# A Safety Assessment of Dexamethasone for Chemotherapy-Induced Nausea and Vomiting in Children Receiving Hematopoietic Stem Cell Transplantation

by

Edric Paw Cho Sing

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Department of Pharmaceutical Sciences
University of Toronto

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## Abstract

Though life-saving, hematopoietic stem cell transplantation (HSCT) carries significant risk for morbidity and mortality. Children receiving chemotherapy to prepare for HSCT also often suffer from poorly controlled chemotherapy-induced nausea and vomiting (CINV). Dexamethasone is an effective antiemetic, but the lack of safety data, especially during HSCT, presents barriers to its routine use. Three projects were undertaken to better understand the safety of dexamethasone in children: (1) a systematic review of the literature; (2) *post-hoc* analysis of its immediate adverse events during HSCT; and (3) a framework to assess its impact on transplant-related mortality. Overall, we identified few high quality studies evaluating the safety of dexamethasone for CINV. Adverse events were transient and of minor clinical significance in the immediate setting. Our framework was designed to feasibly collect and analyze data from multiple centers. Future efforts will refine the overall risk of dexamethasone given as an antiemetic to children undergoing HSCT.

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# Table of Contents

# List of Tables

# List of Figures

**Chapter 1: Introduction**



**Chapter 2: The safety of dexamethasone for the management of chemotherapy-induced nausea and vomiting in pediatric patients: A systematic review**



**Chapter 3: Safety of dexamethasone for nausea and vomiting prophylaxis in children receiving hematopoietic stem cell transplantation**



**Chapter 4: Transplant-related mortality in children receiving dexamethasone for chemotherapy-induced nausea and vomiting during hematopoietic stem cell transplantation: A multi-centre feasibility study**

# List of Appendices

# List of Abbreviations

| | |
|---|---|
| 5-$HT_3$RA | Serotonin-3 receptor antagonist |
| AA | Aplastic anemia |
| ACH | Alberta Children's Hospital |
| AE | Adverse event |
| aGVHD | Acute graft-versus-host disease |
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| ANS | Autonomic nervous system |
| aOR | Adjusted odds ratio |
| ASCO | American Society of Clinical Oncology |
| BBB | Blood-brain-barrier |
| BDNF | Brain-derived neutrophil factor |
| BM | Bone marrow |
| CBCL | Child Behavior Checklist |
| CI | Confidence interval |
| CIN | Chemotherapy-induced nausea |
| CINV | Chemotherapy-induced nausea and vomiting |
| CIV | Chemotherapy-induced vomiting |
| CML | Chronic myeloid leukemia |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTZ | Chemoreceptor trigger zone |
| CYP | Cytochrome P450 |
| DRI | Disease Risk Index |
| EBMT | European Blood and Marrow Transplant |
| EFS | Event-free survival |
| ESMO | European Society of Medical Oncology |
| G-CSF | Granulocyte colony stimulating factors |
| GERD | Gastroesophageal reflux disease |

| | |
|---|---|
| GVHD | Graft-versus-host disease |
| GVL | Graft-versus-leukemia |
| HCT-CI | Hematopoietic Cell Transplantation-specific Comorbidity Index |
| HEC | Highly emetogenic chemotherapy |
| HLA | Human leukocyte antigen |
| HPA | Hypothalamic-pituitary-adrenal |
| HSC | Hematopoietic stem cell |
| HSCT | Hematopoietic stem cell transplantation |
| IFD | Invasive fungal disease |
| IFN-α | Interferon-alpha |
| IL-2 | Interleukin-2 |
| IV | Intravenous |
| LCAT | Liverpool Causality Assessment Tool |
| MASCC | Multinational Association of Supportive Care in Cancer |
| MDS | Myelodysplastic syndrome |
| MEC | Moderately emetogenic chemotherapy |
| NCCN | National Comprehensive Cancer Network |
| NHL | Non-Hodgkin's lymphoma |
| $NK_1RA$ | Neurokinase-1 receptor antagonist |
| PAM | Pretransplantation Assessment of Mortality |
| PeNAT | Pediatric Nausea Assessment Tool |
| PBSC | Peripheral blood stem cells |
| PO | Per os (by mouth) |
| POGO | Pediatric Oncology Group of Ontario |
| PS | Propensity score |
| RR | Risk ratio |
| TBI | Total body irradiation |
| TPN | Total parenteral nutrition |
| TRM | Transplant-related mortality |
| UCB | Umbilical cord blood |

# Chapter 1
# Introduction

## 1.1 Preamble

Hematopoietic stem cell transplantation (HSCT) offers a potentially curative and life-saving option for many children with malignant and non-malignant diseases. This once experimental procedure has transformed the care of childhood cancers and other blood disorders as an internationally recognized and established treatment. In essence, HSCT permits the delivery of intense chemotherapy without subjecting patients to the fatal complications of prolonged, irreversible pancytopenia. Patients with cancer who undergo allogeneic HSCT additionally benefit from the graft-versus-cancer or graft-versus leukemia (GVL) effect of a reformed immunological system. The collective efforts of international research groups coupled with advances in transplant technology continue to refine the delivery of HSCT and improve outcomes.

The marked advantages of HSCT are often offset by substantial morbidity and mortality, related mainly to end-organ damage, serious infection and, in allogeneic HSCT, graft-versus-host disease (GVHD). Identifying patients who experience transplant-related mortality (TRM; death due to causes other than disease recurrence or progression) provides a valuable measure for informing strategies that impact survival. Furthermore, surveillance and management of transplant-related toxicities that contribute to TRM underscore the importance of supportive care.

Children who receive conditioning in preparation for HSCT are often burdened by severe chemotherapy-induced nausea and vomiting (CINV). Dexamethasone is a corticosteroid supported by numerous studies for its efficacy in the treatment and prevention of CINV. However, its use in pediatric patients immediately before and during HSCT is controversial. Concerns stem from the potential interference of immunosuppression with the curative GVL effect of allogeneic HSCT and immune reconstitution following autologous and allogeneic HSCT. There has not yet been direct evidence to support or allay this concern. Overall, the safety of dexamethasone as an antiemetic in pediatric patients is inadequately described.

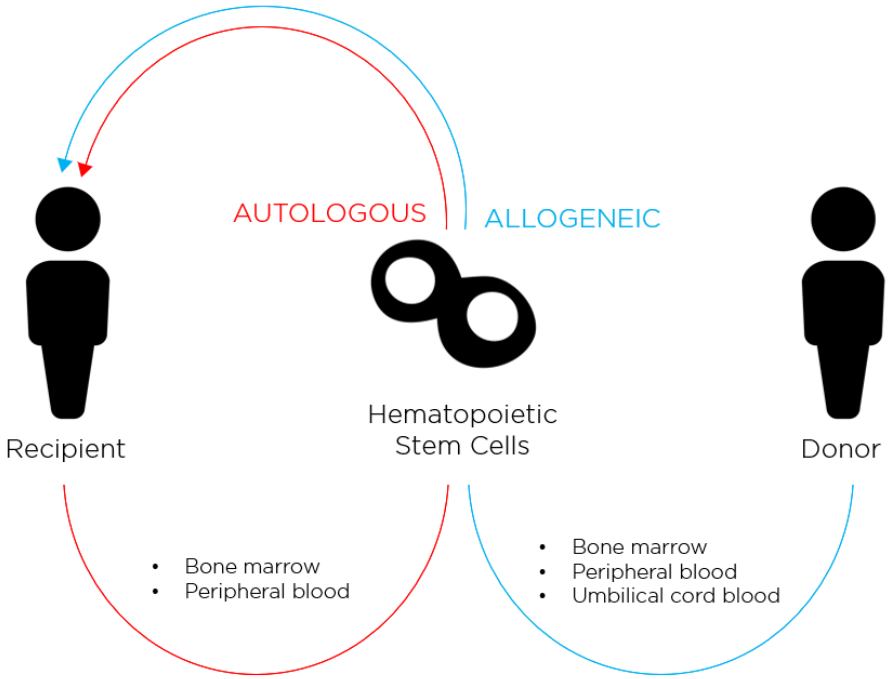
The three projects encompassed by this thesis contribute to the understanding of the risks of using dexamethasone as an antiemetic in children and adolescents undergoing HSCT. This insight will help establish the standard of care for CINV prophylaxis in this setting. The first project is a systematic review of studies that report adverse effects of dexamethasone for CINV. By compiling and summarizing published findings, the current gaps in knowledge are identified. The second project is a single-center, *post-hoc*, retrospective review describing immediate adverse events of dexamethasone in pediatric patients during HSCT. This study characterizes the acute experiences of children and adolescents receiving dexamethasone as recorded in the medical record. Lastly, the framework and feasibility of a multi-center, retrospective study are described. This study will aim to analyze differences in TRM and other HSCT outcomes (event-free survival, invasive fungal disease, acute GVHD, and time to neutrophil engraftment) between children who did and did not receive dexamethasone. A future, large-scale, collaborative investigation will be conducted to determine the effect of dexamethasone on HSCT outcomes with greater certainty.

## 1.2 Hematopoietic Stem Cell Transplantation

Today, over 1 million hematopoietic stem cell transplants (HSCTs) in over 75 countries have been conducted with increasing frequency worldwide.[1] In Canada, over 4,500 HSCTs are performed annually in recipients younger than 18 years.[2] In the United States and Europe, an estimated 12,500 and 4,500 HSCTs are performed each year in recipients younger than 20 years and 18 years, respectively.[3-5] The likelihood of survival following HSCT for various hematological disorders also continues to improve due to ongoing advancements in stem cell technology and research.[6]

HSCT is offered as the only curative treatment available for many children with malignant and non-malignant diseases. The procedure involves the administration of hematopoietic progenitor cells with the capacity to self-renew and differentiate into mature red cells, white blood cells, and platelets. These stem cells are harvested from various sources (bone marrow, peripheral blood, and umbilical cord blood) and donors (autologous or allogeneic).[7,8] Figure 1.1 depicts a basic schematic of these various sources and donors of hematopoietic stem cells (HSCs).

**Figure 1.1** Schematic of autologous and allogeneic HSCT



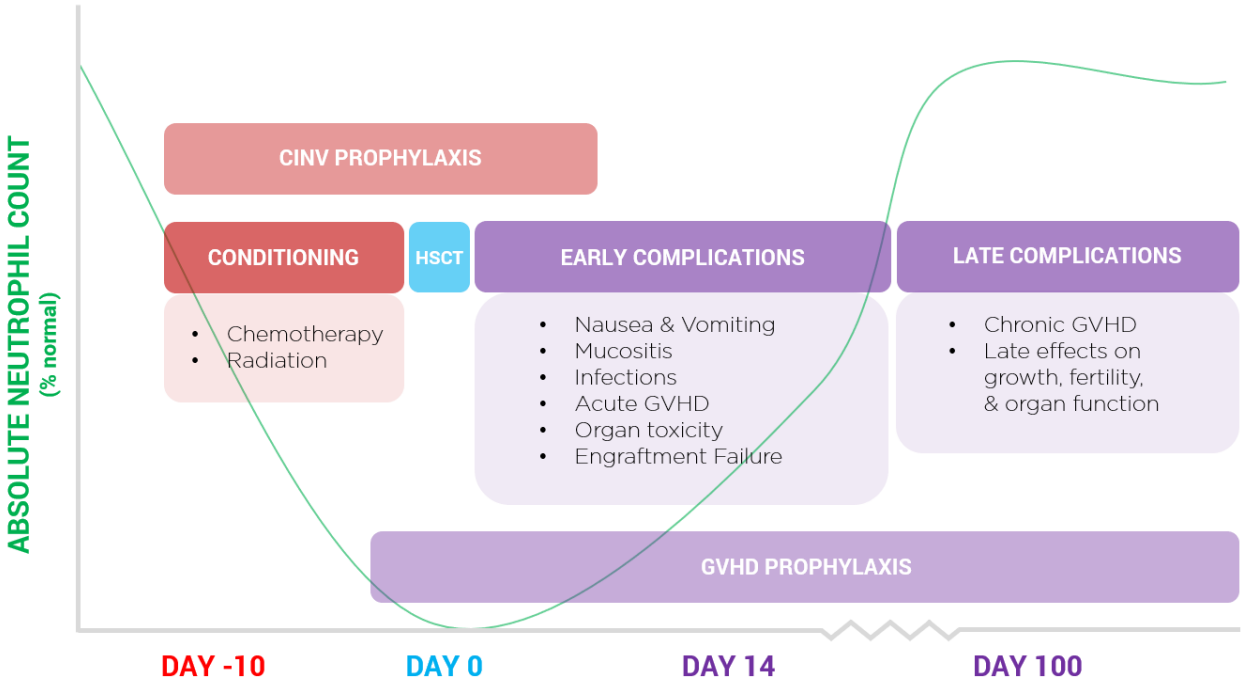
In autologous HSCT, the patient acts as their own source of HSCs. The goal is to rescue the patient from prolonged or irreversible effects of profound pancytopenia caused by high doses of chemotherapy and/or radiation. In allogeneic HSCT, the patient receives HSCs from another individual. The goal is to reconstitute the hematopoietic system of the recipient with the donor's HSCs and, in patients with malignant disease, deliver the curative graft-versus-leukemia effect. More than 75% of pediatric HSCTs are allogeneic as reported by a 2014 EBMT survey of international HSCT practices.[9]

Allogeneic HSC donors are selected carefully according to the compatibility of their human leukocyte antigens (HLA) with those of the recipient. Compatibility is classified as matched (usually from a sibling), haplo-identical (from a first-degree relative with a partial HLA match), or mismatched (usually from live donor registries or umbilical cord blood banks). Matched sibling and related donors are preferred due to an associated higher probability of HSCT success. However, many variables are taken into consideration, such as donor availability, the urgency of HSCT, the underlying condition of the recipient, and donor health status.[7]

The combination of chemotherapy, radiation therapy, and/or immunotherapy given prior to HSC infusion is termed conditioning. The intended effect of conditioning is to prepare the HSCT recipient to receive the donor stem cells by creating space within the bone marrow, eliminating the underlying disease, and providing immune suppression. Conditioning may be classified as myeloablative (regimens given at intensive doses to cause pancytopenia), non-myeloablative (regimens that cause minimal cytopenia), and reduced intensity (regimens that fit neither category and spare patients with advanced age or comorbidities from pancytopenia and further organ toxicity).[7,10]

Various early and late complications associated with HSCT offset its desirable effects. Organ toxicity and infections significantly contribute to the morbidity and mortality of HSCT recipients. The gastrointestinal, pulmonary, cardiac, hepatic, renal, mucocutaneous, and endocrine systems are commonly affected. The time to onset of these complications is largely predictable based on the duration of time elapsed from HSC infusion. Factors known to influence the risk of complications include pre-existing comorbidities, conditioning intensity, and source of stem cells.[7,11] A broad overview of the major events during HSCT are presented in Figure 1.2.

**Figure 1.2** Approximate timeline of major events during myeloablative allogeneic HSCT and absolute neutrophil count recovery[12,13]




Adapted from Storek J. Immunological reconstitution after hematopoietic cell transplantation – its relation to the contents of the graft. *Expert Opinion on Biological Therapy*. 2008;8(5):583-597. CINV=Chemotherapy-induced nausea and vomiting; HSCT=Hematopoietic stem cell transplantation; GVHD=Graft-versus-host disease

Engraftment of donor HSCs and immune reconstitution are essential for a successful HSCT. Immediately after myeloablative conditioning, HSCT recipients experience profound pancytopenia lasting from days to weeks, followed by regeneration of immune cells at varying rates (Figure 1.2 shows approximate absolute neutrophil counts during and after myeloablative allogeneic HSCT). Absolute neutrophil count is a common parameter to clinically evaluate post-transplant engraftment. Time to neutrophil recovery is widely recognized to depend on the source of stem cells. Recipients of growth factor-mobilized peripheral blood stem cells (PBSC) achieve neutrophil recovery in approximately 2 weeks compared to 3 weeks and 4 weeks in recipients of bone marrow (BM) and umbilical cord blood (UCB) grafts, respectively.[12,13]

Failure to establish (primary) or loss of (secondary) functional hematopoiesis after HSCT as indicated by the absolute neutrophil count and/or cytogenetic studies, is known as graft failure. The cause for this complication may be multi-factorial, including HLA-incompatibility, umbilical cord blood as HSC source, T-cell depletion, concomitant infections (e.g.

cytomegalovirus), and myelosuppressive drug therapy.[14] A second HSCT or donor lymphocyte infusions are considered when hematopoietic function is inadequate following HSCT.

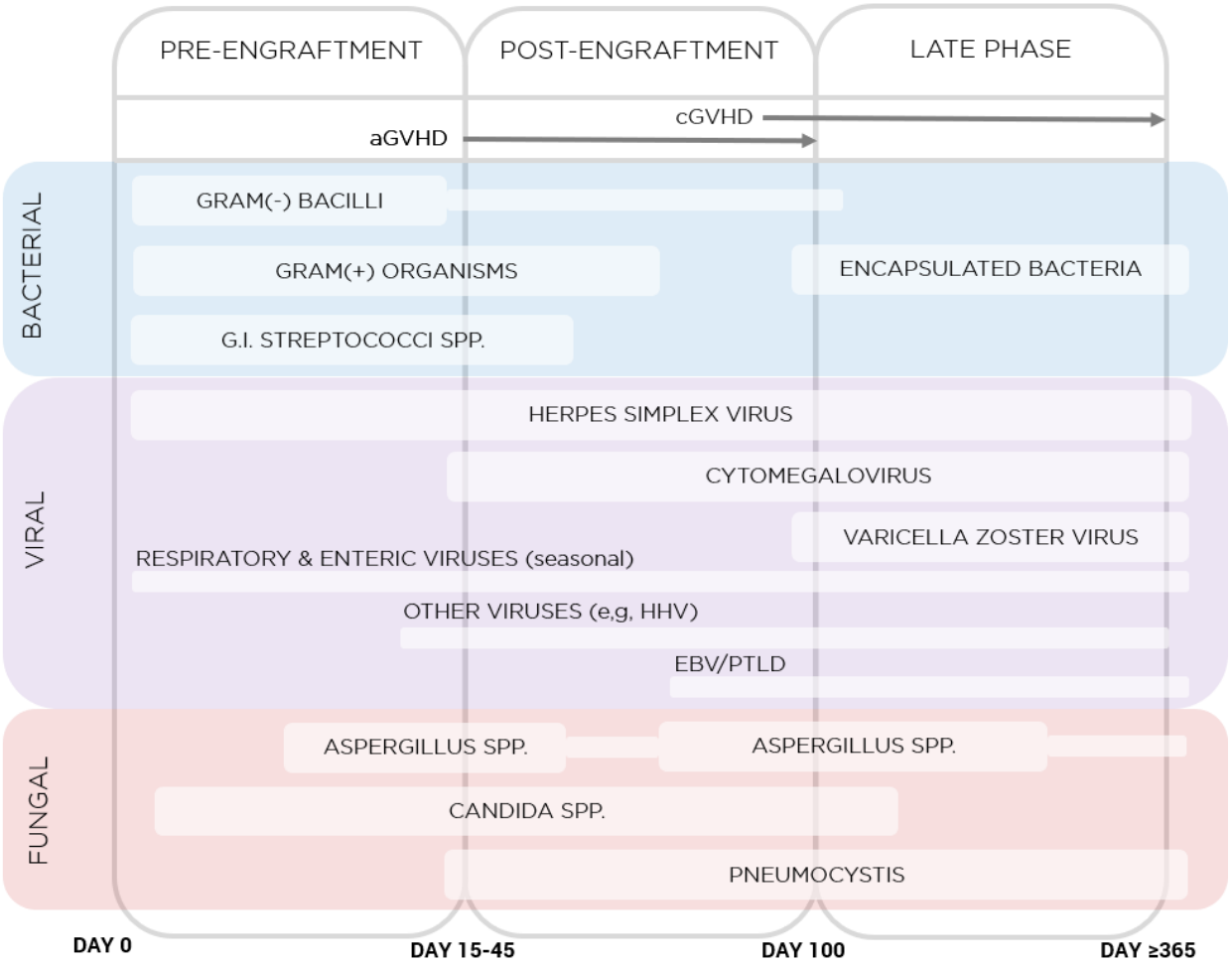
### 1.2.1 Risks of HSCT

Although it offers considerable therapeutic benefit, HSCT remains a clinical intervention with severe and possibly life-threatening risks. Important contributors to the burdens of HSCT include opportunistic infections, graft-versus-host disease, sinusoidal obstructive syndrome, nutritional deficiencies, and chemotherapy-induced nausea and vomiting.[3,7]

The impairment of the innate and adaptive immunity following HSCT provides a wide window of opportunity for infections. Moreover, numerous portals of entry (e.g. mucocutaneous lesions, central venous access devices) and immunosuppressant drug therapy facilitate systemic infection by bacterial, fungal, and viral pathogens. Prior to engraftment, there is a substantial risk for bacteremia with gram-negative and gram-positive organisms and fungal sepsis. Following engraftment, primary infection or reactivation of viruses, such as cytomegalovirus, Epstein-Barr virus, and BK virus become concerning possibilities. A largely preventable pneumonia caused by *Pneumocystis jiroveci* is also possible during this period and warrants routine prophylaxis. The late phase of infectious risk is driven by encapsulated bacteria (e.g. Streptococcus pneumonia) and varicella zoster virus, especially in patients with an ongoing need for immunosuppression. Throughout pre-engraftment to late post-engraftment phases, enteric and respiratory viruses (e.g. adenovirus, respiratory syncytial virus) as well as reactivation of herpes simplex virus present as constant infectious threats. See Figure 1.3 for a summary of the various phases during which opportunistic infection with specific pathogens are most likely during allogeneic HSCT.[12]

Invasive fungal disease (IFD) remains a leading cause of non-relapse mortality in children undergoing allogeneic HSCT. It is estimated to occur in 8-17% of pediatric HSCT recipients and carry a mortality rate of 35 to 50%.[15-20] Invasive aspergillosis and candidiasis represent the most commonly reported IFDs in children undergoing HSCT.[3,21] Pneumonia due to endemic fungi in North America, such as histoplasmosis and coccidioidomycosis, present additional concerns in immunocompromised patients.[22] The depth and duration of neutropenia, high-dose corticosteroid exposure, and acute and chronic graft-versus-host disease are reported risk factors for IFD in children undergoing HSCT.[23]

**Figure 1.3** Phases of opportunistic infections with bacterial, viral, and fungal pathogens among recipients of allogeneic HSCT[12]




Adapted from Tomblyn M, Chiller T, Einsele H, *et al*. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238. aGVHD=Acute graft-versus-host disease; cGVHD=Chronic graft-versus-host disease; Spp.=Species; HHV=Human herpesvirus; EBV=Epstein-Barr virus; PTLD=Post-transplant lymphoproliferative disorder;

Graft-versus-host disease (GVHD) represents a common major complication of allogeneic HSCT. Its incidence is directly associated with the degree of donor-recipient HLA disparity.[24,25] An estimated 28% of patients with an HLA-matched sibling donor and up to 85% of those with an unrelated donor experience grade II to IV acute GVHD (aGVHD).[26-28] Conditioning- or disease-induced tissue damage triggers a chain of events resulting in immune reactivity of donor T-cells against recipient tissues. When this manifests before and after 100 days following HSC infusion (Day +100), this is widely classified as acute and chronic GVHD, respectively.[29] Most commonly, acute manifestations affect the skin, gastrointestinal tract (e.g. stomach, duodenum,

colon), and liver. Chronic GVHD can involve any tissue including the skin, mucosa, muscle, joint, liver, gut, and lungs. Immunosuppressant drug therapy is used to control symptoms until tolerance is achieved between donor T-cells and the healthy tissues of the HSCT recipient.[7]

### 1.2.2 Transplant-Related Mortality

Treatment-related mortality, or at times known as non-relapse mortality, is a common survival metric in pediatric cancer studies. It represents the impact of supportive care strategies and treatment intensity. Describing the proportion of mortality events due to any cause other than those related to the disease is vital for optimizing the safety of treatment protocols, including conditioning prior to HSCT. In the HSCT setting, a distinct yet comparable term has been coined transplant-related mortality (TRM).

Over the last few decades, advancements owing to research and technology have improved TRM rates. A single-center review shows that TRM dramatically dropped from 33% (1984-1992) to 5% (2001-2009) in children with acute lymphoblastic leukemia (ALL) undergoing HSCT.[30] Another review of allogeneic HSCT for the treatment of a variety of conditions documented a reduction from 27% (1983-1999) to 9% (2000-2010).[31] From a multinational study group, the mean 4-year TRM in children with high-risk ALL was found to be 10% and 2% in those transplanted from matched unrelated and sibling donors, respectively.[32] More current estimates of TRM rates in children and adolescents are typically 5-10%, but depend on an array of factors.[7]

Various prediction scores have emerged to facilitate pre-transplant assessment and the decision to proceed with HSCT. The EBMT risk score was initially developed for chronic myeloid leukemia (CML) patients but then was extended to other acquired hematological disorders (ALL, acute myeloid leukemia [AML], myelodysplastic syndrome, non-Hodgkin's lymphoma, aplastic anemia). By combining five disease and transplant characteristics, the score produces a method for a quick assessment of the risk of mortality due to HSCT. The validity of this tool is supported by an analysis suggesting that it explains up to 63% of TRM.[33] With over 10 years of data analyzed, it remains valid irrespective of conditioning intensity and advances in HSCT technology. For research purposes, the EBMT risk score holds promise as a way to balance the baseline risk of TRM among comparator groups.

Other prediction scores have been developed that are also validated in pediatric cancer patients or are intended to complement the EBMT risk score. The Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) is a scoring system validated to comprehensively account for the burden of pre-transplant co-morbidities in risk assessment.[34] The Disease Risk Index (DRI) integrates disease-related parameters, such as cytogenetics, and was designed to complement gold standard prognostic tools, namely the EBMT risk score.[35] Another scoring system specifically for allogeneic HSCTs, the Pretransplantation Assessment of Mortality (PAM) score predicts outcomes using exclusively clinical data.[36] These scoring systems and their relative predictive value and clinical utility have yet to be compared.

An overview of the characteristics of established pretransplantation prognostic risk scoring systems is found in Table 1.1. The PAM score and DRI were not considered for the purposes of this thesis project owing to their lack of experience and validity in a pediatric population. In chapter 4, the rationale for selecting the EBMT risk score over the HCT-CI is discussed.

**Table 1.1** Overview of pretransplantation prognostic risk scoring systems for determination of HSCT eligibility[17,33-40]

| | EBMT | PAM | HCT-CI | DRI |
|---|---|---|---|---|
| Validated Outcomes | TRM, OS, Relapse | 2-year OS | TRM, OS | 2-year OS |
| Validation Cohort | • N=>150,000 via EBMT registry<br>• Auto & Allo HSCT<br>• Adult & Pediatrics | • N=1,549 via 3 cancer sites<br>• Allo HSCT<br>• Adult | • N=19,767 via CIBMTR registry<br>• Auto & Allo HSCT<br>• Adult & Pediatrics | • N=13,131 via CIBMTR registry<br>• Allo HSCT<br>• Adult |
| Variables | 5 variables:<br>• Age<br>• Disease stage<br>• Time interval from diagnosis<br>• Donor type<br>• Donor-recipient sex combination | 5 variables:<br>• Age<br>• Disease risk<br>• Donor type<br>• Forced expiratory volume in 1 second<br>• Donor-recipient CMV serology | 17 variables:<br>• Pulmonary disease<br>• Cardiac disease<br>• Hepatic disease<br>• Renal disease<br>• Other malignancies<br>• Other comorbidities (e.g. diabetes, psychiatric, obesity) | 3 variables:<br>• Disease type<br>• Disease stage<br>• Cytogenetics (AML) |

EBMT=European Group for Blood and Marrow Transplantation; PAM=Pretransplantation Assessment of Mortality; HCT-CI=Hematopoietic Cell Transplantation-specific Comorbidity Index; DRI=Disease Risk Index; TRM=Transplant-related mortality; OS=Overall survival; CIBMTR=Center for International Blood and Marrow Transplant Research; Auto=Autologous; Allo=Allogeneic; HSCT=Hematopoietic stem cell transplantation; CMV=Cytomegalovirus; AML=Acute myeloid leukemia

## 1.3 Chemotherapy-Induced Nausea and Vomiting

Vomiting is defined as the forceful ejection of gastric contents. Together with non-productive attempts to vomit (retching), it is known as emesis.[41] The emetic reflex is an intricate multiple-step pathway leading up to the activation of a cluster of neurons in the medulla oblongata, termed the vomiting centre. Chemical interactions between neurotransmitters (e.g. dopamine, serotonin, neurokinin, acetylcholine, and histamine) and their receptors in the peripheral and central nervous systems are ultimately responsible for driving the emetic reflex.[42-45]

There are several ways that chemotherapy can activate the vomiting center to cause chemotherapy-induced vomiting (CIV). The chemoreceptor trigger zone (CTZ) constantly monitors the blood and cerebral spinal fluid for emetogenic stimuli such as cytotoxic drugs and other noxious substances. This is possible because of a relatively permeable blood-brain-barrier in the area postrema and a dense population of neurotransmitter receptors. Following activation, the CTZ projects signals to the vomiting center to induce emesis. Secondly, chemotherapy-induced destruction of intestinal enterochromaffin cells initiates the mass release of neurotransmitters such as serotonin. Thereafter, vagal afferent nerves transmit impulses to the solitary tract nucleus in the dorsal brain stem. It is the function of the solitary tract nucleus to integrate peripheral input from various organs and relay these signals to the vomiting center. Finally, cognitive anticipation of chemotherapy can trigger the vomiting center even before chemotherapy is administered. Generated by higher cortical structures in the brain, this conditioned response is reinforced by anxiety and distress, especially in patients with previously uncontrolled emesis.[46] Once the vomiting center is activated, efferent impulses are sent to the salivation, respiratory, and vasomotor centers, and to cranial nerves VIII and X. These innervate the pharyngeal, gastrointestinal, and abdominal muscles to coordinate the action of vomiting.[42-45]

Nausea is defined as a feeling of gastric discomfort and an urge to vomit.[47] It is essential to distinguish this phenomenon from vomiting as a distinct, subjective, but likewise distressing consequence of chemotherapy. In contrast, it has been argued that nausea and vomiting operate on a continuum. It has been speculated to be a low-intensity or below-threshold activation of the emetic reflex. Like pain, nausea may act as a specialized warning system derived from signals from the epigastric region.[48] Without a full mechanistic understanding of the inherent neural

pathways involved due to the limitations of animal models, the etiology of chemotherapy-induced nausea (CIN) remains poorly understood.

Existing evidence supports an association between nausea and autonomic nervous system (ANS) activity. Parasympathetic changes accompanying nausea manifest as pupil dilation, cutaneous vasoconstriction, sweating, salivation, tachycardia, and proximal gastric relaxation. Morrow *et al*. demonstrates a consistent pattern of increasing heart rate variability indicative of a rise in cardiac vagal activity preceding the onset of nausea. This suggests parasympathetic outflow may set the stage for the expression of nauseous symptoms.[48-50] Moreover, nausea is known to be one of the clinical characteristics of adrenal insufficiency, which implicates the involvement of the hypothalamic-pituitary-adrenal (HPA) axis in the pathogenesis of CIN. Hursti *et al*. found that lower cortisol levels may predict a higher incidence and magnitude of CINV rationalizing the use and observed efficacy of corticosteroids as antiemetics.[51] Similar to CIV, the beliefs and expectations of cancer patients may shape their prognosis and development of CIN. Kirsch *et al*. proposes the schema theory wherein a patient expecting a symptom (e.g. nausea) will be more likely to interpret sensations as nauseating.[52] Due to its complexity and wide subjectivity and lack of reliable animal models, it is challenging to clearly elucidate the mechanism of CIN. This limits the prospects of developing targeted and effective anti-nausea treatments.

Chemotherapy-induced nausea and vomiting (CINV) are frequently described in phases. The acute phase is typically defined as beginning with administration of the first chemotherapy dose of the block and ending 24 hours after the administration of the last chemotherapy of the block. Delayed phase is defined as beginning at the end of the acute phase and persisting for 3 to 7 days.[49,53-55] The combination of both acute and delayed phases is known as the overall phase. These phases are suggested to differ in the neurotransmitter most predominantly involved: serotonin in the acute phase and substance P in the delayed phase.[56] This justifies the roles of serotonin and neurokinin receptor antagonists in preventing acute and delayed CINV, respectively. In the 24 hours that precede administration of a chemotherapy agent, patients may experience nausea and/or vomiting without an immediate physiological or pharmacological cause.[46] This is known as anticipatory CINV and is a conditioned response to perceptive stimuli, such as personal thoughts or sensations associated with chemotherapy administration.[57]

Complete control of CINV is the optimal outcome in antiemetic trials and clinical practice. The Pediatric Oncology Group of Ontario (POGO) defines complete control as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given during the period of evaluation as prophylaxis, and no nausea-related change in the child's usual appetite and diet.[46] Partial CINV control is defined as one or two emetic episodes within a 24-hour period. Failure of CINV prophylaxis is defined as more than two emetic episodes within a 24-hour period or a maximum Pediatric Nausea Assessment Tool (PeNAT) score of 3 (moderate) or 4 (severe).[58,59]

### 1.3.1 Burden of CINV

The emotional and physical burden associated with CINV has long been recognized. This is particularly profound in patients receiving HSCT conditioning as intensive doses of multiple chemotherapy agents are given over several consecutive days. It is reported that only 5% and 12% of children receiving HSCT conditioning experience complete control of CINV during the acute and delayed phases, respectively.[60]

Nausea and vomiting are consistently ranked as belonging to the top five most severe side effects of chemotherapy according to surveys of adult cancer patients.[61-63] Parents of children receiving cancer therapy ranked nausea as the fourth most prevalent and bothersome treatment-related side effect.[64] In addition to the distress, patients may suffer from complications such as dehydration, electrolyte disturbances, and Mallory-Weiss tears. Uncontrolled vomiting may interrupt or delay scheduled doses of chemotherapy, thereby compromising the chance for a cure.

Inadequate food intake is another consequence of poorly controlled CINV.[65] Undernutrition and weight loss in childhood cancer patients are associated with lower health-related quality of life, particularly in the domains of physical and social functioning.[66] Malnourishment may also contribute to increased susceptibility to febrile neutropenia with bacteremia and reduced survival rates.[67] Without the ability to tolerate an adequate enteral diet, children undergoing HSCT rely on parenteral nutrition to meet their energy requirements. While beneficial as a short-term strategy, there is evidence to suggest that excessive reliance on parenteral nutrition is linked to downstream HSCT complications. These include higher risks of hepatobiliary toxicity and more severe acute GVHD and mucositis.[68-70] For these reasons, it is important to strive for and achieve complete control of CINV in cancer patients, especially those undergoing HSCT.

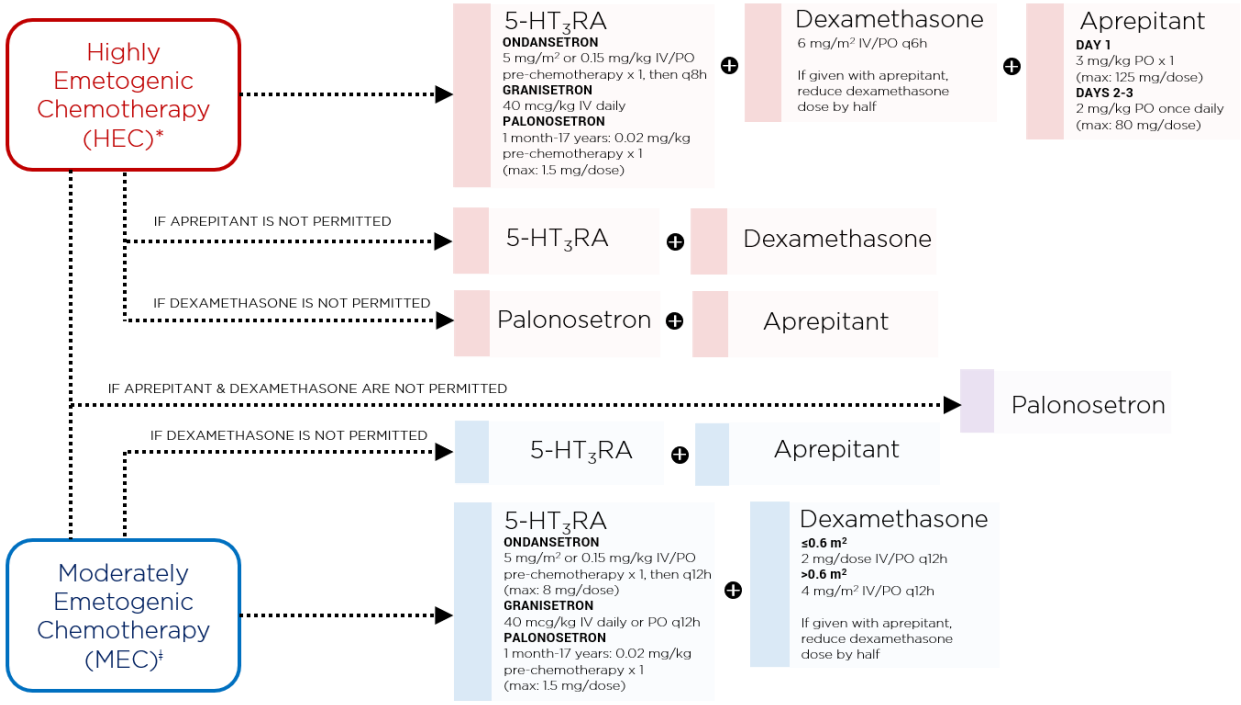
### 1.3.2 Prevention and Treatment of CINV

The proportion of patients who vomit within 24 hours of administration of a chemotherapy agent or regimen in the absence of antiemetic prophylaxis is used to classify its acute emetogenicity.[71] Evidence to support this graded system is predominantly generalized from the experiences in adult patients. Major supportive care practice guidelines in adults stratify emetogenicity into four categories: high, moderate, low, and minimal.[53-55] Many HSCT conditioning regimens cause emesis in >90% of patients who do not receive CINV prophylaxis and are therefore classified as highly emetogenic chemotherapy (HEC). Other agents used in the pediatric HSCT setting, such as busulfan and melphalan, are moderately emetogenic chemotherapy (MEC). Thus, acute emesis is expected to occur in 30 to 90% of patients without CINV prophylaxis who receive these chemotherapy agents.

Several professional associations provide formal recommendations based on emetogenicity to guide the optimal management of CINV in pediatric patients. These are published in guidelines developed by the Pediatric Oncology Group of Ontario (POGO), the Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology (MASCC and ESMO), and the American Society of Clinical Oncology (ASCO).[47,53,54] The first-line antiemetic agents recommended in the prevention and treatment of acute CINV are consistent across clinical practice guidelines. See Figure 1.4 for a summary of the current POGO guideline recommendations in children and adolescents receiving highly and moderately emetogenic chemotherapy.

For patients receiving HEC, a three-drug combination of a 5-$HT_3$ receptor antagonist, dexamethasone, and aprepitant, is strongly recommended. For those receiving MEC, a two-drug combination of a 5-$HT_3$ receptor antagonist and dexamethasone is strongly recommended. In both scenarios, it is the standard of care to include dexamethasone to the prophylactic regimen. The use of an alternative antiemetic reduces the likelihood of complete control of CINV. With the exception of palonosetron, antiemetic agents in place of dexamethasone are weakly recommended or not recommended at all by clinical practice guidelines.[47] The strongest evidence exists for the combination of a 5-$HT_3$ receptor antagonist plus dexamethasone with or without aprepitant. Thus, omission of dexamethasone increases the risk of unnecessary suffering in children undergoing HSCT.

**Figure 1.4** Summary of POGO recommendations of antiemetic agents to prevent CINV in pediatric cancer patients ≥6 months receiving highly or moderately emetogenic chemotherapy (HEC or MEC)[47]




*=Greater than 90% experience emesis in the absence of prophylaxis; ǂ=30-90% experience emesis in the absence of prophylaxis; 5-HT$_3$RA=Serotonin-3 receptor antagonist; IV=Intravenous; PO=By mouth

## 1.4 The Role of Dexamethasone in CINV

Reports observing the antiemetic properties of corticosteroids were first made in the 1980's. Dexamethasone has since emerged as the corticosteroid of choice for CINV prophylaxis due its high potency, prolonged biological effect, and lack of mineralocorticoid activity.[72] When given with other antiemetic agents (5-HT$_3$ receptor antagonists), dexamethasone offers additional protective benefit against CINV in adult and pediatric cancer patients.

The exact antiemetic mechanism of dexamethasone is not fully understood. One prominent theory relates this effect to its anti-inflammatory characteristics. Corticosteroids are postulated to attenuate the downstream effects of inflammatory mediators (e.g. prostaglandins, substance P) released following chemotherapy-induced tissue destruction. Another proposed mechanism involves reducing 5-HT$_3$ production and 5-HT$_3$ receptor expression, thereby suppressing a major neurotransmitter responsible for emesis. Further, CINV may originate from adrenal insufficiency

which implies that corticosteroids could be effective due to the normalization of hypocortisolemia. Lastly, dexamethasone is speculated to exert a central effect on the solitary tract nucleus and antagonize adrenergic receptors in the brain to regulate emesis.[44]

### 1.4.1 Antiemetic Efficacy

The efficacy of dexamethasone for CINV prophylaxis is extensively documented in adult oncology patients. A meta-analysis of 25 randomized clinical trials evaluating 3,714 patients receiving HEC or MEC found that dexamethasone increased the chance that patients would not vomit during the acute phase compared to placebo or no prophylaxis (risk ratio [RR]: 1.26; 95% confidence interval [CI]: 1.21-1.32). In 16 randomized studies of 2,278 patients, a protective benefit of similar magnitude was also demonstrated during the delayed phase (RR: 1.29; 95% CI: 1.18-1.40).[73] When given in addition to a 5-$HT_3$ receptor antagonist, dexamethasone enhances protection against vomiting and nausea compared to 5-$HT_3$ receptor antagonist alone, with superior patient preference and minimal additional side effects.[74-77] A meta-analysis of data of over 3,000 adult patients estimated an increase of 25% and 34% in complete control of acute and delayed vomiting, respectively, when dexamethasone was given in addition to a 5-$HT_3$ receptor antagonist.[73] Moreover, the Italian Group for Antiemetic Research has investigated various intravenous dexamethasone doses ranging from 4 to 20 mg in patients receiving cisplatin.[78] The results of this dose-finding study are reflected in the current dosage recommendation for dexamethasone in consensus guidelines such as MASCC/ESMO, ASCO, and the National Comprehensive Cancer Network (NCCN) (Table 1.2).[53-55]

The pediatric evidence supporting the antiemetic efficacy of corticosteroids is limited but consistently positive. A Cochrane review identified four randomized trials evaluating the comparative effectiveness of corticosteroids in controlling CINV in children. Pooled findings from two of these studies estimating the benefits of adjunctive corticosteroids to first generation 5-$HT_3$ receptor antagonists (e.g. ondansetron, granisetron) showed a higher risk ratio for complete control of vomiting when dexamethasone or methylprednisolone was added (RR: 2.03; 95% CI: 1.35, 3.04).[79] More recently, the authors of a double-blind, randomized controlled trial partly attributed a higher than expected rate of complete vomiting control in their study arm (5-$HT_3$RA + dexamethasone + aprepitant: 48%; vs. 5-$HT_3$RA + dexamethasone + placebo: 12%) to an interaction between aprepitant and dexamethasone. Given together, they speculate that

aprepitant, a moderate CYP3A4 inhibitor, may increase systemic exposure to dexamethasone, resulting in a boosted antiemetic effect.[80]

Despite strong guideline recommendations, there is a lack of trials comparing different corticosteroids, dosing, and routes of administration to reach a strong conclusion on an optimal regimen. Pediatric studies report daily dexamethasone doses ranging widely from 6 to 24 mg/m$^2$/day.[71,79] In practice, the use of dexamethasone as an antiemetic in children has been highly controversial. A survey of 34 Children Oncology Group institutions revealed 29 different dexamethasone dosing regimens in use for children receiving highly emetogenic chemotherapy. Only three respondents indicated that guideline-consistent dexamethasone dosing (6 mg/m$^2$/dose IV/PO every 6 hours) was recommended at their institution while two respondents stated that dexamethasone was never given as an antiemetic.[81] We speculate that this lack of consistency reflects a widespread concern regarding the safety of dexamethasone.

**Table 1.2**. Summary of guideline recommendations of dexamethasone dosing to prevent CINV due to highly and moderately emetogenic (HEC and MEC) chemotherapy in adult and pediatric patients[47,53-55]

| | ADULTS | | | CHILDREN & ADOLESCENTS |
|---|---|---|---|---|
| | NCCN | ASCO | MASCC | POGO |
| HEC | **ACUTE**<br>20 mg PO/IV x 1<br><br>*With NK$_1$RA:*<br>12 mg PO/IV x 1<br><br>**DELAYED**<br>*With aprepitant:*<br>8 mg PO/IV daily on Days 2-4<br><br>*With fosaprepitant:*<br>8 mg PO/IV x 1 on Day 2, then 8 mg BID Days 3-4 | **ACUTE**<br>20 mg PO/IV x 1<br><br>*With NK$_1$RA:*<br>12 mg PO/IV x 1<br><br>**DELAYED**<br>*With aprepitant:*<br>8 mg PO/IV daily on Days 2-3 or 2-4<br><br>*With fosaprepitant:*<br>8 mg PO/IV x 1 on Day 2, then 8 mg BID Days 3-4 | **ACUTE**<br>20 mg x 1<br><br>*With NK$_1$RA:*<br>12 mg x 1<br><br>**DELAYED**<br>8 mg BID for 3-4 days<br><br>*With NK$_1$RA:*<br>8 mg daily for 3-4 days | **ACUTE**<br>6 mg/m$^2$ PO/IV q6h<br><br>If given with aprepitant, reduce the dose by half<br><br>**DELAYED**<br>No recommendation |
| MEC | **ACUTE**<br>12 mg PO/IV x 1<br><br>**DELAYED**<br>8 mg PO/IV daily on Days 2-3 | **ACUTE**<br>8 mg PO/IV x 1<br><br>**DELAYED**<br>8 mg PO/IV daily on Days 2-3 | **ACUTE**<br>8 mg x 1<br><br>**DELAYED**<br>8 mg daily for 2-3 days (many panelists give 4 mg BID) | **ACUTE**<br>*≤0.6 m$^2$*: 2 mg PO/IV q12h<br><br>*>0.6 m$^2$*: 4 mg PO/IV q12h<br><br>If given with aprepitant, reduce the dose by half<br><br>**DELAYED**<br>No recommendation |

NCCN=National Comprehensive Cancer Network; ASCO=American Society of Clinical Oncology; MASCC=Multinational Association of Supportive Care in Cancer; POGO=Pediatric Oncology Group of Ontario; HEC=Highly emetogenic chemotherapy; MEC=Moderately emetogenic chemotherapy

### 1.4.2 Safety Concerns

Dexamethasone is a key cytotoxic component of widely used chemotherapy protocols. The broad activity of dexamethasone involving many organ systems and its complex interactions with the immune system raise concerns and cast doubt regarding its place in the supportive care of oncology patients.

The immunosuppressant effect of dexamethasone is recognized to increase the risk of infections in patients receiving chemotherapy. A large population-based cohort study of pediatric patients with AML determined the duration of corticosteroid therapy to be an independent and significant risk factor for microbiologically and clinically documented infections, sepsis, and infectious death.[82] In the HSCT setting, the risks of bacterial, viral, and fungal infections are already high given the number of other predisposing factors (e.g. intensive chemotherapy, pancytopenia, multiple portals of entry).[83] Higher cumulative doses of corticosteroids are associated with higher rates of invasive fungal disease and non-cytomegalovirus (CMV) viral diseases in HSCT patients.[84] As a result, many clinicians omit corticosteroids or use them sparingly in children undergoing HSCT, despite their potential antiemetic benefits. Further research is warranted to define the critical threshold of corticosteroid exposure to better inform infectious risk.

Interference of dexamethasone on the antitumor effects of chemotherapy in select cancers is another proposed barrier to its use. There are three possible mechanisms: First, experimental and clinical evidence suggest that dexamethasone induces expression of anti-apoptotic genes in certain malignant cells.[85,86] The cytotoxicity of cisplatin was markedly reduced during co-treatment of a human osteosarcoma cell line with dexamethasone.[87] In other non-hematologic malignancies, glucocorticoid therapy is postulated to stimulate tumor growth and metastasis and, at sufficiently high doses, reduce survival.[88-90] While understandably concerning, the clinical response to corticosteroids is closely tied to the cell type. A pro-apoptotic effect is observed in lymphoid cells, bone, and hippocampus. Conversely, non-hematological tissues such as mammary glands, ovaries, and liver cells become less susceptible to chemotherapy when subjected to corticosteroids.[91,92] These differential outcomes reflect the complexity that underlies the downstream effects of corticosteroids in a clinical setting.

Secondly, an intact immune system may be vital for mounting an antitumor response in certain cancers, such as recurrent glioblastoma. A *post-hoc* analysis of a phase III trial found that a daily

dexamethasone dose >4.1 mg given to alleviate neurologic symptoms led to a 2.3-fold and 1.5-fold decrease in the median overall survival of adult patients treated with alternating electrical fields and chemotherapy, respectively. In addition, higher absolute counts of T-lymphocyte subsets were predictive of overall survival. The authors posit that immunosuppression caused by dexamethasone had blunted the antitumor efficacy of glioblastoma treatment.[93]

Lastly, the overall efficacy of chemotherapy may be influenced by dexamethasone through its effect on the blood-brain-barrier. In murine models, glucocorticoids induce expression of p-glycoprotein efflux pumps resulting in reduced uptake of antineoplastic agents. More profoundly, dexamethasone may change the integrity of the barrier. Direct interaction with tight junction proteins and repression of inflammatory mechanisms and neovascularization create a less permeable barrier and may limit chemotherapy access into the central nervous system (CNS).[94] Though demonstrated in *in-vitro* models, the direct benefits of these interactions have not been observable in clinical practice. For example, dexamethasone treatment of cerebral edema secondary to a traumatic brain injury or ischemic stroke did not yield a clear benefit according to several well-conducted clinical trials.[95-97] The size of the effect may be conditional upon the timeframe of initiation, dose, and presence of co-morbidities. Nonetheless, a pharmacokinetic alteration in CNS exposure to chemotherapy could threaten the likelihood of a cure.

Of these concerns, the most under-researched is the impact of dexamethasone on key immunological processes post-HSCT. This pertains to the GVL effect of allogeneic HSCT in patients with leukemia and immune reconstitution following autologous and allogeneic HSCT. The GVL effect has been at the center of various clinical strategies to enhance the curative potential of allogeneic HSCT. The actions of T-lymphocytes, natural killer cells, and immune mediators, such as interleukin-2 (IL-2) and interferon-alpha (IFN-α), contribute to this alloreactive response against residual leukemic cells.[98,99] By downregulating the expression of important cytokines, dexamethasone is thought to disrupt recruitment of the immune cells underlying the GVL effect.[100] Moreover, these cytokines are necessary to stimulate recovery of the hematopoietic system, devastated by the effects of aggressive conditioning. For this reason, dexamethasone is perceived to hinder immune reconstitution. Without timely neutrophil engraftment, the risks of opportunistic infections and other acute complications contributing to TRM become even more concerning. To date, however, there has been no direct evidence of

these clinical interferences. It remains unclear what impact, if any, dexamethasone given for CINV prophylaxis will have on HSCT outcomes.

## 1.5 Rationale for Proposed Research

Children with cancer need and deserve antiemetics that are known to be safe and effective. These patients ultimately suffer when dexamethasone is omitted from routine antiemetic prophylaxis since CINV is less likely to be completely controlled. Yet, the influence of dexamethasone on long-term HSCT outcomes is currently unknown and potentially severe. TRM, disease relapse, IFD, acute GVHD, and delayed or failed engraftment are grave concerns in children undergoing HSCT. The lack of research addressing the adverse effects of dexamethasone dissuades clinicians from using an effective and guideline-recommended antiemetic in vulnerable children. The projects included in this thesis were undertaken to enhance our understanding about the safety of dexamethasone given for CINV prophylaxis. Specifically, we were interested in its untoward effects in children undergoing HSCT.

The first project was part of a larger systematic review of the safety of recommended antiemetic agents for acute CINV in children. For the purposes of this thesis, we solely focused on dexamethasone given for this indication. By identifying and summarizing findings from all relevant studies, we were broadly informed about documented adverse effects of dexamethasone and potential areas for further research. Conducting this comprehensive literature search and systematic review was considered an appropriate first step to our safety evaluation.

A *post-hoc* analysis of a previous single-center, prospective study was completed to describe the safety of dexamethasone in children undergoing HSCT. This was necessary as there were no primary studies that focused on safety of dexamethasone as an antiemetic agent in children. The sparse literature identified from our systematic review evaluated safety as a secondary goal without considering the attribution of adverse events to the drug. Through this retrospective analysis, we aimed to illustrate the immediate concerns of dexamethasone in the HSCT population before embarking on a larger, multi-center exploration of its long-term effects.

The final project was aimed at developing an analytical framework and determining its feasibility for a future study. Ultimately, we aim to assess the effect of dexamethasone on long-term HSCT outcomes, particularly TRM. The lack of previous studies evaluating this

relationship and the significance of TRM warrant attention. Our initial risk estimates will be continuously refined by accumulating data from a growing network of HSCT centers representing diverse practices with respect to the use of dexamethasone as an antiemetic. To appropriately isolate the impact of dexamethasone, our framework was designed to control the effects of important confounders through propensity score methods. The process of pilot testing this framework and assessing its feasibility prior to extending into a large-scale multi-center investigation was essential.

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# Chapter 2
# The Safety of Dexamethasone for the Management of Chemotherapy-Induced Nausea and Vomiting in Pediatric Patients: A Systematic Review

For the purposes of this thesis, the contents of this chapter focus on a single component of a larger systematic review evaluating the safety of guideline-recommended antiemetic drugs in pediatric patients. The full results of the review will be drafted into a manuscript and submitted to a journal.

All authors (E. Paw Cho Sing, P. Patel, L.L. Dupuis) were involved in the conception and planning of the full manuscript. Another author (P. Patel) and I conducted the literature search (with the assistance of a library scientist), reviewed all articles for inclusion/exclusion (title and abstract screening, full-text screening), abstracted data from included articles which were summarized into evidence tables, and assessed the risk of bias of included prospective studies. Any discrepancies in our independent reviews (screening, abstraction, bias assessment) were resolved by a third author (L.L. Dupuis). All authors contributed to the writing of the full manuscript. For this thesis, I developed the following manuscript which focused on the results for dexamethasone from the larger systematic review.

## 2.1 Abstract

*Background*: Dexamethasone is widely recommended for the management of chemotherapy-induced nausea and vomiting (CINV) in adults and children. While effective, there is growing concern over its safety in pediatric patients. The objective of this systematic review was to describe the adverse effects (AEs) of guideline-recommended antiemetic agents used in pediatric patients. The results of dexamethasone for CINV are reported here.

*Methods*: Electronic searches were conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science. All primary studies in English, reporting specific AEs associated with a guideline-recommended antiemetic agent (including dexamethasone for CINV) given as monotherapy in pediatric patients were included. Specific AEs reported by at least three prospective studies were eligible for meta-analysis.

*Results*: A total of 3 randomized cross-over trials of 71 children aged 1.3 to 18 years and 1 prospective observational study of 2 adolescents were included. Dexamethasone dose ranged from 6 to 30 mg/m$^2$/day given over 1 to 2 days. Sedation, insomnia, euphoria, confusion, ataxia, and mood changes were the most frequent AEs reported. These AEs were well tolerated and yielded no major concerns. Osteonecrosis was detected, but unlikely due to dexamethasone given for nausea. AEs could not be synthesized. No studies had safety as a primary aim or used valid and objective methods for AE measurement.

*Conclusions*: Dexamethasone given to pediatric patients for CINV was associated with tolerable AEs. However, there is a clear need for more methodologically robust studies directly evaluating its safety.

## 2.2 Introduction

Dexamethasone has long been used for the treatment and prevention of chemotherapy-induced nausea and vomiting (CINV) in adults and children. When combined with a 5-HT$_3$ receptor antagonist, the complete control of acute and delayed emesis improves significantly compared to a 5-HT$_3$ receptor antagonist alone.[1,2] The growing number of reports supporting the antiemetic value of dexamethasone has cemented its place in adult and pediatric guidelines as strongly recommended for the management of CINV.[3-6]

Across pediatric cancer centers, dexamethasone is not given consistently as a standard antiemetic. A survey of 34 Children's Oncology Group institutions reported 29 different dosing regimens of dexamethasone used in children receiving highly emetogenic chemotherapy with 2 centers omitting it from the standard antiemetic regimen completely.[7] Another audit of 50 inpatient emetic episodes at a national pediatric cancer unit revealed that only one patient received dexamethasone.[8] This variation in practice reflects the uncertainty related to the optimal pediatric dose of dexamethasone and safety concerns associated with corticosteroids in the pediatric population.

The objective of this systematic review and meta-analysis is to describe the adverse effects (AEs) associated with the use of dexamethasone in children when given for CINV. This will offer insight into the current understanding of the safety of dexamethasone when used as an antiemetic and identify gaps in the literature for a future study.

## 2.3 Methods

The search strategy described was established for a larger systematic review of the safety of antiemetic agents recommended for the treatment of acute CINV in children. Selection of studies included in this report was restricted specifically to dexamethasone as the antiemetic drug of interest.

Electronic searches with the assistance of a library scientist were conducted on September 13, 2017. Articles were identified from the following databases: Ovid MEDLINE (1946 to September 13, 2017), EMBASE Classic and EMBASE (1947 to 2017 Week 37), Cochrane Central Register of Controlled Trials (August 2017), and Web of Science (accessed September 13, 2017). The complete search strategy is presented in Appendix 2.1. The reference lists of included studies were reviewed to ensure that all relevant articles were identified. The search was limited to pediatric studies (including neonates, infants, children, and adolescents). There was no restriction by publication date or study design.

The following inclusion criteria were applied to the studies identified by the literature search: (1) published in English as a full-text article, case report, or letter to the editor reporting primary data; (2) included patients aged ≤18 years and either results were reported separately for patients aged ≤18 years or at least 60% of patients were ≤18 years or median/mean age was ≤16 years; (3) at least one study arm that evaluated a guideline-recommended antiemetic agent (serotonin [5-$HT_3$] receptor antagonist or neurokinin [$NK_1$] receptor antagonist for any indication or dexamethasone for the indication of CINV only) as monotherapy; (4) described specific AEs associated with the antiemetic agent; (5) reported the dose of the antiemetic agent or, in the case of poisoning where the dose ingested could not be determined, a blood concentration of the antiemetic agent was reported. The exclusion criteria were as follows: (1) not published in English; (2) conference abstracts or proceedings; (3) not a primary study (such as review articles); (4) study population did not consist exclusively of patients ≤18 years and did not report results separately for patients ≤18 years, at least 60% of patients were not ≤18 years, or median/mean age ≥16 years; (5) did not evaluate a guideline-recommended antiemetic agent as monotherapy or evaluated a guideline-recommended antiemetic agent plus other agents with antiemetic properties (olanzapine, metoclopramide, lorazepam, methotrimeprazine, nabilone, and antihistamines); (6) specific AEs not described or attributed to the antiemetic agent; (7) did not

report the dose or, in the case of poisoning, the blood concentration of the antiemetic agent; (8) duplicate studies; and (9) not retrievable. Duplicate studies were identified electronically and removed using EndNote X7.1 (Bld 7705; Thomson Reuters).

Titles and abstracts of all studies identified by the electronic search were screened by two independent reviewers (EP and PP). Primary articles that evaluated a guideline-recommended antiemetic agent in the pediatric population were selected for full-text screening and reviewed by two independent reviewers (EP and PP). Any discrepancies were discussed and resolved by consensus via a third independent reviewer (LD).

The following data were abstracted from included studies: study design and aim, patient characteristics (sample size, age, sex, and diagnosis), antiemetic dose and regimen, length of antiemetic treatment, pre-defined safety endpoint (AEs to be monitored), AEs reported, and their incidence rate. Data abstraction was verified independently (EP and PP).

The risk of bias of prospective studies was assessed by two independent reviewers (EP and PP). A tool originally developed to describe the quality of prognostic studies was modified and five domains were considered in determining the risk of bias: study participation, study attrition, outcome measurement, study confounding, and statistical analysis and reporting.[9] Each prospective study was classified as having a low, moderate, or high risk of bias. Any discrepancies in risk assignment were resolved by consensus via a third independent reviewer (LD).

The primary outcome was the proportion of patients experiencing specific AEs. AEs were recorded if their presence or absence in the study population was explicitly stated. Where appropriate, AEs were re-classified under accepted terminology from the Common Terminology of Criteria of Adverse Events (CTCAE) version 5.0.[10] A meta-analysis was to be conducted if the proportion of patients experiencing the same AE was reported in at least three prospective studies, including randomized controlled trials and open-label studies. Data synthesis was to be completed using Review Manager (RevMan Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Data from observational studies, case series, and case reports were not eligible for synthesis due to the likelihood of a high risk of bias in the identification and measurement of AEs within these study designs. The natural logarithm of proportions was used since proportions were not expected to be distributed normally. To evaluate

the consistency between independent reviewers, an inter-rater reliability analysis was conducted by calculating the simple Kappa (κ) statistic (SAS Institute Inc.; Cary, NC, USA).

## 2.4 Results

A total of 24,442 articles were identified from the literature search. Of these, titles and abstracts of 18,937 articles were screened and 787 full-text articles were reviewed for eligibility. Agreement between independent reviewers for the final inclusion of studies was moderate (κ = 76.7%). Ultimately, 4 studies evaluating dexamethasone as monotherapy for CINV met inclusion criteria for qualitative analysis. None of the safety data from these 4 dexamethasone studies were eligible for quantitative meta-analysis. Figure 2.1 depicts the flow diagram of study records identified, screened, and included into the present systematic review.

Three prospective randomized cross-over trials involving 71 children, aged 1.3 to 18 years, who received dexamethasone as antiemetic monotherapy were included.[11-13] A single prospective observational study reported cumulative corticosteroid exposure of 32 patients over 4 years.[14] Of these, only two patients were described to receive dexamethasone for the treatment of nausea and thus, were included in our analysis. Assessment of the safety of dexamethasone was not the primary study objective of any of these studies. In two studies (Van Hoff *et al*. and Niinimaki *et al*.), safety endpoints were pre-defined.[13,14] A summary of the study characteristics is presented in Table 2.1. There was a lack of sufficient detail to inform whether outcome measurement was standardized and objective in the three cross-over studies (Sumer *et al*., Basade *et al*., and Vanhoff *et al*.).[11-13] The risk of bias of included studies ranged from low to high (Table 2.2).

The dose of dexamethasone administered in included studies ranged from 6 to 30 mg/m$^2$/day and it was given for 1 to 2 days. Doses were administered intravenously, except in one study which gave the first dose intravenously and then allowed repeat doses given either orally or intravenously.

The most frequent AE of dexamethasone was sedation. Few patients were reported to experience insomnia, euphoria, confusion, ataxia, and mood changes. Insomnia was documented in two studies, while all other AEs were each documented in a single study. There were no AEs severe enough to warrant discontinuation or dose reduction of dexamethasone.

Radiographically detected osteonecrosis was observed in two adolescents reported to have received dexamethasone for nausea. One of these patients also had considerable cumulative exposure to prednisone and dexamethasone as part of their chemotherapy protocol.

A summary of the AEs associated with dexamethasone that were reported in the included studies is presented in Table 2.3.

## 2.5 Discussion

In this systematic review, we described the AEs associated with dexamethasone given to pediatric patients for CINV in three randomized cross-over trials and one prospective observational study. These AEs included sedation, insomnia, and alterations in mood. No patients discontinued dexamethasone or reduced its dose due to AEs. In general, dexamethasone was concluded by authors to be well tolerated in the immediate setting. There were no major concerns in children when it was given for CINV. Overall, there is a shortage of robust studies with a focus on evaluating the safety of dexamethasone.

Insomnia and hypersomnia had been previously reported with the use of corticosteroids. The underlying mechanism remains unclear, though changes in the activity of the hypothalamic-pituitary-adrenal axis are implicated. Opposing influences on sleep are possibly explained by the direct awakening effect of corticosteroids and feedback inhibition of corticotropin-releasing hormone promoting daytime sleepiness. Moreover, corticosteroids disrupt the action of inflammatory cytokines (tumor necrosis factor α, interleukin-1 and -6), which are speculated to regulate sleep.[15] In a study by Hinds *et al*., the sleep activity of children and adolescents with low- or standard-risk acute lymphoblastic leukemia (ALL) were monitored for five days before dexamethasone, followed by another five days while receiving dexamethasone 6 to 12 $mg/m^2$/day. Increased sleep duration and fatigue, night time awakenings, and restless sleep were reported while patients received dexamethasone.[16] In a similar study of children receiving dexamethasone 6 $mg/m^2$/day for five days, Rosen *et al.* documented an increase in the duration of nighttime sleep and the incidence of daytime napping without impairment in the quality of nighttime sleep. These changes in sleep pattern ended 1 day after completion of dexamethasone treatment.[17]

In the current systematic review, almost half of patients in one study receiving a shorter duration of a higher daily dose of dexamethasone (30 mg/m$^2$ over one day) experienced sedation.[13] Insomnia occurred less frequently, but was reported in children receiving a lower daily dose of 6 to 8 mg/m$^2$ over one day.[11,12] The lack of validated methods to assess sleep (actigraphy, standardized questionnaires) in these studies precludes complete understanding of the impact of dexamethasone given for CINV. In the study by Van Hoff *et al*., a simple 4-point severity scale was used to assess sedation. In other studies, a clear description of how insomnia was evaluated is lacking.[13] Moreover, sleep is a complex, neurological process influenced by a multitude of factors especially in children with cancer.[17] Without a comparison group, it is difficult to attribute such reports of insomnia and sedation to dexamethasone.

Alterations in mood and behavior are known to occur in children receiving dexamethasone when given as part of the chemotherapy protocol for ALL. Adverse psychiatric events are speculated to arise from the suppression of brain derived neurotrophic factor (BDNF). In animal models, low levels of BDNF have been correlated with dendritic atrophy and neuronal apoptosis within hippocampal structures.[18,19] Possible links between hippocampal neurotoxicity and psychopathology, such as psychosis and depression, are emerging areas of research. In a qualitative study by McGrath *et al*., interviews of children undergoing ALL treatment and their families reveal the emotional impact of dexamethasone. Aggression, confusion, lethargy, and depression were reported to contribute to a sense of feeling overwhelmed and distress for both child and caregivers.[20] A meta-analysis pooled the results of several randomized controlled trials evaluating dexamethasone during induction therapy in children with ALL. Collectively, neuro-psychiatric AEs (including mood swings, delusional psychoses, and agitation) occurred in 3.6% of children receiving dexamethasone at doses of 6 to 10 mg/m$^2$/day for 28 days consecutively.[21]

Our systematic review included studies that reported euphoria (27%; 3/11) and depression (4%; 1/26) at similar doses of 6 to 8 mg/m$^2$ over one day.[11,12] Confusion (13%; 4/31) and mood changes (6%; 2/31) were also reported, but at a higher daily dose (30 mg/m$^2$ over one day).[13] No patients withdrew due to intolerable AEs, which reflected the mild nature and transiency of these events. The relatively short timeframe of dexamethasone treatment likely limited the negative impact of these psychiatric events. Hence, findings of mood and behavioral disturbances from studies evaluating dexamethasone for ALL treatment cannot be generalized to children receiving brief exposures of dexamethasone for CINV. While it seems psychiatric AEs associated with

short-term use of dexamethasone is unconcerning, we are unable to rule out the possibility of underreporting. Only Van Hoff *et al*. used a 4-point scale to evaluate the presence and severity of a psychiatric AE, hallucinations, which was not observed.[13] None of the included studies used validated tools or objective measures to detect clinically important or subclinical changes in mood and behavior. Due to the lack of standardized definitions, determining the presence of psychiatric AEs was likely at the discretion of the study investigators. Moreover, attribution of subjective symptoms, such as euphoria and confusion, to dexamethasone is uncertain.

Osteonecrosis in weight-bearing bones is a known debilitating consequence of corticosteroid use. Radiologically confirmed osteonecrosis was observed in <1% to 13% of pediatric ALL patients enrolled in large cohort studies.[22-25] In these patients, female sex and age greater than 10 years were significant risk modifiers for the development of osteonecrosis.[25] Smaller retrospective studies estimate the prevalence of symptomatic osteonecrosis to be 7.1% in children with non-Hodgkin's lymphoma (NHL) and 4.4% in those with Hodgkin's disease (HD).[26]

A single prospective cohort study reporting detectable osteonecrosis in two patients who received dexamethasone for nausea met our inclusion criteria. Both patients were adolescents, diagnosed with lymphoma (NHL:1; HD:1), and documented to have a high cumulative corticosteroid exposure for cancer treatment. One patient had been exposed to 1,360 mg/m$^2$ of prednisone for cancer treatment and 24 mg/m$^2$ of dexamethasone (160 mg/m$^2$ in prednisone-equivalent units) for nausea. The other received 2,800 mg/m$^2$ of prednisone and 240 mg/m$^2$ of dexamethasone (1,600 mg/m$^2$ in prednisone-equivalent units) for cancer treatment and 185 mg/m$^2$ of dexamethasone (1,233 mg/m$^2$ in prednisone-equivalent units) for nausea. Thus, the incremental risk of osteonecrosis from dexamethasone given for nausea was considered minor. In fact, the 26 patients who did not develop osteonecrosis received much higher cumulative doses of dexamethasone (up to 1,080 mg/m$^2$ or 7,200 mg/m$^2$ in prednisone-equivalent units) for the treatment of nausea. The authors regarded the intermittent use of dexamethasone for the treatment of nausea as unlikely to contribute to osteonecrosis, despite its occurrence in both patients.[14]

The strength of this systematic review is the level of rigor applied to the criteria for inclusion. We only included studies with at least one treatment arm that evaluated dexamethasone monotherapy, that is, without co-administered antiemetics. This improves the confidence of

attributing emergent AEs to dexamethasone. Although the influence of concomitant chemotherapy agents cannot be fully excluded, this represents the population receiving dexamethasone for CINV.

We acknowledge the limitations of our analysis. The small number of included studies and patients evaluated precluded our ability to synthesize common AEs. This indicates that there is a lack of robust safety assessments of dexamethasone used alone as an antiemetic agent. Moreover, the included studies were not designed to specifically evaluate safety endpoints. For the most part, the methodology for AE measurement and attribution was either inadequately described or omitted. Most reported outcomes were subjective and lacked a standardized approach for severity measurement. It is unclear if AE identification was systematic. For the cross-over studies, the timeframe of assessment was relatively short and did not permit observation of chronic AEs. In general, the lack of studies using standardized and objective reporting is a hindrance to completely understanding the safety profile of dexamethasone when used as an antiemetic. Lastly, our literature search only included articles published in English and thus, relevant publications in other languages may have been missed.

Corticosteroids affect multiple organ systems. The myriad of possible AEs may appear immediately (cardiac and metabolic effects), gradually (bone and lipid changes), or idiosyncratically (alterations in mood and behavior). Several expected AEs of dexamethasone were not captured in this systematic review. A retrospective study of 46 children undergoing HSCT who received CINV prophylaxis that included dexamethasone found high incidences of hyperglycemia (63%), hypertension (52%), and bradycardia (46%).[27] In 60 adult outpatients receiving dexamethasone for prophylaxis of delayed emesis, insomnia (45%), indigestion/epigastric discomfort (27%), and agitation (27%) were frequently reported.[28] This systematic review establishes the absence of robust studies focused on the safety of dexamethasone given to children for CINV. Future studies equipped to measure AEs in a standardized and objective manner are justified to deliver more informative findings.

## 2.6 Conclusion

In this systematic review, we described the AEs associated with the use of dexamethasone for CINV in pediatric patients when administered at doses ranging from 6 to 30 mg/m$^2$/day for 1 to 2 days. The most frequent AE reported was sedation, followed by insomnia, euphoria, confusion,

ataxia, and mood changes. None of these AEs were severe enough to warrant early discontinuation or dose adjustment. Though osteonecrosis is a debilitating complication, the probability that it is associated with dexamethasone given for nausea is likely low. Most importantly, this review emphasized the importance of including standardized and objective methods for measuring AEs when designing antiemetic studies.

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**Figure 2.1** Literature search flowchart

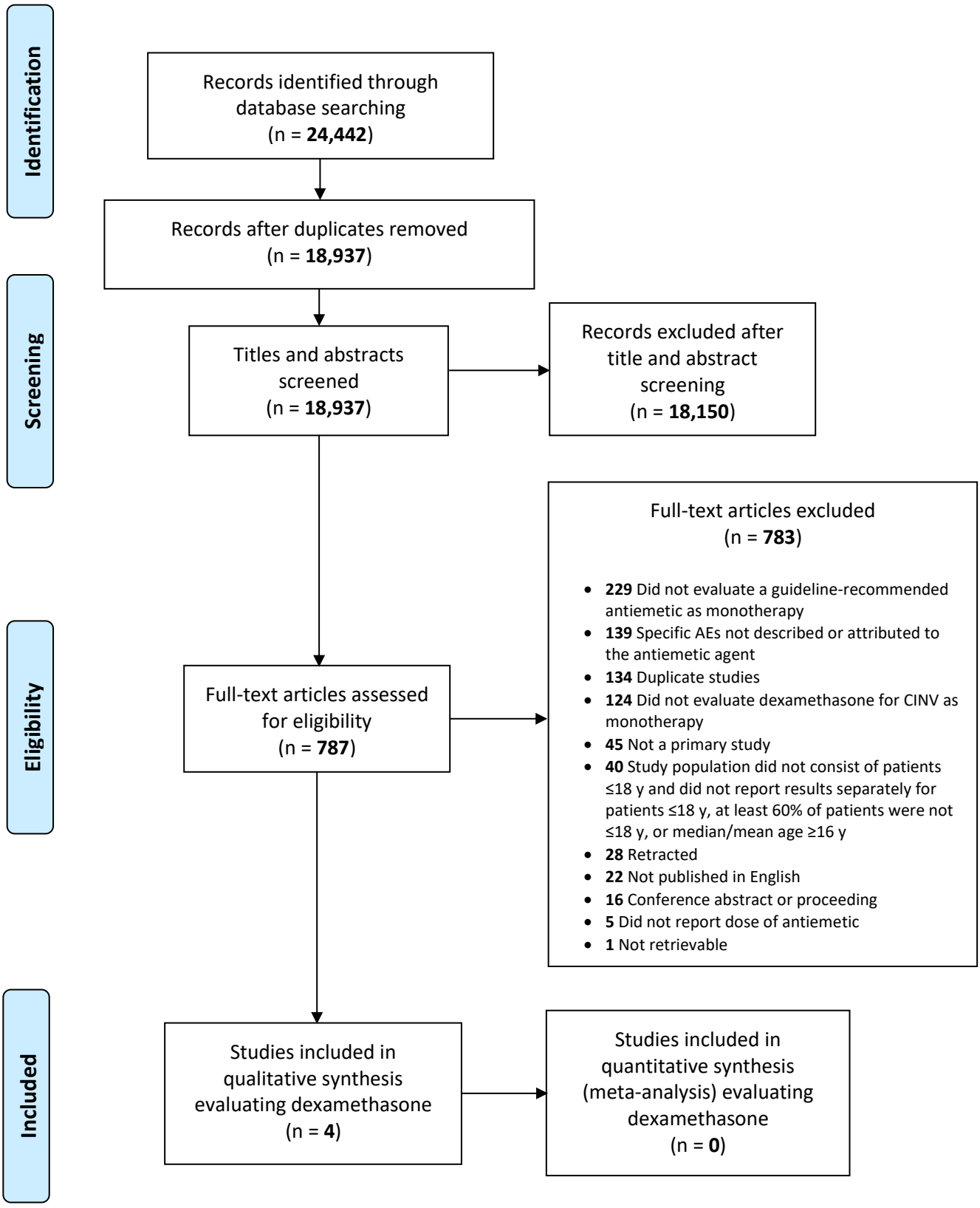

**Table 2.1** Summary of included studies reporting adverse effects associated with dexamethasone used as monotherapy for CINV in children and adolescents

| Author | Year of pub | Study design | Study aim | *N (n)* | Sex, M:F | Mean/median age (range), years | Diagnosis | Dexamethasone regimen | Length of treatment | Pre-defined safety endpoints |
|---|---|---|---|---|---|---|---|---|---|---|
| Basade[10] | 1996 | Randomized, single-blind, cross-over trial | To compare the efficacy and safety of dexamethasone versus metoclopramide in preventing CINV | 27 (26) | 21:6 | 7 (3-14) | Cancer | 8 mg/m$^2$/dose IV | 1 dose | • Insomnia<br>• Depression<br>• Anorexia<br>• Abdominal pain<br>• Dystonia<br>• Elated mood<br>• Headache |
| Sumer[11] | 1988 | Randomized, cross-over trial | To define the antiemetic effect of dexamethasone on children treated with cis-platinum | 11 (11) | 6:5 | 2.9 (1.3-5.4) | Cancer | 1 mg/m$^2$/dose IV 6 hours pre-chemotherapy x 1, then every 4 hours | 10 doses | • Hematologic changes<br>• Electrolyte changes<br>• Liver function test abnormalities<br>• Renal function test abnormalities |
| Van Hoff[12] | 1994 | Randomized, double-blind, placebo-controlled crossover study | To determine the antiemetic efficacy of lorazepam when added to dexamethasone versus placebo plus dexamethasone | 34 (31) | 16:18 | 10.5 (5-18) | Cancer | 10 mg/m$^2$/dose IV pre-chemotherapy followed by repeat doses IV/PO 6 and 12 hours later | 2 doses | • Anxiety<br>• Sedation<br>• Confusion<br>• Ataxia<br>• Hallucinations |
| Niinimaki[13] | 2008 | Prospective observational study/MRI study | To determine the incidence of osteonecrosis in children at the end of treatment for lymphoma or solid tumors | 32 (2*) | 20:12 (1:1)<br><br>Case 1: F<br>Case 2: M | 7.1 (1.3-15.3)<br><br>Case 1: 14 years<br>Case 2: 15 years | Cancer | Cumulative exposure of dexamethasone for nausea treatment:<br>Case 1: 24 mg/m$^2$<br>ǂCase 2: 185 mg/m$^2$ | Varied | • Osteonecrosis |

**Table 2.2** Risk of bias assessment of included studies

| Domains of risk of bias assessment | Basade (1996)[10] | Sumer (1988)[11] | Van Hoff (1995)[12] | Niinimaki (2008)[13] |
|---|---|---|---|---|
| 1. Study participation | High | High | Moderate | Low |
| 2. Study attrition | Low | High | Low | Low |
| 3. Outcome measurement | High | High | Moderate | Low |
| 4. Study confounding | Moderate | Moderate | Moderate | Low |
| 5. Statistical analysis and reporting | Low | Low | Moderate | Low |
| Overall risk of bias | **High** | **High** | **Moderate** | **Low** |

**Table 2.3** Summary of adverse effects associated with dexamethasone administration reported in included studies that evaluated all patients who received dexamethasone for chemotherapy-induced nausea and vomiting

| Adverse effect | First author's name of studies evaluating or reporting adverse effect | Total number of patients evaluated | % reported incidence |
|---|---|---|---|
| Sedation | Van Hoff[12] | 31 | 42 (13/31) |
| Insomnia | Sumer[11] | 11 | 27 (3/11) |
| Euphoria | Sumer[11] | 11 | 27 (3/11) |
| Confusion | Van Hoff[12] | 31 | 13 (4/31) |
| Ataxia | Van Hoff[12] | 31 | 10 (3/31) |
| Mood changes | Van Hoff[12] | 31 | 6 (2/31) |
| Insomnia | Basade[10] | 26 | 4 (1/26) |
| Depression | Basade[10] | 26 | 4 (1/26) |
| Anorexia | Basade[10] | 26 | 4 (1/26) |
| Abdominal pain | Basade[10] | 26 | 4 (1/26) |
| Hallucinations | Van Hoff[12] | 31 | 0 (0/31) |
| Hematologic abnormalities | Sumer[11] | 11 | 0 (0/11) |
| Electrolyte abnormalities | Sumer[11] | 11 | 0 (0/11) |
| Liver function test abnormalities | Sumer[11] | 11 | 0 (0/11) |
| Renal function test abnormalities | Sumer[11] | 11 | 0 (0/11) |

# Chapter 3
# Safety of Dexamethasone for Nausea and Vomiting Prophylaxis in Children Receiving Hematopoietic Stem Cell Transplantation

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All authors were involved in the conception and planning of this manuscript. L.L. Dupuis and I developed the protocol with consultation from other co-authors (T. Schechter, L. Sung, and M. Ali). As primary author, I was responsible for reviewing patient charts, completing data collection forms, and assisted with analyzing, interpreting, and summarizing the data with L.L. Dupuis. Co-author, M. Ali, was consulted for missing follow-up data regarding select patients transferred to external sites.

## 3.1 Abstract

*Background***:** Many children undergoing hematopoietic stem cell transplantation (HSCT) experience chemotherapy-induced nausea and vomiting (CINV) despite receiving prophylaxis. Guideline-consistent CINV prophylaxis includes dexamethasone, but uncertainty regarding safety potentially limits the use of dexamethasone in children. We describe immediate adverse events (AEs) attributable to dexamethasone given for CINV prophylaxis to children during HSCT conditioning.

*Methods***:** Children enrolled in a previous prospective study were retrospectively analyzed. Objective parameters related to specific AEs occurring within five days of dexamethasone administration were abstracted from health records and graded according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03). Their association to dexamethasone was assessed using the Liverpool Causality Assessment Tool (LCAT).

*Results*: Forty-six children (median age 10.2 years) were eligible for analysis. The most frequent AEs attributable to dexamethasone (LCAT category of *probable* or *definite*) were hyperglycemia (63%; CTCAE v4.03 grade 3: 2%), hypertension (52%; CTCAE v4.03 grade 3: 15%), and bradycardia (46%; CTCAE v4.03 grade 3: 0%). Other AEs included dyspepsia or gastro-esophageal reflux disease (24%) and alterations in mood and behavior (9%). No AE exceeded CTCAE v4.03 grade 3 in severity.

*Conclusions*: In children undergoing HSCT who received dexamethasone for CINV prophylaxis, immediate AEs attributable to dexamethasone were most often of minor clinical importance and transient.

## 3.2 Introduction

Children undergoing hematopoietic stem cell transplantation (HSCT) receive conditioning over several days that often consists of highly emetogenic chemotherapy with or without total body irradiation (TBI).[1] However, control of chemotherapy-induced nausea and vomiting (CINV) in these children remains suboptimal, even with prophylaxis.[2] Complications arising from poorly controlled CINV impair functional status and contribute to morbidity and mortality in children with cancer.[3,4]

Several guidelines for the prevention of acute CINV in adult and pediatric patients receiving highly emetogenic chemotherapy including HSCT conditioning strongly recommend the addition of dexamethasone to the antiemetic regimen.[5-8] Despite this, use of dexamethasone as an antiemetic agent in children is not routine and the optimal dose is controversial.[9] Adverse events (AEs) known to be associated with corticosteroid administration include hyperglycemia, hypertension, gastro-esophageal reflux disease (GERD), osteoporosis, changes in mood and behavior, and infectious complications.[10-12] An additional theoretical concern of corticosteroids in the context of HSCT is the potential for immunological interference with engraftment and the graft-versus-leukemia (GVL) effect.[13]

Dexamethasone is an effective antiemetic agent in children receiving chemotherapy,[14] but uncertainty with respect to its safety may present a barrier to its use during HSCT conditioning. This study describes immediate AEs in children and adolescents who received dexamethasone

for the prevention of CINV during HSCT conditioning. This information will enable a broader appreciation of the risks of dexamethasone when used for CINV prophylaxis.

## 3.3 Methods

This study was a post hoc analysis of data collected during a prospective study[2] approved by the Research Ethics Board at SickKids. The primary aim of the prospective study was to describe the prevalence of acute and delayed phase CINV using the Pediatric Nausea Assessment Tool (PeNAT)[15] in children receiving HSCT conditioning. Patients were eligible for the prospective study if they were 4 to 18 years of age, English-speaking, without cognitive or physical impairments which precluded their use of the PeNAT, and receiving conditioning for their first HSCT for any indication other than immunodeficiency.

*Patients:* Children and adolescents 18 years of age or younger who participated in the prospective study were included in this analysis if they received at least one dose of dexamethasone for CINV prophylaxis during HSCT conditioning. Dexamethasone doses recommended in our institutional guideline for CINV prophylaxis during the study period are presented in Table 1. Patient and transplant characteristics were abstracted from the health record.

*Administration of dexamethasone:* Dexamethasone dose and duration were chosen at the discretion of the prescriber. The dose and route, date(s) and time(s) of dexamethasone administration on each day of HSCT conditioning and for seven days afterward were recorded.

*AEs:* The following potential AEs were evaluated based on specific objective measures available in the health record: alterations in mood and behavior, bradycardia, dyspepsia or GERD, hyperglycemia, hypertension, hypotension, increased transaminase concentrations, and tachycardia (see Appendix 3.1, which defines these AEs). In addition, any AE noted in the health record by a health care provider as potentially or actually attributable to dexamethasone was recorded.

AE assessment began with the first dose of dexamethasone for CINV prophylaxis during HSCT conditioning and ended five days after administration of the last dexamethasone dose. The

severity of each AE was graded according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).[16]

*Analysis:* Patient and transplant characteristics, as well as the incidence and severity of AEs attributable to dexamethasone were summarized with descriptive statistics. The Liverpool Causality Assessment Tool (LCAT) was used to evaluate the likelihood (*definite, probable, possible,* or *unlikely*) that AEs were attributable to dexamethasone.[17] An AE was considered to be attributable to dexamethasone if it was assigned an LCAT category of *definite* or *probable*.

## 3.4 Results

Of the 60 patients admitted for HSCT at SickKids between February 2012 and March 2015 and enrolled in the previously mentioned prospective study,[2] 46 received dexamethasone during HSCT conditioning and were included in this analysis. The characteristics of these patients are presented in Table 2.

*Administration of dexamethasone for CINV:* Patients received dexamethasone for CINV prophylaxis for a median duration of 8 (range: 1 to 14) days. The mean daily doses of dexamethasone administered are presented in Table 1. Male and female patients received a mean dexamethasone dose of 14.1±5.7 mg/day and 14.2±5.7 mg/day, respectively.

In 11 patients (24%), concerns regarding possible dexamethasone-related AEs prompted a change in the dexamethasone regimen. The dose was reduced in 2 patients (4%) due to: hyperglycemia and hypertension (1 patient) and bradycardia (1 patient). Dexamethasone was temporarily interrupted in 1 patient due to bradycardia. The drug was discontinued in 8 patients (17%) for the following reasons: bradycardia (4 patients), hypertension (2 patients), mood and behavioral changes (2 patients), hyperglycemia (1 patient), and GERD (1 patient). In these 8 patients, dexamethasone was given for a mean duration of 7.3 (range: 6 to 10) days before being discontinued. Conversely, the dose of dexamethasone was increased in 8 patients (17%) due to inadequate CINV control.

*AEs:* The incidences of the most common AEs attributable to dexamethasone and their CTCAE v4.03 grade distribution are presented in Figure 1.

*Hyperglycemia*: Hyperglycemia attributable to dexamethasone was observed in 29 patients (63%). The severity of hyperglycemia was CTCAE v4.03 grade 1 in 69% (20/29), 2 in 28% (8/29), and 3 in 3% (1/29) of these patients. No patient received insulin or other anti-hyperglycemic medications to manage hyperglycemia. The dextrose content of total parenteral nutrition (TPN) and/or the infusion rate of TPN was reduced in 8 patients (8/29; 28%) who developed hyperglycemia. In 1 patient (1/29; 3%), dextrose was withdrawn from their intravenous (IV) solution.

*Hypertension*: Twenty-four patients (52%) experienced at least one episode of hypertension attributable to dexamethasone. Four patients were receiving chronic anti-hypertensive medication prior to HSCT and, of these, blood pressure control worsened in three while receiving dexamethasone. The severity of hypertension was CTCAE v4.03 grade 1 in 21% (5/24), grade 2 in 50% (12/24), and grade 3 in 30% (7/24) of these patients. Most patients who developed hypertension (22/24, 92%) were treated with nifedipine as needed. Chronic antihypertensive medication was initiated in 5 patients (5/46; 11%), each of whom developed CTCAE v4.03 grade 3 hypertension while receiving dexamethasone.

*Hypotension*: No patients experienced hypotension attributable to dexamethasone.

*Bradycardia*: Twenty-one patients (46%) experienced bradycardia attributable to dexamethasone. The severity of bradycardia was CTCAE v4.03 grade 1 in 67% (14/21) and 2 in 33% (7/21) of these patients. Other than dexamethasone dose reduction or discontinuation, no intervention to manage bradycardia was initiated in any patient and heart rates normalized in all patients after dexamethasone was discontinued.

*Alteration in mood or behavior*: Four patients (9%) received a psychiatric consultation to address mood or behavior changes while receiving dexamethasone (CTCAE v4.03 grade 1: 3 patients; CTCAE v4.03 grade 3: 1 patient). Of these, two patients had a history of corticosteroid-induced behavioral alteration prior to HSCT.

*Other AEs*: The incidence of the remaining AEs which were specifically evaluated and which were found to be probably or definitely attributable to dexamethasone was: dyspepsia or GERD: 24% (11/46; CTCAE v4.03 grade 2: 10 patients; CTCAE v4.03 grade 3: 1 patient); tachycardia: 15% (4/46; CTCAE v4.03 grade 1: 4 patients); and increased transaminase concentrations: 9%

(4/46; CTCAE grade 1: 1 patient; CTCAE grade 2: 2 patients; CTCAE v4.03 grade 3: 1 patient). In addition, one patient experienced vasomotor flushing (CTCAE v4.03 grade 2), which was attributed to dexamethasone by a health care provider.

## 3.5 Discussion

We have described immediate AEs attributable to dexamethasone in children who received it as an antiemetic during HSCT conditioning. The most common of these were: hyperglycemia, hypertension, and bradycardia. AEs were generally transient and of minor clinical importance.

This is the first focused description of immediate AEs associated with the use of dexamethasone given for CINV prophylaxis in children. Previous studies evaluating the antiemetic efficacy of dexamethasone in children have reported AEs as a secondary aim. One cross-over study evaluated the efficacy of a single IV dose of dexamethasone 8 mg/m$^2$ IV given as a single antiemetic agent before chemotherapy in 27 children and reported one case each of insomnia, depression, anorexia and abdominal pain in the dexamethasone arm.[18] Similarly, the efficacy of dexamethasone monotherapy (1 mg/m$^2$/dose IV every 4 hours for 10 doses) was reported in 11 children receiving 22 courses of cisplatin therapy.[19] The only AE associated with dexamethasone was insomnia with euphoria (3 patients). An early trial studying dexamethasone as a single antiemetic agent in adult cancer patients also described AEs of minor clinical significance, most commonly sleepiness and euphoria.[20] In a pilot prospective study, Vardy *et al* asked 60 adult cancer patients receiving dexamethasone 4 mg twice daily as an antiemetic to measure the incidence and severity of various symptoms.[21] Patients reported insomnia (45%), indigestion/epigastric discomfort (27%), agitation (27%) and increased appetite (19%) most commonly.

When assessing the safety of dexamethasone as an antiemetic, the experience of children receiving dexamethasone for the treatment of acute lymphoblastic leukemia (ALL) may be informative. Immediate AEs most commonly reported in 50 children receiving dexamethasone 6 mg/m$^2$/day for 28 days during induction treatment of ALL were: hyperglycemia (20%), gastritis (46%) and hypertension (10%).[22] Transient hyperglycemia, defined as at least two random serum glucose concentrations ≥ 11.1 mmol/L, was observed in 15% of 81 children receiving dexamethasone during induction treatment of ALL.[23] Age ≥ 10 years and body mass index ≥ 85$^{th}$ percentile were independent risk factors for transient hyperglycemia in this population.

Warris *et al.* observed a statistically significant increase in mean fasting blood glucose concentrations on the fourth of five days of dexamethasone 6 mg/m$^2$/day administered to 42 children with ALL (4.4 vs 4.7 mmol/L; $p<0.01$).[24] This increase correlated with serum dexamethasone trough concentrations ($r=0.63$; $p<0.01$). By the fourth day of receiving dexamethasone, these investigators also observed statistically significant, but clinically insignificant increases in mean systolic and diastolic blood pressures. Nevertheless, six patients (14%) who were not hypertensive at baseline had clinical hypertension on the fourth day of receiving dexamethasone.

Bradycardia was the most commonly cited reason for discontinuing or reducing dexamethasone doses in our patient cohort. Reports of corticosteroid-associated bradycardia vary with respect to time of onset (early vs. late in therapy), duration of corticosteroid exposure (single vs. multiple day), route of administration, and dose (high vs. low).[25,26] Van der Gugten *et al.* described changes in heart rate in 61 children with ALL, lymphoma, or acute graft-versus-host disease (aGVHD), receiving either dexamethasone (mean dose: 0.28 ± 0.05 mg/kg/day) or prednisone (mean dose: 0.30 ± 0.05 mg/kg/day dexamethasone equivalents).[27] In this retrospective review, mean pulse rate had decreased significantly from baseline (106 vs. 81 bpm; $p<0.001$) almost 4 days after initiation of corticosteroid therapy. This remained significant after adjustment for age, body temperature and hemoglobin concentration. In various case reports, all patients who received an electrocardiogram had sinus bradycardia.[25-27]

The prevalence of behavioral changes and the way they are defined in children receiving corticosteroids vary widely.[28] For example, Pound *et al.* used several measures (Child Behavior Checklist (CBCL), Pediatric Quality of Life Inventory 3.0 Cancer Module, and the Checklist of Common Complaints) to define and quantify behavioral and emotional changes in 43 children taking dexamethasone (77%) or prednisone (23%) during the maintenance phase of ALL treatment.[11] Patients served as their own controls since the measures were completed once after a five-day course of corticosteroids and again during a period when they had not received corticosteroids for at least 14 to 21 days. When children were taking corticosteroids, mood swings were commonly reported by parents (86%). However, aggressive behavior scores and externalizing problem scale scores, though higher when receiving corticosteroids, were in the normal range. Alteration in mood and behavior associated with dexamethasone were

uncommonly identified in our cohort. However, because our definition required a consult to psychiatry for management, the four patients we identified likely represent the most severe cases.

Overall, few patients in our study experienced clinically important AEs. Indeed, no AE was higher than CTCAE v4.03 grade 3 in severity. Five patients (11%) had clinically important hypertension as they were started on routinely scheduled antihypertensive medications. These patients had also been receiving cyclosporine for aGVHD prophylaxis. The most clinically important bradycardia occurred in 6 patients (13%) such that their dexamethasone dose was reduced or stopped due to low heart rates. One patient had a plasma glucose concentration of CTCAE v4.03 grade 3 severity (14.4 mmol/L; 13.9 to 27.8 mmol/L) that normalized after discontinuation of dexamethasone.

Interpretation of our findings is limited by its retrospective, non-comparative design. Like other retrospective studies, we relied on accurate and complete documentation in the health record. However, we were unable to accurately determine the prevalence of subjective symptoms due to the lack of routine and systematic measurements. Compared to other studies that describe AEs associated with dexamethasone, our study offers the advantage of analyzing the attribution of each AE to drug exposure using a validated pediatric tool, the LCAT. This tool was selected for its good inter-rater reliability, improved performance over the Naranjo tool, and utility in a healthcare context.[17] Nevertheless, as mentioned above, we may have underestimated the prevalence of subjective symptoms such as dyspepsia and overestimated the prevalence of objectively measured AEs. Furthermore, since our evaluation was limited to AEs which manifested during or immediately following dexamethasone administration, we were not able to describe the prevalence of AEs which may be of particular concern in HSCT: impaired engraftment, fungal infection, and cancer relapse.

## 3.6 Conclusion

The most common AEs associated with the use of dexamethasone for CINV prophylaxis in children receiving HSCT conditioning were hyperglycemia, hypertension, and bradycardia. Our use of lenient definitions may have over-estimated the incidence of these AEs. In the absence of co-morbidities which may compound their clinical significance, the most common immediate AEs associated with dexamethasone given for CINV prophylaxis are transient, of minor clinical importance, and do not require medical intervention. This information will be helpful to

clinicians who are weighing the potential benefits of improved CINV control against the potential adverse effects of antiemetic prophylaxis for individual patients.

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**Figure 3.1** Incidence of the most common adverse events (AEs) definitely or probably attributed to dexamethasone and distribution of Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) grades

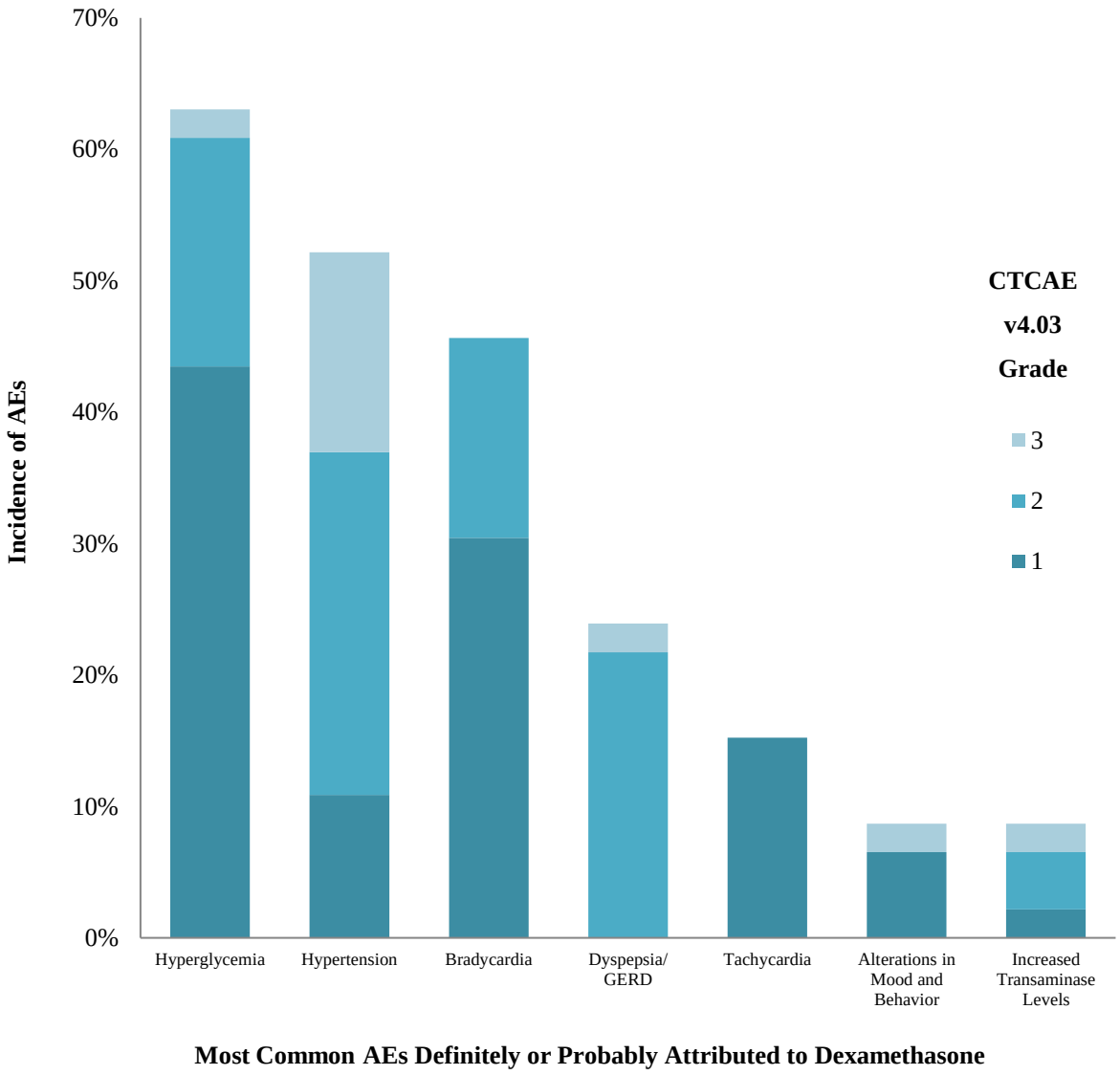

**Table 3.1** Dexamethasone exposure

| Emetogenicity of Conditioning Regimen[1] | Age or BSA | Recommended Dexamethasone Dose for CINV Prophylaxis | Number of Patients | Mean Dexamethasone Dose Administered (± s.d.) |
|---|---|---|---|---|
| **Acute Phase[a]** | | | | |
| High | < 12 years | 24 mg/m$^2$/day ÷ q6h IV/PO[b] | 24 | 15.0 (± 3.4) mg/m$^2$/day |
| | ≥ 12 years | 20 mg/day as a single daily dose IV/PO | 15 | 20.1 (± 5.5) mg/day |
| Moderate | ≤ 0.6 m$^2$ | 4 mg/day ÷ q12h IV/PO | 0 | Not applicable |
| | > 0.6 m$^2$ | 8 mg/day ÷ q12h IV/PO | 7 | 6.5 (± 1.9) mg/day |
| **Delayed Phase[c]** | | | | |
| All | Not applicable | 9 mg/m$^2$/day ÷ q12h PO (maximum 8 mg/dose) | 32 | 9.9 (± 3.6) mg/m$^2$/day |

BSA=Body surface area; CINV=Chemotherapy-induced nausea and vomiting; s.d.=Standard deviation; IV=intravenous; PO=by mouth

[a]Acute phase=Beginning with the first chemotherapy dose and ending 24 hours after the last chemotherapy dose

[b]No maximum single dose

[c]Delayed phase=Beginning at the end of acute phase and ending up to 7 days later

**Table 3.2** Patient and transplant characteristics

| | |
|---|---|
| **Patient Characteristics** | |
| Age, years, median (range) | 10.2 (4.2-17.4) |
| Age Groups, n (%) | |
| ≤ 1 year of age | 0 (0) |
| > 1 to < 12 years of age | 30 (65) |
| ≥ 12 years of age | 16 (35) |
| Sex, n (%) | |
| Male | 23 (50) |
| Female | 23 (50) |
| **HSCT Conditioning Characteristics** | |
| Emetogenicity of Conditioning Regimen, n (%) | |
| High | 39 (85) |
| Moderate | 7 (15) |
| Duration of Conditioning, days, median (range) | 6.1 (2.2-9.0) |
| Conditioning Regimen, n (%) | |
| Cyclophosphamide + TBI | 9 (20) |
| Cyclophosphamide + TBI + Thymoglobulin | 9 (20) |
| Busulfan + Cyclophosphamide | 7 (15) |
| Busulfan + Melphalan | 4 (9) |
| Busulfan + Fludarabine | 2 (4) |
| Other | 15 (33) |
| **HSCT Characteristics** | |
| Type of HSCT, n (%) | |
| Allogeneic | 34 (74) |
| Autologous | 12 (26) |
| Stem Cell Source, n (%) | |
| Peripheral Blood | 14 (30) |
| Bone Marrow | 21 (46) |
| Cord Blood | 11 (24) |

n=Number of subjects; HSCT=hematopoietic stem cell transplantation; TBI=Total body irradiation;

# Chapter 4
# Transplant-Related Mortality in Children Receiving Dexamethasone for Chemotherapy-Induced Nausea and Vomiting During Hematopoietic Stem Cell Transplantation: A Multi-Centre Feasibility Study

The contents of this chapter have been prepared as a manuscript. The authors involved with the conception and implementation of this project are E. Paw Cho Sing, T. Schechter, M. Ali, A. Willan, M. Offringa, L. Sung, and L.L. Dupuis.

As primary author, I developed the protocol with L.L. Dupuis and in consultation with T. Schechter, M. Ali, L. Sung, A. Willan, and M. Offringa. I was responsible for screening patients at The Hospital for Sick Children with the help of a database manager, reviewing patient charts, and entering data into an electronic database. Co-author, M. Ali, was consulted for unavailable data regarding patients transferred to referral sites. Data collection for patients from Alberta Children's Hospital was completed by collaborators, K. McKinnon and J. Jupp. I was responsible for quality assurance and gathering information about the feasibility of data collection. With L.L. Dupuis and the assistance of a biostatistician, I analyzed and summarized the data.

## 4.1 Abstract

*Background***:** The success of hematopoietic stem cell transplantation (HSCT) relies on timely immune reconstitution and, in allogeneic HSCT, the graft-versus-leukemia effect. Possible interference by dexamethasone given to prevent chemotherapy-induced nausea and vomiting (CINV) is concerning. We developed a multi-center framework for retrospective data collection and determined its feasibility for a larger study.

*Methods***:** Patients ≤18 years receiving their first HSCT for an acquired hematological disorder at two centers between January 1, 2012, and July 31, 2017, were included. A feasibility questionnaire was completed by investigators. Feasibility was determined if >60% of data elements were available in an institutional database or if abstraction required ≤90 minutes/patient. Dexamethasone exposed and unexposed groups were compared on HSCT

outcomes (1-year transplant-related mortality [TRM] and event-free survival [EFS], Day +100 invasive fungal disease [IFD], acute graft-versus-host disease [aGVHD], and time to neutrophil engraftment) in a preliminary analysis. We conducted this analysis using propensity score (PS) covariate adjustment and PS matching.

*Results***:** Ninety-seven patients (median age: 8.8 years; range: 0.6-18) were included. Almost 70% of the data elements were easily retrieved from the institutional database at one center while data abstraction required 10 to 30 minutes/patient at the other center. We demonstrated the mechanics of an analysis of outcomes (TRM, EFS, IFD, aGVHD, and time to neutrophil engraftment) using PS covariate adjustment and PS matching for a larger study.

*Conclusions*: We developed an analytical framework to assess the impact of antiemetic dexamethasone on TRM and demonstrated the feasibility of data collection to support its use in a large study.

## 4.2 Introduction

Hematopoietic stem cell transplantation (HSCT) is an increasingly accessible and viable option to cure many high-risk and refractory malignant and non-malignant diseases. Myeloablative pre-transplant conditioning has been a prominent driver of cure. Given just prior to HSCT, conditioning aims to eliminate the underlying disease and prepare the bone marrow to receive donor stem cells. For patients with leukemia receiving allogeneic HSCT, the graft-versus-leukemia (GVL) effect offers additional curative benefit. Experimental data support the importance of cytokine-mediated recruitment of immune cells, especially T-lymphocytes, during this process.[1] Cytokines similarly spur the clonal expansion of the donor-derived immune cells which salvage often permanently impaired bone marrow from intensive doses of chemotherapy and radiation.[2] These key functions of HSCT rely heavily on underlying immunological interactions.

By suppressing cytokine expression, corticosteroids may negatively influence clinical outcomes of HSCT. In particular, dexamethasone is recommended for the treatment and prevention of chemotherapy-induced nausea and vomiting (CINV) and is given proximal to the time of the infusion of HSCs.[3-5] As discussed in previous chapters, clinical data strongly support its antiemetic efficacy in children and adults receiving highly and moderately emetogenic

chemotherapy. Yet, concerns about the immunomodulating effects of dexamethasone have stimulated debate over its safety in HSCT. A theoretical disruption in the GVL effect may increase the risk of relapse and contribute to lower survival in patients with malignant diseases. Without timely recovery of immune function, HSCT recipients are at a prolonged risk of fungal complications and early death. Moreover, a delay in T-lymphocyte reconstitution impacts the occurrence of graft-versus-host disease (GVHD) following allogeneic HSCT.[2,6]

Currently, there is a lack of direct clinical evidence to inform an assessment of the risks of dexamethasone. For this reason, many pediatric HSCT centers are reluctant to routinely include dexamethasone in antiemetic regimens.[7] Omission of this effective antiemetic makes patients more vulnerable to intractable and distressing CINV. Unfortunately, complete control of CINV in children receiving HSCT conditioning is particularly dismal (acute: 5%; delayed: 12%).[8] Preventing CINV not only improves quality of life, but may also mitigate the severity of and risk for downstream complications, such as mucositis and hepatotoxicity, by facilitating enteral nutrition.[9-12] Thus, a greater understanding of the risks of dexamethasone is urgently needed to inform supportive care decisions and improve the safety of HSCT.

To assess the impact of dexamethasone given for CINV on transplant-related mortality (TRM) and other HSCT outcomes, we designed a framework for a multi-center, retrospective study. Before expanding to other centers, we believed it to be important to pilot our methods and identify and address any issues in preparation for full implementation. Here, I describe efforts to determine the feasibility of applying the framework using data from two pediatric HSCT centers. As existing knowledge in this area is lacking, this study also serves to explore and estimate the risks of dexamethasone specific to the HSCT setting.

## 4.3 Methods

### 4.3.1 Feasibility

This multi-center, retrospective study was approved by the Research Ethics Board at The Hospital for Sick Children (SickKids) and Alberta Children's Hospital (ACH). The primary objective of the present research was to determine the feasibility of implementing our framework (below) in a future, large-scale multi-center study. Feasibility was tested using patient data from two sites.

A questionnaire was completed by an investigator or collaborator from each site to determine the proportion of data elements available in the institutional database and the time required for data collection (Appendix C). Site-specific feasibility was met if ≥60% of data elements were available in the institutional database or if <60%, abstraction of the remaining data elements from other sources, such as the health record, required ≤90 minutes per patient. We chose not to define a sample size for the present feasibility study other than the number of eligible patients at the two sites. We acknowledge that a large number of patients will be required in order to provide estimates with certainty and face validity among the HSCT community. For the future study, the sample size will be determined by the number of centers willing to collaborate and the number of eligible patients from each participating center.

### 4.3.2 Framework

*Patients*: Eligible patients were children and adolescents 18 years of age or younger at the time of their first allogeneic or single autologous HSCT and who received myeloablative conditioning for any of the following acquired hematological disorders: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), chronic myeloid leukemia (CML), or aplastic anemia (AA).

Patients were excluded if they had Down syndrome, a diagnosis of severe combined immune deficiency, or a disorder requiring physiological supplementation with glucocorticoid agents, such as adrenal insufficiency. To minimize exposure to corticosteroids other than dexamethasone and for indications other than CINV prophylaxis, patients receiving another corticosteroid, such as methylprednisolone or prednisone, for CINV or aGVHD prophylaxis were excluded. Due to their potential influence on neutrophil counts, patients were excluded if they received sirolimus or cyclophosphamide for aGVHD prophylaxis, granulocyte colony stimulating factors (G-CSF), ganciclovir, or trimethoprim-sulfamethoxazole from the day of HSC infusion to neutrophil engraftment. Patients were also excluded if they were receiving treatment for fungal disease at the time of admission.

*Dexamethasone exposure*: Children and adolescents who received dexamethasone for CINV prophylaxis for a minimum of 72 hours from the start of conditioning through one day prior to stem cell infusion (Day -1) constituted the exposed group. Those who did not receive dexamethasone at any point during the same timeframe constituted the unexposed group.

*TRM:* The primary outcome of the framework was the incidence of TRM at 1-year post-HSCT. TRM was defined as death in the absence of recurrence or progression of prior disease for which the patient's first HSCT was indicated.

*HSCT Outcomes:* The secondary outcomes of the framework were the incidences of event-free survival (EFS) at 1-year post-HSCT; invasive fungal disease (IFD) and aGVHD at 100 days post-HSCT; and the mean time to neutrophil engraftment. To determine EFS, an event was defined as engraftment failure, recurrence or progression of disease, or death. Proven or probable cases of IFD were identified and defined according to the European Organization for Research and Treatment of Cancer (EORTC) criteria (Appendix D). Maximal grade of aGVHD was defined according to the modified Glucksberg scale (Appendix E). The day of neutrophil engraftment was defined as the day of the first of three consecutive measurements separated by at least one day where the absolute neutrophil count is $0.5 \times 10^9$ cells/L or higher.

*Data Collection:* Existing institutional databases were leveraged to retrieve pre-collected data elements such as patient demographics, disease and transplant characteristics, and HSCT outcome measures. If not captured from the internal database, data elements related to receipt of medications were obtained via the pharmacy dispensing software. Data elements not identified in either data source were extracted from patients' health record. Redacted reports of fungal investigations, such as results from sterile/non-sterile cultures and galactomannan assays, were sent directly from each collaborating site to the lead site. Two investigators from the lead site independently reviewed each case and discrepancies were discussed and resolved by consensus via a third independent reviewer. The occurrences of death, recurrence or progression of disease, engraftment failure, aGVHD, and time to neutrophil engraftment, were determined by data collectors using objective sources, such as database entries or diagnostic reports, and were not routinely reviewed by lead site investigators.

*Propensity Score*: A propensity score (PS) was determined for each patient using five independent disease and treatment variables suspected to introduce confounding with respect to dexamethasone exposure: Pre-transplant TRM risk (European Group for Blood and Marrow Transplantation [EBMT] risk score; Appendix F), stem cell source (peripheral blood, bone marrow, or umbilical cord blood), history of documented or suspected invasive fungal disease prior to conditioning (yes or no), receipt of highly emetogenic chemotherapy as conditioning

(yes or no), and receipt of palonosetron for CINV prophylaxis during HSCT (yes or no). A logistic regression analysis of these five covariates was performed to yield a PS as an estimate of the likelihood of receiving dexamethasone.

*Statistical Analysis:* The analysis was developed as a proof of principle in preparation for a larger study. The hypothesis of the larger study will be that dexamethasone given for CINV prophylaxis does not adversely influence TRM in children undergoing HSCT. Demographic data were summarized using descriptive statistics.

We used PS as a covariate in a binary logistic regression model to compare 1-year TRM and EFS between the exposed and unexposed groups. Differences were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). To assess the remaining secondary HSCT outcomes, we planned on using PS-matching or inverse probability of treatment weighting as an alternative. In PS-matching, patients from the exposed and unexposed groups were matched one-to-one to the nearest neighbor based on PS with a caliper distance of 0.1. Matching also occurred within the following age groups: neonates (0 to 27 days), infants (28 days to 1 year), children (≥1 to 10 years), and adolescents (≥10 to 18 years). We aimed to incorporate PS-matched groups or PS-derived weights into a Cox proportional-hazards regression model to assess differences in IFD and aGVHD up to Day +100 and a cumulative incidence analysis to assess differences in the time to neutrophil engraftment. Prior to Day +100, any occurrence of death, disease relapse or recurrence, or receipt of a second HSCT were considered to be competing events for the analysis of IFD and aGVHD. If these events occurred prior to neutrophil engraftment, they were considered to be competing events for the analysis of the outcome, time to neutrophil engraftment. We planned on presenting the differences as adjusted hazard ratios with 95% CI. For the larger study, we will comment on the clinical significance of these differences and the extent of overlap of the CI in all outcomes between the exposed and unexposed groups.

### 4.3.3 Rationale for Methodological Choices

*Study Design*: A retrospective study design was preferred due to the delay in acquiring TRM data. Furthermore, randomization would not have been ethical as some children would be denied a guideline-recommended antiemetic agent depending on the standard of care at the participating site. It would also prove challenging to uproot long-standing beliefs and practices of clinicians who routinely allow or disallow the use of dexamethasone for CINV prophylaxis. Thus, a

randomized controlled trial was not ethical or feasible and a retrospective approach was undertaken. PS was incorporated to control selection bias and confounding inherent to observational study designs.

*Exposure Definition*: The duration of dexamethasone exposure of 72 hours or longer was chosen empirically. At present, there are no clinical data to inform a threshold of corticosteroid exposure above which would be sufficient to impact the GVL effect. A duration ranging from 5 to >10 days of high-dose corticosteroids has been identified to correlate with an increased risk of IFD.[13] However, there is a lack of consensus to support a threshold to define a high dose. For the purposes of this study, our *a priori* bias is towards capturing a higher frequency of adverse events associated with dexamethasone. If it is indeed associated with negative HSCT outcomes, we intended on improving detection of this signal by broadening our exposed group to include those exposed to dexamethasone as short as 72 hours. We compared this to individuals with no exposure to dexamethasone to allow a sufficient difference between groups.

*Outcome Definitions*: We selected TRM as the primary outcome of our framework to understand the impact of a supportive care measure (giving dexamethasone for CINV prophylaxis) on survival independent of the disease being treated. Wide heterogeneity in the classification of treatment-related mortality exists across clinical trials.[14] We adapted a consensus-based definition established by a panel of experts in pediatric cancer supportive care. This system demonstrated excellent reliability when applied by clinical research associates ($\kappa$=0.83, 95% CI 0.60-1.00) and pediatric oncologists ($\kappa$=0.84, 95% CI 0.63-1.00) as well as high criterion validity between consensus classifications ($\kappa$=0.92, 95% CI 0.78-1.00).[15] Due to the lack of a standardized definition in HSCT and the flexibility inherent to the system for classifying treatment-related mortality developed by Alexander *et al*., we adapted this definition for the primary outcome of our framework.

Moreover, we chose to assess EFS to gain comprehensive insight on important undesirable outcomes, including engraftment failure and relapse. IFD and aGVHD are important early complications of HSCT that warrant assessment. They were analyzed using widely accepted and validated measures: the EORTC criteria for proven and probable IFD (Appendix C) and the modified Glucksberg scale for grading aGVHD (Appendix D). The time to neutrophil

engraftment using an established threshold for neutrophil recovery was chosen as an outcome since it is an important HSCT milestone and may influence infection risk.

*PS Estimation*: We recognized that the decision to use dexamethasone may be heavily influenced by various non-random factors. There is a possibility that dexamethasone may be withheld or used more conservatively in children with a higher pre-transplant risk for TRM or in those with a history of IFD. More highly emetogenic conditioning warrants a more effective, steroid-inclusive antiemetic strategy, while concomitant administration of palonosetron permits the omission of dexamethasone without compromising CINV control.[3] Lastly, the choice of stem cell source may influence use of dexamethasone if corticosteroids are perceived to hinder immune reconstitution. At baseline, recovery of neutrophils is slowest with cord blood HSCs and fastest with peripheral blood HSCs.[16] Imbalance of these factors across groups result from having a non-randomized study design. PS was proposed to balance these factors to mitigate their influence on outcomes of interest. Variables incorporated into PS estimation were the EBMT risk score, history of documented or suspected IFD prior to the start of conditioning, receipt of highly emetogenic conditioning, receipt of palonosetron for CINV prophylaxis, and stem cell source.

*EBMT Risk Score*: Susceptibility to TRM is influenced by multiple pre-transplant characteristics. Intergroup differences in these characteristics must be minimal to appropriately estimate the impact of dexamethasone exposure. The EBMT risk score predicts the likelihood of TRM by assessing five pre-transplant factors: patient age, disease stage, time interval from diagnosis to transplant, donor type, and donor-recipient sex combination (Appendix E). Using a large clinical data registry, this tool has been validated in more than 150,000 pediatric and adult recipients of allogeneic and autologous HSCTs.[17] The potential of the EBMT risk score as a tool for clinical decision making has been supported by pediatric research groups.[18-20] Furthermore, its components are readily available allowing for ease of use and widespread applicability.

We identified other similar prognostic risk scores to predict mortality in the HSCT setting. The Pretransplantation Assessment of Mortality score and the Disease Risk Index were excluded due to the lack of validation in a pediatric population at the time of consideration.[21,22] Despite the value of accounting for the burden of pre-transplant comorbidities, The Hematopoietic Cell Transplantation-specific Comorbidity Index was deemed too cumbersome and impractical to

incorporate.[23] The EBMT risk score was selected over other risk scores based on validity in a pediatric population, acceptability by pediatric researchers, and feasibility of implementation.

*PS Methods:* PS was used to adjust for potential confounders and mimic the effects of randomization in this observational study. The lack of a universally preferred PS method prompted careful review of each one to select an approach that suited the needs of our outcome analysis.

To assess TRM and EFS, covariate adjustment using PS was selected as the primary method of analysis. This is supported by a comparative analysis of different PS methods applied to large datasets from cardiovascular observational studies. Stratification performed poorly and was difficult to implement with rare events. Inverse probability of treatment weighting also produced imprecise estimates when covariates were markedly imbalanced and propensity scores clustered towards extreme ends. Covariate adjustment and matching demonstrated the most reliable estimation of treatment effects when applied to 4 datasets ranging in size from 7,500 to 90,000 patients. Although simple and efficient, matching comes at the expense of losing a sizeable proportion of subjects, thus attenuating generalizability and the precision of risk estimates. Up to 60% of patients were excluded from data analysis due to incomplete matching in published reports.[24,25] Considering these limitations, PS covariate adjustment was selected as the method of analysis for its similar performance without the substantial loss of data from the analysis.

To assess IFD, aGVHD, and time to neutrophil engraftment, PS matching and inverse probability of treatment weighting were selected as the primary and alternative methods of analysis. In a series of Monte Carlo simulations, varioius PS methods were compared on their ability to estimate marginal hazard ratios of time-to-event outcomes. Stratification and covariate adjustment using the PS led to substantial bias upon estimation of hazard ratios, while minimal bias was achieved in those analyses that incorporated matching using PS (one-to-one greedy nearest-neighbour matching within caliper width) and inverse probability of treatment weighting. These findings support the choice of PS methods used to analyze our secondary outcomes.[26,27] Given the need for large sample sizes to overcome the effect of attrition on the precision of our estimates, inverse probability of treatment weighting is reserved as an attractive alternative that allows analysis of the full dataset.

*Pediatric Age Bands*: Matching patients on PS within discrete age bands was designed to reflect the pharmacokinetic variability of dexamethasone that exists across the age spectrum. In two studies, children with ALL younger than 10 years old demonstrated higher clearance of dexamethasone compared to that in older children.[28] The elimination half-life was also significantly shorter in patients 1 to 9.9 years old (2.14 ± 0.08 hours) relative to those 10 to 18.8 years old (3.06 ± 0.14 hours).[29] Studies in extremely low-birth weight neonates observed a prolonged half-life following a single dose of dexamethasone (9.26 ± 3.34 hours).[30] This likely reflects the low activity levels of hepatic CYP3A4 enzymes, the main metabolizing enzyme of dexamethasone, in neonates. Due to the dramatic changes of CYP3A4 expression during the first 12 months of life, dexamethasone exposure is also likely prolonged and variable in this age group.[31] These clinical findings support the pediatric age bands that were selected for matching.

## 4.4 Results

All patients who received their first autologous or allogeneic HSCT at SickKids and ACH between January 1, 2012, and July 31, 2017, were assessed for eligibility. Ninety-seven patients (mean age: 8.8 years; range: 0.6-18.1) were enrolled across both sites (SickKids: 72; ACH: 25) and were included in the PS covariate adjustment analysis. Twenty-eight patients (14 matched pairs) were included in the PS matched-pair analysis. A flowchart depicting the number of patients screened, excluded, and included are presented in Figure 4.1.

At SickKids, most patients (81%) were exposed to dexamethasone for a duration of 3 days or longer given as CINV prophylaxis. None of the included patients at ACH were exposed to dexamethasone. A summary of baseline characteristics is found in Table 4.1.

### 4.4.1 Feasibility

At SickKids, almost 70% of the data elements were retrievable from the institutional database (Table 4.2). Data elements related to IFD and engraftment failure were retrieved from the electronic health record. At ACH, only 17% of the data elements were retrievable from the institutional database. However, the time dedicated to abstracting these remaining data elements was approximately 10 to 30 minutes per patient.

### 4.4.2 Framework

To gain more experience with PS methods, a preliminary analysis using PS covariate adjustment and PS matching was conducted.

*PS Covariate Adjustment:* Overall, the TRM rates at 1-year post-HSCT were 9% (5/58) and 5% (2/39) in the exposed and unexposed groups, respectively. The adjusted OR of TRM was 1.0 (95% CI: 0.1-7.9). The rates of EFS were 60% (35/58) and 51% (20/39) in the exposed and unexposed groups, respectively. The adjusted OR of EFS was 3.8 (95% CI: 1.1-13.5).

*PS Matching*: Fourteen patients who did and did not receive dexamethasone were able to be matched. After matching, there were no differences in age groups, the distribution of covariates, and PS between exposed and unexposed groups (Table 4.3). Few patients who were unexposed to dexamethasone were excluded from the matched-pair analysis of secondary outcomes (IFD: 1 patient; aGVHD: 2 patients; time to neutrophil engraftment: 1 patient) due to competing events. The rates of IFD and aGVHD were 14% (2/14) and 43% (6/14) in the exposed group and 15% (2/13) and 25% (3/12) in the unexposed group, respectively. The mean time to neutrophil engraftment was 23 (range: 9-34) days in the exposed group and 20 (range: 14-27) days in the unexposed group. Due to the small number of patients who experienced competing events (death: 1 patient; second HSCT: 1 patient), a Cox proportional-hazards regression and cumulative incidence model with competing events analysis could not be performed. Thus, adjusted hazard ratios were not be presented for IFD, aGVHD, and time to neutrophil engraftment, based on the data from this feasibility cohort.

A summary of the preliminary analysis using PS covariate adjustment and PS matching are found in Table 4.4 and 4.5, respectively.

## 4.5 Discussion

The ramifications of interfering with the GVL effect in children receiving allogeneic HSCT and delaying immune reconstitution after autologous or allogeneic HSCT are serious. The development of a viable, analytical framework is the first step to fully describing the safety or risks of harm of dexamethasone given for CINV to pediatric HSCT recipients. We have developed an analytical framework and demonstrated that data collection to conduct the analysis is feasible.

From the beginning, we valued prompt identification of eligible patients and simplified data collection. These were perceived as integral for successfully implementing our framework as a larger, multi-centre study. Accredited pediatric HSCT centers maintain an internal HSCT database to facilitate reporting to national and international regulatory bodies. Such databases allow rapid retrieval of data elements, including demographics, pre- and post-HSCT disease status, and HSCT information. Our questionnaire indicated that most of our data elements were available by means of a database query at SickKids. While fewer than 60% of data elements were available from a database at ACH, data abstraction from other sources was not time-consuming. At both sites, a record of dispensed and administered medications was easily retrievable from an existing pharmacy software or the computerized physician order entry system. Remaining data elements were abstracted from individual patient health records.

As the largest pediatric oncology center in Canada, SickKids performs virtually all pediatric HSCTs in Ontario as well as those referred from hospitals in the Atlantic provinces. Similarly, ACH acts as the provincial quaternary referral center for pediatric BMT and receives referrals from southwestern British Columbia and western Saskatchewan. Patients referred from other centers presented challenges to data collection in both participating sites. The data elements regarding longer term outcomes (e.g. TRM, EFS) were seldom not available and required follow-up with the referral center. Although post-HSCT follow-up is conducted at regular intervals, it is possible that storage of this data into the health record may be missed especially for patients without active or concerning medical issues. In preparation for the larger study, we will develop an individualized strategy with investigators from collaborating sites to collect required data from referral centers. Lastly, we recognize that our feasibility endpoint may not be met for every site invited to participate in our study. Some may still be willing to participate depending on the systems in place, such as clinical research support staff and internal database access. With each potential collaborator, we will discuss the feasibility of data collection in the unique context of their institution.

Our analytical framework is strengthened by the incorporation of PS methods. The decision to use dexamethasone is possibly influenced by multiple factors left uncontrolled in conventional observational research. Estimating this likelihood to adjust outcome analysis permits creation of quasi-randomized comparisons to attenuate issues of selection bias and confounding. As a result, PS methods are increasingly being used in studies of a similar nature. However, the lack of a

universally supported method prompts close examination of their relative advantages and disadvantages. To better understand PS methodology, we analyzed the data from our feasibility cohort using PS covariate adjustment and PS matching. Both perform well using datasets from large-scale observational studies.[24,25] Comparatively, PS matching appears to offer less biased estimations of time-to-event outcomes. However, the precision of these estimates may be threatened by high attrition rates from unmatched subjects. In our analysis, as many as 70% of patients were left unmatched which substantially reduced our sample size. However, as our dataset grows, the influence of data attrition may become less important. Given these factors, we will continue to use PS covariate adjustment for assessment of TRM and EFS in the larger study. We plan to retain PS matching as the primary method for estimating differences in IFD, aGVHD, and time to neutrophil engraftment, and reserve inverse probability of treatment weighting as an equivalently reliable and efficient alternative.

Incorporating the EBMT risk score, a validated and credible pretransplantation risk assessment tool, into PS estimation facilitates balancing the effect of confounders. We selected the EBMT risk score for its simplicity and validity in a pediatric population. It offers practical advantages that streamline and allow other sites to conduct our proposed study methods feasibly. We demonstrated that all data elements of the EBMT risk score were routinely collected and promptly retrievable from clinical databases. As useful as it is, we must acknowledge that the EBMT risk score does not perfectly predict TRM. Gratwohl *et al*. estimates that only 63% of the variability of TRM can be explained by the risk score.[17] However, none of the other available prognostic risk tools (HCT-CI, PAM, DRI) were deemed superior in predictive ability. Thus, a residual confounding effect remains a possible limitation of our analysis. As previously discussed, we adopted a standardized definition for TRM which demonstrated high reliability and criterion validity when applied by pediatric oncologists and clinical research associates.[15] In addition, establishing a centralized method for assessment of each case of IFD aimed to reduce bias and inter-rater variability. These aspects further strengthen the validity of our analytical framework.

A possible confounding effect that stems from differences between HSCT centers is currently not addressed in our framework. The inclusion of pediatric HSCT centers that either systematically encourage or discourage the use of dexamethasone in all patients may be problematic. Indeed, we included 25 patients from ACH who were all unexposed to

dexamethasone. Uneven distribution of patients from specific centers may confound the association between dexamethasone exposure and our outcomes of interest. These differences include the level of specialization, dedicated services for pediatric care, HSCT volume per year, geographic location, and affiliation with a research consortium. Ideally, we would only include centers with a diversity of antiemetic practices, but recognize that institutional standards of practice limit such inconsistencies. For the future study, we aim to explore the effect of the type of center and region in our framework, which was not possible in our feasibility study of two centers.

Through our preliminary analysis, we evaluated the association between dexamethasone exposure and TRM and other HSCT outcomes using PS covariate adjustment. The low event rates and our small sample size contributed to the wide CIs of our initial estimates. It is important to note that the current investigation is exploratory and serves as a proof of principle with respect to the use of our analytical framework. Valid estimates will be generated in a future study using a much larger sample size.

Our investigation of the risks of dexamethasone used as an antiemetic in HSCT, to the best our knowledge, is the first of its kind. Despite strong guideline support, the use of dexamethasone in children, particularly those undergoing HSCT, remains controversial. TRM, IFD, aGVHD, and delayed or failed engraftment are serious and merit close attention. Ultimately, a better appreciation of the balance between risks and benefits of dexamethasone will help define the standard of care and shape guideline recommendations for CINV prophylaxis in children.

## 4.6 Conclusion

Assessment of the safety of dexamethasone in the context of HSCT is important. Pediatric patients deserve evidence-based supportive care and safe treatments for their underlying diseases. We have developed an analytical framework to estimate the risk of TRM in pediatric HSCT patients who did and did not receive dexamethasone for CINV. We have shown that collection of the data elements required for this analysis is feasible. Data from other pediatric HSCT centers will be sought and incorporated into the analysis. This will allow an assessment of the influence of dexamethasone as an antiemetic on HSCT outcomes with increasing certainty.

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**Figure 4.1** Study flowchart

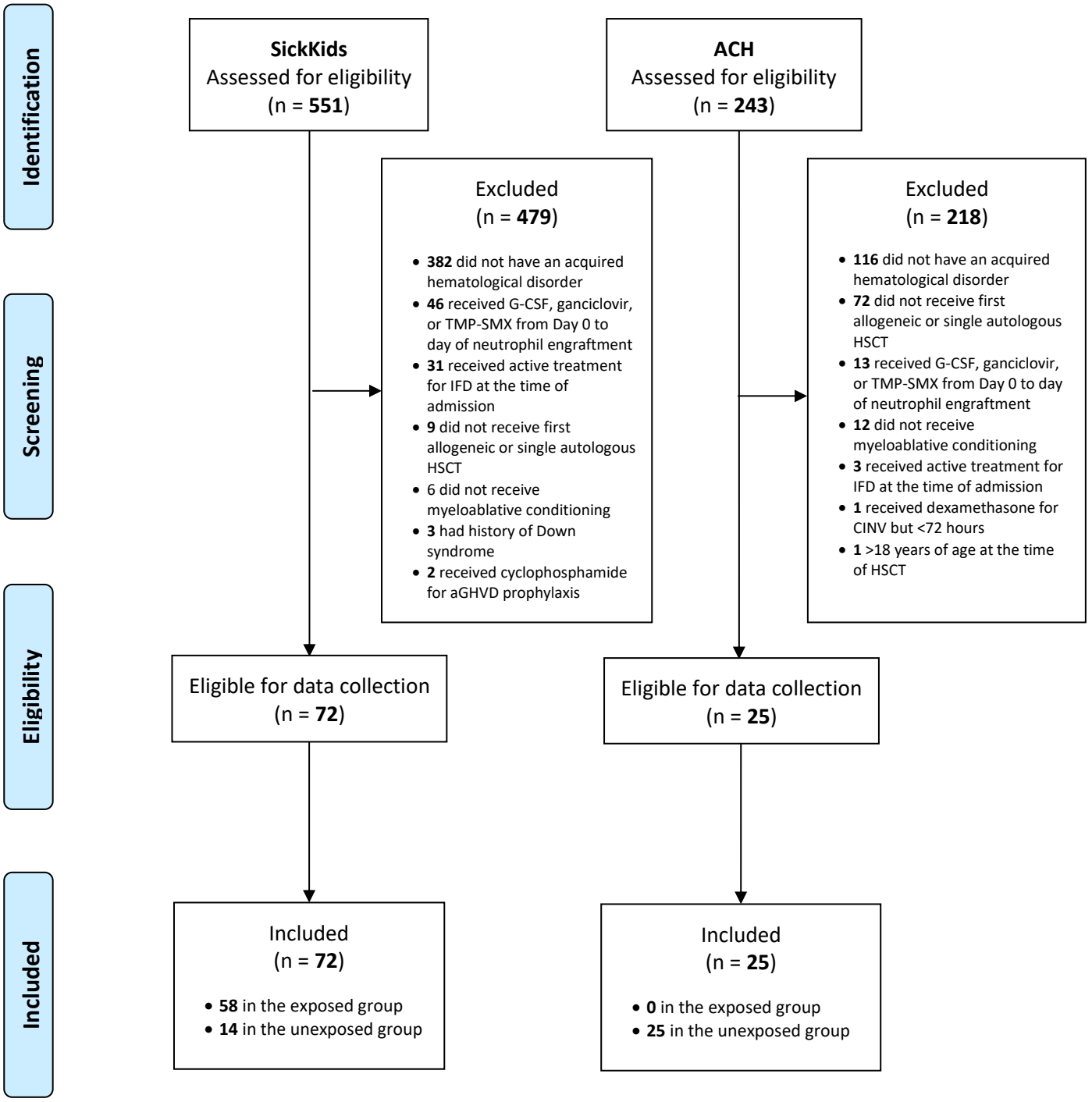

**Table 4.1** Summary of baseline characteristics

| **Demographics** | **N (%)** |
|---|---|
| Total number of patients | 97 |
| Age Groups | |
| 0 to 27 days old | 0 (0) |
| 28 days to 1 year old | 4 (4) |
| ≥1 to 10 years old | 47 (48) |
| ≥10 to 18 years old | 46 (47) |
| Sex | |
| Male | 59 (61) |
| Female | 38 (39) |

| **Disease Characteristics** | **N (%)** |
|---|---|
| Primary diagnosis | |
| ALL | 46 (47) |
| AML | 36 (37) |
| MDS | 9 (9) |
| NHL | 4 (4) |
| CML | 2 (2) |
| AA | 0 (0) |
| Disease stage | |
| Early | 41(42) |
| Intermediate | 37 (38) |
| Late | 19 (20) |
| Time interval from diagnosis to transplant | |
| <12 months | 55 (57) |
| >12 months | 42 (43) |

| **HSCT Characteristics** | **N (%)** |
|---|---|
| Type of HSCT | |
| Allogeneic | 95 (98) |
| Autologous | 2 (2) |
| Stem Cell Source | |
| Bone Marrow | 57 (59) |
| Peripheral Blood | 25 (26) |
| Cord Blood | 15 (15) |
| Donor Type* | |
| HLA-Identical Sibling | 28 (29) |
| Unrelated | 55 (58) |
| Other | 12 (13) |
| Donor-Recipient Sex Combination* | |
| Female Donor, Male Recipient | 26 (27) |
| Other | 69 (73) |
| Conditioning Regimen | |
| Cyclophosphamide + TBI | 38 (39) |
| Busulfan + Cyclophosphamide | 18 (19) |
| Busulfan + Fludarabine + TBI | 24 (25) |
| Busulfan + Fludarabine | 9 (9) |
| Other | 8 (8) |

| **Dexamethasone** | **N (%)** |
|---|---|
| Exposure status | |
| Exposed group | 58 (60) |
| Unexposed group | 39 (40) |

N=Number of subjects; ALL=Acute lymphoblastic leukemia; CR=Complete remission; AML=Acute myeloid leukemia; MDS=Myelodysplastic syndrome; NHL=Non-Hodgkin's lymphoma; CML=Chronic myeloid leukemia; AA=Aplastic anemia; HSCT=Hematopoietic stem cell transplantation; *=Allogeneic HSCT only; HLA=Human leukocyte antigen; TBI=Total body irradiation

**Table 4.2** Availability of data elements in institutional database at The Hospital for Sick Children (SickKids) and Alberta Children's Hospital (ACH)

| Study Stage | Data Element | SickKids | ACH |
|---|---|---|---|
| 1. Eligibility Screening | Date of birth | Yes | Yes |
| | Diagnosis (indication for HSCT) | Yes | Yes |
| | Date of HSCT | Yes | Yes |
| | Type of HSCT | Yes | Yes |
| | Conditioning regimen | Yes | No |
| | Intensity of conditioning | Yes | No |
| 2. Exclusion Screening | Down syndrome | No | No |
| | Diagnosis of severe combined immune deficiency | No | No |
| | Disorders requiring physiological supplementation with corticosteroids | No | No |
| | Receipt of active treatment for IFD at admission for HSCT to initiation of conditioning | No | No |
| | aGVHD prophylaxis regimen | Yes | No |
| | Receipt of ganciclovir, sulfamethoxazole-trimethoprim, and G-CSF from Day 0 to day of neutrophil engraftment | No | No |
| | Receipt of corticosteroids other than dexamethasone for CINV prophylaxis | Yes | No |
| 3. PS Estimation | Recipient sex | Yes | Yes |
| | Donor sex | Yes | No |
| | Donor type | Yes | No |
| | Date of diagnosis | Yes | No |
| | Date of relapse(s) | Yes | No |
| | Stem cell source | Yes | No |
| | History of documented or suspected IFD from date of diagnosis to admission for HSCT | No | No |
| | CINV prophylaxis regimen (including palonosetron) | No | No |
| | Receipt of dexamethasone for CINV prophylaxis | Yes | No |
| 4. Outcome Analysis | Date of death | Yes | No |
| | Cause of death | Yes | No |
| | Recurrence or progression of disease for which HSCT was indicated | Yes | No |
| | Engraftment failure | No | No |
| | Date of neutrophil engraftment | Yes | No |
| | Maximal grade of aGVHD | Yes | No |
| | Redacted reports suggestive of invasive fungal disease within Day +100 | No | No |
| **Percentage of data elements available in institutional database** | | **68.9%** | **17.2%** |

**Table 4.3** Distribution of covariates before and after PS matching

| | **Original** | | ***P*-value** | **Matched** | | ***P*-value** |
|---|---|---|---|---|---|---|
| | Exposed | Unexposed | | Exposed | Unexposed | |
| Total number of patients | 58 | 39 | | 14 | 14 | |
| Age, years, median (SD) | 10.0 (4.6) | 8.0 (5.0) | 0.58 | 7.5 (4.2) | 8.0 (5.5) | 0.51 |
| Age Groups, N | | | | | | |
| 0 to 27 days | 0 | 0 | | 0 | 0 | |
| 28 days to 1 year | 2 | 2 | | 1 | 1 | |
| ≥1 to 10 years | 25 | 22 | | 8 | 8 | |
| ≥10 to 18 years | 31 | 15 | 0.35 | 5 | 5 | 1.0 |
| EBMT risk score, median (SD) | 2.3 (1.3) | 1.9 (1.3) | 0.23 | 2.0 (1.3) | 2.5 (1.2) | 0.88 |
| Stem Cell Source, N | | | | | | |
| Bone Marrow | 43 | 14 | | 12 | 11 | |
| Peripheral Blood | 11 | 4 | | 1 | 2 | |
| Cord Blood | 4 | 21 | <0.05 | 1 | 1 | 0.83 |
| History of Documented /Suspected IFD, N | 9 | 8 | | 4 | 4 | |
| Yes | 49 | 31 | 0.53 | 10 | 10 | 1.0 |
| No | | | | | | |
| Palonosetron for CINV Prophylaxis, N | | | | | | |
| Yes | 0 | 4 | | 0 | 0 | |
| No | 58 | 35 | <0.05 | 14 | 14 | 1.0 |
| Highly Emetogenic Conditioning, N | | | | | | |
| Yes | 8 | 4 | | 11 | 11 | |
| No | 50 | 35 | 0.60 | 3 | 3 | 1.0 |
| Propensity score, mean (SD) | 0.21 (0.15) | 0.68 (0.33) | <0.05 | 0.28 (0.21) | 0.29 (0.20) | 0.95 |

N=Number of patients; SD=Standard deviation; EBMT=European Blood and Marrow Transplantation; IFD=Invasive fungal disease; CINV=Chemotherapy-induced nausea and vomiting

**Table 4.4** Preliminary analysis of TRM and EFS in patients exposed and unexposed to dexamethasone using PS as a covariate

| Outcome | Dexamethasone | | aOR[#] (95% CI) |
|---|---|---|---|
| | Exposed (n=58) | Unexposed (n=39) | |
| TRM, N (%) | 5 (8.6) | 2 (5.1) | 1.0 (0.1-7.9) |
| EFS, N (%) | 35 (60.3) | 20 (51.3) | 3.8 (1.1-13.5) |

PS=Propensity score; N=Number of subjects; TRM=Transplant-related mortality; EFS=Event-free survival; aOR=Adjusted odds ratio by logistic regression adjusted for propensity score; CI=Confidence interval

# Reference group for all outcomes is the unexposed group i.e. aOR >1.00 indicates a higher odds for the outcome in the exposed group relative to the unexposed group.

**Table 4.5** Preliminary analysis of secondary HSCT outcomes in patients exposed and unexposed to dexamethasone within PS-matched pairs

| Outcome | Dexamethasone | |
|---|---|---|
| | Exposed | Unexposed |
| IFD, N (%) | 2/14 (14.3) | 2/13 (15.4)[§] |
| aGVHD*, N (%) | 6/14 (42.9) | 3/12 (25.0)[§] |
| Time to neutrophil engraftment, mean (range), days | 22.6 (9-34) | 19.6 (14-27)[#] |

PS=Propensity score; N=Number of subjects; IFD=Invasive fungal disease; aGVHD=Acute graft-versus-host disease; *=Allogeneic HSCT only; [§]=Excluded patients who experienced death, disease relapse or recurrence, or received a second HSCT prior to Day +100; [#]=1 patient did not engraft

# Chapter 5
# Discussion and Conclusions

## 5.1 Summary of Key Findings

Historically, dexamethasone has played a vital role in the supportive care of children receiving chemotherapy. The gaps in knowledge about its safety and harmfulness during an extremely critical period, HSCT, present serious challenges for optimizing supportive care. These projects described in this thesis contribute to a largely unstudied area and, ultimately, provide a sustainable framework for evaluating TRM and other HSCT outcomes.

The systematic review of the safety of dexamethasone for CINV identified three randomized cross-over trials involving 71 children, ranging in age from 1.3 to 18 years, who received dexamethasone at doses ranging from 6 to 30 mg/m$^2$/day given for 1 to 2 days. The most frequent AE reported was sedation, followed by euphoria, insomnia, confusion, ataxia, and mood changes. These AEs were described as mild and did not require discontinuation of dexamethasone.[1-3] Two adolescents from a single prospective observational study developed serious and irreversible osteonecrosis, though dexamethasone for nausea was a minor contributor to their cumulative steroid exposure over 4 years.[4] More profoundly, this review highlighted the significant lack of robust and controlled studies with the primary aim of assessing dexamethasone safety.

The second project was a *post hoc* review of a previous prospective study to describe immediate adverse events of dexamethasone in children undergoing HSCT. In addition, we applied a validated pediatric tool, LCAT, to analyze the attribution of each adverse event to dexamethasone exposure.[5] In 46 children, we found high incidences of hyperglycemia (63%), hypertension (52%), and bradycardia (46%) and few cases of alterations of mood and behavior (9%). These immediate adverse events of dexamethasone were transient, of minor clinical importance, and did not require medical intervention.[6]

The final project described the design and feasibility of an analytical framework to assess the impact of dexamethasone given for CINV on TRM and other important HSCT outcomes. At the

lead site, we found that over 70% of the data elements required for this study were easily retrievable from an institutional database. At a collaborating site, data abstraction from other sources (e.g. pharmacy records, individual patient chart) required 10 to 30 minutes per patient to collect. Our feasibility endpoints were met, indicating that data collection for a future large study would be feasible. In a preliminary analysis, we evaluated the association between dexamethasone exposure and TRM and other HSCT outcomes (EFS, IFD, aGVHD, and time to neutrophil engraftment) using PS methods. This demonstrated the mechanics of our analysis as an exercise in preparation for a larger study. With the involvement of an international network of accredited pediatric HSCT centers, valid estimates will be generated and described with more certainty.

## 5.2 Strengths and Limitations

The level of rigor applied to isolate the effect of dexamethasone was the greatest strength encompassing these three projects. For the systematic review, we relied on studies assessing the safety of dexamethasone as monotherapy to mitigate contamination from concomitant antiemetic agents. Similarly, a Cochrane review by Phillip *et al*. reported the safety of antiemetic agents in children. However, this review lacked the ability to isolate adverse events specific to dexamethasone due to other antiemetic agents given simultaneously.[7] The second project directly incorporated an attribution tool to qualify the emergence of adverse events with the likelihood of causation. This approach, which had been lacking in previous safety studies, improved the credibility of these observations. Lastly, we used a rigorous approach to study the association between exposure to dexamethasone and HSCT outcomes. Given the inherent limitations of non-experimental studies, we applied two PS methods, covariate adjustment and matching, to minimize the influence of selection bias and potential confounders.

All three projects in this thesis served complementary purposes. The systematic review highlighted the paucity of research focused on the safety of dexamethasone for CINV in pediatric patients. This established the foundation for subsequent projects which contributed to improving our understanding of the safety of dexamethasone specifically in patients undergoing HSCT. Through these projects, we focused on adverse events occurring during or shortly after administration of dexamethasone, as well as the long-term impact on HSCT outcomes. Viewed in conjunction, these projects permit a better appreciation for balancing the benefits and risks of

using dexamethasone as an antiemetic agent. We hope to enhance the quality and strength of evidence-based antiemetic recommendations in pediatric patients receiving chemotherapy.

While serving as a first step for more robust studies, there are limitations to this research. As we identified, high risks of bias in the existing literature lower our confidence in the accurate reporting of adverse events associated with dexamethasone. Our findings from the second project were limited by accurate chart documentation of objective measures of safety. We likely dismissed or underestimated the prevalence of subjective symptoms while overestimating the prevalence of objectively measured adverse events. In developing the framework for the final project, we recognize that the EBMT risk score can only explain up to 63% of our outcome.[8] However, it was deemed the best available and most practical tool to incorporate in our framework. Thus, our analysis may be influenced by residual confounders despite our best efforts. It can also be argued that to detect a significant in TRM, an extremely large dataset is needed. In the present study, we used patient data from two centers to determine feasibility for the larger, future investigation. Our preliminary risk estimates are far from conclusive, yet offer a starting point. Further evaluation involving a network of pediatric HSCT centers to improve these initial estimates is feasible.

## 5.3 Recommendations for Future Research

In this thesis, three projects presented much needed data about the safety of dexamethasone given to pediatric patients for the prevention of CINV. We acknowledge that future studies are required to refine, consolidate, and complete our understanding in this area. For example, prospective studies using valid and reliable objective methods for measuring adverse events and appropriate strategies to mitigate confounders or assess attribution to dexamethasone are needed. Dose-finding studies of dexamethasone in children are lacking and incorporating safety assessments into such studies will help determine an optimal dose. We are hopeful and anticipate that our analytical framework implemented in two Canadian centers will be expanded to other pediatric HSCT centers around the globe. A robust assessment of TRM in children who were exposed and unexposed to dexamethasone during HSCT will help inform specific antiemetic recommendations in this population.

## 5.4 Conclusion

Supportive care measures are important in children receiving HSCT. This includes giving effective antiemetic prophylaxis containing dexamethasone. However, concerns about its safety and theoretical interference with HSCT limit its routine use. The projects in this thesis collectively contribute vital information about the safety of dexamethasone. Adverse events identified in a systematic review and observed in a *post-hoc* analysis of prospectively collected data were transient in nature and of minor clinical importance. Still, high quality prospective studies are needed to understand the overall safety of dexamethasone. We designed a framework to assess the long-term impact of dexamethasone on TRM and other HSCT outcomes and demonstrated its feasibility for a future study.

## 5.5 References


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# Appendices

**Appendix A:** Complete search strategy

**Summary of databases searched**

| Electronic database | Date performed | Number of records |
|---|---|---|
| Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present> | September 13, 2017 | 5143 |
| Web of Science | September 13, 2017 | 2835 |
| Embase Classic+Embase <1947 to 2017 Week 37> | September 13, 2017 | 14670 |
| EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017> | September 13, 2017 | 1794 |
| Total | | 24442 |

**Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>**

| | |
|---|---|
| 1 | Ondansetron/ (3010) |
| 2 | ("avessaron" or "bryterol" or "cedantron" or "cellondan" or "ceramos" or "emeset" or "gr 38032" or "gr 38032f" or "gr 38032f" or "gr c507 75" or "gr38032" or "gr38032f" or "modifical" or "narfoz" or "odansetron" or "ondansetron" or "onsia" or "sakisozin" or "sn 307" or "sn307" or "vomceran" or "zetron" or "zofran" or "zofrene" or "zofron" or "zophran" or "zophren" or "zuplenz").mp. (4736) |
| 3 | Granisetron/ (1107) |
| 4 | ("apf 530" or "apf530" or "brl 43694" or "brl 43694a" or "brl43694" or "brl43694a" or "eutrom" or "granicip" or "granisetron" or "kevatril" or "kytril" or "sancuso" or "sustol" or "taraz").mp. (1756) |
| 5 | ("endoprol" or "endostem" or "ics 205 930" or "ics 205930" or "navoban" or "tropisetron").mp. (1617) |
| 6 | ("aloxi" or "onicit" or "palonosetron" or "rs 25259" or "rs25259").mp. (586) |
| 7 | ("aprepitant" or "emend" or "l 754030" or "l754030" or "mk 0869" or "mk 869" or "mk0869" or "mk869" or "ono 7436" or "ono7436").mp. (1093) |
| 8 | ("anzatric" or "dopin tab" or "jolyon md" or "lanopin" or "lanzac" or "ly 170053" or "ly170053" or "meltolan" or "midax" or "olace" or "oladay" or "olan" or "olandus" or "olanex" or "olansek" or "olanzapine " or "olapin" or "olazax" or "oleanz" or "olexar" or "oltal" or "olzap" or "onza" or "ozapin md" or "psychozap" or "relprevv" or "zalasta" or "zelta" or "zydis" or "zypadhera" or "zyprex" or "zyprexa" or "zyprexav").mp. (9583) |
| 9 | Metoclopramide/ (4988) |

| | |
|---|---|
| 10 | ("ahr 3070 c" or "ahr 3070c" or "ahr3070c" or "ametic" or "anausin" or "apo-metoclop" or "aputern" or "betaclopramide" or "bondigest" or "cerucal" or "clodilion" or "clopamon" or "clopan" or "clopra" or "clopram" or "degan" or "del 1267" or "del1267" or "dibertil" or "duraclamid" or "emenil" or "emetal" or "emetard" or "emitasol" or "emperal" or "encil" or "enzimar" or "gastro timelets" or "gastrobi" or "gastrobid" or "gastronerton" or "gastrosil" or "gastrotem" or "gastrotimelets" or "gavistal" or "gensil" or "hemesis" or "hyrin" or "imperan" or "m 813" or "m813" or "maalox nausea" or "maril" or "maxeran" or "maxeron" or "maxolan" or "maxolon" or "mcp-beta tropfen" or "meclomid" or "meclopamide" or "meclopramide" or "meclopran" or "meramide" or "metaclopramide" or "metagliz" or "metamide" or "methochlopramide" or "methoclopramide" or "methoclopramine" or "metlazel" or "metochlopramide" or "metoclopamide" or "metoclopramid" or "metoclopramide" or "metoclopramine" or "metoclopranide hydrochloride" or "metoclor" or "metoclorpramide" or "metocobil" or "metocyl" or "metodopramide" or "metolon" or "metopram" or "metox" or "metozolv" or "metpamid" or "metram" or "mygdalon" or "nausil" or "neopramiel" or "netaf" or "neu sensamide" or "nilatika" or "normastin" or "octamide" or "opram" or "paspertin" or "perinorm" or "pharmyork" or "plasil" or "pramidin" or "pramin" or "pramotel" or "primperan" or "primperil" or "prinparl" or "prokinyl lp" or "prowel" or "pulin" or "reclomide" or "reglan" or "reliveran" or "rimetin" or "rimetin" or "sensamide" or "sotatic-10" or "terperan" or "tomid" or "vertivom" or "vomitrol" or "zumatrol").mp. (7287) |
| 11 | Methotrimeprazine/ (810) |
| 12 | ("bayer 1213" or "cl 36467" or "cl 39743" or "cl36467" or "cl39743" or "hirnamin" or "levium" or "levo mepromazine" or "levo promazine" or "levomeprazin" or "levomeprazine" or "levomepromazine" or "levopromazin" or "levopromazine" or "levoprome" or "levozin" or "mepromazine" or "methoprazine" or "methotrimeprazine" or "methotrimperazine" or "methozane" or "milezin" or "minozinan" or "neozine" or "neuractil" or "neurocil" or "nirvan" or "nozinan" or "rp 7044" or "rp7044" or "sinogan" or "sk and f 5116" or "skf 5116" or "skf5116" or "tisercin" or "tizercine" or "tizertsin" or "veractil").mp. (1079) |
| 13 | Lorazepam/ (2925) |
| 14 | ("almazine" or "alzapam" or "anxiedin" or "anxira" or "anzepam" or "aplacasse" or "apolorazepam" or "apo-lorazepam" or "aripax" or "ativan" or "azurogen" or "bonatranquan" or "donix" or "duralozam" or "durazolam" or "efasedan" or "emotival" or "idalprem" or "kalmalin" or "kendol" or "larpose" or "laubeel" or "lonza" or "lopam" or "lorabenz" or "loram" or "loranase" or "loranaze" or "lorans" or "lorapam" or "loravan" or "lorax" or "loraz" or "lorazene" or "lorazep" or "lorazepam" or "lorazin" or "lorazon" or "lorenin" or "loridem" or "lorivan" or "lorsedal" or "lorzem" or "merlit" or "mesmerin" or "nervistop" or "novhepar" or "novo lorazem" or "novolorazem" or "nu loraz" or "nuloraz" or "orfidal" or "orifadal" or "pro dorm" or "punktyl" or "quait" or "renaquil" or "rocosgen" or "securit" or "sedatival" or "sedicepan" or "sidenar" or "sinestron" or "somagerol" or "stapam" or "tavor" or "temesta" or "titus" or "tolid" or "tranqipam" or "trapax" or "trapex" or "upan" or "wy 4036" or "wy4036" or "wypax").mp. (4744) |
| 15 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (29686) |
| 16 | exp Dexamethasone/ (49810) |
| 17 | ("adrecort" or "adrenocot" or "aeroseb dex" or "aflucoson" or "aflucosone" or "ak-dex" or "alfalyl" or "anaflogistico" or "arcodexan" or "arcodexane" or "artrosone" or "auxiloson" or "auxison" or "azium" or "bidexol" or "calonat" or "cebedex" or "cetadexon" or |

| | |
|---|---|
| | "colofoam" or "colvasone" or "corsona" or "cortastat" or "cortidex" or "cortidexason" or "cortidrona" or "cortidrone" or "cortisumman" or "dacortina fuerte" or "dalalone" or "danasone" or "decacortin" or "decadeltosona" or "decadeltosone" or "decaderm" or "decadion" or "decadran" or "decadron " or "decadronal" or "decadrone" or "decaesadril" or "decaject" or "decameth" or "decamethasone" or "decasone" or "decasterolone" or "decdan" or "decilone" or "decofluor" or "dectancyl" or "dekacort" or "delladec" or "deltafluoren" or "deltafluorene" or "dergramin" or "deronil" or "desacort" or "desacortone" or "desadrene" or "desalark" or "desameton" or "desametone" or "desigdron" or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexacen 4" or "dexachel" or "dexacort" or "dexacortal" or "dexacorten" or "dexacortin" or "dexacortisyl" or "dexadabroson" or "dexadecadrol" or "dexadreson" or "dexadrol" or "dexagen" or "dexahelvacort" or "dexair" or "dexakorti" or "dexalien" or "dexame" or "dexamecortin" or "dexameson" or "dexamesone" or "dexametason" or "dexametasone" or "dexameth" or "dexamethason" or "dexamethason " or "dexamethasone" or "dexamethasone" or "dexamethasonium " or "dexamethazon" or "dexamethazone" or "dexamethonium" or "dexamonozon" or "dexan" or "dexane" or "dexano" or "dexa-p" or "dexapot" or "dexascheroson" or "dexascherozon" or "dexascherozone" or "dexason" or "dexasone" or "dexavet" or "dexi siozwo" or "dexinoral" or "dexionil" or "dexmethsone" or "dexona" or "dexone" or "dexpak" or "dextelan" or "dextrasone" or "dezone" or "dibasona" or "diodex" or "dosauxison" or "doxamethasone" or "esacortene" or "ex s1" or "exadion" or "exadione" or "firmalone" or "fluormethyl prednisolone" or "fluormethylprednisolon" or "fluormethylprednisolone" or "fluormone" or "fluorocort" or "fluorodelta" or "fluoromethylprednisolone" or "fortecortin" or "gammacorten" or "gammacortene" or "grosodexon" or "grosodexone" or "he 111" or "he111" or "hexadecadiol" or "hexadecadrol" or "hexadiol" or "hexadrol" or "isnacort" or "isopto dex" or "isoptodex" or "lokalison f" or "loverine" or "luxazone" or "marvidione" or "mediamethasone" or "megacortin" or "mephameson" or "mephamesone" or "metasolon" or "metasolone" or "methanesulfonyldexamethasone" or "methazon ion" or "methazone ion" or "methazonion" or "methazonione" or "methylfluorprednisolone" or "metisone lafi" or "mexasone" or "millicorten" or "millicortenol" or "mk 125" or "mk125" or "mymethasone" or "neoforderx" or "neofordex" or "nisomethasona" or "novocort" or "nsc 34521" or "nsc34521" or "oradexan" or "oradexon" or "oradexone" or "orgadrone" or "pidexon" or "policort" or "predni-f" or "prednisolone f" or "prodexona" or "prodexone" or "sanamethasone" or "santenson" or "santeson" or "sawasone" or "soldesam" or "soludecadrol" or "soludecadron" or "solurex" or "spersadex" or "spoloven" or "sterasone" or "sterodex" or "thilodexine" or "totocortin" or "triamcimetil" or "turbinaire" or "vexamet" or "wymesone").mp. (68296) |
| 18 | 16 or 17 (68332) |
| 19 | exp nausea/ or exp vomiting/ (36113) |
| 20 | ("emeses" or "emesis" or "nause*" or "retch*" or "vomit*" or "cinv").mp. (100852) |
| 21 | 19 or 20 (103973) |
| 22 | 18 and 21 (2389) |
| 23 | 15 or 22 (30702) |
| 24 | (infan* or newborn* or new-born* or neonat* or neo-nat* or child* or adolescen* or juvenile* or teen* or girl* or boy* or youth* or toddler* or tot or tots or paediatric* or pediatric*).mp. [***Age group Textword search terms***] (4076008) |

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|---|---|
| 25 | 23 and 24 (5143) |

**Web of Science**
Science Citation Index Expanded (SCI-EXPANDED) --1900-present
Social Sciences Citation Index (SSCI) --1956-present
Arts & Humanities Citation Index (A&HCI) -- 1975-present
Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)-1990-present
Emerging Sources Citation Index (ESCI) -- 2015-present

| | | |
|---|---|---|
| # 16 | 2,835 | #15 AND #14 |
| # 15 | 2,554,880 | TS=(infan* or newborn* or new-born* or neonat* or neo-nat* or child* or adolescen* or juvenile* or teen* or girl* or boy* or youth* or toddler* or tot or tots or paediatric* or pediatric*) |
| # 14 | 33,820 | #13 OR #10 |
| # 13 | 2,363 | #12 AND #11 |
| # 12 | 63,073 | TS=("emeses" or "emesis" or "nause*" or "retch*" or "vomit*" or "cinv") |
| # 11 | 57,304 | TS=("adrecort" or "adrenocot" or "aeroseb dex" or "aflucoson" or "aflucosone" or "ak-dex" or "alfalyl" or "anaflogistico" or "arcodexan" or "arcodexane" or "artrosone" or "auxiloson" or "auxison" or "azium" or "bidexol" or "calonat" or "cebedex" or "cetadexon" or "colofoam" or "colvasone" or "corsona" or "cortastat" or "cortidex" or "cortidexason" or "cortidrona" or "cortidrone" or "cortisumman" or "dacortina fuerte" or "dalalone" or "danasone" or "decacortin" or "decadeltosona" or "decadeltosone" or "decaderm" or "decadion" or "decadran" or "decadron " or "decadronal" or "decadrone" or "decaesadril" or "decaject" or "decameth" or "decamethasone" or "decasone" or "decasterolone" or "decdan" or "decilone" or "decofluor" or "dectancyl" or "dekacort" or "delladec" or "deltafluoren" or "deltafluorene" or "dergramin" or "deronil" or "desacort" or "desacortone" or "desadrene" or "desalark" or "desameton" or "desametone" or "desigdron" or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexacen 4" or "dexachel" or "dexacort" or "dexacortal" or "dexacorten" or "dexacortin" or "dexacortisyl" or "dexadabroson" or "dexadecadrol" or "dexadreson" or "dexadrol" or "dexagen" or "dexahelvacort" or "dexair" or "dexakorti" or "dexalien" or "dexame" or "dexamecortin" or "dexameson" or "dexamesone" or "dexametason" or "dexametasone" or "dexameth" or "dexamethason" or "dexamethason " or "dexamethasone" or "dexamethasone" or "dexamethasonium " or "dexamethazon" or "dexamethazone" or "dexamethonium" or "dexamonozon" or "dexan" or "dexane" or "dexano" or "dexa-p" or "dexapot" or "dexascheroson" or "dexascherozon" or "dexascherozone" or "dexason" or "dexasone" or "dexavet" or "dexi siozwo" or "dexinoral" or "dexionil" or "dexmethsone" or "dexona" or "dexone" or "dexpak" or "dextelan" or "dextrasone" or "dezone" or "dibasona" or "diodex" or "dosauxison" or "doxamethasone" or "esacortene" or "ex s1" or "exadion" |

| | | |
|---|---|---|
| | | or "exadione" or "firmalone" or "fluormethyl prednisolone" or "fluormethylprednisolon" or "fluormethylprednisolone" or "fluormone" or "fluorocort" or "fluorodelta" or "fluoromethylprednisolone" or "fortecortin" or "gammacorten" or "gammacortene" or "grosodexon" or "grosodexone" or "he 111" or "he111" or "hexadecadiol" or "hexadecadrol" or "hexadiol" or "hexadrol" or "isnacort" or "isopto dex" or "isoptodex" or "lokalison f" or "loverine" or "luxazone" or "marvidione" or "mediamethasone" or "megacortin" or "mephameson" or "mephamesone" or "metasolon" or "metasolone" or "methanesulfonyldexamethasone" or "methazon ion" or "methazone ion" or "methazonion" or "methazonione" or "methylfluorprednisolone" or "metisone lafi" or "mexasone" or "millicorten" or "millicortenol" or "mk 125" or "mk125" or "mymethasone" or "neoforderx" or "neofordex" or "nisomethasona" or "novocort" or "nsc 34521" or "nsc34521" or "oradexan" or "oradexon" or "oradexone" or "orgadrone" or "pidexon" or "policort" or "predni-f" or "prednisolone f" or "prodexona" or "prodexone" or "sanamethasone" or "santenson" or "santeson" or "sawasone" or "soldesam" or "soludecadrol" or "soludecadron" or "solurex" or "spersadex" or "spoloven" or "sterasone" or "sterodex" or "thilodexine" or "totocortin" or "triamcimetil" or "turbinaire" or "vexamet" or "wymesone") |
| # 10 | 33,085 | #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 |
| # 9 | 5,441 | TS=("almazine" or "alzapam" or "anxiedin" or "anxira" or "anzepam" or "aplacasse" or "apolorazepam" or "apo-lorazepam" or "aripax" or "ativan" or "azurogen" or "bonatranquan" or "donix" or "duralozam" or "durazolam" or "efasedan" or "emotival" or "idalprem" or "kalmalin" or "kendol" or "larpose" or "laubeel" or "lonza" or "lopam" or "lorabenz" or "loram" or "loranase" or "loranaze" or "lorans" or "lorapam" or "loravan" or "lorax" or "loraz" or "lorazene" or "lorazep" or "lorazepam" or "lorazin" or "lorazon" or "lorenin" or "loridem" or "lorivan" or "lorsedal" or "lorzem" or "merlit" or "mesmerin" or "nervistop" or "novhepar" or "novo lorazem" or "novolorazem" or "nu loraz" or "nuloraz" or "orfidal" or "orifadal" or "pro dorm" or "punktyl" or "quait" or "renaquil" or "rocosgen" or "securit" or "sedatival" or "sedicepan" or "sidenar" or "sinestron" or "somagerol" or "stapam" or "tavor" or "temesta" or "titus" or "tolid" or "tranqipam" or "trapax" or "trapex" or "upan" or "wy 4036" or "wy4036" or "wypax") |
| # 8 | 480 | TS=("bayer 1213" or "cl 36467" or "cl 39743" or "cl36467" or "cl39743" or "hirnamin" or "levium" or "levo mepromazine" or "levo promazine" or "levomeprazin" or "levomeprazine" or "levomepromazine" or "levopromazin" or "levopromazine" or "levoprome" or "levozin" or "mepromazine" or "methoprazine" or "methotrimeprazine" or "methotrimperazine" or "methozane" or "milezin" or "minozinan" or "neozine" or "neuractil" or "neurocil" or "nirvan" or "nozinan" or "rp 7044" or "rp7044" or "sinogan" or "sk and f 5116" or "skf 5116" or "skf5116" or "tisercin" or "tizercine" or "tizertsin" or "veractil") |
| # 7 | 6,292 | TS=("ahr 3070 c" or "ahr 3070c" or "ahr3070c" or "ametic" or "anausin" or "apo-metoclop" or "aputern" or "betaclopramide" or "bondigest" or "cerucal" or "clodilion" or "clopamon" or "clopan" or "clopra" or "clopram" |

| | | |
|---|---|---|
| | | or "degan" or "del 1267" or "del1267" or "dibertil" or "duraclamid" or "emenil" or "emetal" or "emetard" or "emitasol" or "emperal" or "encil" or "enzimar" or "gastro timelets" or "gastrobi" or "gastrobid" or "gastronerton" or "gastrosil" or "gastrotem" or "gastrotimelets" or "gavistal" or "gensil" or "hemesis" or "hyrin" or "imperan" or "m 813" or "m813" or "maalox nausea" or "maril" or "maxeran" or "maxeron" or "maxolan" or "maxolon" or "mcp-beta tropfen" or "meclomid" or "meclopamide" or "meclopramide" or "meclopran" or "meramide" or "metaclopramide" or "metagliz" or "metamide" or "methochlopramide" or "methoclopramide" or "methoclopramine" or "metlazel" or "metochlopramide" or "metoclopamide" or "metoclopramid" or "metoclopramide" or "metoclopramine" or "metoclopranide hydrochloride" or "metoclor" or "metoclorpramide" or "metocobil" or "metocyl" or "metodopramide" or "metolon" or "metopram" or "metox" or "metozolv" or "metpamid" or "metram" or "mygdalon" or "nausil" or "neopramiel" or "netaf" or "neu sensamide" or "nilatika" or "normastin" or "octamide" or "opram" or "paspertin" or "perinorm" or "pharmyork" or "plasil" or "pramidin" or "pramin" or "pramotel" or "primperan" or "primperil" or "prinparl" or "prokinyl lp" or "prowel" or "pulin" or "reclomide" or "reglan" or "reliveran" or "rimetin" or "rimetin" or "sensamide" or "sotatic-10" or "terperan" or "tomid" or "vertivom" or "vomitrol" or "zumatrol") |
| # 6 | 11,976 | TS=("anzatric" or "dopin tab" or "jolyon md" or "lanopin" or "lanzac" or "ly 170053" or "ly170053" or "meltolan" or "midax" or "olace" or "oladay" or "olan" or "olandus" or "olanex" or "olansek" or "olanzapine " or "olapin" or "olazax" or "oleanz" or "olexar" or "oltal" or "olzap" or "onza" or "ozapin md" or "psychozap" or "relprevv" or "zalasta" or "zelta" or "zydis" or "zypadhera" or "zyprex" or "zyprexa" or "zyprexav") |
| # 5 | 2,955 | TS=("aprepitant" or "emend" or "l 754030" or "l754030" or "mk 0869" or "mk 869" or "mk0869" or "mk869" or "ono 7436" or "ono7436") |
| # 4 | 695 | TS=("aloxi" or "onicit" or "palonosetron" or "rs 25259" or "rs25259") |
| # 3 | 1,366 | TS=("endoprol" or "endostem" or "ics 205 930" or "ics 205930" or "navoban" or "tropisetron") |
| # 2 | 1,870 | TS=("apf 530" or "apf530" or "brl 43694" or "brl 43694a" or "brl43694" or "brl43694a" or "eutrom" or "granicip" or "granisetron" or "kevatril" or "kytril" or "sancuso" or "sustol" or "taraz") |
| # 1 | 5,850 | TS=("avessaron" or "bryterol" or "cedantron" or "cellondan" or "ceramos" or "emeset" or "gr 38032" or "gr 38032f" or "gr 38032f" or "gr c507 75" or "gr38032" or "gr38032f" or "modifical" or "narfoz" or "odansetron" or "ondansetron" or "onsia" or "sakisozin" or "sn 307" or "sn307" or "vomceran" or "zetron" or "zofran" or "zofrene" or "zofron" or "zophran" or "zophren" or "zuplenz") |

**Embase Classic+Embase <1947 to 2017 Week 37>**

| | |
|---|---|
| 1 | ondansetron/ (15535) |

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|---|---|
| 2 | ("avessaron" or "bryterol" or "cedantron" or "cellondan" or "ceramos" or "emeset" or "gr 38032" or "gr 38032f" or "gr 38032f" or "gr c507 75" or "gr38032" or "gr38032f" or "modifical" or "narfoz" or "odansetron" or "ondansetron" or "onsia" or "sakisozin" or "sn 307" or "sn307" or "vomceran" or "zetron" or "zofran" or "zofrene" or "zofron" or "zophran" or "zophren" or "zuplenz").mp. (15872) |
| 3 | granisetron/ (5043) |
| 4 | ("apf 530" or "apf530" or "brl 43694" or "brl 43694a" or "brl43694" or "brl43694a" or "eutrom" or "granicip" or "granisetron" or "kevatril" or "kytril" or "sancuso" or "sustol" or "taraz").mp. (5248) |
| 5 | tropisetron/ (3300) |
| 6 | ("endoprol" or "endostem" or "ics 205 930" or "ics 205930" or "navoban" or "tropisetron").mp. (3438) |
| 7 | palonosetron/ (1635) |
| 8 | ("aloxi" or "onicit" or "palonosetron" or "rs 25259" or "rs25259").mp. (1712) |
| 9 | aprepitant/ (2682) |
| 10 | olanzapine/ (30372) |
| 11 | ("anzatric" or "dopin tab" or "jolyon md" or "lanopin" or "lanzac" or "ly 170053" or "ly170053" or "meltolan" or "midax" or "olace" or "oladay" or "olan" or "olandus" or "olanex" or "olansek" or "olanzapine " or "olapin" or "olazax" or "oleanz" or "olexar" or "oltal" or "olzap" or "onza" or "ozapin md" or "psychozap" or "relprevv" or "zalasta" or "zelta" or "zydis" or "zypadhera" or "zyprex" or "zyprexa" or "zyprexav").mp. (32927) |
| 12 | metoclopramide/ (23715) |
| 13 | ("ahr 3070 c" or "ahr 3070c" or "ahr3070c" or "ametic" or "anausin" or "apo-metoclop" or "aputern" or "betaclopramide" or "bondigest" or "cerucal" or "clodilion" or "clopamon" or "clopan" or "clopra" or "clopram" or "degan" or "del 1267" or "del1267" or "dibertil" or "duraclamid" or "emenil" or "emetal" or "emetard" or "emitasol" or "emperal" or "encil" or "enzimar" or "gastro timelets" or "gastrobi" or "gastrobid" or "gastronerton" or "gastrosil" or "gastrotem" or "gastrotimelets" or "gavistal" or "gensil" or "hemesis" or "hyrin" or "imperan" or "m 813" or "m813" or "maalox nausea" or "maril" or "maxeran" or "maxeron" or "maxolan" or "maxolon" or "mcp-beta tropfen" or "meclomid" or "meclopamide" or "meclopramide" or "meclopran" or "meramide" or "metaclopramide" or "metagliz" or "metamide" or "methochlopramide" or "methoclopramide" or "methoclopramine" or "metlazel" or "metochlopramide" or "metoclopamide" or "metoclopramid" or "metoclopramide" or "metoclopramine" or "metoclopranide hydrochloride" or "metoclor" or "metoclorpramide" or "metocobil" or "metocyl" or "metodopramide" or "metolon" or "metopram" or "metox" or "metozolv" or "metpamid" or "metram" or "mygdalon" or "nausil" or "neopramiel" or "netaf" or "neu sensamide" or "nilatika" or "normastin" or "octamide" or "opram" or "paspertin" or "perinorm" or "pharmyork" or "plasil" or "pramidin" or "pramin" or "pramotel" or "primperan" or "primperil" or "prinparl" or "prokinyl lp" or "prowel" or "pulin" or "reclomide" or "reglan" or "reliveran" or "rimetin" or "rimetin" or "sensamide" or "sotatic-10" or "terperan" or "tomid" or "vertivom" or "vomitrol" or "zumatrol").mp. (24660) |
| 14 | levomepromazine/ (5667) |
| 15 | ("bayer 1213" or "cl 36467" or "cl 39743" or "cl36467" or "cl39743" or "hirnamin" or "levium" or "levo mepromazine" or "levo promazine" or "levomeprazin" or "levomeprazine" or "levomepromazine" or "levopromazin" or "levopromazine" or "levoprome" or "levozin" or "mepromazine" or "methoprazine" or "methotrimeprazine" or |

| | |
|---|---|
| | "methotrimperazine" or "methozane" or "milezin" or "minozinan" or "neozine" or "neuractil" or "neurocil" or "nirvan" or "nozinan" or "rp 7044" or "rp7044" or "sinogan" or "sk and f 5116" or "skf 5116" or "skf5116" or "tisercin" or "tizercine" or "tizertsin" or "veractil").mp. (5759) |
| 16 | lorazepam/ (24327) |
| 17 | ("almazine" or "alzapam" or "anxiedin" or "anxira" or "anzepam" or "aplacasse" or "apolorazepam" or "apo-lorazepam" or "aripax" or "ativan" or "azurogen" or "bonatranquan" or "donix" or "duralozam" or "durazolam" or "efasedan" or "emotival" or "idalprem" or "kalmalin" or "kendol" or "larpose" or "laubeel" or "lonza" or "lopam" or "lorabenz" or "loram" or "loranase" or "loranaze" or "lorans" or "lorapam" or "loravan" or "lorax" or "loraz" or "lorazene" or "lorazep" or "lorazepam" or "lorazin" or "lorazon" or "lorenin" or "loridem" or "lorivan" or "lorsedal" or "lorzem" or "merlit" or "mesmerin" or "nervistop" or "novhepar" or "novo lorazem" or "novolorazem" or "nu loraz" or "nuloraz" or "orfidal" or "orifadal" or "pro dorm" or "punktyl" or "quait" or "renaquil" or "rocosgen" or "securit" or "sedatival" or "sedicepan" or "sidenar" or "sinestron" or "somagerol" or "stapam" or "tavor" or "temesta" or "titus" or "tolid" or "tranqipam" or "trapax" or "trapex" or "upan" or "wy 4036" or "wy4036" or "wypax").mp. (25644) |
| 18 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (100415) |
| 19 | dexamethasone derivative/ or dexamethasone/ or dexamethasone 21 mesilate/ or dexamethasone acetate/ or dexamethasone isonicotinate/ or dexamethasone sodium phosphate/ (137666) |
| 20 | ("adrecort" or "adrenocot" or "aeroseb dex" or "aflucoson" or "aflucosone" or "ak-dex" or "alfalyl" or "anaflogistico" or "arcodexan" or "arcodexane" or "artrosone" or "auxiloson" or "auxison" or "azium" or "bidexol" or "calonat" or "cebedex" or "cetadexon" or "colofoam" or "colvasone" or "corsona" or "cortastat" or "cortidex" or "cortidexason" or "cortidrona" or "cortidrone" or "cortisumman" or "dacortina fuerte" or "dalalone" or "danasone" or "decacortin" or "decadeltosona" or "decadeltosone" or "decaderm" or "decadion" or "decadran" or "decadron " or "decadronal" or "decadrone" or "decaesadril" or "decaject" or "decameth" or "decamethasone" or "decasone" or "decasterolone" or "decdan" or "decilone" or "decofluor" or "dectancyl" or "dekacort" or "delladec" or "deltafluoren" or "deltafluorene" or "dergramin" or "deronil" or "desacort" or "desacortone" or "desadrene" or "desalark" or "desameton" or "desametone" or "desigdron" or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexacen 4" or "dexachel" or "dexacort" or "dexacortal" or "dexacorten" or "dexacortin" or "dexacortisyl" or "dexadabroson" or "dexadecadrol" or "dexadreson" or "dexadrol" or "dexagen" or "dexahelvacort" or "dexair" or "dexakorti" or "dexalien" or "dexame" or "dexamecortin" or "dexameson" or "dexamesone" or "dexametason" or "dexametasone" or "dexameth" or "dexamethason" or "dexamethason " or "dexamethasone" or "dexamethasone" or "dexamethasonium " or "dexamethazon" or "dexamethazone" or "dexamethonium" or "dexamonozon" or "dexan" or "dexane" or "dexano" or "dexa-p" or "dexapot" or "dexascheroson" or "dexascherozon" or "dexascherozone" or "dexason" or "dexasone" or "dexavet" or "dexi siozwo" or "dexinoral" or "dexionil" or "dexmethsone" or "dexona" or "dexone" or "dexpak" or "dextelan" or "dextrasone" or "dezone" or "dibasona" or "diodex" or "dosauxison" or "doxamethasone" or "esacortene" or "ex s1" or "exadion" or "exadione" or "firmalone" or "fluormethyl prednisolone" or "fluormethylprednisolon" or |

| | |
|---|---|
| | "fluormethylprednisolone" or "fluormone" or "fluorocort" or "fluorodelta" or "fluoromethylprednisolone" or "fortecortin" or "gammacorten" or "gammacortene" or "grosodexon" or "grosodexone" or "he 111" or "he111" or "hexadecadiol" or "hexadecadrol" or "hexadiol" or "hexadrol" or "isnacort" or "isopto dex" or "isoptodex" or "lokalison f" or "loverine" or "luxazone" or "marvidione" or "mediamethasone" or "megacortin" or "mephameson" or "mephamesone" or "metasolon" or "metasolone" or "methanesulfonyldexamethasone" or "methazon ion" or "methazone ion" or "methazonion" or "methazonione" or "methylfluorprednisolone" or "metisone lafi" or "mexasone" or "millicorten" or "millicortenol" or "mk 125" or "mk125" or "mymethasone" or "neoforderx" or "neofordex" or "nisomethasona" or "novocort" or "nsc 34521" or "nsc34521" or "oradexan" or "oradexon" or "oradexone" or "orgadrone" or "pidexon" or "policort" or "predni-f" or "prednisolone f" or "prodexona" or "prodexone" or "sanamethasone" or "santenson" or "santeson" or "sawasone" or "soldesam" or "soludecadrol" or "soludecadron" or "solurex" or "spersadex" or "spoloven" or "sterasone" or "sterodex" or "thilodexine" or "totocortin" or "triamcimetil" or "turbinaire" or "vexamet" or "wymesone").mp. (148764) |
| 21 | 19 or 20 (148764) |
| 22 | exp "nausea and vomiting"/ (306299) |
| 23 | ("emeses" or "emesis" or "nause*" or "retch*" or "vomit*" or "cniv").mp. (339744) |
| 24 | 22 or 23 (342099) |
| 25 | 21 and 24 (13816) |
| 26 | 18 or 25 (108724) |
| 27 | (infan* or newborn* or new-born* or neonat* or neo-nat* or child* or adolescen* or juvenile* or teen* or girl* or boy* or youth* or toddler* or tot or tots or paediatric* or pediatric*).mp. [***Age group Textword search terms***] (4255547) |
| 28 | 26 and 27 (14670) |
| 29 | ("emeses" or "emesis" or "nause*" or "retch*" or "vomit*" or "cinv").mp. (339745) |
| 30 | 22 or 29 (342100) |
| 31 | 21 and 30 (13820) |
| 32 | 18 or 31 (108725) |
| 33 | 27 and 32 (14670) |

**EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017>**

| | |
|---|---|
| 1 | Ondansetron/ (952) |
| 2 | ("avessaron" or "bryterol" or "cedantron" or "cellondan" or "ceramos" or "emeset" or "gr 38032" or "gr 38032f" or "gr 38032f" or "gr c507 75" or "gr38032" or "gr38032f" or "modifical" or "narfoz" or "odansetron" or "ondansetron" or "onsia" or "sakisozin" or "sn 307" or "sn307" or "vomceran" or "zetron" or "zofran" or "zofrene" or "zofron" or "zophran" or "zophren" or "zuplenz").mp. (2522) |
| 3 | Granisetron/ (357) |
| 4 | ("apf 530" or "apf530" or "brl 43694" or "brl 43694a" or "brl43694" or "brl43694a" or "eutrom" or "granicip" or "granisetron" or "kevatril" or "kytril" or "sancuso" or "sustol" or "taraz").mp. (845) |
| 5 | ("endoprol" or "endostem" or "ics 205 930" or "ics 205930" or "navoban" or |

| | |
|---|---|
| | "tropisetron").mp. (335) |
| 6 | ("aloxi" or "onicit" or "palonosetron" or "rs 25259" or "rs25259").mp. (309) |
| 7 | ("aprepitant" or "emend" or "l 754030" or "l754030" or "mk 0869" or "mk 869" or "mk0869" or "mk869" or "ono 7436" or "ono7436").mp. (312) |
| 8 | ("anzatric" or "dopin tab" or "jolyon md" or "lanopin" or "lanzac" or "ly 170053" or "ly170053" or "meltolan" or "midax" or "olace" or "oladay" or "olan" or "olandus" or "olanex" or "olansek" or "olanzapine " or "olapin" or "olazax" or "oleanz" or "olexar" or "oltal" or "olzap" or "onza" or "ozapin md" or "psychozap" or "relprevv" or "zalasta" or "zelta" or "zydis" or "zypadhera" or "zyprex" or "zyprexa" or "zyprexav").mp. (2443) |
| 9 | Metoclopramide/ (993) |
| 10 | ("ahr 3070 c" or "ahr 3070c" or "ahr3070c" or "ametic" or "anausin" or "apo-metoclop" or "aputern" or "betaclopramide" or "bondigest" or "cerucal" or "clodilion" or "clopamon" or "clopan" or "clopra" or "clopram" or "degan" or "del 1267" or "del1267" or "dibertil" or "duraclamid" or "emenil" or "emetal" or "emetard" or "emitasol" or "emperal" or "encil" or "enzimar" or "gastro timelets" or "gastrobi" or "gastrobid" or "gastronerton" or "gastrosil" or "gastrotem" or "gastrotimelets" or "gavistal" or "gensil" or "hemesis" or "hyrin" or "imperan" or "m 813" or "m813" or "maalox nausea" or "maril" or "maxeran" or "maxeron" or "maxolan" or "maxolon" or "mcp-beta tropfen" or "meclomid" or "meclopamide" or "meclopramide" or "meclopran" or "meramide" or "metaclopramide" or "metagliz" or "metamide" or "methochlopramide" or "methoclopramide" or "methoclopramine" or "metlazel" or "metochlopramide" or "metoclopamide" or "metoclopramid" or "metoclopramide" or "metoclopramine" or "metoclopranide hydrochloride" or "metoclor" or "metoclorpramide" or "metocobil" or "metocyl" or "metodopramide" or "metolon" or "metopram" or "metox" or "metozolv" or "metpamid" or "metram" or "mygdalon" or "nausil" or "neopramiel" or "netaf" or "neu sensamide" or "nilatika" or "normastin" or "octamide" or "opram" or "paspertin" or "perinorm" or "pharmyork" or "plasil" or "pramidin" or "pramin" or "pramotel" or "primperan" or "primperil" or "prinparl" or "prokinyl lp" or "prowel" or "pulin" or "reclomide" or "reglan" or "reliveran" or "rimetin" or "rimetin" or "sensamide" or "sotatic-10" or "terperan" or "tomid" or "vertivom" or "vomitrol" or "zumatrol").mp. (2502) |
| 11 | Methotrimeprazine/ (31) |
| 12 | ("bayer 1213" or "cl 36467" or "cl 39743" or "cl36467" or "cl39743" or "hirnamin" or "levium" or "levo mepromazine" or "levo promazine" or "levomeprazin" or "levomeprazine" or "levomepromazine" or "levopromazin" or "levopromazine" or "levoprome" or "levozin" or "mepromazine" or "methoprazine" or "methotrimeprazine" or "methotrimperazine" or "methozane" or "milezin" or "minozinan" or "neozine" or "neuractil" or "neurocil" or "nirvan" or "nozinan" or "rp 7044" or "rp7044" or "sinogan" or "sk and f 5116" or "skf 5116" or "skf5116" or "tisercin" or "tizercine" or "tizertsin" or "veractil").mp. (106) |
| 13 | Lorazepam/ (694) |
| 14 | ("almazine" or "alzapam" or "anxiedin" or "anxira" or "anzepam" or "aplacasse" or "apolorazepam" or "apo-lorazepam" or "aripax" or "ativan" or "azurogen" or "bonatranquan" or "donix" or "duralozam" or "durazolam" or "efasedan" or "emotival" or "idalprem" or "kalmalin" or "kendol" or "larpose" or "laubeel" or "lonza" or "lopam" or "lorabenz" or "loram" or "loranase" or "loranaze" or "lorans" or "lorapam" or "loravan" or "lorax" or "loraz" or "lorazene" or "lorazep" or "lorazepam" or "lorazin" or "lorazon" or "lorenin" or "loridem" or "lorivan" or "lorsedal" or "lorzem" or "merlit" or "mesmerin" or |

| | |
|---|---|
| | "nervistop" or "novhepar" or "novo lorazem" or "novolorazem" or "nu loraz" or "nuloraz" or "orfidal" or "orifadal" or "pro dorm" or "punktyl" or "quait" or "renaquil" or "rocosgen" or "securit" or "sedatival" or "sedicepan" or "sidenar" or "sinestron" or "somagerol" or "stapam" or "tavor" or "temesta" or "titus" or "tolid" or "tranqipam" or "trapax" or "trapex" or "upan" or "wy 4036" or "wy4036" or "wypax").mp. (1689) |
| 15 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (9580) |
| 16 | exp Dexamethasone/ (2650) |
| 17 | ("adrecort" or "adrenocot" or "aeroseb dex" or "aflucoson" or "aflucosone" or "ak-dex" or "alfalyl" or "anaflogistico" or "arcodexan" or "arcodexane" or "artrosone" or "auxiloson" or "auxison" or "azium" or "bidexol" or "calonat" or "cebedex" or "cetadexon" or "colofoam" or "colvasone" or "corsona" or "cortastat" or "cortidex" or "cortidexason" or "cortidrona" or "cortidrone" or "cortisumman" or "dacortina fuerte" or "dalalone" or "danasone" or "decacortin" or "decadeltosona" or "decadeltosone" or "decaderm" or "decadion" or "decadran" or "decadron " or "decadronal" or "decadrone" or "decaesadril" or "decaject" or "decameth" or "decamethasone" or "decasone" or "decasterolone" or "decdan" or "decilone" or "decofluor" or "dectancyl" or "dekacort" or "delladec" or "deltafluoren" or "deltafluorene" or "dergramin" or "deronil" or "desacort" or "desacortone" or "desadrene" or "desalark" or "desameton" or "desametone" or "desigdron" or "de-sone la" or "dexa cortisyl" or "dexa dabrosan" or "dexa korti" or "dexa scherosan" or "dexa scherozon" or "dexa scherozone" or "dexacen 4" or "dexachel" or "dexacort" or "dexacortal" or "dexacorten" or "dexacortin" or "dexacortisyl" or "dexadabroson" or "dexadecadrol" or "dexadreson" or "dexadrol" or "dexagen" or "dexahelvacort" or "dexair" or "dexakorti" or "dexalien" or "dexame" or "dexamecortin" or "dexameson" or "dexamesone" or "dexametason" or "dexametasone" or "dexameth" or "dexamethason" or "dexamethason " or "dexamethasone" or "dexamethasone" or "dexamethasonium " or "dexamethazon" or "dexamethazone" or "dexamethonium" or "dexamonozon" or "dexan" or "dexane" or "dexano" or "dexa-p" or "dexapot" or "dexascheroson" or "dexascherozon" or "dexascherozone" or "dexason" or "dexasone" or "dexavet" or "dexi siozwo" or "dexinoral" or "dexionil" or "dexmethsone" or "dexona" or "dexone" or "dexpak" or "dextelan" or "dextrasone" or "dezone" or "dibasona" or "diodex" or "dosauxison" or "doxamethasone" or "esacortene" or "ex s1" or "exadion" or "exadione" or "firmalone" or "fluormethyl prednisolone" or "fluormethylprednisolon" or "fluormethylprednisolone" or "fluormone" or "fluorocort" or "fluorodelta" or "fluoromethylprednisolone" or "fortecortin" or "gammacorten" or "gammacortene" or "grosodexon" or "grosodexone" or "he 111" or "he111" or "hexadecadiol" or "hexadecadrol" or "hexadiol" or "hexadrol" or "isnacort" or "isopto dex" or "isoptodex" or "lokalison f" or "loverine" or "luxazone" or "marvidione" or "mediamethasone" or "megacortin" or "mephameson" or "mephamesone" or "metasolon" or "metasolone" or "methanesulfonyldexamethasone" or "methazon ion" or "methazone ion" or "methazonion" or "methazonione" or "methylfluorprednisolone" or "metisone lafi" or "mexasone" or "millicorten" or "millicortenol" or "mk 125" or "mk125" or "mymethasone" or "neoforderx" or "neofordex" or "nisomethasona" or "novocort" or "nsc 34521" or "nsc34521" or "oradexan" or "oradexon" or "oradexone" or "orgadrone" or "pidexon" or "policort" or "predni-f" or "prednisolone f" or "prodexona" or "prodexone" or "sanamethasone" or "santenson" or "santeson" or "sawasone" or "soldesam" or "soludecadrol" or "soludecadron" or "solurex" or "spersadex" or "spoloven" or "sterasone" or "sterodex" or "thilodexine" or "totocortin" or "triamcimetil" or "turbinaire" |

| | |
|---|---|
| | or "vexamet" or "wymesone").mp. (6990) |
| 18 | 16 or 17 (6998) |
| 19 | exp nausea/ or exp vomiting/ (5572) |
| 20 | ("emeses" or "emesis" or "nause*" or "retch*" or "vomit*" or "cniv").mp. (35656) |
| 21 | 19 or 20 (35677) |
| 22 | 18 and 21 (1809) |
| 23 | 15 or 22 (10279) |
| 24 | (infan* or newborn* or new-born* or neonat* or neo-nat* or child* or adolescen* or juvenile* or teen* or girl* or boy* or youth* or toddler* or tot or tots or paediatric* or pediatric*).mp. [***Age group Textword search terms***] (199692) |
| 25 | 23 and 24 (1794) |

**Appendix B:** Definitions of adverse event outcomes

| Adverse Event | Definition |
|---|---|
| Alterations in mood and behavior | Determined by findings of psychiatric consults and psychiatric treatments received (e.g. counseling, mood stabilizing agents, anti-psychotic drugs) while receiving dexamethasone. |
| Bradycardia | Defined as the minimum heart rate below the lower limit of normal (<2$^{nd}$ percentile) based on age group, while receiving dexamethasone. The heart rate range from 2$^{nd}$ to 98$^{th}$ percentiles based on age group is listed below:[1]<br>• <1 day old; 93-154 bpm<br>• 1-2 days old; 91-159 bpm<br>• 3-6 days old; 91-166 bpm<br>• 1-3 weeks old; 107-182 bpm<br>• 1-2 months old; 121-179 bpm<br>• 3-5 months old; 106-186 bpm<br>• 6-11 months old; 109-169 bpm<br>• 1-2 years old; 89-151 bpm<br>• 3-4 years old; 73-137 bpm<br>• 5-7 years old; 65-133 bpm<br>• 8-11 years old; 62-130 bpm<br>• 12-15 years old; 60-119 bpm<br>• >18 years old; 60-100 bpm |
| Dyspepsia, GERD | Initiation of proton-pump inhibitors, histamine $H_2$ receptor antagonists, alginates, antacids, and/or mucosal protective agents during the time period that dexamethasone is administered. |
| Hyperglycemia | Daily maximum plasma glucose level above the upper limit of normal (ULN) based on age group, occurring after initiation of dexamethasone for which adjustment in diet and/or "round-the-clock" or as-needed insulin is prescribed:<br>• <1 year old: >5.5 mmol/L<br>• 1-2 years old: >5.0 mmol/L<br>• 3-11 years old: >6.1 mmol/L<br>• ≥12 years old: >6.1 mmol/L |
| Hypertension | Maximum systolic and/or diastolic blood pressure above the upper limit of normal (>90$^{th}$ percentile) based on gender, age, and height occurring after initiation of dexamethasone for which "round-the-clock" or as-needed antihypertensive medication is prescribed.<br>Recommended upper normal limits (UNL) for blood pressure (BP) in children and adolescents are derived from the National High Blood |

| | |
|---|---|
| | Pressure Education Program (NHBPEP) Working Group on Hypertension Control in Children and Adolescents.[2] |
| Hypotension | Minimum systolic blood pressure below the lower limit of normal (<5th percentile) based on age group, occurring after initiation of dexamethasone:<br>• <60 mmHg in term neonates (0-28 days)<br>• <70 mmHg in infants (1-12 months)<br>• <70 mmHg + (2 x age in years) in children 1-10 years of age<br>• <90 mmHg in children ≥10 years of age |
| Liver function test (LFT) abnormalities | Increase in the blood level of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) by >3 times the upper limit of normal (x ULN) and/or alkaline phosphatase (ALP) by >2.5 x ULN, while receiving dexamethasone. |
| Tachycardia | Defined as the maximum heart rate above the upper limit of normal (>98th percentile) based on age group, while receiving dexamethasone. The heart rate range from 2nd to 98th percentiles based on age group is listed below:[1]<br>• <1 day old; 93-154 bpm<br>• 1-2 days old; 91-159 bpm<br>• 3-6 days old; 91-166 bpm<br>• 1-3 weeks old; 107-182 bpm<br>• 1-2 months old; 121-179 bpm<br>• 3-5 months old; 106-186 bpm<br>• 6-11 months old; 109-169 bpm<br>• 1-2 years old; 89-151 bpm<br>• 3-4 years old; 73-137 bpm<br>• 5-7 years old; 65-133 bpm<br>• 8-11 years old; 62-130 bpm<br>• 12-15 years old; 60-119 bpm<br>• >18 years old; 60-100 bpm |

**Appendix C:** Feasibility questionnaire for collaborating sites

1. For each data element below, please indicate if you obtained this element through a query to your institution's HSCT database:

| Study Stage | Data Element | Available in Institutional HSCT Database? |
|---|---|---|
| 1. Eligibility Screening | Date of birth | ☐ |
| | Diagnosis (indication for HSCT) | ☐ |
| | Date of HSCT | ☐ |
| | Type of HSCT (e.g. allogeneic, autologous) | ☐ |
| | Conditioning regimen | ☐ |
| | Intensity of conditioning (e.g. myeloablative, reduced intensity) | ☐ |
| 2. Exclusion Screening | Down syndrome | ☐ |
| | Diagnosis of severe combined immune deficiency | ☐ |
| | Adreno-insufficiency or other disorders requiring physiological supplementation with corticosteroids | ☐ |
| | Receipt of active treatment for IFD at admission for HSCT to initiation of conditioning | ☐ |
| | aGVHD prophylaxis regimen | ☐ |
| | Receipt of ganciclovir, sulfamethoxazole-trimethoprim, and G-CSF from Day 0 to day of neutrophil engraftment | ☐ |
| | Receipt of corticosteroids other than dexamethasone for CINV prophylaxis | ☐ |
| 3. Propensity Score Estimation | Recipient sex | ☐ |
| | Donor sex | ☐ |
| | Donor type (e.g. matched-sibling donor, unrelated) | ☐ |
| | Date of diagnosis | ☐ |
| | Date of relapse(s) | ☐ |
| | Stem cell source (e.g. bone marrow, peripheral blood) | ☐ |
| | History of documented or suspected IFD from date of diagnosis to admission for HSCT | ☐ |
| | CINV prophylaxis regimen (including palonosetron) | ☐ |
| | Receipt of dexamethasone for CINV prophylaxis | ☐ |
| 4. Outcome Analysis | Date of death | ☐ |
| | Cause of death | ☐ |
| | Recurrence or progression of disease for which HSCT was indicated | ☐ |
| | Engraftment failure | ☐ |
| | Date of neutrophil engraftment | ☐ |
| | Maximal grade of aGVHD | ☐ |
| | Redacted reports suggestive of invasive fungal disease within Day +100 | ☐ |

2. How much time on average did you dedicate to obtaining the data elements that were not obtained from an HSCT database query?

   ☐ <10 minutes per patient

   ☐ 10-30 minutes per patient

   ☐ 30-60 minutes per patient

   ☐ 60-90 minutes per patient

   ☐ >90 minutes per patient

   ☐ Not applicable

3. Please indicate the other sources of data elements that were not obtained through an HSCT database query: (Choose all that apply)

   ☐ Pharmacy records/database

   ☐ Patient health record

   ☐ Consultation with an HSCT team member

   ☐ Other: Click here to enter text.

4. Overall, how easy or hard was it to collect the data for this study?

| ☐ | ☐ | ☐ | ☐ | ☐ |
|---|---|---|---|---|
| Very easy | Easy | Neither easy or hard | Hard | Very hard |

5. If you answered *hard* or *very hard* above, please describe any challenges you may have encountered during data collection:

   Click here to enter text.

**Appendix D:** European Organization for Research and Treatment of Cancer (EORTC) definition for invasive fungal disease

**Proven IFD**: Any one of the following:

- Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy with observation of fungal elements of molds (hyphae, melanized yeast-like forms with associated tissue damage) and yeasts (encapsulated budding yeasts or hyphae)
- Blood culture that yields a mold or yeast
- Culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site that yields a mold or yeast. For molds, this excludes bronchoalveolar lavage fluid, cranial sinus cavity specimen, and urine
- For yeasts, cryptococcal antigen in CSF

**Probable IFD**: One host factor, clinical criterion, and mycological criterion must be present.

- Host factors
    - Recent history of neutropenia ($<0.5 \times 10^9$ neutrophils/L for >10 days) temporally related to onset of fungal disease
    - Receipt of allogeneic stem cell transplant
    - Prolonged use of corticosteroids (mean minimum dose of 0.3mg/kg/day of prednisone equivalent for >3 weeks)
    - Treatment with T-cell immunosuppressants or nucleoside analogues during the past 90 days
    - Inherited severe immunodeficiency
- Clinical criteria
    - Lower respiratory tract fungal disease (1 of 3 CT signs: (1) dense well-circumscribed lesions with or without halos, (2) air-crescent sign, (3) cavity)
    - Tracheobronchitis (ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis)
    - Sinonasal infection (imaging of sinusitis plus 1 of 3 signs: (1) acute localized pain, (2) nasal ulcer with black eschar, (3) extension from paranasal sinus across bony barriers)
    - CNS infection (1 of 2 signs: (1) focal lesions on imaging, (2) meningeal enhancement on MRI or CT)
    - Disseminated candidiasis (1 of 2 entities after an episode of candidemia within previous 2 weeks: (1) small bull's-eye lesions in liver or spleen, (2) progressive retinal exudates on ophthalmologic exam)
- Mycological criteria
    - Direct test (cytology, direct microscopy, culture): mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate indicated by 1 of 2 signs: (1) presence of fungal elements, (2) recovery by culture.
    - Indirect test (detection of antigen or cell-wall constituents): galactomannan in plasma, serum, BAL, or CSF (aspergillosis) or β-D-glucan in serum (IFD other than cryptococcosis and zygomycoses)

**Appendix E:** Modified Glucksberg scale

| aGVHD Grade | Skin | Liver | Gut |
|---|---|---|---|
| **I** | 1-2 | 0 | 0 |
| **II** | 1-3 | 1 | 1 |
| **III** | 2-3 | 2-3 | 2-3 |
| **IV** | 4 | 4 | 4 |

Organ Staging
Skin:

| | |
|---|---|
| 1 | Maculopapular rash <25% BSA |
| 2 | Maculopapular rash 25-50% BSA |
| 3 | Generalized erythroderma |
| 4 | Erythroderma with bullae and desquamation |

*BSA: body surface area

Liver:

| | |
|---|---|
| 1 | Total bilirubin >34 and <52 µmol/L (>2 and <3 mg/dL) |
| 2 | Total bilirubin ≥52 and <103 µmol/L (≥3 and <6 mg/dL) |
| 3 | Total bilirubin ≥103 and <256 µmol/L (≥6 and <15 mg/dL) |
| 4 | Total bilirubin ≥256 µmol/L (≥15 mg/dL) |

Gut:

| Stool volume | mL/m$^2$/day | mL/day |
|---|---|---|
| 1 | >280 and ≤555 | >500 and ≤1000 |
| 2 | >555 and ≤883 | >1000 and ≤1500 |
| 3 | >833 | >1500 |
| 4 | Severe abdominal pain ± ileus | |

**Appendix F:** European Group for Blood and Marrow Transplantation (EBMT) risk score

| Risk Factor | Score Point |
|---|---|
| Age of the patient, years | |
| <20 | 0 |
| 20-40 | 1 |
| >40 | 2 |
| Disease stage[1] | |
| Early | 0 |
| Intermediate | 1 |
| Late | 2 |
| Time interval from diagnosis to transplant, months[2] | |
| <12 | 0 |
| >12 | 1 |
| Donor type[3] | |
| HLA-identical sibling donor | 0 |
| Unrelated donor, other | 1 |
| Donor-recipient sex combination[3] | |
| All other | 0 |
| Donor female, male recipient | 1 |

[1]Disease stage does not apply for aplastic anemia (score 0). See the below text for definitions according to main disease category:

- Early disease stage includes acute leukemia transplanted in first complete remission, myelodysplastic syndrome transplanted either untreated or in first complete remission, chronic myeloid leukemia in first chronic phase, and non-Hodgkin lymphoma and multiple myeloma transplanted untreated or in first complete remission. If haploidentical HSCT, early disease stage includes transplantation in first complete remission.
- Intermediate disease stage includes acute leukemia transplanted in second complete remission, chronic myeloid leukemia in all other stages than chronic phase or blast crisis, myelodysplastic syndrome in second complete remission or in partial remission; and non-Hodgkin lymphoma and multiple myeloma in second complete remission, in partial remission, or stable disease. If haploidentical HSCT, intermediate disease stage includes transplantation in second or subsequent complete remission.
- Late disease stage includes acute leukemia in all other disease stages, chronic myeloid leukemia in blast crisis, myelodysplastic syndromes in all other disease stages, and multiple myeloma and lymphoma in all other disease stages than those defined as early or intermediate. If haploidentical HSCT, late disease stage includes transplantation in the absence of complete remission.

[2]Time interval from diagnosis to transplant does not apply for patients transplanted in first complete remission (score 0).

[3]Does not apply to patients with autologous HSCT (score 0).