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REVIEW

Interventions to reduce the risk of side-effects of cancer treatments in childhood

Bob Phillips[a,b], Jess Morgan[a,b], Ruth Walker[a], Claudia Heggie[c] and Salah Ali[d]

[a]Centre for Reviews and Dissemination, University of York and Hull-York Medical School, York, UK; [b]Regional Department of Paediatric Haematology and Oncology, Leeds Children's Hospital, Leeds, UK; [c]Paediatric Dentistry University of Leeds, Leeds, UK; [d]Department of Pediatric Haematology/Oncology, Cancer Center of Southeastern Ontario, Queens University, Kingston, Ontario, Canada

ABSTRACT

Introduction: Childhood cancers as a group affect around 1 in 500 children but each individual diagnosis is a rare disease. While research largely focuses on improving cure rates, the management of side effects of treatment are high priority for clinicians, families and children and young people.

Areas covered: The prevention and efficient management of infectious complications, oral mucositis, nausea and vomiting and graft-vs-host disease illustrated with examples of implementation research, translation of engineering to care, advances in statistical methodologies, and traditional bench-to-patient development. The reviews draw from existing systematic reviews and well conducted clinical practice guidelines.

Expert opinion: The four areas are driven from patient and family priorities. Some of the problems outlined are ready for proven interventions, others require us to develop new technologies. Advancement needs us to make the best use of new methods of applied health research and clinical trial methodologies. Some of the greatest challenges may be those we're not fully aware of, as new therapies move from their use in adult oncological practice into children. This will need us to continue our collaborative, multi-professional, multi-disciplinary and eclectic approach.

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1. Introduction

Childhood cancers as a group affect around 1 in 500 children before the age of 15 years but each individual diagnostic entity meets the definition of a rare disease. Anti-cancer management is designed based on risk stratifications for each specific pathology. The common components of treatment fall into three key groups – systemic therapies aimed at both local and distant disease control (traditionally cytotoxic chemotherapy, but increasingly also targeted and immuno-therapies and small molecules), radiotherapy (including photons, protons and brachytherapy), and surgery. All three types of intervention carry risks of different complications and side effects, as do the treatments used to manage these adverse events.

The presentation and management of side effects of treatment are high priorities for clinicians, families and children and young people themselves. Priority setting exercises involving key stakeholders in the UK, Canada and the Netherlands have consistently ranked these issues in the top ten [1–5]. The top priority for children's cancer research in the UK is 'Can we find effective and kinder (less burdensome, more tolerable, with fewer short and long term effects) treatments for children with cancer, including relapsed cancer?' The concept of 'kindness' in children's cancer treatment has not been accurately defined in the literature, but considers the burden of therapy, including the common side effects associated with it.

Managing the complications and implications of cancer care, often referred to in pediatrics as supportive care and enhanced supportive care in adult settings, aim to improve the experience of childhood cancer, but also address life threatening situations, and facilitate the intensification of therapy supporting improvements in overall survival. Within this review, we focus on four key areas of supportive care in childhood cancer treatment from the setting of treatments in high-income 'global North' countries, and consider how these might be prevented and/or managed, highlighting how different approaches to supportive care research has underpinned these advances.

2. Infection

The most common life-threatening complication of cancer treatment in children and young people is infection. Prevention of infections in immunocompromised children and young people takes a multi-level approach at individual, institutional and societal levels, using a range of behavioral and pharmacological interventions.

Behavioral interventions at the individual level include good mouth and skin care, and reducing high risk social exposures. Recent evidence based clinical practice guidelines from the Netherlands have advised that many commonly advised behavioral interventions (such as avoiding public transport) are not supported by evidence that they reduce risk [6].

More medical interventions for individual patients include strategies to reduce risk factors for infection, such as reducing mucositis (see later in this review), minimizing episodes of central

CONTACT Bob Phillips bob.phillips@york.ac.uk Centre for Reviews and Dissemination, Alcuin College University of York, York, Yorkshire YO10 5DD, UK of Great Britain and Northern Ireland

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Article highlights

- While childhood cancer and hematopoietic stem cell transplant research focuses on cure, the management of side effects of treatment is a high priority for clinicians, families and children and young people.
- The most common life-threatening complication is infection, and prevention and management of this takes a multi-level approach at individual, institutional and societal levels, using a range of behavioral and pharmacological interventions.
- Photobiomodulation is now a widely available technique to prevent and treat oral mucositis in even very young children; developing and finessing the techniques of this is needed.
- The relative paucity of trial data about nausea and vomiting management in children compared with adults gives us a strong driver to use network meta-analysis techniques to maximize the evidence we have.
- Graft-versus-host disease (GVHD) is one of the most common of the serious specific post-HSCT complications, and prevention by reducing initial injury and treatment through modifying host response are areas under intensive investigation.

venous access and perhaps antimicrobial line locks [7]. Whilst adapted chemotherapy regimes can help to reduce risk, granulocyte colony stimulating factors have a limited role for children and young people with cancer (except in prolonged neutropenia, or in dose interval reduced regimens) [8].

Prophylactic antimicrobials play a role in reducing the risk of infections in various ways. During therapy, Pneumocystis jirovecii prophylaxis is recommended for children and young people on many regimes [9,10]. Meanwhile, fluoroquinolone prophylaxis has been proven to reduce the risk of serious bacterial infection in high risk hematological malignancies [11]. Research to evaluate their benefits in lower risk populations is ongoing [12]. There is also a role for post-exposure prophylaxis to reduce the risk of certain viral infections in those at high risk of infectious complications, with the most commonly encountered being SARS-CoV2 and varicella zoster [13]. The role of prophylactic antifungal medications for those at the highest risk of invasive fungal disease is clearly established [14].

At institutional levels, good infection prevention practices around source isolation, hand hygiene, and water and food safety reduce the risk of outbreaks within pediatric hematology and oncology services. Staff vaccination and human resources practices such as paid sick leave further reduce the likelihood of healthcare acquired infections.

At a societal level, public health interventions to reduce infection risks in the general population particularly support those undergoing anti-cancer treatment. This includes good sanitation, vaccinations, and work around disease surveillance and outbreak control.

In addition to the interventions discussed above which aim to reduce the risk of infections in children and young people with cancer, good management of febrile neutropenia (FN) can also reduce the significance of this complication when it occurs. This is the co-occurrence of fever in children and young people with a low neutrophil count. Various definitions are used both within and between countries, but they tend to include patients with an absolute neutrophil count of < 500 cells/microliter, and a measured core temperature of over 38.3C [15], with some being more expansive and some slightly more restrictive. Ongoing work seeks to more expressly define the most appropriate temperature threshold for intervention [16], as well as the role of wearable technologies in detecting febrile episodes [17].

Febrile episodes on average 0.75 times in every 30 days of neutropenia [18] and, even without severe sepsis, disrupts family life, carries unwanted side effects of antimicrobial therapies, and has significant impacts on healthcare system resources. To minimize these adverse effects, and effectively treat life-threatening situations, early identification of potential infection and early instigation of risk-stratified clinical practice guideline compliant management is essential [19].

Multiple risk stratification tools and clinical practice guidelines have been developed for febrile neutropenia in children and young people, with varying degrees of success [20–22]. More intensive treatment is then administered to those at highest risk of serious complications of infection, and less intensive strategies applied to those at low risk, sparing them the adverse effects of antimicrobial therapies and prolonged hospitalization.

Risk stratification most frequently takes into account the intensity of chemotherapy administered (sometimes using the underlying disease as a proxy marker for this), and the bone marrow function at the time of the episode (using elements of the full blood count). Furthermore, assessment of the clinical condition of the child or young person, as well as the social situation into which they may be discharged, plays an important role. No one risk stratification tool is clearly identified as most suitable for this population, particularly for teenagers and young adults, where neither pediatric nor adult tools perform as effectively. Tools should be used within comprehensive clinical practice guidelines, implemented by those with experience of children and young people with cancer.

An example of such an implementation within the UK system, where cancer in young people up to their 19th birthday is centered around a limited number of defined principal treatment centers, and supportive care delivered across this network and their attached satellite centers, is the AUS tool. [23,24] This simple, robust tool assesses the presenting total white cell count, platelet count, and the intensity of prior chemotherapy (measured against the commonest 'low intensity' regime of lymphoblastic leukemia maintenance) to produce a score from 0 to 3, which relates to the likelihood of bacteremia. It is used in conjunction with a clinical assessment of the child's 'wellness' and individual and social circumstances to offer home-based care with oral antibiotics to patients in around 20% of episodes within the first 24 hours of attending. A national service evaluation demonstrated the safety of this approach, which was well received by parents and families [25].

Antimicrobials in febrile neutropenia should be carefully considered, taking into account evidence for effectiveness and adverse events, the patient's previous infection history, and local pathogens and rates of antimicrobial resistance. Antibiotics carry a number of possible side effects, of which gastrointestinal effects are most common and distressing. Reducing the duration of antibiotics and hospitalization, as well as narrowing the spectrum of antibiotic cover, have

been shown to be safe and effective for selected groups of patients, and bring improved outcomes in terms of experiences of care, measured quality of life, and effective resource management [26]. Furthermore, reducing the exposure to unnecessary antibiotics is consistent with the principles of antimicrobial stewardship.

Research in this area is ongoing, focussing on refinement of the risk stratification systems and advancement of the 'stopping rules' for fever without clear evidence of infection, for example using dynamic assessment of inflammatory biomarkers. As new approaches to treatment become more common, such as chimeric-antigen-receptor T-cell therapy (CAR-T), the paradigm for prevention and treatment of infection may need to shift again.

3. Mucositis

Mucositis is among the most common side effects of cancer treatment, affecting up to 8 in every 10 children [27]. Mucositis describes the inflammation and subsequent damage to otherwise healthy cells. The gastrointestinal tract is particularly susceptible to the stomatotoxic effects of chemotherapeutic agents due to its the high cell turnover [28]. This cell turnover is increased further in children, with a higher proliferation rate of epithelial cells when compared to adults, making this population particularly susceptible to mucositis [29]. Although the clinical signs of mucositis are seen in the epithelium, submucosal tissues and the extra-cellular matrix are involved in its pathophysiology [30]. Initial tissue injury results in a cascade of reactive oxygen species and amplification of pro-inflammatory cytokines resulting in epithelial damage, which compounds with the direct stomatotoxicity of chemotherapeutic agents [30,31].

When severe mucositis occurs, with ulceration of the mouth and gastrointestinal tract, children and young people experience significant pain [32]. This often affect their ability to eat and drink orally and necessitate inpatient stays for parenteral nutrition and pain-relief. Children may also struggle to swallow their own saliva, sleep, or communicate when they have severe disease, with demonstrated negative impacts on quality-of-life during cancer treatment [33].

Mucositis severity is influenced by a number of diagnostic and treatment related factors. These include the underlying condition [34,35], the chemotherapeutic agents such as use of alkylating agents, platinum compounds, anthracyclines, antimetabolites, vinca alkaloids, taxanes, and antibiotics such as bleomycin [36]. Along with choice of chemotherapeutic agent, dose and treatment regime also impacts mucositis risk. Children and young people often receive aggressive, multi-agent chemotherapy over multiple days which increases risk further in this population [37].

Patient related factors in relation to mucositis severity are less well understood. Association with patient age or sex is unclear, and varies between pediatric populations studied. [34,38,39] Children with previous episodes of oral mucositis [37,38], neutropenia [33,38], thrombocytopenia [40], genetic variation [41,42] and a higher level of anxiety [39,43] have been shown to be at increased risk of developing severe oral mucositis. Regarding the oral microbiome, associations with presence of HSV-1 and oral candida have been previously reported [39]. Toothbrushing has been found to reduce severity of mucositis, when compared to use of mouth rinses alone [44].

A Cochrane review in 2011 found evidence in support of 10 interventions for oral mucositis prevention when including all-age patients undergoing chemotherapy, with strongest evidence in support of use of cryotherapy and keratinocyte growth factor [45]. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) subsequently conducted a series of systematic reviews regarding these preventive interventions, which were synthesized into the MASCC clinical practice guidance on mucositis management secondary to cancer treatment [46,47]. However, preventive interventions that are successful in adults may not directly translate to pediatric populations; the later section on nausea and vomiting focuses on new research methods we can use to overcome this challenge. The Pediatric Oncology Group of Ontario (POGO) took a more traditional method and developed a clinical practice guideline for mucositis prevention in pediatric cancer and hematopoietic stem cell transplant patients, reflecting the difference between these populations and the strength of evidence in each [48]. These guidance documents differ in their recommendations (Table 1).

Oral cryotherapy, which is most commonly completed with ice chips, is postulated to prevent mucositis due to oral cooling resulting in vasoconstriction of the blood vessels in the oral cavity, reducing delivery of chemotherapeutic agents to these tissues. Additionally, low temperatures may reduce the metabolic activity in epithelial and basal cells, making them less susceptible to the stomatotoxic effects of chemotherapy [49].

However, the use of ice chips provide only transient reductions in oral temperature before requiring replenishment, which can prove challenging for use in long infusions. There are limited cryotherapy studies in pediatric populations, and children and young people have been shown to have poor compliance with oral cryotherapy [50]. Use of flavored ice-pops or ice cream may make cryotherapy more appealing to young children, [51]. But extended holding of sugar containing liquids in the mouth presents an additional dental decay risk in these children and may negate the influence of oral care protocols.

Keratinocyte growth factor (KGF) is a member of the fibroblast growth factor family. KGF is specific to epithelial cells, and stimulates their proliferation and differentiation throughout the gastrointestinal tract and oral mucosa [52,53]. This proliferative effect is thought to counteract the epithelial atrophy observed in ulcerative oral mucositis. Palifermin is a recombinant human KGF most commonly used in mucositis management [47].

The safety and efficacy of keratinocyte growth factor in children is uncertain, with concern relating to the adverse effects, primarily the development of rash, pruritus, pain in extremities and mucosal thickening [53,54]. Additionally, there is theoretical concern that palifermin presents a risk of secondary malignancy, due to KGF receptor expression on a multitude of epithelial tissues. However, KGF receptors are not expressed on hematopoietic cells, and so KGF should not

Table 1. Summary of recommendations in mucositis prevention guidance documents.

Preventive intervention	MASCC/ISOO Guidance. 2020 [45]	POGO Guidance. 2021 [47]
Benzydamine mouthwash	Recommended in patients receiving: • Moderate dose radiotherapy for head and neck cancer	
Oral cryotherapy	Recommended in patients receiving: • Bolus administration of 5-fluorouracil during chemotherapy • Autologous HSCT where conditioning regime includes high dose melphalan	Strong recommendation in: • Older, cooperative patients receiving short infusions of 5-fluorouracil or melphalan Conditional recommendation in: • Older, cooperative patients receiving other short chemotherapy infusions associated with mucositis
Keratinocyte growth factor	Recommended intravenously in patients receiving: • Autologous HSCT where conditioning regime includes high dose high dose chemotherapy and total body irradiation	Strong recommendation against routine use in paediatric patients receiving treatments for cancer or HSCT
Photobiomodulation	Intra-oral low-level laser recommended in adult patients receiving: • HSCT, receiving high dose chemotherapy (with or without total body irradiation) • Head and neck radiotherapy (without chemotherapy)* • Radiotherapy and chemotherapy for head and neck cancer*	Intra-oral red light spectrum (620-750 nm) photobiomodulation strongly recommended for paediatric patients: • Receiving autologous or allogeneic HSCT • Radiotherapy for head and neck carcinoma Conditionally recommended for paediatric patients: • Receiving radiotherapy for other head and neck cancers
Sucralfate (combined topical and systemic)	Is not recommended in patients receiving: • Radiotherapy for head and neck cancer • Chemotherapy for solid cancers	
Glutamine (parenteral)	Is not recommendation in patients receiving: • HSCT	
Granulocyte colony stimulating factor		Strong recommendation against use in paediatric patients receiving chemotherapy or HSCT

HSCT = haematopoietic stem cell transplant. (*) safety considerations recommended for intra-oral photobiomodulation use in patients with oral cancers.

Table 2. Antiemetic medications currently recommended for children and young people in the clinical practice guidelines of Paediatric Oncology Group of Ontario (POGO) [68–70], multinational association of supportive care in cancer (MASCC) [71] and Children's cancer and leukemia group (CCLG) [72].

Highly emetogenic chemotherapy (HEC)	Moderately emetogenic chemotherapy (MEC)	Low emetogenic chemotherapy (LEC)
An NK-1 antagonist + a 5HT3 receptor antagonist + dexamethasone for prevention of acute CINV (Olanzapine* may also be considered.) An NK-1 antagonist + a 5HT3 receptor antagonist + dexamethasone for prevention of delayed CINV	A 5HT3 receptor antagonist + dexamethasone for prevention of acute CINV]. Dexamethasone for prevention of delayed CINV.	A 5HT3 receptor antagonist for prevention of acute CINV. No routine prophylaxis for prevention of delayed CINV.

Recommended NK-1 antagonists: Aprepitant or fosaprepitant. Recommended 5HT3 receptor antagonists: palonosetron, ondansetron, granisetron or tropisetron. *Use of Olanzapine would be off-label in the UK and Canada.

increase risk of hematological malignancy. These adverse effects, unknown long term effects, and modest treatment effect size are cited as rationale for recommendation against routine use in pediatric guidance [47]. Additionally, there are practical considerations including cost and the lack of routine availability of Palifermin in some jurisdictions, for example Europe and Canada.

Photobiomodulation describes the application of red visible light, or near infra-red wavelengths at low power to encourage tissue repair, reduce inflammation and produce analgesia through changes in cellular activity [55,56]. Historically, this has been administered with 'low-level lasers' in the near infra-red spectrum, but increasingly photobiomodulation utilizes noncoherent light-emitting diode (LED) sources in the red visible light spectrum, rather than low-level lasers [56,57]. The optical window of tissues lies within 650–1200 nm [58]; wavelengths of light with proven proliferative cellular effect utilized in photobiomodulation lie within 600–700 nm for red light, and 780–950 nm for near-infrared. There is a lack of stimulatory biochemical activity observed in wavelengths 700–770, and so these wavelengths are not utilized [59].

The exact cellular mechanism of photobiomodulation has not been fully elucidated, however, a photochemical reaction in the mitochondrial respiratory chain is the leading hypothesis. Reduction of oxygen at the terminal enzyme in the mitochondrial respiratory chain (cytochrome c oxidase) results in adenosine triphosphate (ATP) production which is essential for DNA synthesis and cell proliferation [60]. Nitric oxide competitively inhibits the binding of oxygen, acting as a homeostatic control of mitochondrial respiration, with nitric oxide levels increased in

cells experiencing stress or hypoxia [60]. Photons within the wavelengths utilized in photobiomodulation are absorbed by chromophores on cytochrome c oxidase with resultant photo stimulatory dissociation of nitric oxide, reducing its inhibitory effect and increasing ATP production[60]. Secondary messaging through generation of reactive oxygen species and subsequent activation of transcription factors and Src tyrosine kinases, which have a vital role in cell signaling relating to growth, proliferation and adhesion [61]. The incomplete understanding of mechanism, and inconsistent and suboptimal reporting of dosimetry results in incomplete comprehension of the efficacy of photobiomodulation. However, meta-analyses show pooled benefit in the use prophylactic use of photobiomodulation for mucositis management [26,54], resulting in strong recommendations for use in specific pediatric populations (Table 1). There may be a role for photobiomodulation in management of other oral diseases, with evidence of pain reduction in adults with recurrent herpes labialis receiving 650 nm diode laser when compared to topical aciclovir [62]. Practical limitations to use of low-level laser systems, including specific training and protective equipment, and unknown acceptability to young children are highlighted as areas of uncertainty in pediatric guidance [47].

Of the recommendations made in evidence-based guidance, photobiomodulation is emerging as an intervention with real utility in children and young people as a low-risk intervention with proven feasibility. However, research from members of our group has shown that there is limited uptake in U.K. children's cancer centers [63,64]. Barriers cited included lack of knowledge and skills, unclear professional roles, and limitations in environmental context and resources. The increased use of LED light sources in photobiomodulation may help to overcome some of these barriers and concerns highlighted in pediatric guidance [47], with lower training and practical burden, and increased flexibility of LED systems when compared to traditional low-level lasers. There is limited evidence for the effectiveness of extra-oral approaches, with existing research primarily focusing on intra-oral delivery. Extra-oral delivery is complicated by light attenuation through the multiple layers of the cheek, and anatomical variation in the thickness of these layers and variation in chromophores (such as melanin) in the skin [65]. Research from members of our group has found LED photobiomodulation to be highly acceptable to children and young people receiving cancer treatment, but that intra-oral treatment can present a barrier to acceptance.

Further studies should consider the effectiveness of extra-oral LED approaches compared to intra-oral or combined approaches, and the patient factors affecting light transmission in an such approaches in pediatric clinical practice. Implementation science methods and frameworks could be utilized to robustly explore the barriers to uptake of photobiomodulation, and to test these implementation science theories in the context of children's supportive care.

4. Nausea and vomiting

Nausea and vomiting are common side effects of many cancer treatments that continue to be a problem for an estimated 70% of children and young people receiving chemotherapy. These side effects have profound physical consequences including dehydration, electrolyte imbalance, weight loss, anorexia, weakness and increased susceptibility to infection [66,67]. There is also often psychological impact, in particular, nausea is commonly identified as being a distressing aspect of chemotherapy treatment [66].

Previous research [67–70] has sought to identify randomized control trials (RCTs) comparing anti-sickness medicines for prevention of chemotherapy-induced nausea and vomiting (CINV) in children and young people, and combine their results using meta-analysis. This work has informed recommendations of current clinical practice guidelines [68–72]; See Table 2 that advocate for the use of neurokinin-1 receptor (NK1) antagonists (aprepitant and fosaprepitant), 5-hydroxytryptamine (5-HT3) antagonists (ondansetron, palonosetron and granisetron), dopamine blockers (metoclopramide) and corticosteroids (dexamethasone). These medications are recommended in specific combinations that depend on the emetogenic potential of the chemotherapy being received (i.e. how likely the chemotherapy is to cause vomiting in the absence of prophylaxis).

Emetogenicity of chemotherapy is often categorized into 'low,' causing a 10–30%, 'moderate,' causing a 30–90% and 'high' causing over a 90% incidence of emesis in the absence of prophylaxis [69]. It is notable that the emetogenic potential of extremely commonly used agents is poorly researched, and much of our understanding derives crudely from adult data [73].

Despite the availability of high quality evidence on the effectiveness of antiemetic medications, there exist uncertainties and unanswered questions. Firstly, the standard meta-analysis technique used to combine RCT evidence can only compare two interventions which have been subject to head-to-head trials, and as these are not comprehensive, not all antiemetic medications have been formally compared to every other in these syntheses. The analyses are also limited by the inconsistency in reporting of outcomes in the underlying clinical trials. Added to this are the challenges of describing which antiemetic medications are most effective at preventing infrequently reported, but highly patient-relevant outcomes, such as nausea [67], along with the optimal dosing and scheduling of many commonly used antiemetic medications including dexamethasone [68]. Another limitation of the existing evidence on antiemetic use in children (as with many areas of pediatric medicine) is that RCTs are often few, and those which do exist have small sample sizes. This means that estimates of relative treatment effect are more uncertain than their corresponding estimates in the adult population.

Research is underway to apply an alternative statistical technique called network-meta-analysis (NMA), a method that can simultaneously combine RCT evidence on three or more treatments. Whilst facilitating the comparison of each treatment with every other within a 'network' of treatments, NMA can also be used to estimate the relative treatment effects of treatments not directly compared in clinical trials (referred to as 'indirect' evidence), provided these treatments are present in a 'connected network' of treatments i.e. a network where there is a 'path' (of randomized or 'direct' comparisons) between any two interventions. This is possible

by subtracting the estimate of one direct comparison from another via the common comparator (similar to working out the length of the third edge of a triangle when you have only the length of two edges). These advantages mean NMA may help to address some of the limitations of existing evidence syntheses [74] including allowing assessments of infrequently reported outcomes and understanding more fully the possible effects of dosing and scheduling differences.

To overcome some of the paucity of pediatric trials, methods that can incorporate RCT evidence on the effect of treatments in adults (which is often more plentiful than the child data) may be useful. These methods extrapolate information about treatment effect, from the adult population, to hopefully improve the precision (or certainty) of estimates of treatment effect in children. This is described as 'borrowing strength' from the adult evidence. These methods have successfully been applied in other areas of pediatric medicine, where information about the effect of treatments for plaque psoriasis, was extrapolated from a network of treatments in adults, to inform estimates of treatment effect in children [75]. Preliminary research into using these extrapolation methods to improve understanding of antiemetic use in children, indicates possible differences in the underlying risk of CINV between adults and children, as well as the relative effects of treatments (i.e. the effect of one treatment compared to another). We therefore believe that it would most appropriate for methods of extrapolation applied in this area, to account for potential differences in the way children and adults respond to treatments. This way adult evidence can be included without making the assumption that the data arise for the same population [76].

In addition to estimating average treatment effects in pediatric populations, small sample sizes in children's clinical trials also limits the opportunity to investigate how patients with different characteristics, or given different chemotherapies for example, respond to antiemetic medications. Some patients may gain greater relative benefit from a treatment compared to other i.e. derive more benefit from one treatment than another. However, estimating the relative effect of treatments in different groups requires dividing an already small sample within an RCT into tiny subsets. Published RCT evidence could be combined or 'synthesised' to estimate these effects, but would require each RCT to report treatment effects in the same groups of patients, and to define these groups of patients in the same way (a situation that is uncommon). Because of this, instead of using published or 'aggregate' data, the 'raw' data (also called individual participant data or IPD) acquired from clinical trials may be more useful. Previous research [77] that combined IPD from RCTs of antiemetics in children, has identified that older children, those with a longer acute phase duration (i.e. a longer length of chemotherapy block) that put children at greater risk of CINV in the acute phase, and those who had poor acute phase control had a greater risk of CINV in the delayed phase. However, it remains unknown if these children would benefit more or less from particular antiemetic medications (i.e. where they would derive greater relative benefit from a treatment). This information may be useful to help refine current recommendations for the use of prophylaxis in children at risk of CINV, by targeting individuals who would gain most benefit from particular treatments, something that may be particularly useful when needing to ration more expensive but potentially more effective treatments in resource limited settings, and avoid given treatments to children who would derive little benefit, but may still experience side effects from the medications.

The statistical methods discussed including NMA, extrapolation of adult clinical trial data and synthesis of IPD could help to maximize our understanding of how to best prevent nausea and vomiting in children from the evidence that already exists. This could ultimately help us to reach answers sooner, without the need to conduct so many clinical trials that require long periods of time and resource.

5. Graft vs. Host Disease

Allogeneic hematopoietic stem cell transplantation (HSCT) is a life-saving treatment for several difficult-to-treat conditions including, but not limited, to some malignancies. Patients who have undergone the conditioning regimes required before HSCT may suffer many of the same complications as those who have received treatments for cancer, and in pediatrics their treating teams often overlap in clinical and research roles.

Graft-versus-host disease (GVHD) is one of the most common of the specific post-HSCT complications resulting in significant morbidity and mortality. GVHD is a consequence of the interaction between donor and recipient immune cells. When recipient immune antigen presenting cells (APCs) present several recipient antigens, donor immune cells rapidly proliferate, become activated and attack recipient normal tissues which are considered foreign to eliminate those antigens [78–81].

Tissue injury is a key component to initiate GVHD as the more tissue is damaged, the more antigens exposed to be presented. This tissue injury causes release of inflammatory cytokines and other mediators which leads to APCs activation [81–85]. Tissue injury occurs directly by HSCT conditioning regimen as well as previous chemotherapy treatment of underlying disease. The more intense the condition regimen (e.g. myeloablative and total body irradiation-based regimens), the greater the tissue injury and consequently higher rates of GVHD develop [78,81,86–89].

The pathogenesis of GVHD is not fully understood, and several studies have been conducted to reveal different mechanisms and pathways that are involved in the development of various presentations of GVHD [78,90–94]. GVHD has two forms; acute and chronic. Acute GVHD pathogenesis entails an immune-mediated inflammatory state that usually affects skin, liver and gut, affecting upper gut (nausea, vomiting, loss of appetite) and/or lower gut (ranges from watery diarrhea to bloody diarrhea and ileus). Along with immune mediated inflammation, chronic GVHD pathogenesis involves promoting fibrosis and can affect a variety of organs, most commonly skin, liver, gut, lung, and mucous membranes.

Acute GVHD is classified using the Glucksberg et al. system that was developed in 1974 is still being used. In this classification, involved organs are staged from 1 to 4, then grading of the overall organ involvement is determined (Tables 3 and 4) [95].

Table 3. Acute GVHD staging system.

Stage	Skin based on maculopapular rash	Liver based on bilirubin	Gastrointestinal based on quantity of diarrhoea
1	<25% of surface	34–50 µmol/L	500–1000 mL
2	25–50% of surface	51–102 µmol/L	1001–1500 mL
3	Generalised erythroderma	103–255 µmol/L	>1500 mL
4	Generalised erythroderma with bullae and desquamation	>255 µmol/L	Severe abdominal pain ± ileus

Table 4. Acute GVHD grading system.

Grade	
I	Skin stage 1–2
II	Skin stage 1–3, GI, and/or liver Mild decrease in performance
III	Skin stage 2–3, GI, and/or liver 2–3 Marked decrease in clinical performance
IV	Skin stage 2–4, GI, and/or liver 2–4 Extreme decrease in clinical performance

Diagnostic criteria and clinical features of chronic GVHD were subject to collective efforts to be standardized across HSCT community and to include the atypical features of GVHD to improve research outcomes through several National Institutes of Health (NIH) Consensus Projects. The NIH consensus criteria entails a comprehensive scoring system for each of the main organs involved in chronic GVHD (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, and the genital tract). A 4-point scale (0–3) is applied to each organ or site with 0 representing no involvement and 3 entails severe manifestations. Performance status is included on a 0 to 3 scale. Then an overall severity system (No GVHD, mild, moderate or severe) is applied [96–99].

As acute and chronic GVHD have different pathogenic pathways, treatment strategies differ. Several treatment modalities for GVHD have been used or are currently under investigation with different rates of success. Examples include corticosteroids that reduce GVHD through a variety of mechanisms; the main one is by blocking NF-κB pathways in APCs and T cells, which triggers apoptosis; calcineurin inhibitors are used to reduce T lymphocyte proliferation; mycophenolate mofetil blocks purine synthesis in T and B lymphocytes; anti-thymocyte globulin (ATG) induces depletion of T cells and APCs; alemtuzumab induces lymphocyte depletion; extracorporeal photopheresis induces apoptosis of white blood cells; an increase in anti-inflammatory cytokines and immunosuppressive T regulatory cells; ruxolitinib, a selective (JAK1 and JAK2) inhibitor, reduces GVHD by inhibiting the production of proinflammatory cytokines, thus reducing T-cell proliferation, and mesenchymal stromal cells which are used mainly in chronic GVHD to suppress alloreactive T-cell cytotoxicity, and promote tissue healing [100] Each of these strategies carries significant risk of direct and indirect toxicity, for example the immunosuppressive consequences of many agents leading to overwhelming infection, neuropathic pain from calcineurin inhibitors or thrombocytopenia from ruxolitinib.

Mount Sinai Acute GVHD International Consortium (MAGIC) explores potential predictive biomarkers for acute GVHD. A validated algorithm was generated to predict probability for NRM, and resistance to treatment [101,102] as well as long term outcomes in steroid-resistant GVHD [103].

Mesenchymal stromal cells (MSCs) support hematopoietic stem cells and have been utilized as a safe option to treat steroid resistant GVHD. Efficacy of this strategy seems to depend on patient-specific biomarkers and immune profile. Satisfactory responses to MSC treatment have been reported in pediatric patients with difficult-to-treat GVHD. Children with high-risk GVHD, as defined by MAGIC criteria, who received MSCs had a significantly higher overall survival compared to those who were treated with the best available therapy [104–106].

Because a well-established, low risk, effective treatment for severe GVHD is lacking, efforts have been concentrating on preventive strategies [107]. Various strategies have been proposed, e.g. choice of best matched donors (Human leukocyte antigen; HLA and cytomegalovirus; CMV status and sex matched or male donors especially to male recipients) [86,87], stem cell source that has lowest rate of GVHD provocation, e.g. cord blood stem cell units which have the least number of T cells compared to other stem cell sources, in vitro donor T cell depletion, in vivo donor T cell depletion via administration of ATG or alemtuzumab prior to HSC infusion, prescribing combinations of calcineurin inhibitors, steroids, mycophenolate, methotrexate and cyclophosphamide around and after HSC infusion to suppress the alloreactive immune cells implicated in development of GVHD [78,108–111].

One of the main approaches to reduce risk of GVHD is the utilization of non-myeloablative and reduced intensity conditioning regimens whenever appropriate to alleviate tissue injury. This strategy has shown good effect in reduction of severe forms of GVHD [3,112,113]. Non-chemotherapy condition regimens for Sickle cell disease HSCT are currently being studied to further eliminate the risk of GVHD and other long term complications of chemotherapy [114,115]. Although GVHD is a harmful, potentially lethal complication post HSCT, it is associated with beneficial graft-versus-leukemia (GVL) effect which lowers the risk of leukemia recurrence. Therefore, several studies have proposed ways to augment GVL effect while reducing GVHD. These approaches include graft alpha beta+/CD19+ cells depletion and post-HSCT cyclophosphamide administration [116].

Several other alternative curative approaches to replace chemotherapy and/or avoid allogeneic HSCT are being increasingly utilized. Immunotherapy like blinatumomab substitutes some of the chemotherapy courses in acute lymphoblastic leukemia with promising effects in difficult-to-treat and relapsed leukemia [117–119]. Chimeric antigen receptor T cell (CAR T cell) and other cellular therapies are fast growing field that have a huge potential to replace substantial number of allogeneic HSCT procedures and chemotherapies with no risk of GVHD as those cells are patient's own cells [120,121]. Gene therapy, including gene insertion and editing, is another

promising strategy and active area of research to substitute a considerable number of allogeneic HSCT procedures especially for patients with hemoglobinopathies [122–124]. Precision medicine is rapidly expanding, and several working groups are establishing pathways for targeted therapy against pathogenic mutations with promising results in various diseases that were historically being treated with conventional chemotherapy and allogeneic HSCT. For instance, Philadelphia chromosome positive acute lymphoblastic leukemia is a high risk-disease which in the past was considered to require allogeneic HSCT in most cases to achieve cure. Currently with tyrosine kinase inhibitors which targets the pathogenic translocation, majority of patients are being treated without the need for allogeneic HSCT [125,126].

6. Conclusion

Reducing the side effects of cancer treatments, whether given for cancers (including leukemias and lymphomas and brain tumors) or as part of hematopoietic stem cell transplantation, is a complex field which includes basic and translational science, psychological and social research, and many layers of applied clinical research developing interventions and advancing health care delivery systems to implement them. Reducing the side effects is being approached by changing the anticancer therapies, and use of treatments to ameliorate the adverse effects which still occur, and optimizing the use of these interventions to minimize the 'secondary' side effects.

In the area of infections within the immunocompromised host advances have been made by improving approaches to prevention and management. The refinement of prophylactic interventions including antimicrobials and immune therapies has begun, but there remain open questions about exactly which patients benefit the most from these strategies and the balance between short term efficacy and longer term adverse consequences in antimicrobial resistance. There remains regional variation in the societal and behavioral interventions which are instituted to minimize infection, with many having sparse evidence to support them. The implementation of programmes aimed at identifying lower risk groups who can be managed with shorter, less intensive treatment regimes, has improved the quality of care delivered to many but has the opportunity to develop further.

The approaches in reducing side effects of conditioning regimens for HSCT is a good example of managing the third-level effects of chemotherapies, where the complications arise from unhelpful immune responses aggravated by the tissue injury of the preparatory treatments. Manipulating these using agents which have anti-cancer properties is being investigated to minimize the already considerable morbidity of allogeneic transplantation. Using advanced cellular therapies can be harnessed to ameliorate the side effects, and potentially reduce their occurrence too.

Technological developments outside the sphere of pharmacology and cellular receptor manipulation can also provide hope for recalcitrant side effects. Mucositis can be prevented in some patients and made less problematic in many others with near-infra-red light energy. Appreciating how this is working, including its interactions with the oral microbiome, may allow us to develop better strategies to deliver the photon treatment. Engineers will then be needed to develop the devices which can do this consistently and in a child-friendly manner.

The re-analysis of existing clinical study data, using novel data synthesis methods, could extend the approaches we can use to address side effects (and potentially anti cancer therapies directly). In the setting of preventing and managing chemotherapy-induced nausea and vomiting this includes understanding comparative and differential effectiveness more fully, and using the more extensive trial data in adult patients to supplement the work of pediatricians.

7. Expert opinion

The four areas presented in this paper show how wide and interesting the field of supportive care research, of which side effect management is part, is within pediatric haematology/oncology. The research is driven from patient and family priorities; the priority setting partnerships which have been undertaken all emphasize how important these elements of care are to families and yet how little research has answered their major questions.

Some of the problems outlined are ready for proven interventions to be rolled out in practice. How best to do this, in the resource-constrained environment of healthcare, will be a combination of individual champions and high quality implementation science. We have described such interventions in photobiomodulation and risk-stratified management of febrile neutropenia, but this is also true for some areas our paper has not covered, such as delivering low-level psychoeducational support for families going through cancer treatment and the activity-based prevention and management of fatigue. In many cases, these changes, though relatively simple in terms of treatments, can be considered complex interventions due to the requisite interdisciplinary behaviors and skills interacting in different contexts. Understanding more about which are the key levers to encourage change will improve out delivery.

Other problems require us to develop new technologies; these may be able to detect complications at earlier time points to introduce treatments more quickly. They may also do the reverse; detect when a complication is not happening, so that preventative measures with their own burdens can be discontinued. Within the field of infection, examples under exploration include screening blood with multiplex PCR for earlier detection, and the use of biomarker combinations to rule out significant bacterial infection. Technologies may produce better ways of delivering current treatments, perhaps with prolonged intradermal delivery of agents to treat skin GVHD, or photobiomodulation beyond the pharyngeal and into the other areas of gut which can be affected. Adaptation of existing technologies, such as the genome testing panels for targetable anti-cancer mutations, could look at the pharmacogenetic basis for varied side effect profiles and modify our management strategies. This will only happen if we can invest in combining good quality clinical annotation of the side effects and complications of

therapy alongside the other clinical elements collected in current biobanking projects.

Advancement will only happen with us making best use of new methods of applied health research and clinical trial methodologies. Cancers in children are individually rare, and the treatments varied, leading to a smaller, heterogenous pool of patients who can test varied interventions. Statistical and mathematical advancements, updating how we can see the truth of the world through our clinical observations, are essential as we use more individualized approaches but desire as much assurance as possible that our actions bring more good than harm. These include the use of nuanced approaches to evidence synthesis, but also multi-arm, multi-stage Bayesian trial designs within supportive care, and the use of phase III treatment trials as the backbones into wish to bolt key supportive care questions.

Some of the greatest challenges may be those we're not yet fully aware of, as new therapies move from their use in adult oncological practice into children. The short and longer term toxicities of these agents could potentially differ in children of different ages, with the different physical and physiological milieu of developmental stages. Our communal history of long and close follow-up of patients into adulthood, with all their subsequent health conditions, will need to continue as we evolve our therapeutic approaches.

Our hope, in treating children with cancers and those who need HSCT, is that we will be able to achieve cure with an unaffected quality of life for all patients and their families. The rapidly expanding use of immunotherapy, targeted therapy, autologous cell therapy, and monoclonal antibody-based conditioning regimens would, in 5–10 years from now, enable a considerable decrease in the number of children in need of allogeneic HSCT as well as reduce HSCT-related complications including GVHD. This will greatly enhance the side effect profiles for children with different oncological and hematological diagnoses. This will need us to continue our collaborative, multi-professional, multi-disciplinary and eclectic approach.

We acknowledge that in this Expert Review we have cherry-picked only four areas of supportive care to address. These have been chosen to be illustrative of different approaches, opportunities and locations within the research pipeline. It is in no way to imply that other areas, such as nutritional intervention, psychosocial support, otoprotection or delivery of care closer to home are unimportant. We have also focussed on work in high-income countries. An estimated 80% of childhood cancers are in in low- and middle-income countries, and the overall survival rates sit at around 20%, in contrast to the 80% survival in high-income countries [127]. Again, our intent is not to downplay the challenges in those countries, but discuss the areas in which our primary expertise sits. To address all of the challenges, those we have discussed here, and those we have not, it will need us in academia to continue to work with patients and clinical professionals to understand how we might know things, the things we need to know about, and how to make them work in the real world. And we are on the way.

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