European Journal of Cancer Care*. Jul 2019;28(4)e13045. doi:10.1111/ecc.13045
70. Hullmann SE, Brumley LD, Schwartz LA. Medical and Psychosocial Associates of Nonadherence in Adolescents With Cancer. *Journal of Pediatric Oncology Nursing*. Mar-Apr 2015;32(2):103-113. doi:10.1177/1043454214553707
71. Erickson JM, Ameringer S, Linder L, et al. Using a Heuristic App to Improve Symptom Self-Management in Adolescents and Young Adults with Cancer. *Journal of Adolescent and Young Adult Oncology*. Apr 2019;8(2):131-141. doi:10.1089/jayao.2018.0103
72. Aubin S, Rosberger Z, Petr K, Gerald B, Hafez N. Cancer! I Don't Have Time for That. Using Skype Technology to Help Young Adults Adjust to the Repercussions of Cancer. *Psycho-Oncology*. Oct 2014;23:173-173.
73. Zebrack B, Kwak M, Sundstrom L. First Descents, an adventure program for young adults with cancer: who benefits? *Supportive Care in Cancer*. Dec 2017;25(12):3665-3673. doi:10.1007/s00520-017-3792-7
74. Jibb LA, Stevens BJ, Nathan PC, et al. Implementation and preliminary effectiveness of a real-time pain management smartphone app for adolescents with cancer: A multicenter pilot clinical study. *Pediatric Blood & Cancer*. Oct 2017;64(10)e26554. doi:10.1002/pbc.26554

75. Carson V, Hunter S, Kuzik N, et al. Systematic review of physical activity and cognitive development in early childhood. *Journal of Science and Medicine in Sport*. Jul 2016;19(7):573-578. doi:10.1016/j.jsams.2015.07.011
76. Gotte M, Kesting S, Winter C, Rosenbaum D, Boos J. Experience of Barriers and Motivations for Physical Activities and Exercise During Treatment of Pediatric Patients With Cancer. *Pediatric Blood & Cancer*. Sep 2014;61(9):1632-1637. doi:10.1002/pbc.25071
77. Poitras VJ, Gray CE, Borghese MM, et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. *Applied Physiology Nutrition and Metabolism*. Jun 2016;41(6):S197-S239. doi:10.1139/apnm-2015-0663
78. Ruble KA, Li W, Thornton CP, Hooke MC. Exercise and Physical Activity. In: Hinds PA, Linder LA, eds. *Pediatric Oncology Nursing: Defining Care Through Science*. 1 ed. Springer Publishing Company; 2020.
79. Hooke MC, Garwick AW, Neglia JP. Assessment of Physical Performance Using the 6-Minute Walk Test in Children Receiving Treatment for Cancer. *Cancer Nursing*. Sep-Oct 2013;36(5):E9-E16. doi:10.1097/NCC.0b013e31829f5510
80. Nielsen MKF, Christensen JF, Frandsen TL, et al. Testing physical function in children undergoing intense cancer treatmenta RESPECT feasibility study. *Pediatric Blood & Cancer*. Aug 2018;65(8)e27100. doi:10.1002/pbc.27100
81. Ward-Smith P, Hamlin J, Bartholomew J, Stegenga K. Quality of life among adolescents with cancer. *Journal of Pediatric Oncology Nursing*. May-Jun 2007;24(3):166-171. doi:10.1177/1043454207299656
82. Baumann FT, Bloch W, Beulertz J. Clinical exercise interventions in pediatric oncology: a systematic review. *Pediatric Research*. Oct 2013;74(4):366-374. doi:10.1038/pr.2013.123

83. Thornton CP, Ruble K, Kozachik S. Psychosocial Interventions for Adolescents and Young Adults With Cancer: An Integrative Review. *Journal of Pediatric Oncology Nursing*. Nov 2020;37(6):408-422. 1043454220919713. doi:10.1177/1043454220919713

84. Coccia PF, Pappo AS, Beaupin L, et al. Adolescent and Young Adult Oncology, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. Jan 2018;16(1):66-97. doi:10.6004/jnccn.2018.0001

85. Stinson JN, Jibb LA, Greenberg M, et al. A Qualitative Study of the Impact of Cancer on Romantic Relationships, Sexual Relationships, and Fertility: Perspectives of Canadian Adolescents and Parents During and After Treatment. *Journal of Adolescent and Young Adult Oncology*. Jun 2015;4(2):84-90. doi:10.1089/jayao.2014.0036

86. Geue K, Schmidt R, Sender A, Sauter S, Friedrich M. Sexuality and romantic relationships in young adult cancer survivors: satisfaction and supportive care needs. *Psycho-Oncology*. Nov 2015;24(11):1368-1376. doi:10.1002/pon.3805

87. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer*. Mar 2012;118(6):1710-1717. doi:10.1002/cncr.26459

88. Robinson L, Miedema B, Easley J. Young Adult Cancer Survivors and the Challenges of Intimacy. *Journal of Psychosocial Oncology*. 2014;32(4):447-462. doi:10.1080/07347332.2014.917138

89. Klosky JL, Randolph ME, Navid F, et al. Sperm cryopreservation practices among cancer patients at risk for infertility. *Pediatric Hematology and Oncology*. 2009;26(4):252-260. Pii 911114143. doi:10.1080/08880010902901294

90. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to Oral Mercaptopurine and Risk of Relapse in Hispanic and Non-Hispanic White Children With Acute Lymphoblastic Leukemia: A Report From the Children's Oncology Group. *Journal of Clinical Oncology*. Jun 2012;30(17):2094-2101. doi:10.1200/jco.2011.38.9924
91. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *American Journal of Health Promotion*. Sep-Oct 1997;12(1):38-48. doi:10.4278/0890-1171-12.1.38
92. Çakmak S, Nural N. Incidence of and risk factors for development of oral mucositis in outpatients undergoing cancer chemotherapy. *International Journal of Nursing Practice*. 2019;25(1):e12710. doi:10.1111/ijn.12710
93. Gabriel AdF, Silveira FM, Curra M, et al. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. *Oral Diseases*. 2021;n/a(n/a)doi:10.1111/odi.13863
94. Guimarães JR, Carvalho LG, Damascena LC, et al. The incidence of severe oral mucositis and its occurrence sites in pediatric oncologic patients. *Medicina oral, patología oral y cirugía bucal*. 2021;26(3):e299-e303. doi:10.4317/medoral.24185
95. McCullough RW. US oncology-wide incidence, duration, costs and deaths from chemoradiation mucositis and antimucositis therapy benefits. *Future Oncology*. 2017;13(30):2823-2852. doi:10.2217/fon-2017-0418
96. Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation Therapy. *Journal of the National Cancer Institutes Monographs*. 2019;2019(53)doi:10.1093/jncimonographs/lgz011
97. Pulito C, Cristaudo A, Porta CL, et al. Oral mucositis: the hidden side of cancer therapy. *Journal of Experimental & Clinical Cancer Research*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7

98. Otmani N, Hattad S. Clinical Outcome in Children with Chemotherapy-Induced Mucositis. *Seminars in Oncology Nursing*. 2021;37(3):151160. doi:10.1016/j.soncn.2021.151160

99. Shu Z, Zeng Z, Yu B, et al. Nutritional Status and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study. *Frontiers in Oncology*. 2020;0doi:10.3389/fonc.2020.594687

100. Kishimoto M, Akashi M, Tsuji K, et al. Intensity and duration of neutropenia relates to the development of oral mucositis but not odontogenic infection during chemotherapy for hematological malignancy. *PLOS ONE*. 2017;12(7):e0182021. doi:10.1371/journal.pone.0182021

101. Sobue T, Bertolini M, Thompson A, Peterson DE, Diaz PI, Dongari-Bagtzoglou A. Chemotherapy-induced oral mucositis and associated infections in a novel organotypic model. *Molecular Oral Microbiology*. 2018;33(3):212-223. doi:10.1111/omi.12214

102. Kanagalingam J, Wahid M, Lin J-C, et al. Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT) study. *Supportive Care in Cancer*. 2018;26(7):2191-2200. doi:10.1007/s00520-018-4050-3

103. Hamouda N, Sano T, Oikawa Y, et al. Apoptosis, Dysbiosis and Expression of Inflammatory Cytokines are Sequential Events in the Development of 5-Fluorouracil-Induced Intestinal Mucositis in Mice. *Basic & Clinical Pharmacology & Toxicology*. 2017;121(3):159-168. doi:10.1111/bcpt.12793

104. Basile D, Di Nardo P, Corvaja C, et al. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. *Cancers*. 06/20 2019;11(6):857. doi:10.3390/cancers11060857

105. Sonis ST. The pathobiology of mucositis. *Nature Reviews Cancer*. Apr 2004;4(4):277-284. doi:nrc1318 [pii]

106. Wong HM. Oral Complications and Management Strategies for Patients Undergoing Cancer Therapy. *The Scientific World Journal*. 01/08 2014;2014:581795. doi:10.1155/2014/581795

107. Al-Ansari S, Zecha JAEM, Barasch A, de Lange J, Rozema FR, Raber-Durlacher J. Oral Mucositis Induced By Anticancer Therapies. *Current Oral Health Reports*. 2015;2(4):202-211. doi:10.1007/s40496-015-0069-4

108. Ariyawardana A, Cheng KKF, Kandwal A, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supportive Care in Cancer*. 10/01 2019;27(10):3985-3995. doi:10.1007/s00520-019-04888-w

109. Mahendran VJ, Stringer AM, Semple SJ, Song Y, Garg S. Advances in the Use of Anti-inflammatory Agents to Manage Chemotherapy-induced Oral and Gastrointestinal Mucositis. *Current Pharmaceutical Design*. 2018;24(14):1518-1532. doi:10.2174/1381612824666180409093918

110. Shankar A, Roy S, Bhandari M, et al. Current Trends in Management of Oral Mucositis in Cancer Treatment. *Asian Pacific Journal of Cancer Prevention* 2017;18(8):2019-2026. doi:10.22034/APJCP.2017.18.8.2019

111. Thomsen M, Vitetta L. Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. *Integrative Cancer Therapies*. 2018;17(4):1027-1047. doi:10.1177/1534735418794885

112. Elad S, Cheng KKF, Lalla RV, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 10/01; 2022/01 2020;126(19):4423-4431. doi:https://doi.org/10.1002/cncr.33100
113. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *British Medical Journal.* 2021;372:n71. doi:10.1136/bmj.n71
114. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. Apr 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026
115. Biostat I. Comprehensive Meta-Analysis 2019. Accessed January 21, 2022. https://www.meta-analysis.com/
116. Hattori M, Hagiwara S, Kotani H, et al. A single-arm, phase 2 study of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis in multiple tumor types. *International Journal of Clinical Oncology*. 2019;24(10):1320-1327. doi:10.1007/s10147-019-01476-0
117. Jones VE, McIntyre KJ, Paul D, et al. Evaluation of Miracle Mouthwash plus Hydrocortisone Versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis: A Randomized Phase II Study. *Oncologist.* 2019;24(9):1153-1158
118. Rugo HSDP, Seneviratne LMD, Beck JTMD, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *The Lancet Oncology*. 2017;18(5):654-662. doi:10.1016/S1470-2045(17)30109-2
119. Rastogi M, Khurana R, Revannasiddaiah S, et al. Role of benzydamine hydrochloride in the prevention of oral mucositis in head and neck cancer patients

treated with radiotherapy (>50 Gy) with or without chemotherapy. *Supportive Care in Cancer*. 2017;25(5):1439-1443. doi:10.1007/s00520-016-3548-9

120. Epstein JB, D., Silverman S, et al. and in part at the 11th Multinational Association of Supportive Care in Cancer International Symposium. 1997.
121. Sheibani KM, Mafi AR, Moghaddam S, Taslimi F, Amiran A, Ameri A. Efficacy of benzydamine oral rinse in prevention and management of radiation-induced oral mucositis: A double-blind placebo-controlled randomized clinical trial. *Asia-Pacific Journal of Clinical Oncology*. 2015;11(1):22-27. doi:10.1111/ajco.12288
122. Kazemian A, Kamian S, Aghili M, Hashemi FA, Haddad P. Benzydamine for prophylaxis of radiation-induced oral mucositis in head and neck cancers: a double-blind placebo-controlled randomized clinical trial. *European Journal of Cancer Care*. 2009;18(2):174-178. doi:10.1111/j.1365-2354.2008.00943.x
123. Chitapanarux I, Tungkasamit T, Petsuksiri J, et al. Randomized control trial of benzydamine HCl versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis. *Supportive Care in Cancer*. 2017;26(3) 879-886.
124. Kiran MS, Vidya S, Aswal GS, Kumar V, Rai V. Systemic and Topical Steroids in the Management of Oral Mucosal Lesions. *Journal of Pharmacy & Bioallied Sciences*. 11 2017;9:S1-S3. doi:10.4103/jpbs.JPBS_91_17
125. Savage NW, McCullough MJ. Topical corticosteroids in dental practice. *Australian Dental Journal*. Dec 2005;50(4 Suppl 2):40. doi:10.1111/j.1834-7819.2005.tb00385.x [doi]
126. Zadik Y, Elad S, Shapira A, Shapira MY. Treatment of oral mucosal manifestations of chronic graft-versus-host disease: dexamethasone vs. budesonide. *Expert Opinions in Pharmacotherapy*. 02/11 2017;18(3):235-242. doi:10.1080/14656566.2017.1282464

127. Nicolatou-Galitis O, Bossi P, Orlandi E, René-Jean B. The role of benzydamine in prevention and treatment of chemoradiotherapy-induced mucositis. *Supportive Care in Cancer*. 10 2021;29(10):5701-5709. doi:10.1007/s00520-021-06048-5

128. AlQahtani RM, Mohyeldin A, Yamen Hassan A, Ahmed AbdElhamed E, Raed Ibrahim A. Pharmacological Interventions for Post-operative Sore Throat (POST): A Network Meta-analysis. *Journal of Anesthesia, Intensive Care, Emergency, and Pain Medicine.* 2021; 17(1):169-177

129. Golac-Guzina N, Novaković Z, Sarajlić Z, et al. Comparative Study of the Efficacy of the Lysozyme, Benzydamine and Chlorhexidine Oral Spray in the Treatment of Acute Tonsillopharyngitis - Results of a Pilot Study. *Acta Medica Academica*. Aug 2019;48(2):140-146. doi:10.5644/ama2006-124.252 [doi]

130. Sonis ST, Watkins B, Fey E, Yuschak M, Parenti D. Mechanism of action of benzydamine in the treatment of oral mucositis. *Journal of Clinical Oncology*. 06/01; 2022/01 2005;23(16):8040. doi:10.1200/jco.2005.23.16_suppl.8040; 1910.1200/jco.2005.23.16_suppl.8040

131. Alsheyyab F, Al-Momani D, Kasht R, Kamal A, Abusalem D, Al-Qasem W. Impact of severe oral mucositis in pediatric cancer patients on resource utilization and cancer treatment plans. *International Journal of Clinical Pharmacy*. 2021;doi:10.1007/s11096-021-01253-y

132. Zheng Z, Zhao X, Zhao Q, et al. The Effects of Early Nutritional Intervention on Oral Mucositis and Nutritional Status of Patients With Head and Neck Cancer Treated With Radiotherapy. *Frontiers in Oncology*. 2020;10:595632. doi:10.3389/fonc.2020.595632

133. Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Annals of Oncology*. 2017;28(9):2107-2118. doi:10.1093/annonc/mdx271

134. Kim SH, Lee SM, Jeung HC, et al. The Effect of Nutrition Intervention with Oral Nutritional Supplements on Pancreatic and Bile Duct Cancer Patients Undergoing Chemotherapy. *Nutrients*. 2019;11(5):1145. doi:10.3390/nu11051145
135. Laviano A, Di Lazzaro L, Koverech A. Nutrition support and clinical outcome in advanced cancer patients. *Proceedings of the Nutrition Society*. 2018;77(4):388-393. doi:10.1017/S0029665118000459
136. Lin T, Yang J, Hong X, Yang Z, Ge T, Wang M. Nutritional status in patients with advanced lung cancer undergoing chemotherapy: a prospective observational study. *Nutrition and Cancer*. 2020;72(7):1225-1230. doi:10.1080/01635581.2019.1675720
137. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Journal of Clinical Oncology*. 2014;32(13):1331-1337. doi:10.1200/JCO.2013.52.6962
138. Calip GS, Xing S, Jun D-H, Lee W-J, Hoskins KF, Ko NY. Polypharmacy and Adherence to Adjuvant Endocrine Therapy for Breast Cancer. *Journal of Oncology Practice*. 2017;13(5):e451-e462. doi:10.1200/JOP.2016.018317
139. Chen L-J, Trares K, Laetsch DC, Nguyen TNM, Brenner H, Schöttker B. Systematic Review and Meta-Analysis on the Associations of Polypharmacy and Potentially Inappropriate Medication With Adverse Outcomes in Older Cancer Patients. *The Journals of Gerontology*. 2021;76(6):1044-1052. doi:10.1093/gerona/glaa128
140. Murphy CC, Fullington HM, Alvarez CA, et al. Polypharmacy and patterns of prescription medication use among cancer survivors. *Cancer*. 2018;124(13):2850-2857. doi:10.1002/cncr.31389
141. Plemons JM, Rees TD, Zachariah NY. Absorption of a topical steroid and evaluation of adrenal suppression in patients with erosive lichen planus. *Oral Surgery, Oral*

Medicine, and Oral Pathology. Jun 1990;69(6):688-693. doi:10.1016/0030-4220(90)90349-w

142. Diaz PI, Hong B-Y, Dupuy AK, et al. Integrated Analysis of Clinical and Microbiome Risk Factors Associated with the Development of Oral Candidiasis during Cancer Chemotherapy. *Journal of Fungi*. 2019;5(2):49. doi:10.3390/jof5020049

Chapter 2 Addendum

The cumulative findings from the first two manuscripts in this literature review address psychosocial factors in adolescents and young adults with cancer and illustrate their relationships with symptoms of therapy. Findings from the first manuscript further demonstrate that adolescents and young adults with cancer have unique psychosocial needs not akin to other age groups and likewise, are best tended to with interventions that speak to the developmental and age-appropriate needs of these patients. Importantly, this manuscript also illustrates that psychosocial factors, including stress, are amenable to change. If these factors do contribute to symptoms of therapy, they offer an opportune target for intervention, and interventions have been successfully delivered to patients on therapy. The second manuscript address self-efficacy specifically and illustrates that this interpersonal construct directly influences symptoms of cancer therapy in adolescents and young adults as a potential influencing variable in the relationship between interventions that address behavior changes or psychosocial constructs and toxicities of therapy. This second manuscript provides rationale and scientific merit for the inclusion of self-efficacy as a possible confounding or moderating variable in this study.

The third manuscript in this chapter addresses the inflammatory component of the hypothesized relationship between stress and mucositis. Results from this review and meta-analysis strongly suggest that local reduction of the inflammatory profile of persons receiving cancer-directed therapy reduces the incidence and severity of mucositis development. Together, these reviews provide justification to evaluate psychosocial factors (stress and self-efficacy) as well as physiologic factors (inflammation) as components of mucositis development.

CHAPTER 3: METHODS

This methods chapter is presented in one part. Manuscript four (Thornton, Kozachik, & Ruble; Nursing Research, 2022) outlines the methodology of this novel prospective observational study. The manuscript provides rationale for conducting this study including justification for the prospective design and how this methodological approach uses nursing science to fulfill an important step in the translational science pathway. An addendum to this manuscript is provided at the end of this chapter to discuss additional variables that were collected for analysis and how these fit into the research methodology described within the manuscript.

Manuscript Four: Study protocol to evaluate influences of stress and inflammation on mucositis in adolescents and young adults with cancer

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Abstract

Background: Adolescent and young adult (AYA) cancer diagnoses are on the rise and gains in survivorship are falling behind for this age group. Dose-limiting toxicities of therapy, including mucositis, are more frequent in this age group and may be contributing to poorer survivorship. Animal models and observational studies suggest that stress and inflammation may be contributing to the high prevalence of dose-limiting mucositis in this age demographic. The AYA oncology population has been an overlooked and under-researched oncology demographic, leading to poor understanding of why this age group has high side effect burdens and poorer cancer survival.

Objectives: This methods paper describes a novel prospective clinical study in AYAs receiving chemotherapy. The purpose of the study is to evaluate if stress at the time of chemotherapy administration predicts the development of dose-limiting mucositis and determines if this relationship is mediated by stress-induced inflammatory profiles. This is the first study to translate these stress and inflammation findings from animal models to a nurse-centered research design in humans.

Methods: Persons aged 15-39 years who are receiving chemotherapy with a significant (>20%) risk of developing mucositis will be recruited for a prospective study. Baseline stress is measured through participant questionnaires and blood is collected to analyze for inflammatory markers. Participants receive chemotherapy as clinically planned and complete a daily survey of mucositis symptoms for 14 days after chemotherapy. Regression and mediation analysis will determine if stress and inflammatory profiles predict the development of dose-limiting mucositis.

Results: This model of inquiry through a nursing framework uses a biobehavioral model considers physiologic and psychologic risk factors for chemotherapy toxicities. This study is also an important step along the translational science pathway that is essential in bringing data from laboratory studies to the clinical arena. This study design also has

important implementation science aspects by assessing the ability for critically ill individuals to participate in low-burden clinical studies that may yield important findings to improve care delivery.

Discussion: Findings from this work will identify potentially modifiable factors that may be manipulated to minimize chemotherapy toxicities and lead to improved survival. Data from this study will inform larger research endeavors to better understand symptom development in this high-risk oncologic population.

Introduction

In this year, there will be an estimated 88,260 adolescents and young adults (AYAs) diagnosed with cancer that will lead to nearly 10,000 deaths.[1] Over the past 20 years, annual cancer incidence among AYAs, defined as those 15-39 years of age, has increased despite the overall decreased cancer incidence noted in the general population. While steady progress is noted in improving cancer survival, the slowest rate of improved outcomes is in the AYA population.[1] Many AYAs are treated following pediatric protocols because their cancers are biologically more similar to those of younger children and have better chance of cure on pediatric regimens. However, while survival rates have improved on pediatric therapies, they still do not have survival rates as high as younger counterparts.[2] Therefore, AYAs with cancer remain an oncologic demographic that deserve careful attention and dedicated research efforts to better determine why their cancers are particularly difficult to treat and why they have not yet attained the same degree of benefit in treatment breakthroughs as other age groups. Unfortunately, AYAs are often under-represented in the scientific literature and have low involvement in clinical studies, further limiting advances in knowledge about their cancer biology, therapy, and experiences unique to this group.

An important area of inquiry includes a better understanding of the development of dose-limiting toxicities of therapy. Cancer-directed therapies are inherently toxic and introduce potential for significant adverse effects and burdensome side effect profiles. When these are severe in intensity or decrease organ function, they necessitate therapy interruptions, de-escalation of treatment intensity, or withholding of treatment altogether.[3] This is clinically significant not only because these toxicities impact quality of life, but also because reductions in treatment intensity reduces cancer survival. Importantly, many dose-limiting toxicities are more prevalent in AYAs and may be partially

contributing to poorer cancer outcomes.[4-6] A particularly important dose-limiting toxicity is mucositis.

Mucositis as a Dose-Limiting Toxicity

Mucositis is an ulcerative condition of the gastrointestinal tract associated with many chemotherapy regimens. Mucositis typically develops over the course of 5-10 days after chemotherapy, progressively increasing in intensity until resolution and may last as long as 10 days. The condition is painful and interrupts the ability to eat, drink, and communicate because ulcers most commonly present in the mouth and throat. Patients frequently cite mucositis as one of the most distressing adverse effects of therapy.[7, 8] Development in young persons has been associated with decreased weight/BMI, reduced physical activity, longer hospital stays, increased costs, and significant delays in chemotherapy administration,[8] At this time, there is no universally adopted evidence-based strategy for effectively preventing mucositis outside of oral hygiene and once it develops, treatment remains only symptomatic in nature.[9-11] This situation necessitates a better understanding of mucositis development so that preventative strategies can be developed, especially amongst AYAs since they experience a disproportionate burden of mucositis.

Most of what is known about the pathobiology of mucositis is derived from animal models. The current understanding is that chemotherapy introduces an initial insult to mucosal cells and tissues leading to cell damage and death. Reactive oxygen species are released in response to cell and tissue damage which activate amplification of inflammatory responses that exacerbate severity of the ulcers.[12] Increases in proinflammatory cytokines like interleukin (IL)-1a, IL-6, IL-12, tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ) and nuclear factor kappa b (NF-κB) correlate with worsening mucositis in animal models but have not been thoroughly studied in

humans.[12] Due to the involvement of the inflammatory cascade in mucositis development, it stands to reason that persons with higher inflammatory markers at the time of chemotherapy administration could be more susceptible to mucositis. What remains unknown, is why mucositis is more prevalent and severe in AYA populations. A possible explanation is that AYAs experience a high degree of stress, which is a known stimulus of the inflammatory response.

Role of Stress and Inflammation in Mucositis

AYAs with cancer report worse severity of stress than younger and older counterparts with cancer[13] with up to 48% of patients reporting PTSD symptoms during therapy.[14] Stress, distress, and psychosocial functioning alone have negative impacts on toxicity profiles in AYAs during therapy[15,16] but may also be introducing physiologic responses that worsen the side effect profile of treatment. Chronic and acute stress stimuli elicit a cascade of pro-inflammatory responses and correlate with a number of adverse health outcomes.[17,18] In the oncology population, higher degrees of inflammation have been associated with more severe symptom burden and symptom clusters.[19-22] Some human and animal studies suggest that the inflammatory response may be involved with the development of chemotherapy-induced mucositis.[23-26] However, these animal studies that display causative relationships have not been replicated in human models and the in-vivo studies in humans have not assessed the degree to which stress or inflammation may contribute to mucositis development.

This cumulation of evidence depicts a concerning situation for AYAs with cancer. They have inferior outcomes compared to other age groups with cancer that may be explained by higher incidence of dose-limiting toxicities that develop from a combination of psychosocial and physiologic factors. Research must focus on improving the understanding of mucositis development in this age group through a holistic approach

that considers biologic, physiologic, and psychosocial influences. The purpose of this paper is to describe the protocol for a National Institutes of Health funded prospective study examining biobehavioral influences of mucositis in adolescents and young adults with cancer. This methods paper describes a project that fits within an important phase of clinical science and translates findings from in-vitro studies and animal models to clinical studies involving human subjects.

Materials and Methods

Study Design

This study employs a prospective longitudinal design to determine if stress or inflammation at the time of chemotherapy administration predict risk of mucositis incidence and severity in AYAs with cancer. The study also explores if inflammation is a mediator in the relationship between stress and mucositis and is designed with consideration of the National Institutes of Health Symptom Science Model[27] and Theory of Unpleasant Symptoms.[28] The Symptom Science Model guides research through identification of a symptom, phenotyping the symptom, and describing biomarkers for clinical investigation and intervention.[27] This project is serving to fulfill the latter portion of this model, identifying important biomarkers to explain symptom development.

In recognizing that symptom development is complex and influenced by a multitude of factors, the Theory of Unpleasant Symptoms was used to scaffold additional relationships for investigation. The theory is a recursive and bi-directional model, identifying that physiological, psychologic, and situational factors all influence symptom development (as well as each other) and should be considered when investigating symptom etiology.[28] This study therefore considers influences from inflammation (physiological), stress (psychological), and treatment-related (situational) factors in the development of mucositis.

Study Specific Aims

This study will describe relationships between stress and inflammation in AYAs at the time of chemotherapy administration and evaluates if these factors are significantly associated with mucositis development via 3 specific aims (figure 1).

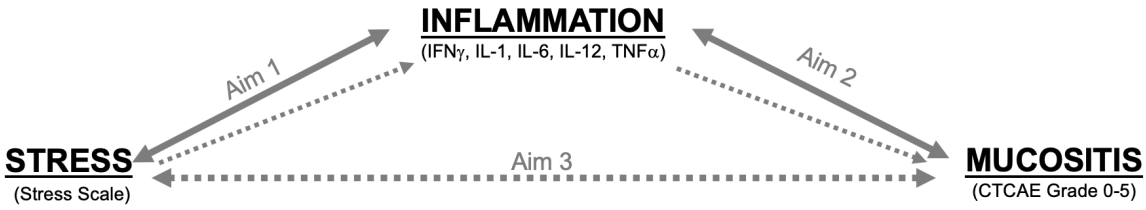

Figure 1: Study specific aims

Aim 1

Determine the association between self-reported psychological stress and inflammatory biomarkers (IFNγ, IL-1, IL-6, IL-12, TNFα) in AYAs receiving chemotherapy. We hypothesize that there will be a positive correlation between reported stress and inflammatory biomarkers.

Aim 2

Determine the association between inflammatory biomarkers (IFNγ, IL-1, IL-6, IL-12, TNFα) at the time of chemotherapy administration and the incidence/severity of oral mucositis post-chemotherapy in AYAs. We hypothesize that there will be a positive correlation between these serum inflammatory biomarkers and mucositis.

Aim 3

Explore the direct relationship between stress and post-chemotherapy mucositis and the indirect effect through inflammatory biomarkers as mediators in this relationship in AYAs

receiving chemotherapy. We hypothesize that there will be a positive correlation between perceived stress at the time patients receive chemotherapy and the presence/intensity of subsequent mucositis (direct effect). We also hypothesize that inflammatory biomarkers at the time of chemotherapy administration mediate the relationship between stress and mucositis (indirect effect).

Sampling, Recruitment, and Retention

Participants will be recruited from two clinical sites, a large university-affiliated academic hospital and a community-based hospital from the same city. Both institutions treat patients across the age spectrum from infancy into adulthood and respective Institutional Review Boards have provided approval for the study at both sites. Potential participants will be identified by a member of the research team through review of the electronic medical records, chemotherapy schedules, and clinic schedules. A $20 online gift card is advertised as incentive for participation and provided upon completion of the study to compensate participants for their time. Due to restrictions of in-person research recruitment, electronic recruitment will also be performed via targeted messaging through the patient portal within the electronic medical records system. Patients who signed up for the portal and have provided consent to receive advertisements for research will be sent an advertisement for the study.

To be included in this study, participants must be between the ages of 15 and 39 years at the time of study enrollment and receiving chemotherapy with at least a 20% risk of dose-limiting mucositis.[29-31] These regimens include Methotrexate, Ifosfamide & Etoposide, Mitoxantrone, Cytarabine, Doxorubicin, or myeloablative conditioning for stem cell transplant. Participants may enroll with any cycle of therapy but will not be approached for enrollment with their first cycle to minimize burden during the diagnosis period, which is a particularly stressful time. They will be excluded if they have a

documented cognitive deficit that would preclude being able to complete the stress measures or if they have a pre-existing stress disorder as these would alter stress measures. Participants will also be excluded if they used steroids or have had an infection requiring antibiotics within 14 days prior to study enrollment as these will alter the inflammatory profile.

Power Analysis

Power analysis was conducted using PASS version 14 software. For Aim 1, a moderate effect size of 0.3 was set as the goal for minimum detectable correlation between continuous variables. With alpha at 0.05 and power of 80%, correlation of 0.28 or greater will be able to be detected with a sample size of 100. Aims 2 and 3 will utilize logistic regression with mucositis as a dichotomous outcome in two forms 1) the presence of any mucositis and 2) the presence of dose-limiting mucositis. The presence of dose-limiting mucositis was used in power analysis to be conservative, since this is the less common outcome. Based on the number and type of chemotherapy regimens at the recruiting sites, it was determined that the average participant has a 34% chance of developing dose-limiting mucositis. This proportion was used in the power analysis with differing levels of variance explained by covariates in the model and determined that detectable odds ratios at each level. With power of 0.8, alpha of 0.05, sample size of 100, and base rate of dose-limiting mucositis at 34%, 100 participants will have statistical power to detect an odds ratio of 1.84-1.94 for each one unit increase in predictor variables. These are clinically significant effect sizes, so a recruitment goal of 100 participants was set.

Variables and Measurement

Variables, instruments, and measurement characteristics of included measures are depicted in table 1.

Table 1: Variables and measurement

Variable	Instrument	Measurement Characteristics
Perceived Stress	National Institutes of Health Perceived Stress Ages 13-17 v2.0 and 18+ v2.0	10 question 5-point Likert scale Cronbach alpha (13-17 year old): 0.89 Cronbach alpha (18+ year old): 0.91 Comparative fit index (13-17 year old): 0.99 Comparative fit index (18+ year old): 0.98
Inflammatory Markers	Milliplex Human High Sensitivity immunology multiplex assay	150μL human serum processed via Mesoscale Diagnostic Multi-Spot Assay Intra-assay variability is <6% for all measured markers
Oral Mucositis	Patient-reported outcomes (PRO) version of Common Terminology Criteria for Adverse Events (CTCAE)	5-Point Likert scale, assessing symptoms of mucositis over past 24-hour period 0: No pain, no sores or pain in mouth/throat 1: Mild pain, but I did not need to take any pain medicine 2: Moderate pain, but I did not change what I could eat or drink 3: Severe pain, I stopped eating or drinking normally 4: Very severe pain, I had to go to the hospital or clinic
Lymphocyte Count Neutrophil Count	Medical records review	Lower limit of detection = 0, upper limit is 10,000,000/μL
Diagnosis	Medical records review	Categorical, as hematologic (leukemia) and non-hematologic (solid tumor) d
Chemo agent		Categorical including assignment to one of the categories listed in inclusion criteria
Chemo dose		Dosing of chemotherapy administered on day 0 (enrollment day) of this study
Sex and Race		As identified via medical records

Stress

This predictor variable will be assessed using the NIH Toolbox Perceived Stress Scales, versions are available for ages 13-17 and 18+. The scale includes 10 items asking participants to consider how they have felt over the past month and measures reported stress over this timeframe. These instruments were chosen to measure participant-reported perceived stress because of brevity, ease of completion, and established validity and reliability in both children and adults.[32-34] The instrument yields a raw score that is translated to a T-score to compare to general population normative means.

Inflammatory Markers

Inflammatory biomarkers hypothesized to increase following stress and also impact the development of mucositis will be analyzed from blood serum collected at the time of chemotherapy administration. Markers include IFNγ, TNFα, IL-1, IL-6, and IL-12 and will be analyzed with Milliplex Human High Sensitivity multiplex assay and run in tandem to ensure quality of results and will be re-processed if differences exceed 5%.

Mucositis

The National Cancer Institute Patient-Reported Outcomes (PRO) version of the Common Terminology Criteria for Adverse Events (CTCAE) will be used to assess oral mucositis.[35] The grading system is the standard lexicon for assessing and grading toxicities from therapy[36] and is used in all NCI-sponsored trials. The patient-reported measure is recommended for use to capture symptoms of cancer therapy in research[35] and has demonstrated high validity and reliability over a 7-day recall period for AYAs.[35, 37, 38] In this study, participants will be asked to rank intensity of mucositis symptoms daily for 14 days which captures the typical onset and peak of symptom development.

The patient-reported version of the CTCAE scale has high correlation with clinician-assigned mucositis severity[35] Mucositis will be treated as a dichotomous variable in two forms: as the presence of any (grade $\geq$1) and presence of dose-limiting (grade $\geq$3) mucositis. Most treatment protocols require dose modifications if patients have symptoms of grade $\geq$3 mucositis at any point following chemotherapy[5, 39-41] so this measurement approach is consistent with clinical practice and remains highly clinically relevant.

Demographic and Confounder Variables

Age, race/ethnicity, and primary oncology diagnosis will be collected from medical records to be evaluated as confounders. Because mucositis may be related to

degree of immunosuppression at the time of chemotherapy administration, absolute lymphocyte count and absolute neutrophil count will be collected and evaluated as confounders in mucositis to gauge degree of immunosuppression. Risk of developing mucositis varies with chemotherapy agent and dose so the type and dose of chemotherapy administered on the day of study enrollment will be used to account for this variability. Because inflammatory markers are frequently elevated with leukemia, primary oncology diagnosis will be entered as a covariate in analyses to control for underlying cancer as an influence on inflammatory markers.

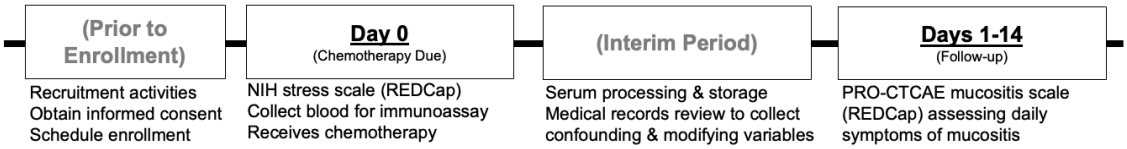

Figure 2: Data collection procedure

Data Collection Procedures

Data collection procedures are outlined in figure 2. The duration of study involvement for each participant is 14 days. Prior to enrollment, study team members will obtain informed consent; for participant sunder 18 years of age, assent from the patient will be obtained. On the day participants are scheduled for the start of any chemotherapy cycle (day 0), they will receive an email with a secure link to complete the age-appropriate NIH perceived stress scale via REDCap with instructions to complete by the end of day. Clinical nursing or phlebotomy staff will collect an extra 5mL of whole blood while drawing clinical labs, this typically occurs 2-6 hours prior to the patient receiving chemotherapy. Research staff perform initial processing of blood by spinning in refrigerated centrifuge, pipetting serum into microtubes, and storing frozen at -80C.

Starting the following day (day 1) participants will begin to receive 14 daily emails containing a link to a REDCap survey with the single-item PRO-CTCAE evaluation of mucositis. Participants will be prompted to score the severity of mucositis symptoms they have experienced over the past day, ranging from “none” to “severe”. Nonresponse to the survey by 1:00pm prompts a reminder email to minimize missing data and the link is deactivated by midnight, ensuring that responses reflect symptoms only for the specified date. During this time, research staff will perform medical records review to collect confounding variable data.

Data Analysis Plan

Aim 1

Linear regression will be used to evaluate the association between self-reported psychological stress and each inflammatory biomarker. Perceived stress scores are a continuous measurement and will be treated as a predictor of each biomarker, also a continuous measure. Diagnosis of leukemia may impact inflammatory markers[42] and so a categorical diagnosis of oncologic diagnosis will be included as a covariate to control for the influence of a hematologic malignancy impacting inflammation. Stratification based on participant sex, age, and race/ethnicity will be conducted to account for the impacts that these personal and developmental factors may have on the inflammatory stress response.

Aim 2

Logistic regression will be used to evaluate the relationship between inflammatory markers and the development of subsequent mucositis. Mucositis will be treated as a dichotomous outcome in two ways; first as the presence of any mucositis (grade 0 vs. grade $\geq$1) and secondly as the presence of dose-limiting mucositis (grade

<3 vs. grade ≥3) since these cut points are highly clinically significant. Inflammatory biomarkers will be regressed individually on mucositis score. Mucositis risk varies with chemotherapy agent/dose, and degree of immunosuppression at the time of chemotherapy administration so chemotherapy agent, dose, and lymphocyte/neutrophil count will be included as covariates to control for possible confounding.

Aim 3

Logistic regression will explore the direct relationship between stress and oral mucositis with stress score as a continuous predictor and mucositis as a dichotomous outcome in two forms, in the same fashion as Aim 2. As with Aim 1, sex, age, and race/ethnicity will be entered into the model to evaluate their moderating effects on this relationship. Sobel's test[43] will be used to determine if inflammatory biomarkers mediate the effects of stress on mucositis through a series of regressions. Sobel's testing approach with product coefficients has been shown to be a powerful method for estimating indirect effects.[44] In this approach, each mediator (inflammatory biomarkers) is predicted from the independent variable (perceived stress) which is accomplished through aim 1 in this study. Then, change in the outcome (mucositis) will be predicted from the independent variable (stress) and mediator (inflammatory biomarkers) which is accomplished through the first part of aim 3 and aim 2 in this study, respectively. Sobel's test will be used to estimate the indirect effect through product coefficients and confounders utilized in aim 2 will again be used in this analysis. Execution of this aim will determine if stress at the time of chemotherapy administration effectively predicts subsequent mucositis development and if inflammatory markers explain the variance in this prediction as mediators of the relationship.

Discussion

There are two major innovative aspects to this study. First, the use of nursing frameworks to evaluate symptom development allows for the blending of research methodologies from multiple fields, broadening the impact of this work and making it applicable to a number of clinical arenas. Presently, few studies consider multiple domains that impact mucositis development and typically focus only on disease or therapy-related factors like diagnosis, chemotherapy dose, chemotherapy agent, and rate of chemotherapy administration. Findings from this study will be relevant to biomedical, nursing, and psychosocial clinicians and researchers and will inform preventative interventions from each field respectively. The study design is also patient-centric and patient-informed, addressing a symptom of cancer therapy that persons with cancer frequently identify as burdensome and distressing,[7, 8] ensuring that findings remain highly relevant to patients and families. Furthermore, this study focuses on adolescents and young adults with cancer, a demographic frequently overlooked in the oncology literature, further reinforcing the need for a patient-directed inquiry on mucositis.

Second, this study fulfills important steps in the translational and implementation science continuum by assessing if findings identified in animal models hold true in humans and the clinical setting. This study will provide findings to inform additional inquiries such as effect sizes, potential mediating variables, and confounder variables to consider in larger studies. Furthermore, this methodology allows for the evaluation of the feasibility of using daily symptom reports in critically ill persons delivered via email during therapy. The prospective design and daily emailed symptom surveys allows for the collection of real-time data reflective of clinical practice without introducing significant burden to participants. This may prove to be a strategy that is low burden for participants allowing researchers to address the paucity of work done with AYAs in a methodology

that facilitates participation. Implication findings will be useful for the design and conduct of future larger studies evaluating additional toxicities from therapy in young persons with cancer. Importantly, evaluation of study participation, enrollment, and response will inform models for future similar study designs.

Conclusion

This study will evaluate newly hypothesized contributors to mucositis in adolescents and young adults being treated for cancer through a biobehavioral, nursing model of inquiry. The use of a nursing model allows for the incorporation of domains relevant to biomedical, nursing, and psychosocial clinicians. This study constitutes an important step in translational research in bringing clinical discovery to patient care through a patient-centric and informed approach. The long term goal of this research is to inform preventative strategies that will reduce the burden of cancer-directed therapy in young persons and to inform future studies investigating symptoms and toxicities of cancer therapy.

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Chapter 3 References

1. Institutes NC. Surveillance, Epidemiology, and End Results Program. Accessed January 20, 2022. https://seer.cancer.gov/
2. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *Cancer*. 2020;70(6):443-459. doi:10.3322/caac.21637
3. Coccia PF, Pappo AS, Beaupin L, et al. Adolescent and Young Adult Oncology, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2018;16(1):66-97. doi:10.6004/jnccn.2018.0001
4. Burke MJ, Devidas M, Chen Z, et al. Outcomes in adolescent and young adult patients (16 to 30 years) compared to younger patients treated for high-risk B-lymphoblastic leukemia: report from Children's Oncology Group Study AALL0232. *Leukemia*. 2021; doi:10.1038/s41375-021-01460-6
5. Gupta A, Damania RC, Talati R, O'Riordan MA, HMatloub YH, Ahuja SP. Increased Toxicity Among Adolescents and Young Adults Compared with Children Hospitalized with Acute Lymphoblastic Leukemia at Children's Hospitals in the United States. *Journal of Adolescent and Young Adult Oncology*. 2021;10(6):645-653. doi:10.1089/jayao.2020.0154
6. Sarangdhar M, Whiteway SL, Heath JL, et al. High-Density Data Mining to Identify Unique Toxicities of Adolescent/Young Adult Cancer Treatment: A Report from the Children's Oncology Group. *Blood*. 2017;130(Supplement 1):2562-2562. doi:10.1182/blood.V130.Suppl_1.2562.2562
7. Kanagalingam J, Wahid MIA, Lin JC, et al. Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT)

study. *Supportive Care in Cancer*. 2018;26(7):2191-2200. doi:10.1007/s00520-018-4050-3

8. Otmani N, Hattad S. Clinical Outcome in Children with Chemotherapy-Induced Mucositis. *Seminars in Oncology Nursing*. 2021/06/01/ 2021;37(3):151160. doi10.1016/j.soncn.2021.151160
9. Bensinger W, Schubert M, Ang K-K, et al. NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care. *Journal of the National Comprehensive Cancer Network*. 2008 2008;6(S1):S-1-S-21. doi:10.6004/jnccn.2008.2001
10. Brown TJ, Gupta A. Management of Cancer Therapy–Associated Oral Mucositis. *Journal of Clinical Oncology - Oncology Practice*. 2020;16(3):103-109. doi:10.1200/jop.19.00652
11. Mazhari F, Shirazi AS, Shabzendehdar M. Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. *Pediatric Blood & Cancer*. 2019;66(3):e27403. doi: 10.1002/pbc.27403
12. Sangild PT, Shen RL, Pontoppidan P, Rathe M. Animal models of chemotherapy-induced mucositis: translational relevance and challenges. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2018;314(2):G231-G246. doi:10.1152/ajpgi.00204.2017
13. Kazak AE, Derosa BW, Schwartz LA, et al. Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. *Journal of Clinical Oncology*. 2010;28(12):2002-2007. doi:10.1200/JCO.2009.25.9564
14. McCarthy MC, McNeil R, Drew S, et al. Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents.

Journal of Adolesccent and Young Adult Oncology. 2016;5(4):322-329. doi:10.1089/jayao.2016.0015

15. Haase JE, Phillips CR. The Adolescent/Young Adult Experience. *Journal of Pediatric Oncology Nursing*. 2004;21(3):145-149. doi:10.1177/1043454204264385
16. Thornton CP, Ruble K, Kozachik S. Psychosocial interventions for adolescents and young adults with cancer: an integrative review. *Journal of Pediatric Oncology Nursing*. 2020;37(6):408-422. doi: 10.1177/1043454220910713
17. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2017;9(6):7204-7218. doi:10.18632/oncotarget.23208
18. Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: The Common Pathway of Stress-Related Diseases. *Frontiers in Human Neuroscience*. 2017;11:316-316. doi:10.3389/fnhum.2017.00316
19. Jakovljevic K, Kober KM, Block A, et al. Higher Levels of Stress Are Associated With a Significant Symptom Burden in Oncology Outpatients Receiving Chemotherapy. *Journal of Pain and Symptom Management*. 2021;61(1):24-31.e4. doi:10.1016/j.jpainsymman.2020.07.019
20. Kwekkeboom KL, Tostrud L, Costanzo E, et al. The Role of Inflammation in the Pain, Fatigue, and Sleep Disturbance Symptom Cluster in Advanced Cancer. *Journal of Pain and Symptom Management*. 2018;55(5):1286-1295. doi:10.1016/j.jpainsymman.2018.01.008
21. Ma J, Kavelaars A, Dougherty PM, Heijnen CJ. Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source. *Cancer*. 2018;124(11):2289-2298. doi:10.1002/cncr.31248
22. Weber D, O'Brien K. Cancer and Cancer-Related Fatigue and the Interrelationships With Depression, Stress, and Inflammation. *Journal of Evidence-Based*

Complementary and Alternative Medicine. 2017;22(3):502-512. doi:10.1177/2156587216676122

23. Hall PD, Benko H, Hogan KR, Stuart RK. The influence of serum tumor necrosis factor-alpha and interleukin-6 concentrations on nonhematologic toxicity and hematologic recovery in patients with acute myelogenous leukemia. *Experimental Hematology*. 1995;23(12):1256-60.
24. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100(9 Suppl):1995-2025. doi:10.1002/cncr.20162
25. Sonis ST, Peterson RL, Edwards LJ, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncology*. 2000;36(4):373-81. doi:10.1016/s1368-8375(00)00012-9
26. Ye Y, Carlsson G, Agholme MB, et al. Pretherapeutic plasma pro- and anti-inflammatory mediators are related to high risk of oral mucositis in pediatric patients with acute leukemia: a prospective cohort study. *PLoS One*. 2013;8(5):e64918. doi:10.1371/journal.pone.0064918
27. Cashion AK, Gill J, Hawes R, Henderson WA, Saligan L. National Institutes of Health Symptom Science Model sheds light on patient symptoms. *Nursing Outlook*. 2016;64(5):499-506. doi:10.1016/j.outlook.2016.05.008
28. Lenz ER, Pugh LC, Milligan RA, Gift A, Suppe F. The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*. 1997;19(3):14-27. doi:10.1097/00012272-199703000-00003
29. Bardellini E, Schumacher F, Conti G, Porta F, Campus G, Majorana A. Risk factors for oral mucositis in children receiving hematopoietic cell transplantation for primary immunodeficiencies: a retrospective study. *Pediatric Transplant*. Aug 2013;17(5):492-7. doi:10.1111/petr.12094

30. Bowen JM, Wardill HR. Advances in the understanding and management of mucositis during stem cell transplantation. *Current Opinionis on Supportive and Palliative Care*. Dec 2017;11(4):341-346. doi:10.1097/spc.0000000000000310
31. Curra M, Soares Junior LAV, Martins MD, Santos P. Chemotherapy protocols and incidence of oral mucositis. An integrative review. *Einstein (Sao Paulo)*. 2018;16(1):eRW4007. doi:10.1590/s1679-45082018rw4007
32. Hodes RJ, Insel TR, Landis SC, Research NIHBfN. The NIH toolbox: setting a standard for biomedical research. *Neurology*. 2013;80(11 Suppl 3):S1-S1. doi:10.1212/WNL.0b013e3182872e90
33. Kupst MJ, Butt Z, Stoney CM, et al. Assessment of stress and self-efficacy for the NIH Toolbox for Neurological and Behavioral Function. *Anxiety Stress and Coping*. 2015;28(5):531-44. doi:10.1080/10615806.2014.994204
34. Victorson D, Manly J, Wallner-Allen K, et al. Using the NIH Toolbox in special populations: considerations for assessment of pediatric, geriatric, culturally diverse, non-English-speaking, and disabled individuals. *Neurology*. 2013;80(11 Suppl 3):S13-S19. doi:10.1212/WNL.0b013e3182872e26
35. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Journal of Pain and Symptom Management*. 2014;106(9)doi:10.1093/jnci/dju244
36. Institute NC. *Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*. United States Department of Health and Human Services, National Institutes of Health; 2017.
37. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common

Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncology*. Nov 2015;1(8):1051-9. doi:10.1001/jamaoncol.2015.2639

38. Reeve BB, McFatrich M, Pinheiro LC, et al. Cognitive Interview-Based Validation of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events in Adolescents with Cancer. *Journal of Pain and Symptom Management*. 2017;53(4):759-766. doi:10.1016/j.jpainsymman.2016.11.006
39. Advani AS, Sanford B, Luger S, et al. Frontline-Treatment Of Acute Lymphoblastic Leukemia (ALL) In Older Adolescents and Young Adults (AYA) Using a Pediatric Regimen Is Feasible: Toxicity Results of the Prospective US Intergroup Trial C10403 (Alliance). *Blood*. 2013;122(21):3903-3903. doi:10.1182/blood.V122.21.3903.3903
40. Canner JA, Alonzo TA, Franklin J, et al. Treatment outcomes in older adolescent and young adult (AYA) patients with newly diagnosed AML. *Journal of Clinical Oncology*. 2011;29(15):9506-9506. doi:10.1200/jco.2011.29.15_suppl.9506
41. Woods WG, Franklin ARK, Alonzo TA, et al. Outcome of adolescents and young adults with acute myeloid leukemia treated on COG trials compared to CALGB and SWOG trials. *Cancer*. 2013;119(23):4170-4179. doi:10.1002/cncr.28344
42. Giordano P, Molinari AC, Del Vecchio GC, et al. Prospective study of hemostatic alterations in children with acute lymphoblastic leukemia. *American Journal of Hematology*. 2010;85(5):325-30. doi:10.1002/ajh.21665
43. Hayes AF. Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs*. 2009/12/01 2009;76(4):408-420. doi:10.1080/03637750903310360
44. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*. 2002;7(1):83-104. doi:10.1037/1082-989x.7.1.83

Chapter 3: Addendum

In addition to the variables discussed in the above manuscript, self-efficacy will also be collected in this study due to the construct's established relationship with therapy-induced symptoms in AYAs receiving chemotherapy, as discussed in chapter 2. The NIH toolbox Self-Efficacy measure will be administered along with the stress scale for all participants. Similar to the stress scale, the self-efficacy instrument has established reliability for respective age groups in this study and its brevity in length has been favorable for use in this population. Self-efficacy scores will be converted to t-scores which are more comparable to normative values and more reliable for use in analyses. Self-efficacy will be entered into analysis models predicting mucositis to control for the construct's confounding effects.

Additional inflammatory biomarkers will also be analyzed from the same blood sample and explored as potential new biomarkers that predict mucositis. These include epidermal growth factor (EGF), granulocyte-monocyte colony stimulating factor (GMCSF), interleukins 6, 8, 10, 12p40, 12p70, 13, and 18, monocyte chemoattractant proteins (MCP) 1 and 3, and vascular endothelial growth factor (VEGF). These biomarkers are analyzed with the same serum sample on the same immunoassay and have been established as having a connection with stress levels. Several (EGF and VEGF) have also been correlated with the development of mucositis in in-vitro studies and warrant further investigation in clinical studies. The inclusion of these additional biomarkers serve as a useful step in identifying new markers for mucositis development and also to further elucidate relationships between the inflammatory process and symptom development in AYAs with cancer.

Finally, this pilot study not only serves to evaluate relationships to produce initial effect size estimates for future research, but also serves to evaluate the feasibility of this research approach with AYAs receiving chemotherapy and to determine if this study can be realistically replicated within a larger sample.

CHAPTER 4: FINDINGS

Results of this research are presented as a single manuscript. Manuscript five (Thornton, Perrin, Kozachik, Lukkahatai, & Ruble, 2022) describes the sample of this pilot study, the landscape of stress and self-efficacy for this sample, and incidence of mucositis specific to this age group. This manuscript also details relationships between stress, inflammation, and mucositis amongst 30 AYAs receiving chemotherapy and provides initial effect size estimates for these relationships. Findings are discussed within the relative limitations and strengths of this study design and a discussion of how these findings can be applied in clinical practice is provided.

Manuscript Five: Biobehavioral influences of stress and inflammation on mucositis in adolescents and young adults with cancer: Results from a pilot study

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Abstract

Objectives: Chemotherapy-induced mucositis is a prevalent and burdensome toxicity among adolescent and young adults (AYAs) with cancer and impedes the delivery of optimal therapy. Its development is not well understood but baseline stress and inflammation may be contributory factors. This pilot study evaluates stress and inflammation as risk factors for mucositis, identifies effect size estimates, and evaluates feasibility of a prospective study to investigate mucositis development.

Data Sources: Thirty AYAs receiving chemotherapy with substantial risk of mucositis completed baseline stress measures and serum collected for inflammatory biomarker analysis. Regression and mediation analyses determined relationship between stress/inflammation and mucositis.

Conclusion: Stress appears to be a significant risk factor for incidence of mucositis (OR 1.13, p=0.125) and predicts total mucositis score (β=0.281, p=0.023) as well as peak incidence (β=0.052, p=0.018). Baseline levels of IL1a and EGF predicted mucositis development and EGF and IL-8 may mediate the relationship between stress and mucositis. Findings suggest that stress-induced inflammation exacerbates symptom development.

Implication for Nursing Practice: Results from this pilot study inform mucositis symptom models, suggesting that psychosocial and physiologic factors are involved in development. Importantly, this pilot study provides initial effect size estimates, including magnitude and direction of relationships, that are essential to informing larger, more robustly powered studies. High enrollment, low attrition, and minimal missing data in this study suggest this model is feasible for research in this population. Importantly, this work is a first step in identifying new risk factors for mucositis and targets for nurse-led interventions to prevent toxicity development.

Introduction

Chemotherapy-induced mucositis is a frequent adverse effect and burdensome toxicity of cancer-directed therapy.[1-4] Patients frequently cite mucositis as the most distressing side effect of treatment because it can be acutely and intensely painful and create difficulties with the ability to eat, drink, and speak normally.[5, 6] Limitations in intake lead to malnutrition and dehydration that further worsen quality of life and lengthen time needed to recover after chemotherapy.[4, 6, 7] Mucositis also develops concurrently with therapy-induced immunosuppression, creating a significant risk for life-threatening infections.[6, 8, 9] Due to the gravity and risks of mucositis, development of severe symptoms at any point following chemotherapy necessitates treatment de-escalation through interrupting therapy, reducing doses, or withholding agents entirely. In this regard, mucositis becomes a life-threatening toxicity of therapy because a solitary incidence may be severe enough to change the course of treatment and compromise overall cancer survival. There are currently no evidence-based treatments for mucositis; symptomatic care remains the only available management once the condition develops[10-12] making prevention a desirable clinical goal. Unfortunately, evidence-based interventions to prevent mucositis are lacking. A number of preventative approaches have been identified including use of probiotics, nutritional supplements, laser therapy, cryotherapy, antimicrobial mouthwashes, and oral hygiene protocols (among many others) but these have not proven to be universally effective[13, 14] and mucositis continues to develop in many patients. An improved understanding of mucositis pathobiology and development is needed to better inform the development of evidence-based prevention approaches.

Mucositis development follows administration of several chemotherapy agents. Chemotherapy alone is likely not sufficient to cause mucositis,[15] but is the first step in a cascade leading to ulcer formation. Chemotherapy inhibits cellular growth, limits cell

differentiation, and damages DNA structure ultimately leading to cell death.[16, 17] The breakdown of these cells initiates an inflammatory cascade that worsens cell and tissue damage and exacerbates lesion development.[16-19] Increases in oxidative stress generate reactive oxygen species and damage-associated pattern molecules that promote transcription of nuclear factor kappa-B which recruits a swift inflammatory response.[16-19] High concentrations of inflammatory cytokines damage the endothelium, dissolve connective tissue, and impair cell oxygenation and repair mechanisms.[16-19] At the same time, chemotherapy reduces the number and function of other cells including fibroblasts, lymphocytes, and macrophages that assist with cellular repair. The end result is a decaying mucosal layer with damage exacerbated by the inflammatory response and a dysfunctional repair system that is unable to slow progression or promote healing. Overall, chemotherapy is the instigating factor in mucositis development, but it is the patient's inflammatory response that further contributes to the development of mucosal lesions.[15] Baseline levels of inflammatory markers have been suggested as risk factors for mucositis development in radiation therapy.[20] Literature reviews suggest epidermal growth factor (EGF), tumor necrosis factor alpha (TNFα), and interleukins IL-1, IL-6, and IL-12 may predict radiation-induced oral mucositis.[20] Modulating the inflammatory response, therefore, may be an opportune target for preventative interventions and more attractive approach than reducing the intensity (and therefore efficacy) of treatment.

Mucositis incidence is highest in the adolescent and young adult (AYA) population. Up to 43% of patients aged 15-39 years develop dose-limiting mucositis when treated for cancer - higher than both younger and older patient populations.[21-25] The higher incidence of severe mucositis in this population is particularly concerning since AYAs have seen the slowest improvements in cancer survival over the past 20 years and are concurrently the only age group experiencing increases in annual cancer incidence.[26] Focused attention on prevention of dose-limiting toxicities in this cohort of

oncology patients is particularly important. Unique to other age groups, AYAs also report the highest rates and severity of stress and distress during treatment[27-31] which is a known stimulator of the inflammatory cascade.[32, 33] Since inflammation has a known role in developing mucositis, stress may also be contributing to development by way of stress-induced inflammation, priming patients for mucositis development by elevating inflammatory markers that will exacerbate ulcer development after chemotherapy administration. Animal models suggest that acute stress-induced inflammation significantly increases the risk of mucositis development.[34, 35] In these models, TNFα, interferon gamma (IFNγ), EGF, and interleukins IL-1, IL-6, and IL-12 correlate with stress and also predict mucositis development.[34, 35] It is not well understood, however, if this relationship also exists in humans and clinical studies of this sort have yet to be conducted in persons receiving chemotherapy, with AYA populations, or adequately explore causes of increased inflammatory markers at baseline.

The primary purpose of this study is to explore the associations between stress, inflammation, and mucositis among AYAs receiving chemotherapy and evaluate if inflammation mediates the relationship between stress and mucositis. This pilot study will identify initial effect size estimates for these relationships and evaluate feasibility of this study design and findings will be pivotal to inform future work that definitively describes these relationships and ultimately identify potential targets for mucositis prevention.

Methods

This prospective longitudinal study recruited AYAs receiving chemotherapy from two clinical sites; a large academic hospital and a community hospital in the same city in

the mid-Atlantic region of the United States. The Institutional Review Boards at each center provided approval for this study (Johns Hopkins IRB# 00245176).

Sample and Setting

To be eligible, participants must have been between the ages of 15 and 39 years at the time of study enrollment and be receiving a cytotoxic agent with a 20% or greater incidence of dose-limiting mucositis. These regimens include the use of methotrexate, ifosfamide & etoposide, mitoxantrone, cytarabine, doxorubicin, or myeloablative conditioning for stem cell transplant.[36-38] Participants were excluded if they had a documented cognitive deficit that would preclude completion of the stress measure.

Recruitment and Data Collection

Participants were also excluded if they had used anti-inflammatory medications or had an infection in the past 14 days, as these would alter the inflammatory profile. Eligible participants were identified by clinical staff members and referred for study enrollment. The study team also reviewed chemotherapy schedules and approached eligible participants for enrollment and advertised the study through the patient messaging portal within the electronic medical records system. Informed consent was obtained and patients were enrolled in the study to begin with their subsequent cycle of chemotherapy. Participant responses were collected through REDCap surveys emailed to the participant, demographic and clinical data were extracted from the medical record by the study team.

Measures

Demographic and Clinical Data

Age, sex, chemotherapy agent(s) administered, doses for each agent, primary oncology diagnosis, and absolute lymphocyte count at the time of chemotherapy administration were extracted from the medical records. Lymphocyte count was collected to account for degree of immunosuppression at the time of chemotherapy administration since this has a known influence on mucositis development. Participants reported their race as a free-text response. The risk of mucositis for each participant was determined by reviewing toxicity profiles from clinical trials of their chemotherapy regimen. The incidence of dose-limiting mucositis for each participant[36-38] was used to stratify patients to be categorized as “high” (20-25% chance) versus “very high” (>25%) risk of developing dose-limiting mucositis to control for confounding by chemotherapy in analyses.

Stress and Self-Efficacy

The National Institutes of Health (NIH) Toolbox Perceived Stress Scale was used to measure baseline stress. Because self-efficacy has been identified as a potential moderating factor for the symptom experience in AYAs with cancer,[39] the NIH Toolbox Self-Efficacy measure was also completed by participants to evaluate if this attenuated the relationships under investigation. Validated and reliable versions of each measure are available for ages 13-17 and 18+, each contain 10-items with Likert responses, have high internal consistency (alpha >0.89),[40, 41] and comparative fit index exceeding 0.89.[42] The measures have normative data available so that corrected t-scores can be calculated and used for more accurate analysis.[42-44] Stress scores were used as continuous predictors and to identify participants who were categorized as “high stress” if they had scores one standard deviation or higher above normative means. Participants

completed these measures prior to blood collection on the day they received chemotherapy.

Inflammatory Markers

Inflammatory markers were measured via serum collected prior to chemotherapy administration and were drawn with clinical labs to prevent additional venipuncture or central line use. Biomarkers hypothesized in the relationship between stress and mucositis evaluated included EGF, TNFα, IFNγ, IL-1(a and b), IL-6, and IL-12. Additional exploratory markers included granulocyte-monocyte stimulating factor (GMCSF), monocyte chemoattractant proteins 1 and 3 (MCP1, MCP3), vascular endothelial growth factor (VEGF), and interleukins IL-8, IL-10, IL-12p40, IL-12p70, IL-13, and IL-18. Inflammatory biomarkers were analyzed quantified at the Johns Hopkins Immune Core Monitoring Laboratory using the Milliplex MAP Human High Sensitivity multiplex assay following the manufacturer's protocol. Each sample was tested in duplicates and the mean value was used for analysis. The value of half the lower limit was used for samples that had inflammatory marker levels below the assay's lower detection level. This was done in lieu of entering the lower limit itself to maintain variability within the measures and to also avoid entering zero and over-estimating variability.[45]

Mucositis symptoms

Participants reported symptoms daily over the 14 day period following chemotherapy via the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) mucositis grading scale.[46] The PRO-CTCAE tool has demonstrated high validity and reliability over a recall period of up to 7 days for AYAs.[46-48] With this scale, participants rank daily mucositis severity on a single-item 0-4 scale that correlates with clinician-assigned CTCAE severity.[46] For analysis, mucositis

was evaluated in three ways; 1) mucositis incidence as a bivariate outcome, identifying participants who reported no symptoms vs. those who reported any symptoms, 2) as peak severity determined by highest intensity per participant, and 3) total mucositis score calculated by adding daily score across all 14 days which accounts for severity and duration.

Analysis

Descriptive analyses including frequencies, percentages, means and standard deviations were used to describe the sample's demographic and clinical characteristics. Linear regression was used to evaluate influences of age on stress, self-efficacy, and inflammatory markers. Independent sample t-tests explored differences in inflammatory markers between groups based on sex, race, diagnosis, stress level (dichotomized), and mucositis incidence. Chi square analyses evaluated mucositis incidence between groups based on chemotherapy regimen, diagnosis, and those identified as high stress. Regression models were used to evaluate prediction of inflammation from stress levels as well as mucositis outcomes from stress and inflammation.

Structural equation modeling was employed to evaluate the role of inflammatory markers in mediating the relationship between stress and mucositis (figure 1). In these models, the primary pathway between stress and inflammation was compared to the hypothesized mediation pathway through each inflammatory marker. Effect sizes and p-values were compared in mediation analyses utilizing logistic regression for the bivariate outcome of mucositis incidence and Sobel's test of mediation for mucositis peak and total mucositis score. For Sobel's test of mediation, the percentage of effect of stress that is mediated by each inflammatory marker was determined by dividing the indirect effect through the mediation path by the total effect in each model.

Results

Thirty participants were recruited over the course of a 14-month period ending in November 2021. One participant did not complete the stress and self-efficacy survey and another could not have inflammatory biomarkers analyzed due to sample hemolysis. Otherwise, there were no missing data. One participant in this study was undergoing transplant for sickle cell disease and had inflammatory markers that were all greater than 5 times the level of other participants, likely due to their underlying diagnosis. Because they were the only participant receiving therapy for a non-cancerous disease and had outlier data, they were excluded from analyses involving inflammatory markers.

Participants had a mean age of 19.3 years (SD 4.8 years) and ranged from 15-34 years (median 18 years) and this sample equivocally represents male and female participants (table 1). Two thirds (66.7%) of participants reported their race as White, and 33.3% identified as Black/African American. This sample represents primary oncology diagnoses of sarcoma (36.7%), lymphoma (33.3%), leukemia (20%), or other tumors (10%) translating to a variety of chemotherapy regimens employed (table 1). Mean stress t-scores for this population were 55.6 (SD 11.4) which is higher than normative scores (mean 50, SD 10, $p<0.002$). Eleven participants (37.9%) endorsed stress scores at least one standard deviation above normative means (denoted as “high stress” in this study). Stress scores did not vary by age ($\beta=0.269$, $p>0.1$) and were not different based on sex or race ($p>0.8$).

All measures of mucositis are also displayed in table 1. Sixteen participants (53.3%) developed mucositis at some point over the course of the study period, the remaining 14 (46.7%) did not report any symptoms. Of those who reported mucositis symptoms, 8 (26.67%) had peak pain severity described as mild and 5 (16.67%) developed moderate pain; neither of which is dose-limiting severity. Three participants (10%) developed dose-limiting toxicity; two with grade 3 (severe pain) and one with

grade 4 (very severe pain). The mean total mucositis score, accounting for severity and duration for this sample was 3.83 (SD 5.87).

Table 1: Demographics and clinical characteristics	
Age (mean years)	19.3 (SD 4.8)
Sex	
Male	14 (46.7%)
Female	16 (53.3%)
Race	
White	20 (66.7%)
Black	10 (33.3%)
Diagnosis	
Leukemia	6 (20%)
Sarcoma	11 (36.7%)
Lymphoma	10 (33.3%)
Other	3 (10%)
Chemotherapy	
Ifosfamide & Etoposide	7 (23.3%)
Doxorubicin	4 (13.3%)
Methotrexate	4 (13.3%)
Cyclophosphamide & Doxorubicin	4 (13.3%)
Cyclophosphamide, Doxorubicin & Etoposide	3 (10%)
Cytarabine	2 (6.7%)
Cytarabine & Daunorubicin	2 (6.7%)
Cyclophosphamide & Fludarabine	2 (6.7%)
Cytarabine & Etoposide	1 (3.3%)
Cyclophosphamide & Etoposide	1 (3.3%)
Stress (mean t-score)	55.6 (SD 11.4)
Stress categories	
High stress (score $\geq$1 SD above normal)	11 (37.9%)
Normal stress (score +/- 1 SD within normal)	19 (63.3%)
Mucositis risk	
High (20-25% chance)	16 (53.3%)
Very High (>25% chance)	14 (46.7%)
Mucositis Incidence	
No mucositis symptoms	16 (53.3%)
Mucositis symptoms present	14 (46.7%)
Peak Mucositis Severity	
Grade 0: No symptoms or pain	14 (46.67%)
Grade 1: Mild pain, no need for pain medication	8 (26.67%)
Grade 2: Moderate pain, but no change in oral intake	5 (16.67%)
Grade 3: Severe pain, stopped eating or drinking normally	2 (6.67%)
Grade 4: Very severe pain, had to go to hospital or clinic	1 (3.33%)
Total mucositis score (mean)	3.83 (SD 5.87)

SD: Standard deviation

Relationships Between Stress, Inflammation and Mucositis

Stress-Induced Inflammation

Some mean inflammatory biomarkers were different between groups based on race and oncology diagnosis. Persons who identified as Black had higher GMCSF (74.24 vs 6.1, p=0.036) and VEGF (941.22 vs 302.02, p=0.002) and patients being treated for leukemia had higher levels of IL-8 (17.02 vs. 7.65, p=0.029) and MCP1 (1000.73 vs. 526.76, p=0.011). Because of differences of inflammatory markers based on race and diagnosis of leukemia, these variables were included as confounders in linear regression models predicting inflammation from stress scores. In these analyses, stress only reliably predicted levels of IL-8 (β = -0.297, p=0.040), but was not in the hypothesized direction (table 2).

Table 2: Predicting inflammation from stress, controlling for race and leukemia diagnosis

Biomarker	β	p-value
EGF	-0.566	0.741
GMCSF	-1.502	0.246
IFNγ	-0.786	0.268
IL1a	-0.102	0.116
IL1b	-0.039	0.199
IL6	-0.061	0.335
IL8	-0.297	0.040
IL10	-0.054	0.667
IL12p40	-0.259	0.407
IL12p70	-1.00	0.238
IL13	-1.73	0.328
IL18	-2.77	0.390
MCP1	-1.47	0.826
MCP3	-0.141	0.839
TNFα	-0.562	0.448
VEGF	-2.98	0.701

β = standardized beta coefficient

Inflammation-Induced Mucositis

Regression models and Chi2 analyses did not suggest that mucositis incidence varied by age, race, or diagnosis (all $p \geq 0.2$) but the odds of developing mucositis decreased with higher lymphocyte counts (OR 0.99, p=0.026) suggesting that degree of immunosuppression influences mucositis development. Mucositis incidence was higher for patients who received high risk chemotherapy (71% incidence among this group) compared to those who received lower risk chemotherapy (37.5% incidence, Chi2 p=0.06). Additionally, mean mucositis total scores were higher for those receiving high risk chemotherapy compared to low risk (5.14 vs 2.69, p=0.26). Given the known

correlation between chemotherapy regimen and mucositis, this risk stratification was maintained in the prediction models to be controlled as a confounder. Because self-efficacy has also been established as a factor associated with symptom development in AYAs with cancer, [39] self-efficacy t-scores were also included in prediction models when mucositis was the primary outcome to control for confounding from this construct.

Table 3 displays results of regression models that predicted mucositis from inflammatory markers while controlling for lymphocyte count, self-efficacy, and chemotherapy. Logistic regression models identify that IL1a levels predict the incidence of mucositis (OR 2.66, p=0.084). With every 1-unit increase in baseline IL1a levels, participants were 2.6 times as likely to develop mucositis symptoms at any point following chemotherapy. Linear regression models identified that baseline EGF levels also reliably predict total mucositis score (β=-0.024, p=0.030) as well as peak mucositis severity (β=-0.004, p=0.025). In these models, higher levels of EGF at baseline corelated with lower mucositis scores after chemotherapy administration. The remaining inflammatory markers did not have significant relationships with mucositis development.

Table 3: Prediction of mucositis from inflammatory markers and stress, controlling for lymphocyte count, self-efficacy, and chemotherapy

	Mucositis Incidence		Total Mucositis		Peak Mucositis	
Biomarker	OR	p-value	β	p-value	β	p-value
EGF	0.997	0.583	**-0.024**	**0.030**	**-0.004**	**0.025**
GMCSF	0.994	0.467	-0.008	0.555	-0.002	0.523
IFNγ	0.992	0.638	-0.012	0.656	-0.002	0.619
IL1a	**2.66**	**0.084**	0.229	0.509	0.056	0.362
IL1b	1.00	0.996	-0.689	0.307	-0.092	0.442
IL6	1.02	0.950	0.134	0.693	0.021	0.727
IL8	1.02	0.715	-0.134	0.338	-0.018	0.463
IL10	1.03	0.648	-0.043	0.782	-0.014	0.614
IL12p40	0.957	0.192	0.063	0.301	0.005	0.657
IL12p70	0.993	0.596	-0.017	0.451	-0.003	0.465
IL13	0.996	0.545	-0.006	0.583	-0.001	0.563
IL18	1.00	0.857	0.004	0.465	-0.001	0.526
MCP1	0.997	0.285	0.001	0.596	-0.001	0.662
MCP3	0.983	0.230	-0.013	0.636	-0.003	0.477
TNFα	0.990	0.484	-0.024	0.325	-0.004	0.339
VEGF	1.00	0.722	-0.002	0.451	-0.001	0.626
Stress	1.13	0.125	**0.281**	**0.023**	**0.052**	**0.018**

OR: odds ratio, β: standardized beta-coefficient

Stress-Induced Mucositis

As with models predicting mucositis from inflammation, participant lymphocyte count, self-efficacy scores, and chemotherapy regimen were included in models predicting mucositis from stress to control for the confounding effects of these variables (table 3). In logistic regression models, stress was not a reliable predictor of mucositis incidence (OR 1.13, p=0.125). However, in linear regression models, stress level at the time of chemotherapy administration reliably predicted total mucositis score (β=0.281, p=0.023) such that higher stress at the time of chemotherapy correlated with higher total mucositis score. Likewise, baseline stress also predicted peak mucositis severity (β=0.052, p=0.018) with higher stress again correlating with higher mucositis severity.

Inflammation as Mediator

Structural equation modeling used for mediation analysis (figure 1) evaluated the indirect effect that each inflammatory marker has on mucositis development (table 4). When predicting the incidence of mucositis from stress, several inflammatory markers (GMCSF, IFNγ, IL1b, IL-6, IL12p40, IL12p70, IL-13, MCP3, and TNFα) improved mucositis prediction by the model to some degree. Sobel's test of mediation identified several inflammatory markers that mediated the relationship between stress and total mucositis score. Interleukin 8 explained 8.1% of the effect of stress on total mucositis score as did EGF (3.7%) and VEGF (1.4%). Similarly, EGF is mediated the relationship between stress and peak mucositis score (3.2% of effect) as well as IL-8 (2.9%).

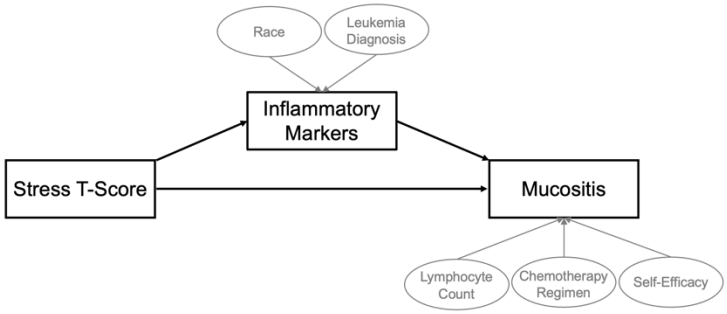

Figure 1: Structural equation modeling. Black squares identify independent, mediating, and outcome variables; gray ovals identify confounding variables

Table 4: Indirect effects of inflammation on relationship between stress and mucositis

	Mucositis Incidence		Total Mucositis			Peak Mucositis		
Biomarker	β	p	Coefficient	p	% effect	Coefficient	p	% effect
EGF	0.124	0.137	0.009	0.763	3.7%	0.002	0.763	3.2%
GMCSF	0.185	0.089*	0.000	0.922	-	0.000	0.910	-
IFNγ	0.183	0.091*	0.000	0.953	-	0.000	0.950	-
IL1a	16.1	1.00	0.001	0.903	-	0.000	0.889	-
IL1b	0.190	0.094*	0.001	0.891	-	0.000	0.858	-
IL6	0.184	0.094*	0.000	0.936	-	0.000	0.932	-
IL8	0.162	0.133	0.023	0.488	8.1%	0.002	0.779	2.9%
IL10	0.194	0.108	0.000	0.955	-	0.000	0.952	-
IL12p40	0.182	0.092*	0.001	0.901	-	0.000	0.895	-
IL12p70	0.187	0.086*	0.000	0.975	-	0.000	0.975	-
IL13	0.190	0.083*	0.000	0.996	-	0.000	0.996	-
IL18	0.181	0.106	0.000	0.962	-	0.000	0.798	-
MCP1	0.189	0.108	0.000	0.974	-	0.000	0.974	-
MCP3	0.182	0.083*	0.000	0.918	-	0.000	0.885	-
TNFα	0.187	0.084*	0.000	0.925	-	0.000	0.906	-
VEGF	0.158	0.101	0.004	0.698	1.4%	0.000	0.801	-

β: standardized beta coefficient, p: p-value
*Indicates improvement in prediction with inflammatory markers (p-value reduces with addition of mediators)
% effect indicates the percentage of effect of stress that is mediated by inflammatory marker, only displayed if >1%

Discussion

This study aimed to provide initial descriptions of the relationships between stress, inflammation, and mucositis in AYAs being treated for cancer and to evaluate if inflammation mediates the relationship between stress and inflammation. Findings provide initial effect sizes for these relations and identify valuable new insight into the complex processes that contribute to mucositis development.

Stress and Inflammation as Novel Predictors of Mucositis

Results from this study mimic those identified in animal models and suggest that stress may serve as a risk factor for the development of chemotherapy-induced mucositis. The odds of developing mucositis following chemotherapy increased by 13% for every 1-unit increase in baseline stress score (p=0.125). Because this study is a pilot study, it was not appropriately powered to identify conclusive relationships, but does

demonstrate that the relationship is in the hypothesized direction (increases in stress increased mucositis incidence). When considering mucositis severity and peak, stress becomes a significant predictor of mucositis. Peak mucositis severity was reliably predicted by baseline stress (β=0.052, p=0.018) and when accounting for both mucositis intensity and duration, stress also reliably predicted symptoms in this regard (β=0.281, p=0.023). These models suggest that stress at the time of chemotherapy administration significantly predicts the development of symptoms while controlling for relevant confounding variables of immunosuppression, chemotherapy, and self-efficacy. These findings identify stress as a potential new avenue for mucositis prevention in the clinical setting.

Stress is a component of the complex psychosocial profile of young people with cancer and might be a modifiable factor in this age group.[49] Effective interventions exist that can improve stress and/or distress in this population,[49-51] but they are difficult to implement and are time-intensive undertakings. Irrespective, this pilot study suggests that stress may emerge as an important modifiable risk factor for mucositis and reductions in stress might alleviate the burden of cancer care, improve quality of life, and reduce the intensity of an important dose-limiting toxicity. Larger, more robustly powered studies need to be conducted in order to better understand the role of stress in mucositis development. Specifically, future studies should be able to more adequately control for mucositis risk due to chemotherapy agent(s) and dose. This study was also not able to adequately evaluate if inflammation mediated the relationship between stress and mucositis due to sample size limitations, but identified several markers that might function in this role including EGF, GMCSF, IFNγ, IL1b, IL-6, IL-8, IL12p40, IL12p70, IL-13, MCP3, TNFα, and VEGF. Future studies evaluating the influence of stress on mucositis should consider these markers as potential mediators in this relationship and

attempt to better explain the physiologic response to stress in this population that might be driving mucositis development.

Inflammatory Biomarkers as Mediators of Stress-Induced Inflammation

In addition to stress, this pilot study has also identified several inflammatory markers and growth factors that may serve as baseline risk factors for mucositis. Several of these (TNFα, IFNγ, EGF, and interleukins IL-1, IL-6, and IL-12) have been previously explored in this regard.[15, 35] Of these, only IL-1a and EGF were predictive of mucositis development in this study.

Interleukins 1a and 1b are potent stimulators of acute and chronic inflammatory processes and are both associated with a number of physiologic responses that correlate with numerous conditions and diseases.[52-54] IL1a is an important component of maintaining cell homeostasis and defense in mucosal tissues[54]and is expressed from many cell types. Production increases in response to growth factors, other pro-inflammatory cytokines, and stress.[52, 54] In this pilot study, the hypothesis that IL1a levels increased in response to stress in AYAs with cancer was not supported. However, the hypothesis that higher baseline levels of IL1a correlate with mucositis development might hold true. Higher levels of IL1a at the time of chemotherapy administration were associated with a hazard ratio of 2.66 for the development of mucositis when controlling for relevant impacts of lymphocyte count, self-efficacy, and chemotherapy regimen ($p=0.084$). Considering the small sample size of this pilot study, it appears as though IL1a levels could potentially emerge as a predictor of mucositis and possible target for prevention. However, IL1a did not reliably predict total mucositis score or peak mucositis score, suggesting that this relationship with mucositis development remains incompletely understood and requires additional research to more comprehensively understand.

EGF is a polypeptide growth factor that plays a pivotal role in the homeostasis of mucosal tissues and leads to increased growth and differentiation of epidermal and mucosal cells.[55-58] Expression and up-regulation of EGF production leads to more durable mucosal cells, improved intestinal barrier integrity, and higher cell proliferation in mucosal tissues.[58] The role of stress-induced changes to EGF concentration is not well understood at this time[59] but it is understood that EGF attenuates the inflammatory response through anti-inflammatory actions.[60-62] In this pilot study, EGF levels did not correlate with stress, but did reliably predict total mucositis score ($\beta = -0.024$, $p=0.030$) and peak mucositis incidence ($\beta = -0.004$, $p=0.025$). While these effect sizes are small, findings support the hypothesis that inflammatory profiles contribute to mucositis and since EGF has anti-inflammatory functions, it correlates with improved mucositis symptom profiles. In this study, baseline levels of EGF were associated with lower total mucositis scores and lower peak mucositis intensities for participants. Prior to applications in the clinical setting, this would also require additional investigation to better elucidate the magnitude of these relationships.

Relevance to Clinical Practice & Research

While previous studies describe proposed mechanisms of inflammation in mucositis development during radiation or in animal models, this study identified several inflammatory markers that potentially serve as risk factors or protective factors for mucositis developing during chemotherapy in humans. The prospective design of this study allowed for the identification of emerging causal relationships over correlational relationships from cross-sectional studies. The inclusion of AYAs is especially important since they have higher toxicity profiles and inferior survival outcomes than other age groups treated on similar protocols.[26-31, 63]

Identification of these factors is important for future clinical practice and these findings inform the design of larger studies that can further detail these relationships. Additionally, these findings begin to inform new approaches to understanding mucositis development that extend beyond the role of chemotherapy alone and considers the impact that stress and inflammation have on symptom development. While the inflammatory markers included in this study were not identified as mediators in the relationship between stress and inflammation, it is important to note that stress and inflammatory markers both reliably predicted mucositis development. This further supports the hypotheses that stress and inflammation are both important risk factors for mucositis development, even if they themselves may not be related. This study also supports the justification for additional studies expanding upon this pilot work.

Initial findings suggest that AYAs with cancer may benefit from early interventions to reduce baseline stress and subsequent stress-induced mucositis. As mentioned, effective interventions to moderate stress in this population exist, but are difficult to implement. Clinical services in this domain are scarce; in a national survey of 142 pediatric oncology palliative care clinicians, only one third (33.3%) of these programs had a psychologist, 19% had an art therapist, and only 7.5% had a psychiatrist. Furthermore, only 35% had an AYA program available for patients.[64] These services, which are intended to assist with symptom management, remain composed primarily of medical staff and are not well-prepared to address the psychosocial needs of AYAs with cancer. This pitfall in healthcare access and delivery may partially explain the higher stress rates for AYAs. Improved clinical care delivery that address the psychosocial needs of this population might serve to reduce symptom profiles by way of improved stress profiles. By demonstrating that broad-reaching impacts of improved psychosocial care, clinicians may be in a position to better advocate for these interdisciplinary services

Modulation of the inflammatory profile through the use of anti-inflammatory agents may also improve mucositis development,[65-68] but further clinical studies need to be conducted to more definitively determine their roles in this regard. These include the use of anti-inflammatory mouthwashes, which impact local inflammatory profiles limited to the oral cavity. Since this study evaluated systemic inflammatory markers via whole blood, studies evaluating salivary inflammatory markers may also assist with determining impacts of localized inflammatory profiles on mucositis development.

Limitations and Strengths

This prospective pilot study has several limitations due to the design and included variables. Attempts were made to consistently collect inflammatory markers immediately prior to chemotherapy administration, but because lab draws for this study were performed with clinical lab draws, there are variations in the timing of specimen collection with some up to 5 hours prior to chemotherapy. Diurnal variations of inflammatory markers were not accounted for in this study, but all labs were drawn prior to noon for each participant, which adds some consistency in biomarker assessment. There are also no well-established normative values for the inflammatory markers included in this study which makes comparison to the general population difficult. The use of half the lower limit of detection for samples that had undetectable levels did not accurately represent the true variability in the inflammatory markers. Participants could join this study at any time during treatment, but they were not approached during their first cycle. This approach allowed for the inclusion of more participants but did not account for the potential of past experiences with mucositis influencing stress going into subsequent chemotherapy cycles. It should be noted that this study was conducted during the COVID-19 pandemic and discussions of school/university closures were in national discourse. This social environment likely influenced baseline stress levels in

AYA participants since it complicated their typical social environment (schooling) as well as clinical care.

Irrespective of these limitations, the pilot study has strengths in its prospective design allowing for the evaluation of causal relationships to be inferred from these findings. It also provided effect size estimates for larger studies that can be better powered to address some of the limitations of this work. Inclusion of participant-reported symptoms provided a consistent measure for each participant and is in line with recommendations for symptom assessment in this population.[5, 69] Only one participant approached for this study declined enrollment, citing that it seemed too burdensome during therapy; but the high enrollment rate and low attrition/missing data suggests that this model of inquiry is appropriate for this population.

Recommendations for Future Research

In future research on this topic, studies should focus on the recruitment of a larger participant sample that can adequately investigate these relationships while controlling for relevant confounders. This study, for example, controlled for the effect of chemotherapy on mucositis by stratifying participants into risk categories, but it may be more appropriate to stratify participants based on chemotherapy agent and control for the dose administered to better manage these confounders. A larger sample will also better elucidate the inflammatory profile of these patients while considering variations due to diagnosis, demographics, and age-related changes and provide statistical power to detect true relationships in this regard. Exploration of salivary inflammatory markers may also hold promise as a means to better understand mucositis development in this population.

Conclusions

This pilot study sought to estimate effect sizes for the relationships between stress, inflammation, and mucositis and to provide initial investigation into stress and inflammation as risk factors for mucositis development. Findings suggest that stress, IL1a, and EGF at the time of chemotherapy administration may reliably predict mucositis development, but the relationships between stress and inflammation remain incompletely understood. Stress and inflammation might be important factors to address as a means to reduce mucositis development. Results from this work provide important insight for the future direction and design of clinical studies to better examine biobehavioral predictors of mucositis development and identify new targets for interventions to prevent mucositis.

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Chapter 4 References

1. Çakmak S, Nural N. Incidence of and risk factors for development of oral mucositis in outpatients undergoing cancer chemotherapy. *International Journal of Nursing Practice*. 2019;25(1):e12710. doi:10.1111/ijn.12710
2. Gabriel AdF, Silveira FM, Curra M, et al. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. *Oral Diseases*. 2021;In Pressdoi:10.1111/odi.13863
3. Guimarães JR, Carvalho LG, Damascena LC, et al. The incidence of severe oral mucositis and its occurrence sites in pediatric oncologic patients. *Medicina Oral, Patología Oral y Cirugía Bucal*. 2021;26(3):e299-e303. doi:10.4317/medoral.24185
4. McCullough RW. US oncology-wide incidence, duration, costs and deaths from chemoradiation mucositis and antimucositis therapy benefits. *Future Oncology*. 2017;13(30):2823-2852. doi:10.2217/fon-2017-0418
5. Kanagalingam J, Wahid M, Lin J-C, et al. Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT) study. *Supportive Care in Cancer*. 2018;26(7):2191-2200. doi:10.1007/s00520-018-4050-3
6. Otmani N, Hattad S. Clinical Outcome in Children with Chemotherapy-Induced Mucositis. *Seminars in Oncology Nursing*. 2021;37(3):151160. doi:10.1016/j.soncn.2021.151160
7. Shu Z, Zeng Z, Yu B, et al. Nutritional Status and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study. *Frontiers in Oncology*. 2020; doi:10.3389/fonc.2020.594687

8. Kishimoto M, Akashi M, Tsuji K, et al. Intensity and duration of neutropenia relates to the development of oral mucositis but not odontogenic infection during chemotherapy for hematological malignancy. *PLOS ONE*. 2017;12(7):e0182021. doi:10.1371/journal.pone.0182021
9. Sobue T, Bertolini M, Thompson A, Peterson DE, Diaz PI, Dongari-Bagtzoglou A. Chemotherapy-induced oral mucositis and associated infections in a novel organotypic model. *Molecular Oral Microbiology*. 2018;33(3):212-223. doi:10.1111/omi.12214
10. Bensinger W, Schubert M, Ang K-K, et al. NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care. *Journal of the National Comprehensive Cancer Network*. 2008 2008;6(S1):S-1-S-21. doi:10.6004/jnccn.2008.2001
11. Brown TJ, Gupta A. Management of Cancer Therapy–Associated Oral Mucositis. *JCO Oncology Practice*. 2020;16(3):103-109. doi:10.1200/jop.19.00652
12. Mazhari F, Shirazi AS, Shabzendehdar M. Management of oral mucositis in pediatric patients receiving cancer therapy: A systematic review and meta-analysis. *Pediatric Blood & Cancer*. 2019;66(3):e27403. doi:https://doi.org/10.1002/pbc.27403
13. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, Filipauskas A. Prevention and Treatment of Chemotherapy and Radiotherapy Induced Oral Mucositis. *Medicina*. 2019;55(2):25.
14. Thomsen M, Vitetta L. Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. *Integrative Cancer Therapies*. 2018;17(4):1027-1047. doi:10.1177/1534735418794885
15. Sonis ST. The pathobiology of mucositis. *Nature Reviews Cancer*. 2004;4(4):277-284. doi:10.1038/nrc1318

16. Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation Therapy. *Journal of the National Cancer Institutes Monographs*. 2019;2019(53)doi:10.1093/jncimonographs/lgz011
17. Pulito C, Cristaudo A, Porta CL, et al. Oral mucositis: the hidden side of cancer therapy. *Journal of Experimental & Clinical Cancer Research*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7
18. Basile D, Di Nardo P, Corvaja C, et al. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. *Cancers*. 2019;11(6):857. doi:10.3390/cancers11060857
19. Hamouda N, Sano T, Oikawa Y, et al. Apoptosis, Dysbiosis and Expression of Inflammatory Cytokines are Sequential Events in the Development of 5-Fluorouracil-Induced Intestinal Mucositis in Mice. *Basic & Clinical Pharmacology & Toxicology*. 2017;121(3):159-168. doi:10.1111/bcpt.12793
20. Normando AGC, Rocha CL, de Toledo IP, et al. Biomarkers in the assessment of oral mucositis in head and neck cancer patients: a systematic review and meta-analysis. *Supportive Care in Cancer*. 2017;25(9):2969-2988. doi:10.1007/s00520-017-3783-8
21. Advani AS, Sanford B, Luger S, et al. Frontline-Treatment Of Acute Lymphoblastic Leukemia (ALL) In Older Adolescents and Young Adults (AYA) Using a Pediatric Regimen Is Feasible: Toxicity Results of the Prospective US Intergroup Trial C10403 (Alliance). *Blood*. 2013;122(21):3903-3903. doi:10.1182/blood.V122.21.3903.3903
22. Bukowinski AJ, Burns KC, Parsons K, Perentesis JP, O'Brien MM. Toxicity of cancer therapy in adolescents and young adults (AYAs). *Seminars in Oncology Nursing*. 2015;31(3):216-226. doi:10.1016/j.soncn.2015.05.003

23. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology*. 2016;34(20):2380-U129. doi:10.1200/jco.2015.62.4544
24. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. *Blood*. 2006;109(7):2773-2780. doi:10.1182/blood-2006-07-036673
25. Relling MV, Fairclough D, Ayers D, et al. Patient characteristics associated with high-risk methotrexate concentrations and toxicity. *Journal of Clinical Oncology*. 1994;12(8):1667-1672. doi:10.1200/jco.1994.12.8.1667
26. National Cancer Institutes. Surveillance, Epidemiology, and End Results Program. Accessed January 20, 2022. https://seer.cancer.gov/
27. Geue K, Brähler E, Faller H, et al. Prevalence of mental disorders and psychosocial distress in German adolescent and young adult cancer patients (AYA). *Psycho-Oncology*. 2018;27(7):1802-1809. doi:10.1002/pon.4730
28. Harlan LC, Lynch CF, Keegan TH, et al. Recruitment and follow-up of adolescent and young adult cancer survivors: the AYA HOPE Study. *Journal of Cancer Survivorship*. 2011;5(3):305-314. doi:10.1007/s11764-011-0173-y
29. McCarthy MC, McNeil R, Drew S, et al. Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents. *Journal of Adolesccent and Young Adult Oncology*. 2016;5(4):322-329. doi:10.1089/jayao.2016.0015

30. Quinn GP, Gonçalves V, Sehovic I, Bowman ML, Reed DR. Quality of life in adolescent and young adult cancer patients: a systematic review of the literature. *Patient Related Outcome Measures*. 2015;6:19-51. doi:10.2147/PROM.S51658
31. Zebrack BJ, Corbett V, Embry L, et al. Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*. 2014;23(11):1267-1275. doi:10.1002/pon.3533
32. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunology Research*. 2014;58(2-3):193-210. doi:10.1007/s12026-014-8517-0
33. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain, Behavior, and Immunity*. 2013;30doi:10.1016/j.bbi.2012.06.015
34. Sonis ST, Peterson RL, Edwards LJ, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncology*. 2000;36(4):373-81. doi:10.1016/s1368-8375(00)00012-9
35. Wardill HR, Tissing WJE, Kissow H, Stringer AM. Animal models of mucositis: critical tools for advancing pathobiological understanding and identifying therapeutic targets. *Current Opinion in Supportive and Palliative Care*. 2019;13(2)
36. Bardellini E, Schumacher F, Conti G, Porta F, Campus G, Majorana A. Risk factors for oral mucositis in children receiving hematopoietic cell transplantation for primary immunodeficiencies: a retrospective study. *Pediatric Transplant*. 2013;17(5):492-7. doi:10.1111/petr.12094
37. Bowen JM, Wardill HR. Advances in the understanding and management of mucositis during stem cell transplantation. *Current Opinion in Supportive and Palliative Care*. 2017;11(4):341-346. doi:10.1097/spc.0000000000000310

38. Curra M, Soares Junior LAV, Martins MD, Santos P. Chemotherapy protocols and incidence of oral mucositis. An integrative review. *Einstein (Sao Paulo)*. 2018;16(1):eRW4007. doi:10.1590/s1679-45082018rw4007
39. Thornton CP, Li M, Yeh CH, Ruble K. Self-efficacy in symptom management for adolescents and young adults with cancer: a systematic review. *Supportive Care in Cancer*. 2021;29:2851-2862. doi:10.1007/s00520-020-05960-6
40. Kupst MJ, Butt Z, Stoney CM, et al. Assessment of stress and self-efficacy for the NIH Toolbox for Neurological and Behavioral Function. *Anxiety, Stress, & Coping*. 2015;28(5):531-44. doi:10.1080/10615806.2014.994204
41. Salsman JM, Butt Z, Pilkonis PA, et al. Emotion assessment using the NIH Toolbox. *Neurology*. 2013;80(11 Suppl 3):S76-86. doi:10.1212/WNL.0b013e3182872e11
42. Kupst MJ, Butt Z, Stoney CM, et al. Assessment of stress and self-efficacy for the NIH Toolbox for Neurological and Behavioral Function. *Anxiety, Stress, and Coping*. 2015;28(5):531-44. doi:10.1080/10615806.2014.994204
43. Hodes RJ, Insel TR, Landis SC, Research NIHBfN. The NIH toolbox: setting a standard for biomedical research. *Neurology*. 2013;80(11 Suppl 3):S1-S1. doi:10.1212/WNL.0b013e3182872e90
44. Victorson D, Manly J, Wallner-Allen K, et al. Using the NIH Toolbox in special populations: considerations for assessment of pediatric, geriatric, culturally diverse, non-English-speaking, and disabled individuals. *Neurology*. 2013;80(11 Suppl 3):S13-S19. doi:10.1212/WNL.0b013e3182872e26
45. Cole SR, Chu H, Nie L, Schisterman EF. Estimating the odds ratio when exposure has a limit of detection. *International Journal of Epidemiology*. 2009;38(6):1674-1680. doi:10.1093/ije/dyp269
46. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for

adverse events (PRO-CTCAE). *Journal of Pain and Symptom Management*. 2014;106(9)doi:10.1093/jnci/dju244

47. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncology*. Nov 2015;1(8):1051-9. doi:10.1001/jamaoncol.2015.2639
48. Reeve BB, McFatrich M, Pinheiro LC, et al. Cognitive Interview-Based Validation of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events in Adolescents with Cancer. *Journal of Pain and Symptom Management*. 2017;53(4):759-766. doi:10.1016/j.jpainsymman.2016.11.006
49. Thornton CP, Ruble K, Kozachik S. Psychosocial Interventions for Adolescents and Young Adults With Cancer: An Integrative Review. *Journal of Pediatric Oncology Nursing*. 2020;37(6):408-422. 1043454220919713. doi:10.1177/1043454220919713
50. Greup SR, Kaal S, E. J. , Janse R, et al. Post-Traumatic Growth and Resilience in Adolescent and Young Adult Cancer Patients: An Overview. *Journal of Adolescent and Young Adult Oncology*. 2018;7(1):1-14. doi:10.1089/jayao.2017.0040
51. Victorson D, Murphy K, Benedict C, et al. A randomized pilot study of mindfulness-based stress reduction in a young adult cancer sample: Feasibility, acceptability, and changes in patient reported outcomes. *Psycho-Oncology*. 2020;29(5):841-850. doi:10.1002/pon.5355
52. Di Paolo NC, Shayakhmetov DM. Interleukin 1α and the inflammatory process. *Nature Immunology*. 2016;17(8):906-913. doi:10.1038/ni.3503
53. Khazim K, Azulay EE, Kristal B, Cohen I. Interleukin 1 gene polymorphism and susceptibility to disease. *Immunological Reviews*. 2018;281(1):40-56. doi:https://doi.org/10.1111/imr.12620

54. Mantovani A, Dinarello CA, Molgora M, Garlanda C. Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. *Immunity*. 2019;50(4):778-795. doi:10.1016/j.immuni.2019.03.012

55. Berlanga-Acosta J, Gavilondo-Cowley J, López-Saura P, et al. Epidermal growth factor in clinical practice – a review of its biological actions, clinical indications and safety implications. *International Wound Journal*. 2009;6(5):331-346. doi:https://doi.org/10.1111/j.1742-481X.2009.00622.x

56. Lacouture M, Sibaud V. Toxic Side Effects of Targeted Therapies and Immunotherapies Affecting the Skin, Oral Mucosa, Hair, and Nails. *American Journal of Clinical Dermatology*. 2018;19(Suppl 1):31-39. doi:10.1007/s40257-018-0384-3

57. Tang X, Liu B, Wang X, Yu Q, Fang R. Epidermal Growth Factor, through Alleviating Oxidative Stress, Protect IPEC-J2 Cells from Lipopolysaccharides-Induced Apoptosis. *International Journal of Molecular Sciences*. 2018;19(3):848.

58. Tang X, Liu H, Yang S, Li Z, Zhong J, Fang R. Epidermal Growth Factor and Intestinal Barrier Function. *Mediators of Inflammation*. 2016;2016doi:10.1155/2016/192734

59. Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. *Molecular Oncology*. 2018;12(1):3-20. doi: 10.1002/1878-0261.12155

60. Choi SY, Lee YJ, Kim JM, Kang HJ, Cho SH, Chang SE. Epidermal Growth Factor Relieves Inflammatory Signals in Staphylococcus aureus-Treated Human Epidermal Keratinocytes and Atopic Dermatitis-Like Skin Lesions in Nc/Nga Mice. *BioMed Research International*. 2018;2018:9439182. doi:10.1155/2018/9439182

61. Hardbower DM, Singh K, Asim M, et al. EGFR regulates macrophage activation and function in bacterial infection. *The Journal of Clinical Investigation*. 2016;126(9):3296-3312. doi:10.1172/JCI83585

62. Wang L, Huang Z, Huang W, et al. Inhibition of epidermal growth factor receptor attenuates atherosclerosis via decreasing inflammation and oxidative stress. *Scientific Reports*. 2017;7(1):45917. doi:10.1038/srep45917
63. National Cancer Institute. Cancer Disparities: National Cancer Institute. Accessed June 28, 2021. https://www.cancer.gov/about-cancer/understanding/disparities
64. Weaver MS, Rosenberg AR, Tager J, Wichman CS, Wiener L. A Summary of Pediatric Palliative Care Team Structure and Services as Reported by Centers Caring for Children with Cancer. *Journal of Palliative Medicine*. 2018;21(4):452-462. doi:10.1089/jpm.2017.0405
65. Chitapanarux I, Tungkasamit T, Petsuksiri J, et al. Randomized control trial of benzydamine HCl versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis. *Supportive Care in Cancer*. 2017;26(3):879-886. doi:10.1007/s00520-017-3904-4
66. Hattori M, Hagiwara S, Kotani H, et al. A single-arm, phase 2 study of steroid-containing mouthwash for the prevention of everolimus-associated stomatitis in multiple tumor types. *International Journal of Clinical Oncology*. 2019;24(10):1320-1327. doi:10.1007/s10147-019-01476-0
67. Jones VE, McIntyre KJ, Paul D, et al. Evaluation of Miracle Mouthwash plus Hydrocortisone Versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis: A Randomized Phase II Study. *Oncologist*. 2019;24(9):1153-1158. doi:10.1634/theoncologist.2018-0340
68. Rugo HSDP, Seneviratne LMD, Beck JTMD, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. *The Lancet Oncology*. 2017;18(5):654-662. doi:10.1016/S1470-2045(17)30109-2

69. Leahy AB, Feudtner C, Basch E. Symptom Monitoring in Pediatric Oncology Using Patient-Reported Outcomes: Why, How, and Where Next. *Patient-Patient Centered Outcomes Research*. 2018;11(2):147-153. doi:10.1007/s40271-017-0279-z

CHAPTER 5: SYNTHESIS/DISCUSSION

Introduction

The goal of this research was to describe the relationships that exist between stress, inflammation, and mucositis in adolescents and young adults undergoing therapy for cancer with the intention of better understanding development of this impactful toxicity of therapy. Chemotherapy has been long understood as the primary risk factor associated with mucositis development. However, the underlying mechanisms and factors associated with mucositis development are complex and extend beyond pharmacologic properties of cytotoxic agents to also include psychosocial and physiological characteristics of the patient. Results of this study suggest that psychosocial constructs of stress and self-efficacy along with physiologic activity of inflammatory biomarkers partially contribute to mucositis development. Identification of these new risk factors and improved understanding of their impacts on symptom profiles presents new opportunities for research and clinical practice. This chapter shares a summary of the results of this dissertation presented by study aim followed by an exploration of the strengths and limitations for this study overall. The chapter concludes with the implications of the study's findings with regard to nursing theory and research as well as recommendations for clinical practice.

Findings by Aim

Aim 1: Determine the associations between self-reported psychological stress and inflammatory biomarkers in AYAs receiving chemotherapy.

Hypothesis: There is a positive correlation between reported stress and inflammatory biomarkers.

Findings: Analysis of this sample of AYAs found significant differences in some inflammatory markers based on race and primary oncologic diagnosis. Persons who identified as Black had higher GMCSF levels (74.24 vs. 6.1, p=0.036) as well as VEGF levels (941.22 vs. 302.02, p=0.002) when compared to White participants. Participants being treated for leukemia had higher IL-8 levels (17.02 vs 7.65, p=0.029) and higher MCP1 levels (1000.73 vs. 526.76, p=0.011) than patients with other diagnoses. Because of these differences, Race and diagnosis of leukemia were included in regression models that evaluated the influence of stress on inflammatory markers. Interleukin 8 (IL-8) was reliably predicted by stress (β = -0.297, p=0.040) but this was not in the hypothesized direction; in this study sample, higher stress predicted lower IL-8 levels. The remaining inflammatory markers had no relationship with stress. Overall, this hypothesis was not supported by this study.

Aim 2: Determine the association between inflammatory biomarkers at the time of chemotherapy administration with the development and intensity of post-chemotherapy mucositis in AYAs.

Hypothesis: There is a positive relationship between inflammatory biomarkers at the time patients receive chemotherapy and the presence and intensity of oral mucositis following chemotherapy.

Findings: Previous literature has suggested that self-efficacy influences symptom development in AYAs receiving therapy for cancer[1] and it is well-established that different chemotherapy agents and dosages confer differing risks of mucositis development. In this sample, immunosuppression, as measured by the absolute lymphocyte count, significantly predicted mucositis incidence (OR 0.998, p=0.026) such that higher lymphocyte count reduced mucositis development. Self-efficacy, chemotherapy regimen, and absolute lymphocyte count were therefore included in

regression models predicting mucositis to control for these confounding variables. Baseline levels of interleukin-1a (IL-1a) predicted mucositis incidence (OR=2.66, p=0.084), but this was only significant at the α=0.1 level. No other inflammatory markers predicted mucositis incidence. Baseline levels of epidermal growth factor, an important anti-inflammatory biomarker, reliably predicted total mucositis score (β=-0.024, p=0.030) and peak mucositis severity (β=-0.004, p=0.025). The remaining inflammatory biomarkers investigated in this study did not predict mucositis total score or peak severity. Findings support the hypothesis that a higher inflammatory profile (or lower anti-inflammatory profile) at the time of chemotherapy administration is a risk factor for mucositis development following chemotherapy.

Aim 3: Explore the direct relationship between stress and post-chemotherapy oral mucositis and the indirect effect through inflammatory biomarkers as mediators of this relationship in AYAs receiving chemotherapy.

Hypothesis: There is a positive correlation between perceived stress at the time patients receive chemotherapy and the presence/intensity of mucositis following chemotherapy (direct effect). There is also a mediating relationship of inflammatory biomarkers at the time of chemotherapy administration that explain the relationship between stress and subsequent mucositis development (indirect effect).

Findings: As with the above rationale, self-efficacy, chemotherapy regimen, and absolute lymphocyte count were all included as covariates in regression models used to predict mucositis development from stress. Stress scores did not reliably predict the incidence of mucositis (OR=1.13, p=0.125) but did predict the total mucositis score (β=0.281, p=0.023) and peak mucositis incidence (β=0.052, p=0.018). Structural equation

modeling was used to evaluate inflammatory biomarkers as mediators in the relationship between stress and mucositis.

When evaluating incidence of mucositis, adding GMCSF, IFNγ, IL1b, IL6, IL12p40, IL12p70, IL13, MCP3, and TNFα levels to the model marginally improved the predictive power of the model. When evaluating total mucositis score and peak mucositis incidence, Sobel's test of mediation was utilized to evaluate the proportion of the effect of stress on mucositis that is mediated by each inflammatory biomarker. Interleukin-8 mediated 8.1% of the effect of stress on total mucositis score although this relationship was not in the hypothesized direction and stress correlated with lower IL-8 levels. The understanding of relationships between stress, IL-8, and mucositis warrant further investigation to better elucidate the physiological link between these constructs. EGF was also a significant mediator between stress and total mucositis score (3.7% of effect) as well as VEGF (1.4% of effect). The remaining markers mediated less than 1% of the relationship between stress and total mucositis score. EGF was also identified as a mediator in the relationship between stress and peak mucositis incidence (3.2% of effect) along with IL-8 (2.9% of effect). Similarly, IL-8 remains poorly understood in this regard since, similar as above, the relationship between stress and IL-8 were not in the hypothesized direction. The remaining biomarkers mediated less than 1% of the relationship between stress and peak mucositis incidence.

The first hypothesis of this aim was supported by these data; there is a correlation between baseline stress and subsequent development of mucositis when evaluating mucositis by total score and peak incidence. Stress does not, however, seem to predict the overall incidence of mucositis in this study. The second hypothesis of this aim was also partially supported by this study and several inflammatory biomarkers mediated some of the relationship between stress and mucositis.

Summary of Findings

Cumulatively, findings from the above specific aims identify stress as an emerging psychosocial construct that places patients at higher risk for developing worse mucositis, but not necessarily as a risk factor that increases the incidence of mucositis. Participants who had higher stress were not more likely to develop mucositis but were more likely to have more severe mucositis during this study period. This is highly clinically significant and relevant to the delivery of cancer therapy since individuals who develop severe mucositis at any point following chemotherapy may require therapy de-escalations. Self-efficacy was also independently predictive of mucositis development, suggesting that this psychosocial construct plays a role in improving symptom awareness and management, although identifying this role specifically was not an intention of this study. Irrespective, findings highlight the power of psychosocial factors in symptom development. Physiologic inflammatory responses to stress may provide explanation to this phenomenon and in this study some inflammatory biomarkers were identified as potential mediators in this relationship. While this holds biologic plausibility, the means by which inflammation is involved in this relationship requires additional research.

Limitations and Strengths

A number of limitations and strengths related to this research should be remarked upon. The first of these limitations relates to the relatively small sample size of this work. A power analysis was conducted for this project and a sample size of 100 participants was determined to have the most relevant and significant effect sizes identified. However, due to the logistical demands of this study, recruiting 100 participants was not feasible and this power analysis was conducted on presumed relationships extrapolated from other work. Restrictions of in-person research activities

due to the coronavirus-19 pandemic and transition to virtual clinical visits severely limited the ability to recruit a robust number of participants since on-site blood collection was needed for this study. Additionally, these relationships have not been well-researched in human models and effect sizes to accurately inform a power analysis were not available. Power analyses were performed by estimating the incidence of dose-limiting mucositis based on expected treatment regimens. The small sample size also offers limited variability in the constructs measured within this study which restricts the ability to accurately assess for the presence of mediation in this work. Future studies should include the biomarkers included in this study in addition to new inflammatory biomarkers as potential mediators in future work evaluating the impact of stress on mucositis.

The prospective non-therapeutic design of this study also introduces some limitations. Due to the nature of cancer-directed therapy, patients often receive varied doses and combinations of chemotherapy agents which each confer differing degrees of risk for mucositis. This was accounted for in this study by determining the risk for dose-limiting mucositis for each participant and then stratifying analyses based on two risk categories. A more appropriate approach in a larger sample would be to stratify participants based on chemotherapy agent and control analyses based on the dose of chemotherapy and/or cycle of therapy to further standardize the research approach. Additionally, there were no limitations on participants' use of additional supportive care measures regarding mucositis prevention which may have unstudied impacts on symptom outcomes. The benefit of this research design is that it allows for the capture of symptom development in real world practice and is directly translatable to clinical practice.

There are a number of study strengths that also warrant consideration and discussion. This research is an important first step in the translational science pathway and is the first to translate findings from animal models to humans and from cross-

sectional work to a prospective design. Past research within animal models has suggested that stress-induced inflammation impacts mucositis development[2, 3] but until this point, these relationships have not been well-explored in humans receiving chemotherapy. Findings from this work suggest that these relationships are transferrable to the clinical care of patients and warrant further attention. Past research in human models only involved participants receiving radiation therapy and have been limited to cross-sectional designs. Therefore, causative relationships between stress, inflammation, and mucositis could only be inferred from past findings. By employing a prospective design, causation can more confidently be established through establishment of a temporal relationship between the predictor variables and outcomes.

This study design also utilizes daily symptom reports which adds important detail and improved understanding of the symptom profile in these patients. Previous research approaches typically measure symptom presence and severity by extracting clinician-assigned severity from the medical records. This approach introduces significant bias due to multiple clinicians assigning symptom severity and also limits accuracy because follow-up times are not consistent. By assessing symptom severity daily in this study, an accurate and systematic approach to symptom measurement is obtained. Furthermore, the use of patient-reported measures offers consistency among participants, is comparable to clinician-assigned severity,[4, 5] and is in line with current recommendations for symptom assessment in this population.[6] This approach also yielded no missing data in the outcome variable and no participants were lost to follow-up or attrition, suggesting that this research design is feasible to use with this population and can be readily translated to larger, multi-site studies that would address the issues with sample size discussed above. Missing data overall were very low; one participant had missing inflammatory biomarker data due to lab draw error. One participant did not complete the

baseline stress and self-efficacy surveys, so only 3.3% of participant-reported data were missing in this study.

Implications for Future Work

Implications for Nursing Theory

The results of this study increase the understanding of the complex relationships between stress, inflammation, and mucositis in adolescents and young adults with cancer. These research results suggest that baseline stress and inflammation may influence mucositis development and are important potential additional constructs in an improved model that better informs the understanding of mucositis development. Previous models have focused heavily on pathobiology of mucositis that is limited to physiologic mechanisms within the mucosa of patients[7-11] but fail to consider psychosocial factors that may also influence symptoms. In the adolescent and young adult oncology population, these factors have been identified as constructs related to therapy-induced toxicities.[12-19] To date, there are no models of mucositis development that include both physiologic and psychologic factors even though the consideration of a combination of factors in symptom development have been recommended in multiple prevalent symptom models.[20-22] Findings herein, inform constructs that should be included in future models that can be used to direct future research in mucositis development and to inform research investigating interventions to prevent symptom development as well.

Implications for Nursing Research

Future research is needed to address the above-identified limitations imposed by this study design with improved sample size and ability to control for additional confounding variables. Specifically, research should be conducted in a manner that can

adequately account for mucositis development due to varying chemotherapy regimens and dosages. Findings from this study are helpful for designing subsequent models of inquiry. Primarily, this study identified prevalence of mucositis in AYAs undergoing therapy for cancer with high-risk chemotherapy regimens (46.7% from this pilot study). Additionally, 3 out of the 30 participants (10%) developed dose-limiting mucositis, which is important to consider as a less-frequent, yet highly clinically relevant outcome for future studies.

Power analyses conducted with non-significant ($p>0.05$) effect sizes determined from this pilot study confirm that a larger sample size is needed to more conclusively evaluate aims of this study. In order to ascertain the true effect of stress on inflammatory markers, effect size for EGF (β=-0.566, 95%CI=-4.06-2.93, p=0.741, R^2=0.0259) and IL-1a (β=-0.102, 95%CI=-0.232-0.027, p=0.116, R^2=0.1318) were utilized and a sample size of 289 and 54 participants would be needed, respectively to identify $\beta>0.3$ in these relationships. For aim 2 evaluating the role of inflammation predicting mucositis, the odds ratio of IL-1a predicting mucositis incidence was used (OR=2.66, 95%CI=0.877-8.098, p=0.084, R^2=0.5482) and a sample size of 32 participants would be necessary to detect an odds ratio of at least 2.0 in these analyses. Finally, a sample size of 2,111 would be necessary to identify an odds ratio of at least 2.0 via logistic regression of stress on mucositis incidence based on effect sizes from this pilot study (OR=1.13, 95% CI=0.966-1.33, p=0.125, R^2=0.3859). While some of these necessary sample sizes are quite high, findings from this pilot study are reassuring in that the approach and research design appear to be feasible to conduct with this patient sample. There were very few missing data with only 3.3% of participant-reported data unaccounted for and only two potential participants approached declined enrollment into the study. This methodology,

therefore, would not need much adjustment when up-scaled to include a larger cohort of individuals.

Additional prospective studies can also be designed to standardize supportive care measures that may impact mucositis development to add clarity to the understanding of these relationships. Participants undergoing transplant for non-oncologic diagnoses also warrant special attention since their underlying disease may influence stress or inflammatory profiles. In this study, one participant was undergoing transplant for sickle cell anemia, for example, and was excluded from analysis due to biological differences in disease pathology that may also be seen in persons undergoing transplant for benign hematologic, genetic, or congenital disorders.

Implications for Policy and Clinical Practice

Because there is no treatment for mucositis outside of supportive care once it develops, prevention has become a desirable clinical goal. Improved understanding of the biobehavioral influences of mucositis from this study can be used to inform practice changes. Primarily, this study found that stress predicts mucositis intensity and total mucositis score. While this study does not specifically assess whether or not reductions in stress improve mucositis development, it may be inferred that stress is an appropriate target for intervention. Unfortunately, psychosocial needs of AYAs with cancer are frequently overlooked and under-addressed in clinical practice.[12,13,16,18,19, 23-28] Findings from this study provide justification for clinicians to advocate for improved psychosocial care for patients as this may correlate with improved toxicity profiles during treatment. Again, these services are not well-established at many healthcare centers[29] which is also an important area for advocacy on behalf of pediatric and AYA oncology clinicians. Furthermore, costs are at times prohibitive for patients to receive psychosocial services that may improve stress. If future research reliably establishes that reducing stress may reduce toxicities, clinicians will

have more justification to advocate for insurance to cover the costs of psychosocial care. Because mucositis contributes to poorer cancer survival, reduced quality of life, and significantly higher healthcare costs, there is motivation for insurance to cover interventions to prevent mucositis. This also opens the opportunity for cost analyses to be conducted in this regard to evaluate the degree to which stress reduction also reduces healthcare costs.

Similar practice conclusions can be drawn regarding understanding about the inflammatory profile contributing to mucositis from this study, but these are not as robust as those relating to stress and mucositis. However, the use of agents that improve the inflammatory profile may hold promise as a second avenue to prevent mucositis as well as the use of growth factors. Future research is needed to better define the relationships between these markers and mucositis development as well as clinical trials that examine the efficacy of using anti-inflammatory and growth factors to mitigate mucositis development.

Summary

This prospective study provides preliminary evidence that stress and inflammation at the time of chemotherapy administration influence the development of an important toxicity of cancer-directed therapy in AYAs. Findings are useful in continuing to promote the translation of research from in-vitro and animal models into clinical practice and this is the first study to do so in this arena of chemotherapy toxicities. While stress and inflammation appear to have significant influence on the development of mucositis, the connection between these variables is not yet completely understood. Additional research must be performed to better elucidate the details of these relationships. Until that time, results from this research can be used to inform more robustly-powered studies, to inform symptom science models that better explain mucositis development, and inform future interventional studies to limit the development of mucositis after chemotherapy administration.

References

1. Thornton CP, Li M, Yeh CH, Ruble K. Self-efficacy in symptom management for adolescents and young adults with cancer: a systematic review. *Supportive Care in Cancer*. 2021;29:2851-2862. doi:10.1007/s00520-020-05960-6
2. Sonis ST, Peterson RL, Edwards LJ, et al. Defining mechanisms of action of interleukin-11 on the progression of radiation-induced oral mucositis in hamsters. *Oral Oncology*. 2000;36(4):373-81. doi:10.1016/s1368-8375(00)00012-9
3. Wardill HR, Tissing WJE, Kissow H, Stringer AM. Animal models of mucositis: critical tools for advancing pathobiological understanding and identifying therapeutic targets. *Current Opinion in Supportive and Palliative Care*. 2019;13(2)
4. Reeve BB, McFatrich M, Pinheiro LC, et al. Cognitive Interview-Based Validation of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events in Adolescents with Cancer. *Journal of Pain and Symptom Management*. 2017;53(4):759-766. doi:10.1016/j.jpainsymman.2016.11.006
5. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Journal of Pain and Symptom Management*. 2014;106(9)doi:10.1093/jnci/dju244
6. Leahy AB, Feudtner C, Basch E. Symptom Monitoring in Pediatric Oncology Using Patient-Reported Outcomes: Why, How, and Where Next. *Patient-Patient Centered Outcomes Research*. 2018;11(2):147-153. doi:10.1007/s40271-017-0279-z
7. Basile D, Di Nardo P, Corvaja C, et al. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. *Cancers*. 06/20 2019;11(6):857. doi:10.3390/cancers11060857
8. Hamouda N, Sano T, Oikawa Y, et al. Apoptosis, Dysbiosis and Expression of Inflammatory Cytokines are Sequential Events in the Development of 5-

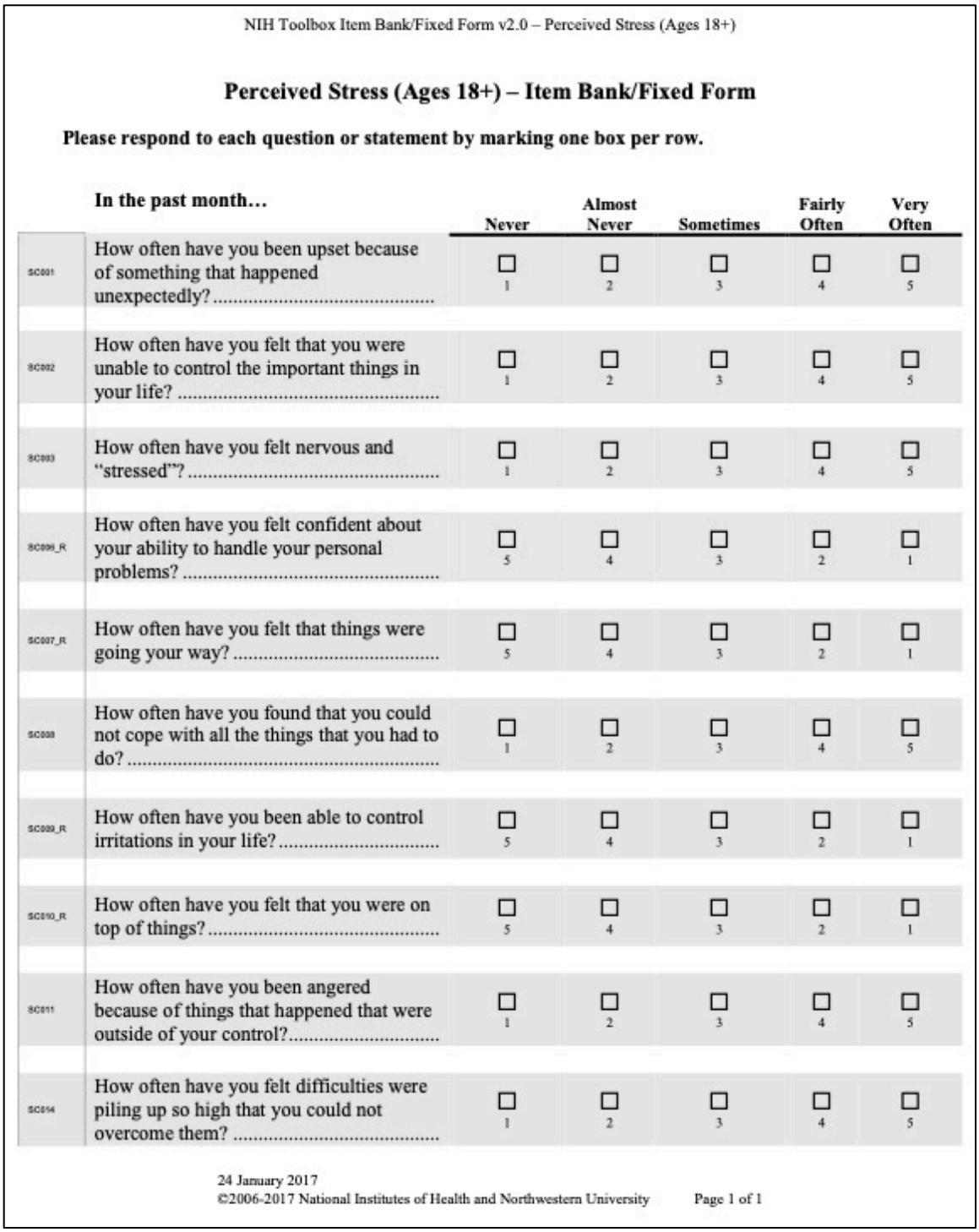
Fluorouracil-Induced Intestinal Mucositis in Mice. *Basic & Clinical Pharmacology & Toxicology*. 2017;121(3):159-168. doi:10.1111/bcpt.12793

9. Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation Therapy. *Journal of the National Cancer Institutes Monographs*. 2019;2019(53)doi:10.1093/jncimonographs/lgz011
10. Pulito C, Cristaudo A, Porta CL, et al. Oral mucositis: the hidden side of cancer therapy. *Journal of Experimental & Clinical Cancer Research*. 2020;39(1):210. doi:10.1186/s13046-020-01715-7
11. Sonis ST. The pathobiology of mucositis. *Nature Reviews Cancer*. 2004;4(4):277-284. doi:10.1038/nrc1318
12. Kazak AE, Derosa BW, Schwartz LA, et al. Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. *Journal of Clinical Oncology*. 2010;28(12):2002-2007. doi:10.1200/JCO.2009.25.9564
13. McCarthy MC, McNeil R, Drew S, et al. Psychological Distress and Posttraumatic Stress Symptoms in Adolescents and Young Adults with Cancer and Their Parents. *Journal of Adolesccent and Young Adult Oncology*. 2016;5(4):322-329. doi:10.1089/jayao.2016.0015
14. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain, Behavior, and Immunity*. 2013;30doi:10.1016/j.bbi.2012.06.015
15. Richter D, Koehler M, Friedrich M, Hilgendorf I, Mehnert A, Weissflog G. Psychosocial interventions for adolescents and young adult cancer patients: A systematic review and meta-analysis. *Critical Reviews in Oncology Hematology*. Sep 2015;95(3):370-386. doi:10.1016/j.critrevonc.2015.04.003

16. Seitz DCM, Besier T, Goldbeck L. Psychosocial interventions for adolescent cancer patients: a systematic review of the literature. *Psycho-Oncology*. 2009;18(7):683-690. doi:10.1002/pon.1473
17. Thornton CP, Ruble K, Kozachik S. Psychosocial Interventions for Adolescents and Young Adults With Cancer: An Integrative Review. *Journal of Pediatric Oncology Nursing*. 2020;37(6):408-422. 1043454220919713. doi:10.1177/1043454220919713
18. Wiener L, Kazak AE, Noll RB, Patenaude AF, Kupst MJ. Standards for the Psychosocial Care of Children With Cancer and Their Families: An Introduction to the Special Issue. *Pediatric Blood & Cancer*. 2015;62 Supplement 5:S419-24. doi:10.1002/pbc.25675
19. Zebrack BJ, Corbett V, Embry L, et al. Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*. 2014;23(11):1267-1275. doi:10.1002/pon.3533
20. Cashion AK, Gill J, Hawes R, Henderson WA, Saligan L. National Institutes of Health Symptom Science Model sheds light on patient symptoms. *Nursing Outlook*. 2016;64(5):499-506. doi:10.1016/j.outlook.2016.05.008
21. Cashion AK, Grady PA. The National Institutes of Health/National Institutes of Nursing Research intramural research program and the development of the National Institutes of Health Symptom Science Model. *Nursing Outlook*. 2015;63(4):484-7. doi:10.1016/j.outlook.2015.03.001
22. Lenz ER, Pugh LC, Milligan RA, Gift A, Suppe F. The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*. 1997;19(3):14-27. doi:10.1097/00012272-199703000-00003

23. Barakat LP, Galtieri LR, Szalda D, Schwartz LA. Assessing the psychosocial needs and program preferences of adolescents and young adults with cancer. *Supportive Care in Cancer*. Feb 2016;24(2):823-832. doi:10.1007/s00520-015-2849-8
24. Barnett M, McDonnell G, DeRosa A, et al. Psychosocial outcomes and interventions among cancer survivors diagnosed during adolescence and young adulthood (AYA): a systematic review. *Journal of Cancer Survivorship*. Oct 2016;10(5):814-831. doi:10.1007/s11764-016-0527-6
25. Geue K, Brähler E, Faller H, et al. Prevalence of mental disorders and psychosocial distress in German adolescent and young adult cancer patients (AYA). *Psycho-Oncology*. 2018;27(7):1802-1809. doi:10.1002/pon.4730
26. Haase JE, Phillips CR. The Adolescent/Young Adult Experience. *Journal of Pediatric Oncology Nursing*. 2004/05/01 2004;21(3):145-149. doi:10.1177/1043454204264385
27. Walker E, Martins A, Aldiss S, Gibson F, Taylor RM. Psychosocial Interventions for Adolescents and Young Adults Diagnosed with Cancer During Adolescence: A Critical Review. *Journal of Adolescent and Young Adult Oncology*. 2016;5(4):310-321. doi:10.1089/jayao.2016.0025
28. Zebrack B, Kent EE, Keegan THM, Kato I, Smith AW, Grp AHSC. "Cancer Sucks," and Other Ponderings by Adolescent and Young Adult Cancer Survivors. *Journal of Psychosocial Oncology*. 2014;32(1):1-+. doi:10.1080/07347332.2013.855959
29. Weaver MS, Rosenberg AR, Tager J, Wichman CS, Wiener L. A Summary of Pediatric Palliative Care Team Structure and Services as Reported by Centers Caring for Children with Cancer. *Journal of Palliative Medicine*. 2018;21(4):452-462. doi:10.1089/jpm.2017.0405

Appendix A: NIH Perceived Stress Scale Ages 18+



NIH Toolbox Item Bank/Fixed Form v2.0 – Perceived Stress (Ages 18+)

Perceived Stress (Ages 18+) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

	In the past month…	Never	Almost Never	Sometimes	Fairly Often	Very Often
SC001	How often have you been upset because of something that happened unexpectedly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC002	How often have you felt that you were unable to control the important things in your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC003	How often have you felt nervous and "stressed"?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC006_R	How often have you felt confident about your ability to handle your personal problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC007_R	How often have you felt that things were going your way?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC008	How often have you found that you could not cope with all the things that you had to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC009_R	How often have you been able to control irritations in your life?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC010_R	How often have you felt that you were on top of things?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC011	How often have you been angered because of things that happened that were outside of your control?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC014	How often have you felt difficulties were piling up so high that you could not overcome them?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

24 January 2017

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Page 1 of 1

Appendix B: NIH Perceived Stress Scale Ages 13-17

Perceived Stress (Ages 13-17) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

	In the past month…	Never	Almost Never	Sometimes	Fairly Often	Very Often
SC011	How often have you been angered because of things that happened that were outside of your control?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC014	How often have you felt difficulties were piling up so high that you could not overcome them?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC007	How often have you felt that things were going your way?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC001	How often have you been upset because of something that happened unexpectedly?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC009	How often have you been able to control irritations in your life?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC002	How often have you felt that you were unable to control the important things in your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC003	How often have you felt nervous and "stressed"?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC010	How often have you felt that you were on top of things?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SC008rv	How often have you found that you could not handle (OR manage) all the things that you had to do?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SC006	How often have you felt confident about your ability to handle your personal problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

23 January 2017

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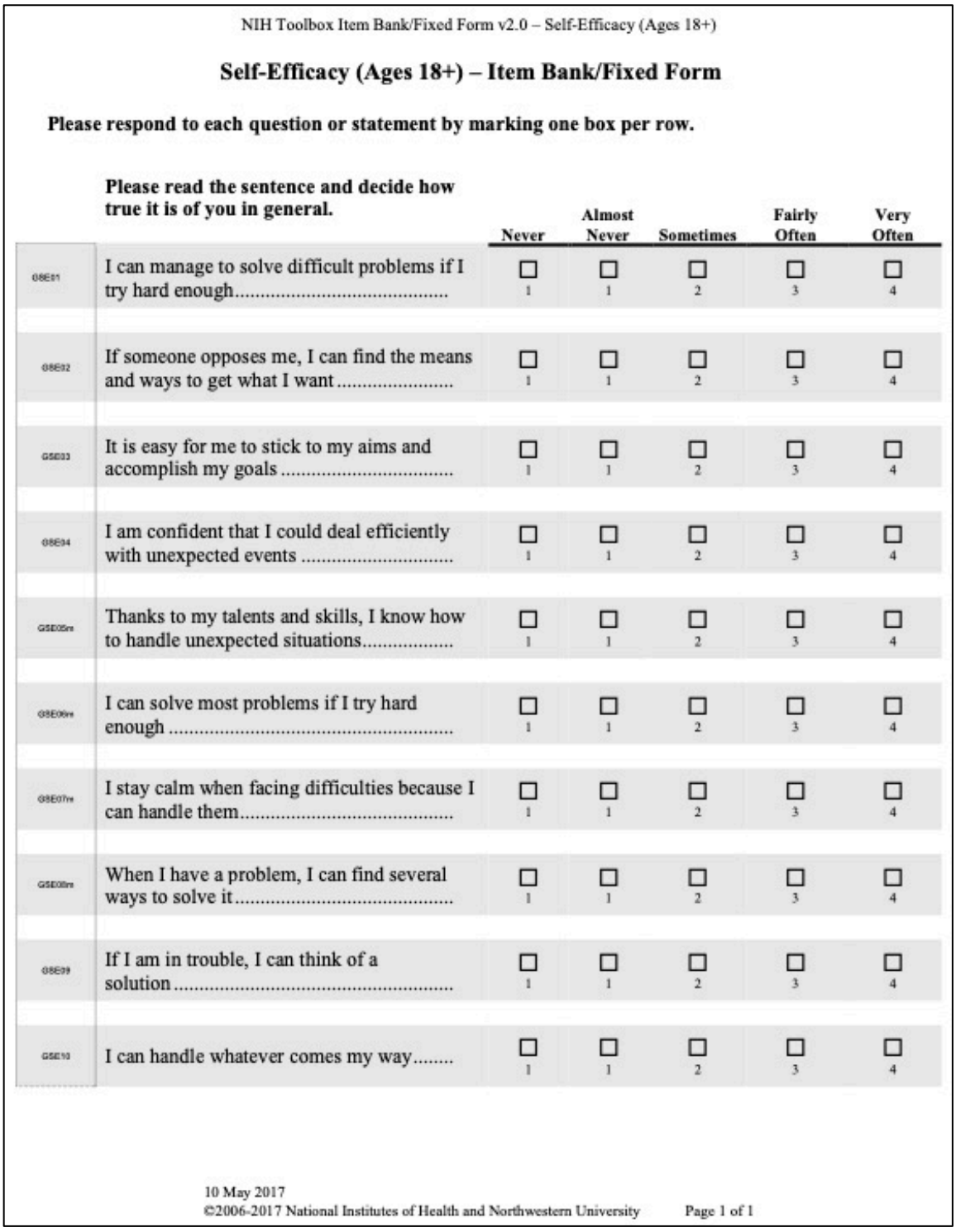
Appendix C: NIH Self-Efficacy Scale Ages 18+



NIH Toolbox Item Bank/Fixed Form v2.0 – Self-Efficacy (Ages 18+)

Self-Efficacy (Ages 18+) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

	Please read the sentence and decide how true it is of you in general.	**Never**	**Almost Never**	**Sometimes**	**Fairly Often**	**Very Often**
08E01	I can manage to solve difficult problems if I try hard enough.....	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
08E02	If someone opposes me, I can find the means and ways to get what I want	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE03	It is easy for me to stick to my aims and accomplish my goals	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
08E04	I am confident that I could deal efficiently with unexpected events	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE05rv	Thanks to my talents and skills, I know how to handle unexpected situations.....	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE06rv	I can solve most problems if I try hard enough	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE07rv	I stay calm when facing difficulties because I can handle them.....	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE08rv	When I have a problem, I can find several ways to solve it.....	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
08E09	If I am in trouble, I can think of a solution	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4
GSE10	I can handle whatever comes my way.....	☐ 1	☐ 1	☐ 2	☐ 3	☐ 4

10 May 2017

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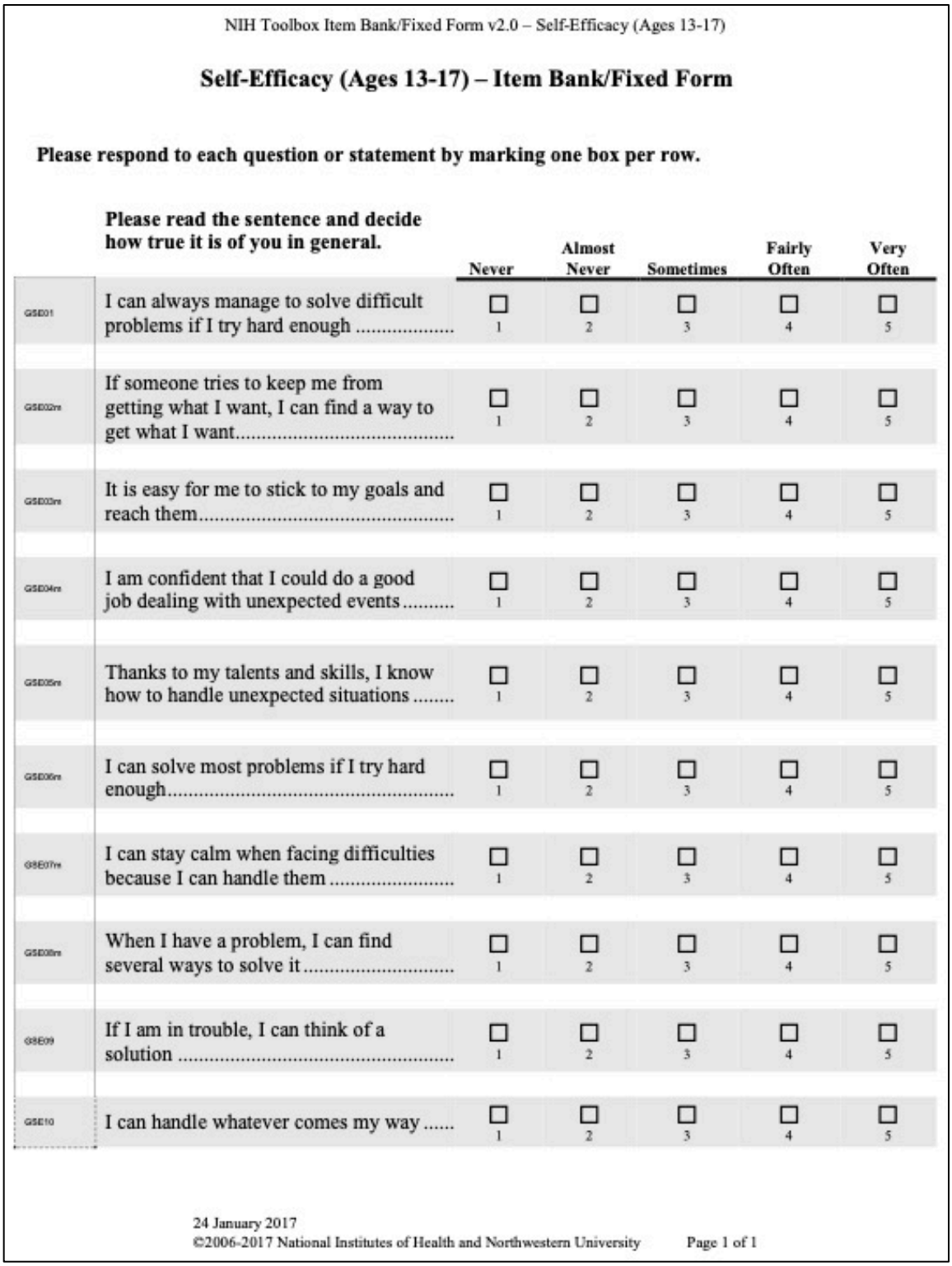
Appendix D: NIH Self-Efficacy Scale Ages 13-17



NIH Toolbox Item Bank/Fixed Form v2.0 – Self-Efficacy (Ages 13-17)

Self-Efficacy (Ages 13-17) – Item Bank/Fixed Form

Please respond to each question or statement by marking one box per row.

	Please read the sentence and decide how true it is of you in general.	**Never**	**Almost Never**	**Sometimes**	**Fairly Often**	**Very Often**
GSE01	I can always manage to solve difficult problems if I try hard enough	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE02rv	If someone tries to keep me from getting what I want, I can find a way to get what I want.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE03rv	It is easy for me to stick to my goals and reach them.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE04rv	I am confident that I could do a good job dealing with unexpected events.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE05rv	Thanks to my talents and skills, I know how to handle unexpected situations	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE06rv	I can solve most problems if I try hard enough.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE07rv	I can stay calm when facing difficulties because I can handle them	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE08rv	When I have a problem, I can find several ways to solve it.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE09	If I am in trouble, I can think of a solution	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
GSE10	I can handle whatever comes my way	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

24 January 2017

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Appendix E: NIH Stress Scale and Self-Efficacy Scale Scoring Tool

NIH Toolbox Perceived Stress Bank/Fixed Form Ages 13-17 v2.0			
Raw Sum Score	Theta Score	Theta SD	Uncorrected T- Score
10	-3.04	0.43	20.4
11	-2.75	0.42	23.2
12	-2.50	0.40	25.8
13	-2.27	0.39	28.0
14	-2.06	0.37	30.1
15	-1.87	0.37	32.0
16	-1.69	0.36	33.9
17	-1.51	0.36	35.6
18	-1.34	0.35	37.3
19	-1.18	0.35	39.0
20	-1.01	0.35	40.7
21	-0.85	0.35	42.3
22	-0.69	0.35	43.9
23	-0.53	0.35	45.5
24	-0.38	0.35	47.0
25	-0.22	0.35	48.6
26	-0.06	0.35	50.2
27	0.09	0.35	51.7
28	0.25	0.35	53.3
29	0.40	0.35	54.9
30	0.55	0.35	56.4
31	0.70	0.35	57.9
32	0.85	0.35	59.4
33	1.00	0.35	60.8
34	1.14	0.35	62.3
35	1.29	0.34	63.7
36	1.43	0.34	65.1
37	1.57	0.34	66.5
38	1.71	0.34	67.9
39	1.85	0.34	69.3
40	1.99	0.34	70.7
41	2.13	0.34	72.2
42	2.27	0.35	73.6
43	2.43	0.35	75.1
44	2.58	0.36	76.7
45	2.75	0.37	78.4
46	2.92	0.37	80.1
47	3.10	0.38	81.9
48	3.28	0.36	83.7
49	3.44	0.34	85.3
50	3.57	0.30	86.6

NIH Toolbox Perceived Stress Bank/Fixed Form Ages 18+ v2.0			
Raw Sum Score	Theta Score	Theta SD	Uncorrected T-Score
10	-2.76	0.49	22.7
11	-2.45	0.46	25.8
12	-2.19	0.44	28.5
13	-1.95	0.42	30.9
14	-1.74	0.40	33.0
15	-1.54	0.39	35.0
16	-1.36	0.38	36.9
17	-1.18	0.38	38.7
18	-1.01	0.37	40.4
19	-0.85	0.37	42.0
20	-0.69	0.37	43.7
21	-0.53	0.37	45.3
22	-0.37	0.37	46.9
23	-0.22	0.37	48.4
24	-0.07	0.37	49.9
25	0.09	0.37	51.5
26	0.24	0.37	53.0
27	0.39	0.37	54.5
28	0.54	0.37	56.1
29	0.69	0.37	57.5
30	0.83	0.37	59.0
31	0.98	0.37	60.5
32	1.12	0.37	61.9
33	1.26	0.37	63.4
34	1.40	0.37	64.8
35	1.54	0.37	66.2
36	1.68	0.36	67.6
37	1.82	0.36	69.0
38	1.96	0.36	70.4
39	2.09	0.36	71.8
40	2.23	0.36	73.1
41	2.37	0.36	74.5
42	2.51	0.37	75.9
43	2.65	0.37	77.4
44	2.80	0.37	78.9
45	2.95	0.38	80.4
46	3.10	0.37	81.9
47	3.25	0.36	83.4
48	3.38	0.34	84.8
49	3.51	0.31	86.0
50	3.61	0.28	87.1

NIH Toolbox Self Efficacy Bank/Fixed Form Ages 8-12 v2.0			
Raw Sum Score	Theta Score	Theta SD	Uncorrected T-Score
10	-3.23	0.38	17.1
11	-3.01	0.38	19.4
12	-2.85	0.38	21.0
13	-2.69	0.36	22.7
14	-2.54	0.35	24.1
15	-2.41	0.34	25.5
16	-2.28	0.34	26.8
17	-2.16	0.33	28.0
18	-2.04	0.33	29.2
19	-1.93	0.33	30.3
20	-1.82	0.33	31.4
21	-1.71	0.33	32.6
22	-1.60	0.33	33.7
23	-1.49	0.33	34.8
24	-1.38	0.33	35.9
25	-1.27	0.34	37.0
26	-1.16	0.34	38.1
27	-1.04	0.34	39.3
28	-0.93	0.34	40.4
29	-0.82	0.34	41.5
30	-0.71	0.34	42.7
31	-0.59	0.34	43.8
32	-0.48	0.34	45.0
33	-0.37	0.34	46.1
34	-0.25	0.34	47.3
35	-0.14	0.34	48.4
36	-0.03	0.33	49.6
37	0.09	0.33	50.7
38	0.20	0.33	51.9
39	0.32	0.33	53.1
40	0.44	0.34	54.3
41	0.56	0.34	55.5
42	0.69	0.34	56.8
43	0.82	0.35	58.1
44	0.96	0.36	59.5
45	1.11	0.38	61.1
46	1.27	0.40	62.7
47	1.45	0.42	64.5
48	1.66	0.45	66.7
49	1.88	0.47	68.9
50	2.21	0.53	72.2

NIH Toolbox Self-Efficacy Bank/Fixed Form Ages 18+ v2.0			
Raw Sum Score	Theta Score	Theta SD	Uncorrected T-Score
10	-3.26	0.33	16.2
11	-3.02	0.31	18.7
12	-2.81	0.28	20.8
13	-2.63	0.26	22.6
14	-2.47	0.24	24.3
15	-2.32	0.24	25.8
16	-2.17	0.25	27.4
17	-2.01	0.25	29.0
18	-1.85	0.26	30.6
19	-1.69	0.26	32.2
20	-1.54	0.26	33.8
21	-1.39	0.26	35.3
22	-1.25	0.25	36.7
23	-1.11	0.24	38.2
24	-0.97	0.24	39.6
25	-0.83	0.24	41.0
26	-0.70	0.25	42.4
27	-0.56	0.25	43.8
28	-0.42	0.25	45.2
29	-0.28	0.26	46.7
30	-0.14	0.26	48.1
31	0.00	0.25	49.5
32	0.14	0.25	50.9
33	0.28	0.24	52.4
34	0.42	0.25	53.8
35	0.58	0.26	55.4
36	0.74	0.28	57.1
37	0.94	0.32	59.1
38	1.20	0.39	61.7
39	1.50	0.47	64.8
40	1.84	0.55	68.3

Appendix F: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Mucositis Scale

Mucositis Symptom Survey

National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) V5.0
Symptom survey adopted from NCI Patient-Reported Outcomes (PRO-CTCAE) Item Library Version 1.0

The survey system (REDCap) will send the below survey question to the participant's email daily for 14 days beginning the day following chemotherapy administration (day 0). If not completed by 1300 hours, the system will re-send the link to the study participant. This question will only allow the respondent to select one answer.

Instructions: Please take a moment to think about if you have had pain in your mouth or throat over the PAST 24 HOURS and select the statement below that best applies to you.

1. In the last 14 days, how severe were your mouth or throat sores at their WORST?
   - ☐ None, no sores or pain in my mouth or throat
   - ☐ Mild pain, but I did not need to take any pain medicine
   - ☐ Moderate pain, but did not change what I could eat or drink
   - ☐ Severe pain, I stopped eating or drinking normally
   - ☐ Very severe pain and I had to go to the hospital or clinic

Scoring instructions: mucositis intensity is determined by patient-reported symptoms consistent with CTCAE grading and NCI PRO Criteria per below definitions:

None, no sores or pain in my mouth or throat	Grade 0 (absent)
Mild pain, but I did not need to take any pain medicine	Grade 1
Moderate pain, but did not change what I could eat or drink	Grade 2
Severe pain, I stopped eating or drinking normally	Grade 3
Very severe pain and I had to go to the hospital or clinic	Grade 4

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake, modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by ulceration or inflammation of the oral mucosa

National Cancer Institute Common Terminology Criteria for Adverse Events V5.0

CURRICULUM VITAE

Clifton P. Thornton

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EDUCATION

2018-2022	PhD – Nursing	Johns Hopkins University	Baltimore, MD
2013-2014	MSN – Pediatric Nurse Practitioner	Johns Hopkins University	Baltimore, MD
2012-2013	BSN – Nursing	Johns Hopkins University	Baltimore, MD
2007-2011	BS – Nuclear Medicine Technology	Ferris State University	Big Rapids, MI
2007-2011	MIN – Biology; Health & Illness in Society	Ferris State University	Big Rapids, MI
2006-2007	AAS – Applied Science Studies	Ferris State University	Big Rapids, MI

LICENSURE

2015-Present	Pediatric Nurse Practitioner - Primary Care	Pediatric Nursing Certification Board	20150248
2015-Present	Certified Registered Nurse Practitioner	Maryland Board of Nursing	R207681
2013-Present	Registered Nurse	Maryland Board of Nursing	R207681
2011-2020	Certified Nuclear Medicine Technologist	Nuclear Medicine Technology Certification Board	035729

CERTIFICATIONS

2022-Present	Certified Pediatric Hematology & Oncology Nurse	Oncology Nursing Certification Corporation (ONCC)	740708
2016-Present	Controlled Substance Registration	Maryland Department of Health, Office of Controlled Substance Administration	N89796
2016-Present	Chemotherapy and Biotherapy Provider	Association of Pediatric Hematology/Oncology Nurses	N/A

2015-Present	Drug Enforcement Administration Registration	US Department of Justice Office of Diversion Control	MT3619509
2015-Present	National Provider Index Registration	National Plan & Provider Enumeration System	1336520402
2013-Present	Pediatric Advanced Life Support	American Heart Association	N/A
2010-Present	Basic Life Support Provider, Cardiopulmonary Resuscitation	American Heart Association	N/A

PROFESSIONAL EXPERIENCE

08/21-Present	Isabel Hampton Robb Teaching Fellow	Johns Hopkins School of Nursing	Baltimore, MD
07/21-Present	Predoctoral Fellow	National Institutes of Health & Johns Hopkins School of Medicine	Baltimore, MD
11/18-Present	Lead Pediatric Hematology & Oncology Nurse Practitioner	Herman & Walter Samuelson Children's Hospital at Sinai	Baltimore, MD
11/16-1/21	Pediatric Nurse Practitioner (Per Diem)	PM Pediatric Urgent Care (formerly Kinder Mender)	Columbia, MD
9/16-9/18	Pediatric Oncology Nurse Practitioner	Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center	Baltimore, MD
10/15-9/16	Pediatric Hematology & Oncology Nurse Practitioner	Banner Thunderbird Medical Center, MD Anderson Cancer Center	Glendale, AZ
05/14-03/16	Nurse Practitioner, Project Manager	Tener Consulting Group, LLC	Penfield, NY
08/13-06/15	Senior Associate Research Nurse	Johns Hopkins School of Nursing	Baltimore, MD
08/10-05/11	Nuclear Medicine Technology Intern	University of Michigan Health System	Ann Arbor, MI

HONORS AND AWARDS

2021	Isabel Hampton Robb Teaching Fellow *Johns Hopkins School of Nursing. Baltimore, MD*
2021	Research Article of the Year *International Academy of Nursing Editors, on behalf of Journal of Emergency Nursing*
2021	Young Investigator *Children's Oncology Group*
2021	Clinical and Translational Science Award *National Institutes of Health Center for Advancing Translational Science & Johns Hopkins University*
2021	Baltimore's Top Nurses, Excellence in Nursing Award for Oncology *Baltimore Magazine*
2021	Baltimore's Top Nurses, Excellence in Nursing Award for Pediatrics *Baltimore Magazine*
2020	Nursing Research Award *Sigma Theta Tau International Honor Society of Nursing, Nu Beta at Large Chapter*
2018	Conway Scholar, PhD Program *Johns Hopkins School of Nursing*
2016	Linda Strangio Editor's Award, Article of the Year *Association for Radiologic and Imaging Nursing*
2014	Graduate Commencement Speaker *Johns Hopkins School of Nursing*
2014	Student Shining Star Award *Johns Hopkins School of Nursing*
2013	Baccalaureate Commencement Speaker *Johns Hopkins School of Nursing*
2013	Research Honors Program *Johns Hopkins School of Nursing*
2010	Honors Program Senior Leadership Award *Ferris State University*
2008	University Rising Star *Ferris State University*
2008	Honors Program Outstanding Volunteer *Ferris State University*

SCHOLARSHIPS

2021	Nurse Practitioner Doctoral Scholarship, PhD *American Academy of Nurse Practitioners*

2021 Rita Reis Wieczorek Maternal/Infant & Pediatric Nursing Doctoral Scholarship & Grant
Nurses Educational Funds

2021 Oncology Nursing Society Doctoral Education Scholarship
Oncology Nursing Foundation

2021 Institute for Clinical and Translational Research Predoctoral Fellowship Training
Johns Hopkins School of Medicine

2020 Institute for Clinical and Translational Research Recruitment Scholarship Award
Johns Hopkins University

2019 Dean's Conference Travel Award
Johns Hopkins School of Nursing

2018 Dean's Conference Travel Award
Johns Hopkins School of Nursing

2018 Joanne and William Conway Full Ride Nursing Scholarship, PhD Program
Johns Hopkins School of Nursing

2013 Nurse Corps Full Ride Graduate Scholarship, MSN (Nurse Practitioner) Program
United States Health Resource and Services Administration

2012 Dean's Academic Merit Scholarship, Undergraduate Program
Johns Hopkins University

2010 Study Abroad Scholarship, United Nations & World Health Organization
Barbara Chapman Foundation, Ferris State University

2009 John Smith Memorial Endowed Leadership Scholarship
Ferris State University

2008 Alumni Association Legacy Scholarship
Ferris State University

2007 Michigan Competitive Scholarship
State of Michigan

2007 Dean's Academic Scholarship
Ferris State University

GRANTS AND SCHOLARLY FUNDING

CURRENT SUPPORT

2021-2022 Understanding influences of dose-limiting mucositis in adolescents and young adults with cancer. Role: Predoctoral fellow/principal investigator. NIH National Center for Advancing Translational Sciences; TL1 Clinical and Translational Science Award. $50,102.88

2021-2022 Psychosocial and biological predictors of mucositis in adolescents and young adults with cancer. Role: Principal investigator. Johns Hopkins University School of Nursing Discovery and Innovation Award. $2,000.00

2020-2021 Recruitment of adolescents and young adults with cancer through electronic health records systems: Methodology and application to clinical research. Role: Principal investigator. Johns Hopkins School of Medicine Institute for Clinical and Translational Research. $2,100.00

2020-2021 Biobehavioral influences of mucositis in adolescents and young adults receiving chemotherapy. Role: Principal investigator. Funded by Sigma Theta Tau International Honor Society of Nursing – Nu Beta Nursing Research Award. $1,000.00

COMPLETED SUPPORT

2020-2021 Analysis of advanced practice registered nurses' educational preparation, practice parameters, and patient outcomes in United States emergency departments. Principal Investigators: Tener Veenema and Roberta Lavin. Role: Associate Scientist. Funded by the National Council of State Boards of Nursing. $300,000.00 total direct costs

2019-2020 National nurse readiness for radiation emergencies and nuclear events. Principal investigator: Tener Veenema. Role: Associate Scientist. Funded by the Radiation Emergency Assistance Center/Training Site and Oak Ridge Associated Universities. $75,000.00 total direct costs

2016-2018 Evidence-based recommendations for the appropriate level of sedation to manage pain in pediatric oncology patients requiring procedures: A systematic review from the Children's Oncology Group. Principal Investigator: Marilyn J. Hockenberry. Role: Research associate. Funded by the National Institutes of Health National Clinical Trials Network and Scientific Leadership Grant (U10CA180886)

NON-RESEARCH GRANTS

2021-2022 Mindfulness and wellness program for children and adolescents with cancer at Sinai Hospital of Baltimore and Mount Washington Hospital. (Philanthropic grants for healthcare services). Role: grant co-author. Funded by the Children's Cancer Foundation. $25,000.00

ACADEMIC SCHOLARSHIP & RESEARCH

** indicates data-based*

IN REVIEW

1. ***Thornton, C.P.** Bandeen-Roche, K., Roberts Lavigne, L.C., Dolinar, M., George Lansey, D., Hladek, M., & Imus, P. (in review). Factors influencing clinical trial participation of older adults receiving allogeneic blood and marrow transplantation.

2. Carey, L.B., Harkins-Brown, A., Ruble, K., Paré-Blagoev, E.J., Milla, K., **Thornton, C.P.,** Henegan, S., & Jacobson, L.A. (in review). Improving assistive technology access for students with health impairments: Lessons learned from young cancer survivors.
3. ***Thornton, C.P.,** Perrin, N., Kozachik, S., Lukkahatai, N., & Ruble, K. (in review). Biobehavioral influences of stress and inflammation on mucositis in adolescents and young adults with cancer: Results from a pilot study.
4. ***Thornton, C.P.**, Semerjian, C., Carey, L.B., Milla, K., Ruble, K.A., Paré-Blagoev, E.J., & Jacobson, L.A. (in review). Why psychosocial care matters: Parent preparedness predicts psychosocial function when children return to school after a cancer diagnosis.

PEER REVIEWED

1. **Thornton, C.P.,** Li, M., Budhathoki, C., Yeh, C.H., & Ruble, K. (2022). Anti-inflammatory mouthwashes for the prevention of oral mucositis in cancer therapy: An integrative review and meta-analysis. *Supportive Care in Cancer*. (in press)
2. **Thornton, C.P.,** Kozachik, Sharon, & Ruble, K.A. (2022). Study protocol to evaluate influences of stress and inflammation on mucositis in adolescents and young adults with cancer. *Nursing Research*. (in press)
3. ***Thornton, C.P.,** Henegan, S., Carey, L.B., Milla, K., Cork, K., Cooper, S.L., Jacobson, L.A., Ruble, K., & Paré-Blagoev, E.J. (2022). Addressing schooling in children with cancer – it's everybody's job so it's nobody's job: An explanatory mixed-methods evaluation. *Journal of Pediatric Oncology Nursing, 39*(3), doi:10.1177/1016/S2155-8256(22)000010-2
4. *Lavin, R.P., Veenema, T.G., Sasnett, L., Schneider-Firestone, S., **Thornton, C.P.,** Saenz, D., Cobb, S., Shahid, M., Peacock, M., & Couig, M.P. (2022). Analysis of nurse practitioners' educational preparation, credentialing, and scope of practice in US Emergency Departments. *Journal of Nursing Regulation, 12*(4), 50-62, doi:10.1016/S2155-8256(22)00010-2
5. **Thornton, C.P.**, Ruble, K., & Jacobson, L.A. (2022). Education for children with chronic illness: Moving forward in online and virtual learning. *JAMA Pediatrics*. doi:10.1001/jamapediatrics.2021.5643
6. Carey, L., Ruble, K., Paré-Blagoev, E.J., Milla, K., **Thornton, C.P.,** Henegan, S., & Jacobson, L.A. (2021). Childhood cancer survivors and distance education challenges: Lessons learned from the COVID19 pandemic. *Journal of Pediatric Psychology*. doi:10.1093/jpepsy/jsab103
7. *Rodney, T., Heidari, O., Miller, H. N., **Thornton, C.P.,** Jenkins, E., & Kang, H.K. (2021). Post-traumatic stress disorder in nurses in the United States: Prevalence and effect on role. *Journal of Nursing Management, 30*(1). doi:10.1111/jonm.13478
8. Veenema, T.G., Lavin, R. P., **Thornton, C. P.,** Schneider-Firestone, S., & Seal, S. (2021). Alignment of nurse practitioner educational preparation and scope of practice in United States emergency departments: A systematic review of the literature. *Journal of Emergency Nursing*, 47(4), 563-581. doi: 10.1016/j.jen.2021.04.005

9. **Thornton, C. P.,** Li, M., Yeh, C. H., & Ruble, K. (2021). Self-efficacy in symptom management for adolescents and young adults with cancer: A systematic review. *Journal of Supportive Care in Cancer, 29*(6). 2851-2862. doi: 10.1007/s00520-020-05960-6

10. Kang, H, K., Rhodes, C., Rivers, E., **Thornton, C. P.,** Rodney, T. (2020). Prevalence of mental health disorders among undergraduate university students in the United States: A review. *Journal of Psychosocial Nursing and Mental Health Services, 59*(2), 17-24. doi:10.3928/02793695-20201104-03

11. Miller, H. N., **Thornton, C. P.**, Rodney, T., Thorpe, R. J., & Allen, J. (2020). Social cohesion in health: A concept analysis. *Advances in Nursing Science, 43*(4), 375-390. doi:10.1097/ANS.0000000000000327

12. ***Thornton, C. P.**, Ruble, K., & Jacobson, L. (2020). Beyond risk-based stratification: Impacts of processing speed and executive function on adaptive skills in adolescent and young adult cancer survivors. *Journal of Adolescent and Young Adult Oncology, 10*(3), 288-295. doi:10.1089/jayao.2020.0059

13. *Bowen, A., Veenema, T. G., Schneider-Firestone, S., Iddins, C., Boyce, D., Davis, J. & **Thornton, C. P.** (2020). Exploring national nurse readiness for a radiological or nuclear incident: A cross-sectional study. *Journal of Emergency Nursing, 46*(5), 600-610. doi: 10.1016/j.jen.2020.06.002

14. **Thornton, C. P.,** Rivers, E., Rhodes, C., Kang, H. K., & Rodney, T. (2020). Development of the condensed heuristic academic research model (CHARM) framework for short-term nursing research groups. *Nursing Outlook, 68*(5), 573-580. doi:10.1016/j.outlook.2020.04.001

15. **Thornton, C. P.,** Ruble, K., & Kozachik, S. (2020). Psychosocial interventions for adolescents and young adults with cancer: An integrative review. *Journal of Pediatric Oncology Nursing, 37*(6), 408-422. doi: 10.1177/1043454220919713

16. *Cooper, S. L., Zhang, L., **Thornton, C. P.,** Ruble, K. (2020). Post chemotherapy titer status and need for re-vaccination after treatment for childhood cancer. *Clinical Pediatrics, 59*(6), 606-613, doi: 10.1177/0009922820915884

17. Duffy, E. A., Adams, T., **Thornton, C. P.**, Fisher, B., Misasi, J., & McCollum, S. (2019). Evidence-based recommendations for the appropriate level of sedation to manage pain in pediatric oncology patients requiring procedures: A report from the Children's Oncology Group. *Journal of Pediatric Oncology Nursing, 36*(4), 6-20. doi:10.1177/1043454319858610

18. Gresh, A., Robinson, K., **Thornton, C. P.,** & Plesko, C. (2019). Caring for women experiencing breast engorgement: A case report. *Journal of Midwifery & Women's Health, 64*(6), 763-768. doi:10.1111/jmwh.13011

19. Duffy, E. A., Dias, N., Hendricks-Ferguson, V., Hellsten, M., Skeens-Borland, M., **Thornton, C. P.,** & Linder, L. (2019). Perspectives on cancer pain assessment and management in children. *Seminars in Oncology Nursing, 35*(3), 261-273. doi:10.1016/j.soncn.2019.04.007

20. Veenema, T. G., Lavin, R. P., Bender, A., **Thornton, C. P.**, & Schneider-Firestone, S. (2018). National nurse readiness for radiation emergencies and nuclear events: A systematic review of the literature. *Nursing Outlook, 67*(1), 54-88. doi:10.1016/j.outlook.2018.10.005

21. Veenema, T. G., **Thornton, C. P.,** Lavin, R. P., Bender, A. K., Seal, S., & Corley, A. (2017). Climate change related water disasters' impact upon population health. *International Journal of Nursing Scholarship,* 49(6), 625-634. doi: 10.1111/jnu.12328

22. Corley, A. G., **Thornton, C. P.**, Glass, N. E. (2016). The role of nurses and community health workers in confronting neglected tropical diseases in Sub-Saharan Africa: A systematic review. *PLOS Neglected Tropical Diseases*, 1-24. doi: 10.1371/journal.pntd.0004914

23. **Thornton, C. P.** (2016). Best practice in teaching male adolescents and young men to perform testicular self-examinations: A review. *Journal of Pediatric Health Care, 30*(6), 518-527. doi: 10.1016/j.pedhc.2015.11.009

24. Veenema T. G., & **Thornton, C. P.** (2015). Enhancing child health and welfare following disasters and public health emergencies in schools and university health centers. *Pediatrics and Neonatal Nursing Open Journal, 2*(3), 75-84. doi: 10.17140/PNNOJ-2-113

25. **Thornton, C. P.,** & Veenema, T. G. (2015) Caring for children after a radiological disaster. *Journal of Radiology Nursing, 34*(4), 200-208. doi:10.1016/j.jradnu.2015.09.007

26. **Thornton, C. P.**, Veenema, T. G. (2015) Children seeking refuge: A review of the escalating humanitarian crisis of child sexual abuse and HIV/AIDS in Latin America. *Journal of the Association of Nurses in AIDS Care, 26*(4), 432-43. Doi: 10.1016/j.jana.2015.01.002

27. Veenema, T. G., **Thornton, C. P.** (2015) Guidance in managing patients following radiation events. *Advanced Emergency Nursing Journal 37*(3). 197-208. doi: 10.1097/TME.0000000000000058

28. Veenema, T. G., **Thornton, C. P.** (2014). Understanding nursing's role in health systems response to large-scale radiological disasters. *Journal of Radiology Nursing, 34*(2), 63-72. doi: 10.1016/j.jradnu.2014.11.005

29. Veenema, T. G., **Thornton, C. P.**, Corley, A. (2014) The public health crisis of child sexual abuse in low and middle income countries: An integrative review of the literature. *International Journal of Nursing Studies, 52*(4), 864-881. doi: 10.1016/j.ijnurstu.2014.10.017

TEXTBOOK PUBLICATIONS

1. **Thornton, C.P.** & Seidl, K. [2022]. Physical activity and exercise. *Essentials of Pediatric Hematology/Oncology Nursing: A core curriculum, 5th Edition.* Association of Pediatric Hematology/Oncology Nursing. Chicago, IL.

2. **Thornton, C. P.** & Ruble, K. A. (2022). Nursing Care of a Family When a Child or Adolescent has a Malignancy. In Silbert-Flagg, J. & Pillitteri, A. (Eds.). *Maternal and Child Health Nursing: Care of the Childbearing and Childrearing Family, 9th Edition*. Philadelphia, PA. Lippincott Williams & Wilkins.

3. Ruble, K. A., Li, W., **Thornton, C. P.,** & Hooke, C. (2020). Exercise and Physical Activity. In Hinds, P. S., & Linder, L. A. (Eds.). *Pediatric Oncology Nursing: Defining Care Through Science, 1st Edition.* New York, NY. Springer Publishing Company.

4. Veenema, T. G., **Thornton, C. P.**, & Lavin, R. P. (2020). The politics and policy of disaster response and public health emergency preparedness. In Mason, D. J., Leavitt, J. K., &

Chaffee, M. W. (Eds.) *Policy and Politics in Health Care and Nursing, 9th Edition.* St. Louis, MO: Elsevier Saunders

5. Veenema, T. G., Corley, A., & **Thornton, C. P.** (2018). Natural Disasters. In Veenema, T. G. (Ed.) *Disaster Nursing and Emergency Preparedness, 4th Edition*. New York, NY: Springer Publishing Company
6. Veenema, T. G., **Thornton, C. P.,** & Corley, A. G. (2018). Environmental Disasters and Emergencies. In Veenema, T. G. (Ed.) *Disaster Nursing and Emergency Preparedness, 4th Edition*. New York, NY: Springer Publishing Company
7. Veenema, T. G., **Thornton, C. P.**, & Lavin, R. P. (2018). The politics and policy of disaster response and public health emergency preparedness. In Mason, D. J., Leavitt, J. K., & Chaffee, M. W. (Eds.) *Policy and Politics in Health Care and Nursing, 8th Edition.* St. Louis, MO: Elsevier Saunders
8. Veenema, T. G., **Thornton, C. P.**, & Lavin, R. P. (2015). The politics and policy of disaster response and public health emergency preparedness. In Mason, D. J., Leavitt, J. K., & Chaffee, M. W. (Eds.) *Policy and Politics in Health Care and Nursing, 7th Edition.* St. Louis, MO: Elsevier Saunders
9. **Thornton, C. P.** (2014). Emergency and Disaster Preparedness. In Lopez, M. E., & Spencer, K. A. (Eds). *Developing the Whole Child: Best Childcare Practices in Limited Resource Settings for Children.* Los Angeles, CA: Whole Child International
10. **Thornton, C. P.** (2014) Sexual Development and Child Abuse. In Lopez, M. E., & Spencer, K. A. (Eds). *Developing the Whole Child: Best Childcare Practices in Limited Resource Settings for Children.* Los Angeles, CA: Whole Child International

PRESENTATIONS

International

[July 2022] Lund, S., **Thornton, C.P.,** Li, J., Park, J., & Lukkahatai, N.
Correlates between physical activity and fatigue in persons with cancer.
Sigma Theta International Nursing Research Congress
Edinburgh, Scotland (Podium)

[July 2022] Jacobson, L.A., **Thornton, C.P.,** & Ruble, K.A.
An interdisciplinary team model to support schooling and education of children with chronic illnesses
Sigma Theta International Nursing Research Congress
Edinburgh, Scotland (Podium, co-first authors)

[July 2022] Ruble, K.A., Jacobson, L.A., & **Thornton, C.P.**
Engaging stakeholders to inform care of children with neurocognitive challenges: Case exemplar from pediatric oncology.
Sigma Theta International Nursing Research Congress.
Edinburgh, Scotland (Podium)

Oct. 2021 **Thornton, C.P.,** Jacobson, L.A., Henegan, S., Carey, L.B., Milla, K., Cork, K., Ruble, K.
Perspectives on supporting schooling for children with cancer: Findings from two PCORI engagement projects.

Association of Pediatric Hematology/Oncology Nursing
Salt Lake City, UT (Podium, virtual)

July 2021 Henegan, S., Jacobson, L., Paré-Blagoev, J., Carey, L.B., Milla, K., **Thornton, C.P.,** & Ruble. K.
The impact of COVID-19 on schooling in children with cancer.
Sigma Theta Tau International Nursing Research Congress.
Singapore (Poster, virtual)

Sept. 2020 **Thornton, C.P.,** Kozachik, S., & Ruble, K.
Psychosocial interventions for adolescents and young adults with cancer.
Association of Pediatric Hematology/Oncology Nursing.
Virtual Conference (Podium)

Sept. 2019 **Thornton, C.P.,** Adams, T., & Duffy, E.
Best Practices and Recommendations for Managing Pain for Children Undergoing Cancer-Related Procedures.
Association of Pediatric Hematology/Oncology Nursing.
San Jose, California (Podium)

Oct. 2018 Duffy, E., Adams, T., Fisher, B., Misasi, J., **Thornton, C.P.,** & McCollum, S.
Evidence-Based Recommendations for the Level of Sedation Required for Adequate Pain Control in Pediatric Oncology Patients Requiring Procedures.
Children's Oncology Group Annual Meeting.
Dallas, Texas (Podium, Invited)

June 2015 **Thornton, C.P.** & Veenema, T.G.
Addressing Child Sexual Abuse in Latin America as a Means to Stop HIV/AIDS.
Sigma Theta Tau International Nursing Research Congress.
San Juan, Puerto Rico (First Author, Podium)

National

[April 2022] **Thornton, C.P.** & Ruble, K.A.
Biobehavioral predictors of dose-limiting toxicities of cancer therapy: Identification of areas for preventative intervention
Association for Clinical and Translational Science
Chicago, IL (Podium)

[April 2022] Paré-Blagoev, J., **Thornton, C.P.,** Ruble, K., & Jacobson, L.A.
Stakeholders: A not-so-secret weapon in a QI clinical education focused dissemination and implementation project.
Association for Clinical and Translational Science
Chicago, IL (Symposium)

Jan 2022 Carey, L.B., **Thornton, C.P.,** Jacobson, L.A.
Educational needs of pediatric oncology patients and survivors.
Council for Exceptional Children
Orlando, FL (Podium, Virtual)

Nov 2021 Milla, K., Carey, L., **Thornton, C.P.,** Henegan, S., Cork, K., Paré-Blagoev, J., Jacobson, L., & Ruble, K.

Integrating patient and family lived-experiences into research and practice: Pediatric cancer as a developmental disability
Association of University Centers on Disabilities
Virtual conference. (Poster)

June 2021 Ruble, K., Carey, L., Paré-Blagoev, J., Milla, K., Henegan, S., Cork, K., **Thornton, C.P.,** & Jacobson, L. Lessons from COVID-19, challenges of remote learning for childhood cancer survivors.
American Society of Clinical Oncology Annual Conference
Virtual Conference. (Poster)

March 2021 Ruble, K., Paré-Blagoev, J., Carey, L. B., Milla, K., Henegan, S., **Thornton, C.P.,** & Jacobson, L. Strategies to improve neuropsychological (NP) care in pediatric oncology: Quality improvement findings.
National Comprehensive Cancer Network Annual Conference.
Virtual Conference. (Poster)

May 2014 **Thornton, C.P.,** Corley, A., & Veenema, T. G.
The Public Health Crisis of Child Sexual Abuse: What Nurses Need to Know.
Association for Community Health Nurse Educators
San Antonio, Texas (Poster, co-first authors)

Dec. 2014 **Thornton, C.P.**
Increasing Testicular Self-Exams in Adolescents.
Johns Hopkins School of Nursing Research Symposium.
Baltimore, Maryland (Poster)

June 2013 **Thornton, C.P.** & Ruble, K.
Effectiveness of Parent Proxy Reports in Pediatric Oncology Survivors.
Johns Hopkins University School of Nursing Research Honors Program.
Baltimore, Maryland (Poster)

NON-PEER REVIEWED AND OTHER PUBLICATIONS

1. Carey, L.B. (2021). Expert interview with **Clifton Thornton**: supporting childhood cancer survivors through medical and school team communication. *Kennedy Krieger Institute: Linking Research to Classrooms*. (blog).
2. **Thornton, C. P.** (2021). Childhood cancer survivors may face neurocognitive challenges. Johns Hopkins' SUCCESS Lab works to ensure they receive a quality education. *Johns Hopkins Nursing Magazine*. bit.ly/3bZHqEx
3. **Thornton, C.P.** & Veenema, T.G. (2012) Disaster Nursing. Smartphone-based clinical-decision support system for clinicians to use during a disaster. *Unbound Medicine.* http://www.unboundmedicine.com/products/disaster_nursing

EDITORIAL ACTIVITIES

Editorial Positions

2022-Present Editorial Board Member *Cancer Control*

Peer Review Activities

2021-Present	Peer Reviewer	*Cancer Control*
2021-Present	Peer Reviewer	*International Journal of Disaster Risk Reduction*
2020-Present	Peer Reviewer	*Journal of Pediatric Oncology Nursing*
2020-Present	Peer Reviewer	*Journal of Emergency Nursing*

Additional Editorial Activities

2018-Present	Abstract Reviewer for Annual Meeting	*Association of Pediatric Hematology/Oncology Nurses*

PROFESSIONAL MEMBERSHIPS AND ACTIVITIES

2021-Present	Council for Exceptional Children	Member
2021-Present	International Psycho-Oncology Society	Early Investigator Group
2020-Present	American Association of Nurse Practitioners	Member
2016-Present	Children's Oncology Group	Nursing Scholar EBP Committee Young Investigator
2015-Present	Association of Pediatric Hematology & Oncology Nursing	Member
2012-Present	Sigma Theta Tau International Honor Society of Nursing	Member
2012-2015	Association of Community Health Nurse Educators	Member

TEACHING EXPERIENCE

ACADEMIC & COURSE DEVELOPMENT

2020-2021	Kids with Cancer Still Need School: The Provider's Role *Graduate Medical Education Course* *Johns Hopkins School of Medicine & Kennedy Krieger Institute. Baltimore, MD*
2020-2021	Doctoral Student Representative *PhD Program Transformation Task Force* *Johns Hopkins School of Nursing. Baltimore, MD*
2019-Present	Pathophysiology – Hematology and Oncology Subjects, Graduate Program *Johns Hopkins School of Nursing. Baltimore, MD*
2017-Present	Pediatric Oncology Seminar (Pediatric and Family Nurse Practitioner Programs) *Johns Hopkins School of Nursing. Baltimore, MD*
2014 Fall	Disaster Preparedness for the Healthcare Professional (Online open course) *Johns Hopkins School of Nursing & Johns Hopkins School of Public Health. Baltimore, MD*

INSTRUCTOR

2022 Spring — Clinical Reasoning I - Clinical Management for the Pediatric Nurse Practitioner: Common Acute Illnesses in Pediatrics (62 students)
Doctor of Nursing Practice, Pediatric Nurse Practitioner Program
Johns Hopkins School of Nursing. Baltimore, MD

2021 Fall — The Research Process and its Application to Evidence-Based Practice (25 students)
Master's Entry to Nursing Program
Johns Hopkins School of Nursing. Baltimore, MD

2011 Fall — Introductory Algebra (67 students, 2 sections)
Structured Learning Assistance Program
Ferris State University. Big Rapids, MI.

2011 Spring — Introductory Chemistry (58 students)
Structured Learning Assistance Program
Ferris State University. Big Rapids, MI.

2010 Fall — Fundamentals of Mathematics (48 students)
Structured Learning Assistance Program
Ferris State University. Big Rapids, MI

2010 Spring — Introductory Chemistry (52 students)
Structured Learning Assistance Program
Ferris State University. Big Rapids, MI

2009 Fall — Introductory Algebra (64 students, 2 sections)
Structured Learning Assistance Program
Ferris State University. Big Rapids, MI.

CLINICAL INSTRUCTOR

2016-Present — Graduate Clinical Preceptor
Pediatric Hematology & Oncology Clinic - Sinai Hospital & Johns Hopkins Hospital
Pediatric Primary Care and Acute Care Nurse Practitioner Program
Johns Hopkins School of Nursing. Baltimore, MD

2014-2015 — Clinical Instructor
Pre-Licensure Public Health Nursing & International Public Health
Johns Hopkins School of Nursing. St Croix, US Virgin Islands

TEACHING ASSISTANT

Sum 2021 — Principles of Pharmacology (Doctoral Program, 129 students)
Johns Hopkins School of Nursing. Baltimore, MD

Spring 2021 — Pathophysiology (Master's Program, 132 students)
Johns Hopkins School of Nursing. Baltimore, MD

Fall 2020 — Pathophysiology (Master's Program, 180 students)
Johns Hopkins School of Nursing. Baltimore, MD

Sum 2020	Leadership for Professional Nursing (Master's Program, 158 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Spring 2020	Pathophysiology (Master's Program, 126 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2019	Health Assessment for Nursing (Master's Program, 162 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Sum 2019	Biostatistics for Evidence-Based Practice (Master's Program, 142 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2014	Principles of Pathophysiology (Baccalaureate Program, 116 students) Physiological & Pathophysiological Basis for Advanced Nursing Practice (MSN, 72 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Sum 2014	Principles of Pathophysiology (Baccalaureate Program, 158 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Spring 2014	Principles of Pharmacology (Baccalaureate Program, 161 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Spring 2014	Physiological & Pathophysiological Basis for Advanced Nursing Practice (MSN, 68 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2013	Principles of Pharmacology (Baccalaureate Program, 71 students) *Johns Hopkins School of Nursing. Baltimore, MD*

STUDY SESSION FACILITATOR AND TUTOR

Spring 2015	Pharmacology (Baccalaureate Program, 120 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2014	Principles of Pathophysiology (Baccalaureate Program, 122 students) *Pharmacology (Baccalaureate Program, 118 students)* *Johns Hopkins School of Nursing. Baltimore, MD*
Spring 2014	Pharmacology (Baccalaureate Program, 135 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2013	Principles of Pathophysiology (Baccalaureate Program, 134 students) *Johns Hopkins School of Nursing. Baltimore, MD*
Fall 2013	Pharmacology (Baccalaureate Program, 136 students) *Johns Hopkins School of Nursing. Baltimore, MD*
2012-2014	Tutor – Pathophysiology, Pharmacology, Child Health (Baccalaureate & Master's program) *Johns Hopkins School of Nursing. Baltimore, MD*
2008-2011	Tutor – Chemistry, Mathematics, Physics, Nuclear Medicine, Allied Health *Ferris State University. Big Rapids, MI*

ADDITIONAL and EXTRACURRICULAR ACTIVITIES

2020-2021	PhD Program Representative – Johns Hopkins Nursing Student Senate *Johns Hopkins School of Nursing. Baltimore, MD*
2020-2021	Curriculum Committee Student Representative – PhD Student Organization *Johns Hopkins School of Nursing. Baltimore, MD*
2017-2018	Provider Representative – Comprehensive Unit-Based Safety Program *Johns Hopkins Hospital, Bloomberg Children's Center, Pediatric Oncology Unit*
2012-2014	President – Johns Hopkins Men in Nursing *Johns Hopkins School of Nursing. Baltimore, MD*
2012-2013	Executive President – Student Government Association *Johns Hopkins School of Nursing. Baltimore, MD*
2009-2011	Member – Ferris State University Nuclear Medicine Association *Ferris State University. Big Rapids, MI*
2007-2008	President – Residence Hall Council *Ferris State University. Big Rapids, MI*
2006-2011	President – Ferris Stars for Make-A-Wish *Ferris State University. Big Rapids, MI*

SERVICE & VOLUNTEER EXPERIENCES

2022	Pediatric Ward Nurse and Nurse Practitioner *Mercy Ships. Dakar, Senegal.*
2020	COVID-19 Command Center, Triage line and consultation *Johns Hopkins University. Baltimore, MD*
2013-2016	Nurse Practitioner, Construction *Hope of Life International. Zacapa, Guatemala*
Jan 2014	Nurse Practitioner and Textbook Contributor *Whole Child International. Managua, Nicaragua*
2006-2012	Volunteer Staff and Wish Interviewer *Make-A-Wish Foundation of Michigan. Grand Rapids, MI.*