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Editor's Message

The long wait: A discussion of emergency department wait time and its impact on clinical outcomes

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A trip to any emergency department (ED) across the country is usually associated with long wait times that can sometimes stretch over a full day or a night. Recently, wait times have been increasing to a distressing rate and emergency medicine teams having been sounding the alarms. Despite the growing population and the increased demand on emergency departments due to the extreme shortage of family physicians, emergency medicine remains under serviced[1]. While doctors, nurses and the entire interprofessional health team continue to deliver their best efforts to care for patients in timely matter, the lack of resources and space hurdle their efforts.

The impact of ED wait times begins with a concerning percentage of patients leaving without being seen by a healthcare team member. A cohort study from the major emergency departments in Ontario showed that 4.2% of patient visiting EDs across Ontario between 2003-2007 left without being seen[2]. The same study showed that longer wait times were associated with higher risk of adverse events and/or being admitted to the hospital. Depending on the acuity of the presentation, wait times can vary significantly with higher acuity patients typically seen sooner. However, resources do not exist to monitor patients' conditions during extended wait times, and changes in acuity have become an increasing issue. Finally, the location of emergency departments contributes to different wait times. A retrospective study of wait times in rural and urban EDs in Ontario revealed that rural emergency departments tend to have shorter wait times[3]. However, it is important to highlight that large urban centers regularly receive higher acuity transfers from smaller rural EDs which contribute to increasing wait times.

Several strategies have been proposed to reduce wait times in EDs. These strategies have been mostly focused on increasing the capacity, decreasing wait time for results after intake and decreasing intake. Several trials across the country showed some degrees of success of these strategies including introduction of satellite health clinics for patients returning to the ED for follow up in British Columbia[4]. A similar study conducted in Saskatchewan showed a positive impact of the reduction of physician reassessment time on wait times in the ED[5]. Finally, a study by Wong et al. showed that many patients prefer to access after-hours family medicine practices over EDs, therefore reducing the demand of patients with lower acuity presentation on EDs[6].

Despite these proposed solutions, wait times continue to increase in EDs across the country. The response to this demand continues to fall short and a system-wide solution is increasingly needed to enhance patient outcome and prevent physician burnout.

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Case Report

A 10-month-old infant with respiratory distress and hypoxemia

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Abstract

A 10-month-old infant with Prader-Willi Syndrome presented with a 7 month history of increased work of breathing, wheeze, inspiratory crepitations, and mild hypoxemia. Subsequent investigations including chest CT suggested the diagnosis to be neuroendocrine cell hyperplasia of infancy (NEHI). NEHI is a rare cause of children's interstitial lung disease. Childhood interstitial lung disease should be considered in an infant with persistent tachypnea, crepitations, and hypoxemia.

Case Presentation

A 10-month-old girl with Prader-Willi Syndrome presented to hospital with respiratory distress, tachypnea, and a history of three previous emergency department visits and two admissions over seven months with similar symptoms. During her previous visits, she was thought to have acute viral bronchiolitis with increased work of breathing, tracheal and subcostal indrawing, wheeze, inspiratory crepitations, and mild hypoxemia (SpO2 88%). Between visits her mother reported increased work of breathing with intermittent grunting and tracheal and subcostal indrawing.

Other than the diagnosis of Prader-Willi Syndrome made during the neonatal period her previous history had been unremarkable. She had been feeding normally and gaining weight.

On admission she required oxygen by nasal prongs at 0.5 L/min to keep her SpO2 greater than 90%. Her weight was 7.45 kg (10th-25th percentile), heart rate 156 per minute, respiratory rate 48 per minute, temperature 37.9oC. She demonstrated increased work of breathing with tracheal and subcostal indrawing, no cough, and on auscultation, symmetrical breath sounds, no wheeze, but bilateral inspiratory crepitations. She had no finger clubbing and the remainder of the exam was consistent with her Prader-Willi Syndrome.

The nasopharyngeal aspirate was negative for respiratory viruses (as it was on four previous occasions). Capillary gas pH 7.34, pCO2 57.1, base excess 3.5, bicarb 30. Cardiology assessment and echocardiogram were normal. Chest radiograph showed mild increase in the size of the retrosternal airspace with flattening of the diaphragms. There was evidence of mild atelectasis in the region of the right middle lobe. A previous barium/formula feeding study was normal. Newborn screening was negative for Cystic Fibrosis. The clinical findings and investigations were not consistent with viral bronchiolitis, asthma, cystic fibrosis, pulmonary aspiration, or pneumonia. Because of the persisting clinical picture and radiographic evidence of air trapping, a chest computed tomogram (chest CT) was performed.

Chest CT revealed diffuse ground glass opacities of the right middle lobe and minimal subsegmental atelectasis (see figure). The clinical picture and chest CT findings were felt to be most consistent with neuroendocrine cell hyperplasia of infancy (NEHI) in consultation with Pediatric Respirology.

Discussion

NEHI is a rare cause of children's interstitial lung disease (cHILD) previously known as persistent tachypnea of infancy. It manifests in otherwise well infants with tachypnea, retractions, crepitations, hypoxemia, and rarely cough. The pathogenesis is thought to be linked to pulmonary neuroendocrine cell prominence, although the exact process is unknown. When performed, lung biopsy demonstrates staining for neuropeptide bombesin in distal airway cells. High resolution CT (HRCT) findings of ground glass opacities in the right middle lobe and lingula, in some patients,

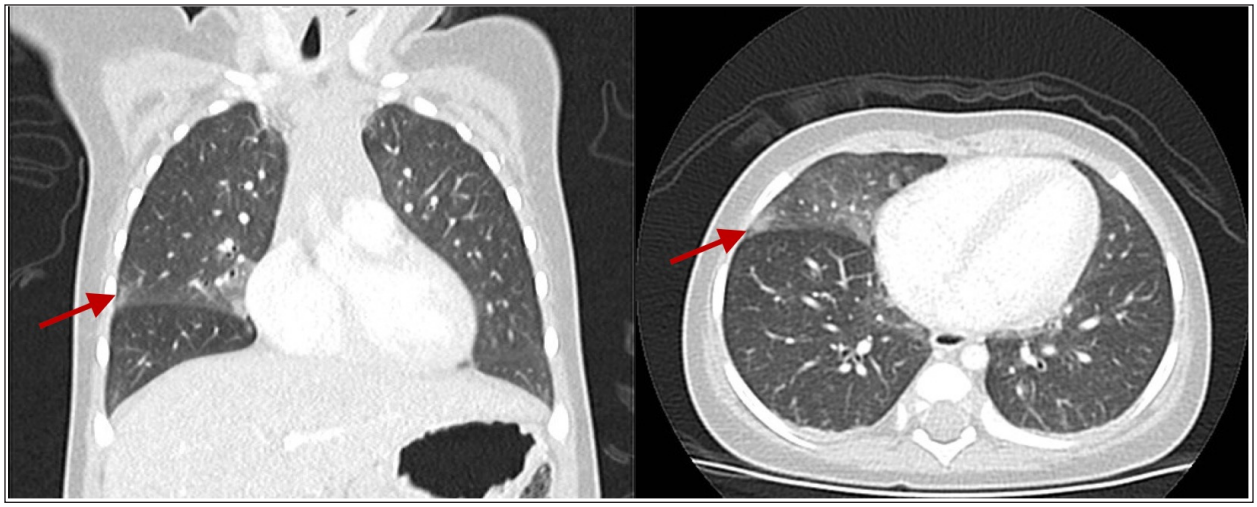

Figure 1.

have been suggested to be diagnostic and avoiding the need for a lung biopsy[1,2].

The treatment of NEHI is supportive; providing extra calories to optimize nutritional status, if failing to thrive, and oxygen supplementation. Caution will be required in our patient because of the weight increase seen around 18-36 months in Prader-Willi Syndrome and the risk of obstructive sleep apnea. Some patients require oxygen 24 hours per day while others only at night and with illnesses. Most patients gradually reduce and cease their need for supplemental oxygen although in follow-up some may develop asthma[3]. Seasonal influenza shots and respiratory syncytial virus prophylaxis are recommended as for all children with significant respiratory problems.

Our patient was initially thought to have viral bronchiolitis but the prolonged course (7 months) made this extremely unlikely. Cardiac assessment was normal and there was no clinical nor imaging evidence of swallowing dysfunction or gastroesophageal reflux.

The etiology of NEHI is unknown but genetic mechanisms may play a role as familial patterns are seen in some cases associated with hypothyroidism. Our patient had normal thyroid function. We are not aware of any association between Prader-Willi Syndrome and NEHI.

In preparation for growth hormone therapy for Prader-Willi Syndrome, a pediatric polysomnogram was performed which showed, in room air, mild hypoxemia and a central apnea-hypoxia index (CAHI) of 16.3 per hour; with supplemental oxygen the CAHI fell to 4 per hour. The fall in this index with oxygen is the usual response in a patient with PWS.

Our patient was discharged on supplemental oxygen for both the central apneas of Prader-Willi Syndrome and the hypoxemia of NEHI and follow-up arranged.

Clinical Pearls

1. Childhood interstitial lung disease should be considered in an infant with persistent tachypnea, crepitations, and hypoxemia.
2. While lung biopsy is the gold standard for NEHI, the classic clinical picture and characteristic CT findings are felt to be diagnostic.

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Education

A medical student's guide to the slit lamp examination

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Abstract

The slit lamp is an essential tool for the diagnosis of common eye pathology. Despite many eye conditions presenting initially to primary care, medical students do not typically receive formal training with the slit lamp in standard medical education curriculum. This guide provides a consistent, systematic framework that may be used by students and clinicians when approaching a slit lamp examination. Additionally, suggestions intended to optimize examination outcomes are described. It is our hope that this guide serves to enhance medical student comfort and proficiency with eye examinations, be it in an ophthalmology clinic, primary care, or emergency department setting.

Introduction

Far too often, slit lamp examination (SLE) is thought to be used exclusively by eyecare specialists. However, the slit lamp is also frequently found in many emergency department and primary care settings[1,2]. Previous studies have found that medical school graduates do not receive sufficient exposure to SLE and lack confidence in their eye examinations[3]. Given the high proportion of eye complaints that present first to primary care offices, it is important for all physicians in training to have a standard approach to operating the slit lamp. This guide outlines a systematic, standard approach to SLE which may be used in eye examinations in any required care setting. It is our hope that this will increase proficiency and confidence in diagnosing and managing common ocular conditions.

First formally introduced in 1911[4], the slit lamp has undergone many changes to evolve into the tool used today. The slit lamp is a microscope with a bright illuminating light. It is used to closely examine different parts of the eye. The slit lamp operates by focusing a beam of light, which may be adjusted in width, height, and angle by the slit lamp operator. This beam of light allows the examiner to visualize in detail the 3-dimensional structures of the eye to identify potential pathology. This, in combination with clinical history, is key to the diagnosis of many ocular conditions. In this guide, we outline a stepwise approach to be used by examiners when operating the slit lamp to investigate eye pathology.

Anatomy of the Eye

This section provides a brief overview and description of the anatomy of the eye. Knowledge of basic eye anatomy is key to identifying landmarks and describing findings during SLE. A comprehensive review of anatomy, including illustrations, may be found in the referenced text[5].

Orbit – Bony structure that contains the globe. Made up of seven bones: sphenoid bone, ethmoid bone, lacrimal bone, frontal bone, palatine bone, maxillary bone, zygomatic bone.

Palpebral Fissure – The ellipsoid space between the eyelids (palpebra).

Lateral Canthus – Where the upper and lower eyelids meet temporally.

Medial Canthus – Where the upper and lower eyelids meet nasally.

- *Caruncle* – Pink, globular structure at the medial canthus of the eye.
- *Superior punctum* – A superior opening at the medial canthus through which tears drain into the lacrimal ducts.
- *Inferior punctum* – An inferior opening at the medial canthus through which tears drain into the lacrimal ducts.

Conjunctiva – A clear mucous membrane that covers the sclera (bulbar conjunctiva) and the inner surface of the eyelids (palpebral conjunctiva).

Sclera – The white, collagenous structure of the eye that serves as protective covering. Extends from the border of the cornea (limbus) to the optic nerve.

Cornea – Clear, avascular tissue that transmits and refracts light.

Anterior Chamber – The anterior portion of the eye between the cornea and iris.

The Iridocorneal Angle – Where the iris meets the cornea. The iridocorneal angle contains trabecular meshwork and Schlemm's canal through which aqueous humour drains from the eye. Various angle pathologies can lead to diverse types of glaucoma. For example, obstruction of the angle by the iris results in a rapid increase in intraocular pressure in acute angle closure glaucoma.

Lens – Biconvex, avascular structure located behind the pupil and suspended by the zonule. Refracts light onto the retina.

Uvea – The middle vascular layer of the eye, including the iris, ciliary body and choroid.

- *Iris* – Forms the anterior portion of the uvea. Contains a central aperture (Pupil) which dilates and constricts to regulate the amount of light that enters the eye.
- *Pupil* – Central aperture of the iris.
- *Ciliary Body* – A ring-like structure located behind the iris. Forms the middle portion of the uvea. Attached by zonule to the lens. Contraction and relaxation of ciliary muscles allows for lens accommodation.
- *Choroid* – The highly vascular portion of the uvea that extends from the ciliary body posteriorly to the optic nerve.

Vitreous – A clear, gelatinous structure that fills the posterior segment of the eye.

Retina – A thin, multilayered sheet of neural tissue that lines the inner portion of the posterior eye.

Macula – The central portion of the retina that has a high proportion of cone photoreceptors.

- *Fovea* – A depression in the central macula that contains a high density of cone photoreceptors. Responsible for "high acuity" vision.

Optic Nerve – Contains over 1 million axons, transmits visual information from the retina to visual pathways in the brain. Also carries the central retinal artery and vein.

Slit Lamp Examination

A systematic approach is an important aspect of a thorough SLE. Keeping this approach consistent can prevent the examiner from missing key findings critical to a correct diagnosis. The slip lamp apparatus with labelled components is illustrated in Figure 1. A systematic, stepwise approach to the SLE is described as follows:

1. Prior to SLE, begin by examining the external structures of the eye. Even in patients with monocular complaints, both eyes are always examined. Look for asymmetry, skin abnormalities, obvious orbital deformities or pathology surrounding the eye.

2. Position yourself such that the slit lamp table is at a comfortable position and height for you and the patient and adjust the oculars to your pupillary distance. Position the patient such that their chin and forehead rest in the correct position on the slit lamp apparatus, and so that their lateral canthi are in line with the landmark markings on the slit lamp. Turn on the light source and unlock the slit lamp.

3. You are now ready to begin the SLE. Conventional examination begins with the patient's right eye, starting with the front part of the eye and moving toward the back. Starting from the medial canthus, sweep the light beam across the superior lid margin. Repeat this for the lower lid margin, starting from the lateral canthus.

4. Examine the palpebral and bulbar conjunctiva by gently lifting the upper and lower lids, sequentially and asking the patient to look in four directions of the gaze. Optional maneuver: use a Q-tip to evert the patient's upper lid to better visualize the superior palpebral conjunctiva. Eyelid eversion is useful in cases with conjunctivitis and in cases with suspicion of a foreign body.

5. Examine the cornea. The cornea should be transparent, and of regular surface. Look for any opacities, surface irregularities, or localized thickness changes. The cornea is better examined with a higher magnification. If indicated, corneal epithelial defects can be visualized using fluorescein dye and using the blue light filter. Visualize the layers of the cornea by narrowing and angling the light beam obliquely.

6. Visualize the anterior chamber by shortening and widening the light beam such that it takes the shape of a square. Toggle between the cornea and iris to focus on the anterior chamber. The anterior chamber is normally optically empty, meaning that nothing should be seen between the cornea and the iris/pupil/lens complex. Look for potential cells and

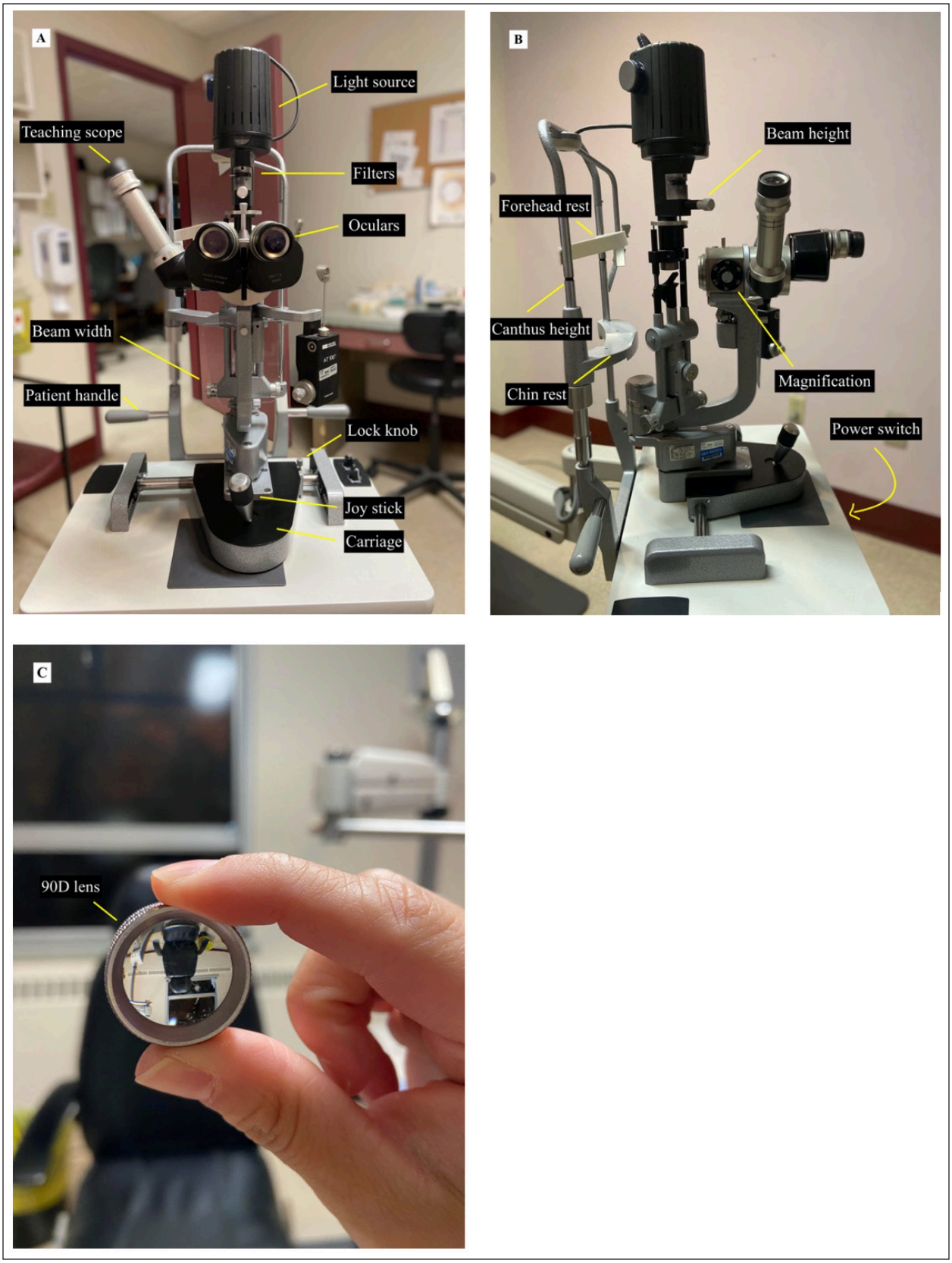

Figure 1. Slit lamp apparatus from examiner's view (A) and lateral view (B) with the 90D lens which is used to examine retina (C).

flare, which may indicate infection, inflammation or hyphema. Cells will appear as floating dust specs, whereas flare appears as a haze. Cells and flare are better appreciated in a dark room and with a high magnification.

7. Continuing posteriorly, visualize the iris, looking for any masses or transillumination defects. To assess for iris transillumination defects, the patient's pupil should be undilated. Narrow the beam of the light source and direct an axial light beam through the undilated pupil. Transillumination is seen as red light reflected back from the retina through defects in the iris. The pattern of transillumination can reveal defects/breaks in the iris and characteristic patterns of certain conditions, such as pigmentary glaucoma, herpetic uveitis and albinism[6].

8. Visualize the lens for any opacities which would be indicative of cataract formation. The lens should be examined using an axial light beam to assess the red reflex, then subsequently with a tangential light beam to visualize the layers of the lens from anterior to posterior.

9. To visualize the vitreous, move the light slightly obliquely and look beyond the pupil. Strands of vitreous should be visible. It may be difficult to visualize the vitreous if the pupil is not dilated pharmacologically.

10. The retina is best visualized when the patient's pupil is pharmacologically dilated. However, if dilation is not possible, the optic nerve head and macula can be examined through a non-dilated pupil in a cooperative patient. A 78 or 90 Diopters lens is required to visualize the retina for any abnormalities. Ask the patient to look with their fellow eye at your ear. Align the light beam coaxially through the pupil and visualize the red reflex. Hold the lens steady between your thumb and index finger about 1-2 cm from the patient's eye. Slowly pull back on the slit lamp apparatus until the retina comes into focus. Visualize the macula and optic disc. You may ask the patient to look in various directions to visualize the retina in its entirety.

11. Complete steps 1-10 for the left eye. Document all findings. Templates for documentation are included as supplemental material. Documentation should describe the location and characteristics of each finding. Locations are typically described in terms of clock hour.

Contraindications

There are no absolute contraindications to slit lamp examination. However, there are relative contraindications that are worthy of inclusion. In the event of chemical burn/exposure to a patient's eye, copious irrigation of the eye is recommended prior to examination. Some patients may have physical limitations that restrict their ability to undergo standard SLE[7]. In such situations, portable slit lamps may be used. Patients may ask whether exposure to light from the slit lamp is damaging to the eye. Examiners should reassure patients that the light exposure from the slit lamp may cause some discomfort but is not harmful.

Tips and Tricks

1. Ergonomics is key – Make sure you are positioned comfortably, as well as the patient. A common pitfall is to forget about your own comfort/positioning. This can take a toll on practitioners after repeated examinations[8].

2. Dim the lights – Decreasing ambient light in the room can allow structures to be better visualized during the examination.

3. Fight the fog – When visualizing the retina, the handheld lens can sometimes become clouded when a patient exhales, particularly if the patient is wearing a mask. Taping the patient's mask to their cheek for the duration of the examination can help with this. Stabilizing the hand holding the lens by resting the 4th or 5th finger against the patient's forehead can also help keep the hand steady.

4. Leverage the light – The width and height of the light beam may be adjusted by the user by manipulating the beam width and height knobs labelled in Figure 1. The light source may also be moved up or down by rotating the knob on the joystick.

5. Don't forget to dial in – Glasses-wearers may find it helpful to remove their glasses and dial in their prescription in the oculars.

6. Don't forget the patient's contact lenses – Remember to ask the patient to remove any contact lenses prior to using fluorescein dye.

7. Mentorship can help – Having someone demonstrate the exam and assist your technique can assist in overcoming any difficulties with the examination technique.

8. Be systematic – Always start with the same eye and visualize structures sequentially in a consistent order. Doing so can prevent missing key findings.

9. Practice makes perfect – Many learners have

difficulty with some of the SLE techniques at first, particularly with using lenses to visualize the retina. Practice and repetition with various settings are key.

Conclusions

In this guide we outline a basic, systematic approach to operating the slit lamp to assist with diagnosis of eye pathology. With slit lamps more commonly found in primary care and emergency settings, it is our hope that this guide provides framework to assist students and clinicians with their assessment and approach to basic findings suggestive of ocular pathology.

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Supplement 1

nova scotia health authority

Eye Care Centre

Initial Visit

Date

Chief Complaint	Clinician Note

Systemic Medications	Ocular Medications

Allergies

Past Ocular History

☐ Amblyopia	☐ Glaucoma (type)	☐ Laser Treatment (type)
☐ Strabismus	☐ Trauma	☐ Surgery (type)
☐ ARMD	☐ Uveitis	☐ Other
☐ Diabetic retinopathy	☐ CTLs (type/duration)	

Past Medical & Surgical History

☐ Angina / IHD / MI	☐ Diabetes	☐ Lupus	_____
☐ Arrhythmia	☐ Thyroid disease	☐ Rheumatoid arthritis	_____
☐ CHF	☐ Migraine	☐ Cancer	_____
☐ Hypercholesterolemia	☐ Seizure	☐ HIV / AIDS	_____
☐ Hypertension	☐ Stroke / TIA	☐ Hepatitis	_____
☐ Asthma	☐ Inflammatory bowel disease		_____
☐ COPD			_____

Family History		Social History
☐ Glaucoma	☐ Macular degeneration	☐ Smoking (amount)
☐ Retinal detachment	☐ Blindness	☐ EtOH (amount)
		Occupation _____

Assessment Forms

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Supplement 2

nova scotia health authority

Eye Care Centre

Initial Visit

Examination

CC SC	DV$_A$	PH	NV$_A$	W
OD				
OS				

PUPILS	Light	Dark	Acc	RAPD (lu)	T$_P$/T$_A$	Colour	VISUAL FIELDS	MOTILITY
OD							OS OD	OD OS
OS								

CT 1/3 m 6 m

HERTEL

GONIO OD OS

OTHER

OD OS

AC

I/P / Lens

OD **OS**

C/D

☐ Dilated @ _____
With _____

C/D

Vitreous

Impression	Plan	Investigations to Book
	Consults F / U _____	☐ Photos ☐ OCT/HRT ☐ IVF/ICG ☐ VF (10-2/24-2/GVF) ☐ Topography ☐ PAM ☐ Orthoptics **RN/Tech** _____ **Res** _____ **Staff** _____ **Dictation #** _____

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Original Research

The Child and Family Traumatic Stress Intervention in Canadian child and youth advocacy centres

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Abstract

Background: The Child and Family Traumatic Stress Intervention (CFTSI) is an evidence-based early intervention shown to reduce post-traumatic stress in children and adolescents. This intervention has not been explored in the context of the Canadian healthcare landscape, and more specifically at Child and Youth Advocacy Centres (CYACs); multi-disciplinary service hubs who serve those exposed to trauma.
Objective: Examine the feasibility and usefulness of the CFTSI in the context of Canadian CYACs.
Methods: A mixed-methods design was utilized, consisting of a validated, nationally distributed online survey which served as an environmental scan, and key informant interviews, which were thematically analyzed.
Results: 15 of 29 invited centres participated. Prior to this study, six of 15 respondents had been aware of the CFTSI. Furthermore, two participants reported current use of the CFTSI. Of the 13 centres not using it, 10 expressed that the CFTSI would be an acceptable and relevant intervention at their centre, and there was significant interest in possible future implementation. Interviews with experienced clinicians revealed benefits and challenges of the CFTSI's format, and the influence of family structure, culture and trauma history on outcomes. Finally, some considerations specific to Canadian centres were uncovered and direction for future research suggested.
Conclusion: Our findings collectively underscore the potential of the CFTSI to bolster mental health services, which are a priority area requiring improvement at Canadian CYACs. Additionally, this study highlights benefits and challenges relevant to Canadian practice and wide-spread implementation of the CFTSI in this country.

Background

Childhood trauma is a pervasive, yet relatively unspoken issue which can have impacts on the mental, physical health and overall wellbeing of exposed children and adolescents. Child and Youth Advocacy Centres (CYACs) serve this demographic and reduce system-based trauma by integrating the work of child protection, criminal justice and mental health services[1]. The CYAC structure has been shown to generally improve accessibility, efficiency, productivity and coordination of care, compared to traditional community-based approaches[2]. However, a review by the Department of Justice described mental health services as a shortcoming in these centres, with many Canadian CYACs using a patchwork of internal and external services in attempt to meet patients' needs[3]. Timely and effective mental health services are particularly important for children and youth exposed to trauma, given the detrimental impacts this can have on development[4].

According to the General Social Survey on Victimization, 30% of Canadians experience some form of physical or sexual abuse by the age of 15 years[5]. A recent review of referrals to mental health partner agencies of Canadian CYACs found that 53.4% of children had exposure to multiple forms of maltreatment, and most had greater than five presenting concerns or symptoms[6]. Many victims of trauma immediately experience some form of psychological stress[7], and between 10-18% continue to experience chronic symptoms[8,9]. Post-traumatic stress disorder (PTSD) can develop in traumatized youth and adults alike, with a Canadian lifetime prevalence of 9.2%[10]. Early intervention can address initial symptoms and bridge the gap between acute treatment and longer-term interventions, thereby preventing chronic trajectories of mental health issues[11].

The Child and Family Traumatic Stress Intervention (CFTSI) is an evidence-based early intervention that was developed over a decade ago at the Yale Child Study Center. It can be used with children aged seven to 18 years from diverse ethnic backgrounds, with single or multiple trauma exposures. It is initiated within 45 days of a traumatic event or disclosure of trauma. The goals of the CFTSI are to improve identification of children impacted by trauma, reduce downstream psychological impacts, address stressors and practical needs, assess the need for longer-term treatment, and strengthen familial communication and coping skills[12].

Delivered by a trained mental health practitioner, the CFTSI consists of five to eight sessions de-

livered over four to six weeks, and includes individual sessions with the child and caregiver, as well as joint sessions. Stress symptoms are assessed in both parties using validated objective materials. Goals around communication and coping skills are established and psychoeducation about trauma is provided. Progress in these areas, as well as distress, are reassessed throughout, and additional treatment and/or case management needs are identified for follow-up[13]. This approach is regarded as beneficial because it focuses on bolstering protective factors in the recovery process, such as internal reaction management and external support[14,15,16].

The CFTSI can significantly lower post-traumatic symptom scores over time, and reduces full and partial PTSD diagnoses at three-month follow-up[17]. Additionally, this intervention increases concordance between caregiver and child-reported traumatic stress symptoms, suggesting improved communication between parties[18]. Finally, use of the CFTSI has been shown to result in meaningful improvements in symptoms of caregivers with clinical levels of post-traumatic stress. This is significant, as parental post-traumatic stress is associated with negative outcomes for children, and thus improvements in the mental health of caregivers may have a compounding, critical impact on the health of their children[19].

As an intervention designed to improve outcomes in the immediate aftermath of a traumatic event or disclosure of such, the CFTSI is directly relevant and applicable to the work of CYACs. However, the current literature pertaining to this intervention is limited to the United States, and the CFTSI has only been adopted by a small number of CYACs in Canada. The fact that CYACs are relatively novel establishments in the Canadian healthcare framework[2] provides a unique opportunity for proactive research and implementation of effective mental healthcare, such as the CFTSI, at these centres. This study aims to examine the feasibility and usefulness of the CFTSI in the context of the Canadian healthcare landscape, with the goal of shaping and improving practice at CYACs in Canada.

Methods

Approval was obtained from the IWK Health Centre Research Ethics Board in Halifax, Nova Scotia, Canada. Between June 2020 and January 2021, a two-part mixed-methods design was utilized, consisting of a nationally distributed online survey and key informant interviews.

A survey was developed to ascertain awareness and current use of the CFTSI at Canadian CYACs. Prior to distribution of the survey, content and response process validity were assessed by four experts in the fields of therapeutic practice and trauma-informed care. This assessment of validity was used to establish the reliability and appropriateness of the survey tool[20]. The panel provided feedback on the survey using a content validity index (CVI), by rating items for relevance via Likert scale (1 = highly irrelevant to 4 = highly relevant). Response process validity was assessed using the think-out-loud model, in which participants shared their thoughts on each survey item and the overall clarity of the survey with respect to its objectives[20]. Feedback was incorporated into refinement of the survey. A brief description of the CFTSI and its implementation requirements (Figure 1) was included in the survey, to standardize the level of knowledge for those without prior awareness or experience with the CFTSI.

The survey was built using the secure online platform Research Electronic Data Capture (REDCap) and was distributed via email to 29 Canadian CYACs

Consider the following information when answering questions in this section.

The Child and Family Traumatic Stress Intervention (CFTSI) is an evidence-based, family-centred early intervention which is initiated within 45 days of a potentially traumatic event or disclosure of trauma experienced by children age 7 to 18 years. The overarching goals of this intervention are to improve identification of children impacted by trauma, prevent downstream psychological impacts and assess the need for continued support. Post-traumatic stress symptomology, caregiver-child communication and coping skills are primary outcome measures of this program.

Implementation Requirements:
• Agencies must be trained in teams that include a minimum of one supervisor and two clinicians.
• Standard training protocol includes:
(a) 2-day, in-person training
(b) minimum of 9 out of 12 one-hour consultation calls within approximately six months following the initial training
(c) minimum of 3 cases during the consultation period
(d) collection and submission of clinical and continuous quality improvement data using the CFTSI data system

Figure 1. Standardized information about the CFTSI provided to survey participants, as it appeared in REDCap.

in operation at the time of study. The Dillman Method was employed to maximize response rate[21]. The invitation to participate was sent to the site lead, director or manager at each CYAC, who in turn selected one most appropriate representative to complete the survey. All survey data was anonymized, via participant ID number, prior to analysis.

Key informants were identified for interview based on practical knowledge or experience with the CFTSI, according to their anonymized survey data. Interviews were conducted to more fully understand current practice involving the CFTSI in Canadian CYACs. Individual interviews took place securely over Zoom for Healthcare, and a validated, semi-structured interview guide was used, which allowed each participant to set priority areas for discussion. Interviews were recorded on a hospital-authorized recording device and were transcribed and stored on a secure, encrypted hard-drive. Transcripts underwent manual thematic content analysis[22,23], using a coding guide. All interview data was also anonymized and reported without identifiers.

Results

Part I: CYAC characteristics, practice patterns & awareness of CFTSI

The survey was completed by 15 of 29 invited CYACs. Of the 14 centres that did not participate, nine did not respond to the invitation and five were operating under models that precluded them from providing adequately qualified participants.

The team composition and scale of participating centres varied, but Social Work was the most common profession represented, with 11 of 15 centres having this profession in their care team. Nine of 15 centers offered direct mental health services, the most common modality being Trauma-Focused Cognitive Behavioural Therapy (CBT) (n = 8). The other six centres had partner agencies for therapy referrals, mainly Victim Services (n = 4) and Community-Based Mental Health & Addictions Services (n = 5). Nine centres offered interventions specific to the prevention, diagnosis and/or management of post-traumatic stress. All 15 centres serviced a client population within seven to 18 years of age.

Prior to this study, nine of 15 centre respondents had been unaware of the CFTSI. The six respondents who were previously aware of this intervention were located mainly in Western provinces and Ontario. Additionally, 4/7 of those in operation for >5 years were aware of the CFTSI, while 2/8 of those in operation for >5 years were aware. The National Child Traumatic Stress Network was the most common way (4/6) clinicians were made aware of the CFTSI. Of those respondents who were aware of the CFTSI, two were currently using it at their centre, and each had been offering it for less than two years. These centres expressed strong agreement that the CFTSI is an acceptable and relevant intervention for use at their CYAC.

Of those not using the CFTSI, 10 of 13 expressed agreement or strong agreement that the CFTSI would be an acceptable and relevant intervention at their centre, while three were unsure. 12/13 expressed interest in learning more about the CFTSI and 7/13 expressed interest in implementing the CFTSI at their centre in the future. None of these centres were aware of other departments or agencies currently offering the CFTSI in their catchment area.

Part II: Thematic analysis of key informant interviews

Three key informants were identified for follow-up interview. All three participants were trained in the field of Social Work, and were evenly distributed in locations across Canada. One of the three participants did not use the CFTSI directly, but was previously aware of it and was currently involved with a similar therapeutic model in both structure and objective. Several prominent themes emerged from the interviews with these clinicians.

Benefits & challenges of a family-focused, highly structured approach

> *"I have many good things to say about the model, but there are times when kids and families spin out of the model, and sometimes there needs to be redirections and alternative approaches".*

Firstly, the caregiver-child approach was consistently recognized as a major benefit of the CFTSI. Education for caregivers was cited as a source of reinforcement of the skills taught to children in therapy, and family support was identified as a protective factor. Additionally, the well-defined time frame and clear clinical goals were identified as appealing aspects of the CFTSI, for both clinicians and families. Clinicians benefit in that the approach is well-organized and deliverable, and families benefit in that they have realistic expectations of the therapy and receive it at the point of maximal impact, rather than later when life circumstances may have changed.

However, the highly structured approach of the CFTSI presented a series of challenges as well. The redundancy of questionnaires, although important to the integrity of the model, was cited as a difficulty for some pa-

tients and families. According to an informant whose caseload was primarily composed of younger clients, the heavy emphasis on psychometrics was identified as a particular challenge for this age group. Additionally, real-world complexities such as pressing emotional or situational issues that may arise in session would sometimes take priority and hinder proper completion of clinical materials.

Overall, training for the CFTSI was highly regarded by interviewees who had participated. Training must be completed by Masters, PhD or MD-level mental health clinicians, and consists of a two-day in-person session, nine to 12 additional consultation calls, and a minimum of three cases reviewed via follow-up consultation (Carrie Epstein, personal communication, June 6, 2020). The required post-training consultation was noted as being focused on adherence to the model and lacking in case-driven clinical richness. As a solution to this, one participant noted that clinicians at their centre engage in regular peer consultation to review cases more fully. Also, one informant expressed concern regarding potential difficulties that clinicians familiar with less-directive therapies, such as play therapy, may face when implementing the very structured CFTSI.

Significance of family structure, culture & trauma history

> *"...Parental support often leads to better outcomes... I can do the work within those sessions when I have supportive, receptive caregivers, but I cannot do the work when that's not a strong skill set within the family".*

Another common theme that emerged was the importance of context. The caregiver-child approach was consistently recognized as a major benefit of the CFTSI, however the effectiveness of the intervention was described as being significantly reduced in cases without a close, receptive and supportive guardian willing to engage in communication. One participant noted that this premise of the CFTSI directly opposes the values of families from cultural backgrounds with strong stigma surrounding open discussion of trauma, while another described some perceived cross-cultural efficacy within their caseload. Furthermore, language barriers and the use of interpreters was cited as having a negative impact on the efficiency of delivery and overall effectiveness of the intervention. Finally, the CFTSI was described as particularly effective in cases of acute trauma, where communication and coping skills are adequate catalysts in the recovery process. However, in more complex cases, such as those involving relational or developmental trauma, the CFTSI often served simply as a stepping-stone to more targeted therapies.

Considerations for Canadian centres

> *"...We're the only ones that offer therapy services... We are a non-profit that kind of took the lead of creating the CYAC, so funding is always an issue".*

Adequate case load/referral base (i.e. police service, child welfare and/or medical clinics), staffing and administrative support, and funding were all identified as important considerations for centres looking to implement the CFTSI. These issues have been recognized by developers of the intervention, as the application process includes an organizational readiness assessment, detailing a centre's peri-traumatic case load and eligible trainees (Carrie Epstein, personal communication, June 6, 2020). Considering that Canada's CYAC network is comparatively less developed and robust than that of the United States, these may be significant limiting factors for many centres, especially non-profits and those serving less-populated regions.

Another consideration was presented by one informant who explained that, although the materials for the CFTSI have been translated to Spanish, this language was rarely used in their practice. Thus, the value of translation in a single language is limited for Canadian centres serving densely-populated regions with extremely diverse demographics and multiple languages spoken.

Finally, a participant proposed that CYACs in Canada are relatively less strained than those of the United States, allowing for greater availability of long-term therapies. According to this clinician, such therapies are often preferential for those with complex traumas and/or requiring more sustainable supports; thus, it may be justified to bypass the CFTSI, regardless of its convenience, provided more appropriate longer-term therapies are readily available and accessible.

Discussion

Childhood trauma has enduring and detrimental effects, as demonstrated by the Adverse Child Experiences (ACE) Study[24]. Felitti and colleagues concluded that a proportional relationship exists between traumatic exposures early in life and risk factors for leading causes of death and disease in adulthood. Poor health outcomes associated with childhood trauma increase demand on the healthcare system and carry profound economic implications as well. A systematic review and meta-analysis examining the lifetime consequences and associated costs of adverse childhood experiences found the total annual cost of ACEs in North America

to be $748 billion USD and that a modest 10% reduction in ACEs could lead to potential annual savings of $105 billion USD or 3 million disability-adjusted life years (DALYs)[25]. Given the breadth and degree with which childhood trauma impacts long-term health status, coupled with the striking financial burden, the importance of investment in tools to address childhood trauma is clear. The CFTSI makes a compelling candidate to help address current gaps in mental health services at Canadian CYACs.

Based on the lack of familiarity with the CFTSI demonstrated in our environmental scan, increased awareness of this intervention among Canadian CYACs may be a good first step to enhance mental health services. However, the CFTSI is certainly not a one-size-fits-all model, and commitment, flexibility and adaptation will be important in facilitating more widespread adoption of this intervention.

Survey results revealed that the US-based National Child Traumatic Stress Network was the most common means by which clinicians were made aware of the CFTSI. Although this is an American network, it may be a valuable avenue to increase awareness of CFTSI in Canada moving forward. Improved awareness and engagement might also be achieved by offering more accessible training modalities, beyond in-person sessions at the Yale Child Study Center. Such options are currently in development, however several stipulations, including a minimum group size of 10 (Carrie Epstein, personal communication, June 6, 2020) may perpetuate barriers for some Canadian centres. Although respondents in this study did not identify financial constraints as a barrier, travel and other associated costs may be limiting factors for less-developed Canadian centres to partake.

Thematic analysis revealed several benefits of the CFTSI. In particular, the combined approach involving both child and caregiver was identified as a strength of the intervention. This is consistent with the existing body of literature regarding early intervention for traumatized youth, which states that outcomes are optimized with caregiver education and involvement[26,27,28,29]. Several challenges with implementing the CFTSI in the context of Canadian CYACs were identified as well. Some of these issues lend themselves to relatively simple solutions, such as alleviating language barriers by expanding the languages in which therapeutic materials are translated. Others, such as complex developmental traumas, lack of supportive caregivers and stigma surrounding mental health, present more significant challenges which require further consideration.

It is pertinent to note that the significance of our findings is potentiated by the manner in which this study was conducted. The merits and pitfalls of an intervention are not necessarily best measured by parameters distantly removed from it. Rather, insights from those who directly work with and deliver the intervention may be more valuable[1]. Thus, the input provided by survey and interview participants is underscored by their experience and working knowledge.

Despite these strengths, this study also had some limitations. All interview participants were trained in the same field, therefore, perspectives from other professions were not reflected in the data. However, this was also somewhat of a benefit, in that profession was eliminated as a variable when reflecting on results. Another limitation was that none of the key informants could speak objectively to the effectiveness of the CFTSI in terms of rates of PTSD in their client population at follow-up. This is due to the relatively short period they have been using the intervention, as well as their designated role in delivery of the therapy and lack of involvement in outcome analysis. However, one clinician noted a perceived decrease in symptoms in most clients, while caregiver distress was not consistently measured.

Overall, there is strong evidence for the CFTSI as an intervention which improves outcomes of childhood traumatic exposures[17,18,19]. Based on our evaluation of its feasibility and usefulness, the CFTSI holds potential to contribute to the enhancement of mental healthcare at Canadian CYACs, by bridging a gap in existing services and providing a family-focused, integrative approach to recovery. This is a crucial area for improvement, as CYACs are still a relatively novel addition to the Canadian healthcare landscape. Moving forward, priority should be set on research and investment in efforts aimed at augmenting mental health services and optimizing outcomes of childhood trauma. Adoption of the CFSTI at CYACs across Canada could offer promise in achieving these goals.

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Case Report

A case of transient constrictive pericarditis in rural Nova Scotia

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Abstract

This case report describes a 32-year-old female who presented with severe dyspnea and exertional intolerance to an emergency department in a rural area of Nova Scotia. The diagnosis was made by corroborating the value of the erythrocyte sedimentation rate, the level of N-terminal prohormone of brain natriuretic peptide, and a transthoracic echocardiogram, which respectively showed an inflammatory pattern, myocardial strain, and classic sonographic findings consistent with constrictive pericarditis. The patient was treated with oral colchicine, naproxen, and prednisone resulting in complete resolution of laboratory and sonographic abnormalities. Availability of echocardiography in a rural setting can promptly and definitively diagnose and rule out many structural and functional disorders of the heart, including rare pathologies such as constrictive pericarditis.

Case

A 32-year-old woman developed painful, erythematous, swollen feet with a CRP of 170 (mg/L), and no systemic unwellness or other findings. She had otherwise no known allergies or sensitivities. Dermatology assessment included post-viral etiology, erythromelalgia, and chilblains in the differential. She tested negative for COVID-19.

Six months later, she experienced new left-sided pleuritic chest pain, gradually worsening fatigue, dyspnea, and orthopnea over three days. This culminated in a presentation to the emergency department with severe dyspnea. She settled on presentation but remained tachycardic at 124 bpm with other vitals within normal. The jugular venous pulse was elevated. A pericardial knock was audible in early diastole. Initial bloodwork was notable for a normocytic anemia, an elevated CRP, and an elevated NT-proBNP (Table 1). ECG showed sinus tachycardia and CXR showed new cardiomegaly with small bilateral pleural effusions (Figure 1).

The initial echocardiogram showed marked pericardial thickening up to 1.2 cm extending along the inferior and lateral aspects of the left ventricle (Figure 2). There was a leftward ventricular septal motion on inspiration and a marked septal bounce. Mitral and tricuspid inflows showed inspiratory variation: mitral valve 14% and tricuspid valve 30%. The IVC and hepatic veins were plethoric, demonstrating an expiratory diastolic flow reversal. The combination of these findings were diagnostic of constrictive pericarditis[1].

The patient was started on outpatient colchicine 0.6mg daily and naproxen 500mg BID[2], and experienced the resolution of symptoms within the first week. She underwent follow-up echocardiogram at 2 weeks, 6 weeks, and 4 months. Due to an intolerance, colchicine was changed to prednisone 30mg daily after 2 weeks[3]. Subsequent imaging showed resolution of pericardial thickening, respiratory leftward ventricular septal motion, septal bounce, mitral and tricuspid valve inflow variation, and diastolic flow reversal in the IVC (Figure 2), indicating complete reversal of constrictive physiology. Inflammatory markers and the NT-proBNP normalized (Table 1).

Constrictive pericarditis is a member of pericardial syndromes comprising pericarditis, pericardial effusion, and cardiac tamponade[4]. These syndromes typically occur from an inflammatory process of the pericardium. Under normal physiological conditions, the pericardium is a thin elastic sack that stretches to accommodate the dynamic expansion of the ventricles. Whereas in constrictive pericarditis, the pericardium becomes thicker and more rigid, turning into a cage that counters the expansion of the ventricles[1]. This alters normal hemodynamics of the heart, mainly by increasing filling pressures in the right ventricle during inspiration, which leads to congestive findings of elevated jugular venous pulse and hepatic vein flow reversal. The increased pressures in the right ventricle also force the interventricular septum into the left ventricle, which produces the septal bounce and inspiratory septal variation as seen on echocardiography (Figure 2). These hemodynamic changes lead to the clinical presentation of heart failure.

The most common reported causes of constrictive pericarditis are idiopathic and viral (42–49%), cardiac

Table 1. Comparison of select laboratory values at presentation and 1 month following treatment.

Marker		Value at presentation	Value after 1 month
WBC	[x 109/L]	10.1	9.3
Hgb	[g/L]	98	132
Plt	[x 109/L]	457	457
MCV	[mcm3]	86.3	87.6
CRP	[mg/L]	122	10.4
Troponin	[mcg/L]	< 0.012	-
NT-proBNP	[ng/L]	870	105

CRP: C-reactive protein. Hgb: hemoglobin. MCV: mean corpuscular volume. NT-proBNP: N-terminal pro-hormone B-type natriuretic peptide. Plt: platelets. WBC: white blood cells.

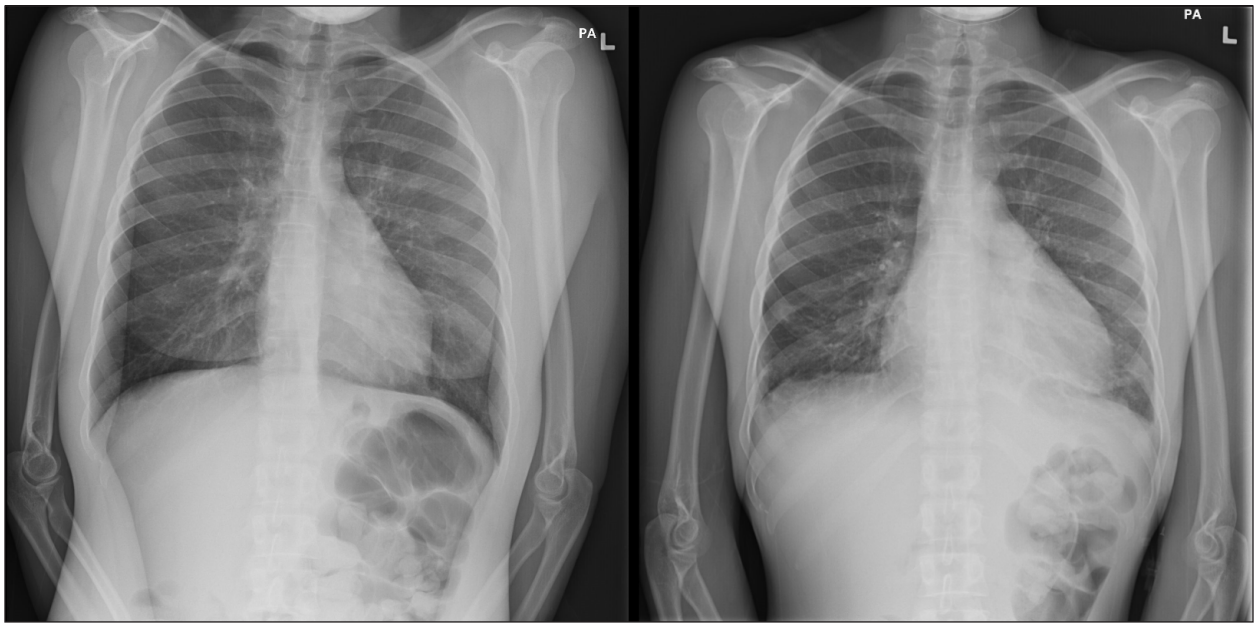

Figure 1. Comparison of diagnostic x-ray images of the chest in the posteroanterior view 6 months prior to onset of symptoms (left) and at clinical presentation (right) showing new and significant cardiomegaly, small pleural effusions bilaterally, linear opacities in the lung bases, and noticeable weight loss.

surgery (11–37%), radiation therapy (9–31%) (especially for Hodgkin's lymphoma and breast cancer), and connective tissue disorders (3–7%)[4]. The mainstay of diagnostic work up is a chest x-ray and a transthoracic echocardiogram. If echocardiographic evidence is inconclusive, a multi-modal approach is recommended that involves cardiac MRI to further ascertain the presence structural and inflammatory pericardial abnormalities[4,5].

First-line treatment is medical therapy with anti-inflammatory medications that includes dual therapy with colchicine and an NSAID, and triple therapy that adds steroids for more severe or refractory cases4. The constrictive pericarditis is labeled as transient when pathology resolves without residual disease[4,5], and is often attributed to viral or idiopathic cause. This was the case with our patient, and so, no further investigations into etiology were performed. In other cases, diagnosis is often delayed with average work up duration of up to 2 years. Longer chronicity tends to be more refractory to medical treatment due to pericardial fibrosis and calcification[5]. Failure of symptoms resolution with medical therapy after 3 months necessitates further investigations for underlying causes (e.g. rheumatological work up, cardiac MRI), addressing any new findings, and an assessment for a pericardiectomy[4].

Availability of echocardiography in a rural setting can definitively diagnose and rule out many structural and functional disorders of the heart. This exemplary case of a rare pericardial pathology was discovered with echocardiography and completely reversed with anti-inflammatory agents, which possibly prevented progression to pericardial fibrosis and irreversible constriction[4].

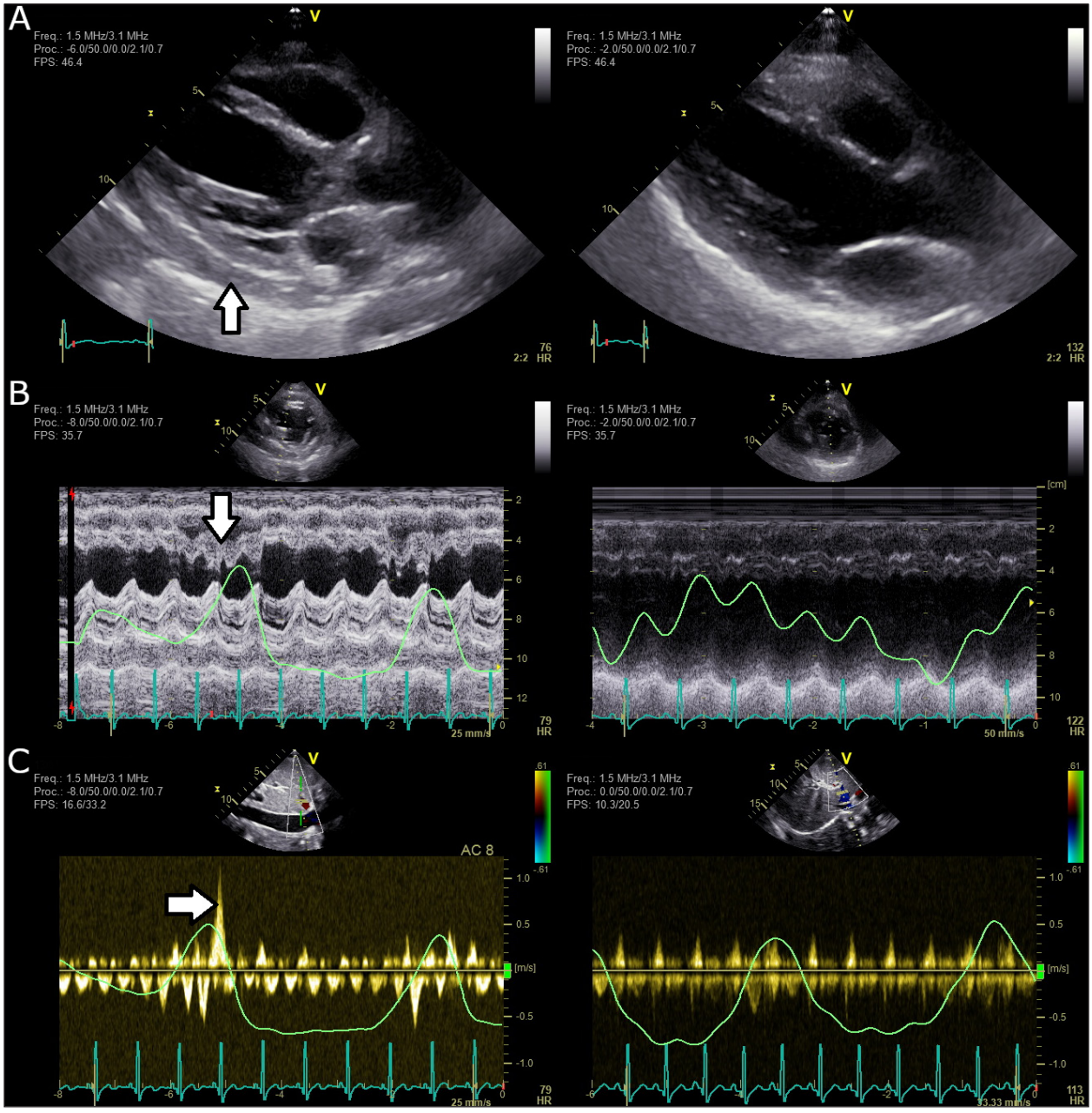

Figure 1. Comparison of echocardiographic images of the pericardium in the transthoracic long view (A), the septal motion in the M mode of transthoracic transverse view (B), and blood flow through the hepatic vein in the subcostal view (C). The cardiac rhythm and respiratory strips are present where appropriate. At clinical presentation (left), the images showed thickened pericardium of 1.2 cm (arrow), leftward inspiratory ventricular septal motion (arrow), and retrograde inspiratory hepatic vein flow (arrow), in keeping with constrictive pericarditis, whereas these features resolved at 4 months following treatment (right).

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Original Research

The efficacy and toxicity of dexrazoxane use in children with cancer: A pupulation-based study from Maritimes, Canada

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Abstract

Anthracycline induced cardiotoxicity is a well-recognized complication in pediatric oncology. The use of the cardio-protective drug dexrazoxane has gained traction despite its unclear efficacy and toxicity. A retrospective, population-based study was completed using chart and database information on children treated with anthracycline at the IWK Health Centre from 2009-2015 (n=178). The efficacy of dexrazoxane was defined as a lack of undesirable deviations in identified cardiac parameters on echocardiogram. Toxicity of dexrazoxane was defined as chemotherapy delays from any of decreased absolute neutrophil count (ANC), decreased platelets, increase in viral/bacterial episodes and febrile neutropenia (FN) episodes. Patients were stratified into groups based on the total amount of anthracycline received and whether they received dexrazoxane. Regardless of anthracycline dose, we found no significant relationships regarding cardiac function in the untreated and dexrazoxane treated groups. However, we found that patients who were treated with >250mg/m2 of anthracycline and received dexrazoxane experienced significantly more platelet delays but no cardiac benefit (p=0.007). When classified by diagnosis, we also found that dexrazoxane treated patients diagnosed with low-risk acute lymphocytic leukemia (LR-ALL) were likely to experience a delay in treatment due to both low ANC (p=0.0001) and the development of FN (p=0.02) whereas high-risk acute lymphocytic leukemia (HR-ALL) patients were likely to experience treatment delays due to thrombocytopenia (p=0.03), low ANC (p=0.0001) and FN (p=0.0001). Despite finding no significant differences regarding the efficacy of dexrazoxane as a cardio-protectant, we have shown that its use induces non-cardiac toxicities in children with cancer that contribute to treatment delays.

Introduction

In Canada, approximately 1700 children are diagnosed with cancer each year1. Observed 5-year survival rates are approximately 78%[1,2]. Therapies used to treat children with cancer can have long-lasting effects that cause serious health complications during survivorship and efforts are ongoing to try and minimize the consequences of delayed treatment toxicities[3]. Of particular significance, is the effect of cumulative dose of anthracyclines on cardiac function[4].

Doxorubicin and daunorubicin were among the first anthracyclines to be incorporated into clinical use[5]. Since their discovery, these agents have been used to treat a number of cancers with curative intent. Although effective, anthracyclines are the primary cause of chemotherapy induced cardiotoxicity whose mechanism remains only partially understood with free radical formation an important contributor[6,7]. In 2014, Top2β was shown to be the key mediator of anthracycline induced cardiomyocyte apoptosis and deletion of Top2β prevented defective mitochondrial biogenesis and reactive oxygen species formation ultimately protecting cardiomyocytes[8]. This process is currently thought to occur at the time of exposure, beginning first at the level of cardiomyocytes and eventually leading to overt heart failure[9]. Therefore, clinical presentation may occur much late[r] than the initial exposure highlighting the importance of either early detection or prevention.

To date, multiple cardio-protectant strategies have been proposed. Some of which include using smaller divided doses of anthracycline, administering concurrent antioxidant drugs or administering medications such as beta-blockers and calcium channel blockers[10–14].

Many of these strategies have minimal efficacy in either primary prevention or improving anthracycline-induced cardiotoxicity[15–17]. To date, the only clinically approved cardio-protective agent is dexrazoxane which is a cyclic derivative of ethylenediaminetetraacetic acid (EDTA).

Dexrazoxane readily penetrates cell membranes where it is subsequently hydrolyzed into two active compounds which chelate iron and prevent cardiomyocyte damage by reducing the release of free radicals[18]. Multiple studies have evaluated the cardio-protective efficacy of dexrazoxane[19–21]. Chow et al. 2016 found that long-term survivors who received dexrazoxane had more preserved systolic function and reduced myocardial wall stress compared with those who did not receive dexrazoxane[22].Others have questioned the safety of dexrazoxane, arguing that it may not only lack cardioprotective properties but may also increase a patient's chance of developing a secondary malignancy or cause delays in treatment due to myelosupression[23]. Whether or not dexrazoxane should be used as a cardioprotective agent remains unclear.

To determine the relative risks and benefits of dexrazoxane use as a cardioprotectant, we retrospectively analyzed pediatric patients who received anthracyclines with or without dexrazoxane at the IWK Health Centre.

Methods

To assess the efficacy and toxicity associated with dexrazoxane, a retrospective, population-based cohort study was completed using chart and database information on children treated with anthracyclines at the IWK Health Centre from 2009-2015. The IWK Health Centre is the only Children's Cancer Centre in Maritime Canada. In 2012, there was a policy change stating dexrazoxane was no longer to be administered to children receiving less than 300 mg/m^2 cumulative dose of anthracycline. Prior to this change, all patients receiving >150 mg/m^2 cumulative anthracycline dose and all those less than 5 years old received dexrazoxane. The cardiotoxic index, or doses of anthracycline used was daunorubicin and doxorubicin 1:1, mitoxantrone 4:1 and idarubicin 5:1.

Data was collected from several databases including, 1) the IWK oncology patient database 2) the IWK pharmacy drug database and chart system; used to collect information on anthracycline and dexrazoxane exposure and 3) the IWK cardiology echocardiography database; used to provide information on cardiac size and function measurements for the participants identified.

Toxicity of dexrazoxane was defined as chemotherapy delays (by 3 days or more) from any of: decreased absolute neutrophil count (ANC), decreased platelets, increase in viral/bacterial episodes and febrile neutropenia (FN) episodes. Viral/bacterial episodes are defined by a positive culture or PCR positive. ANC is defined as the sum of the counts of mature neutrophils and band forms. Febrile neutropenia is defined as an absolute neutrophil count (ANC) less than 0.5 x 109/L and a fever of 38.3°C or oral or tympanic temperature greater than or equal to 38°C for 1 hour or more. The efficacy of dexrazoxane was defined as a lack of undesirable deviations in identified cardiac parameters on echocardiogram (ECHO) associated with anthracycline toxicity. These included decreased ejection fraction (LVEF), decreased fractional shortening (LVFS), increased LV mass (g/m^2) and increased z-scores (>2) for left ventricular internal diameter at end diastole and systole (LVIDd, LVIDs) or decreased z-scores (<-2) for left ventricular posterior wall thickness at end diastole (LVPWD). A reduction in left ventricular ejection fraction (<55%) or shortening fraction (<30%) or the presence of symptomatic cardiotoxicity was used as a threshold for defining cardiac toxicity of anthracyclines.

We collected all available information regarding the outcomes listed above. Information was available on a total of 136 patients which were stratified into groups based on the total dose of anthracycline received.

All efficacy outcomes were measured either 1) after anthracycline treatment (LV mass, LVEF, LVFS) or, 2) both before and after anthracycline treatment (LVIDd, LVIDs, LVPWD). The outcomes measured after treatment were plotted using the raw scores reported by echocardiography databases. The outcomes measured before and after treatment were plotted using z-scores to determine whether there was a significant change from baseline in these variables post anthracycline treatment.

Statistics

All graphs were made using GraphPad Prism 4 Software. In all cases where efficacy is analyzed a non-parametric Wilcoxin-Mann-Whitney t-test was used comparing patients who received solely anthracycline (either <150, 150-250 or >250mg/m^2) and those who received both anthracycline and dexrazoxane. Stars indicate the strength of the relationship ($p<0.05^*$, $p<0.01^{**}$, $p<0.001^{***}$).

Toxicity information was available for a total of 177 patients (including the 136 used for efficacy analysis. First, we analyzed all 177 patients regardless of dexrazoxane administration to look for toxic effect differences between patients receiving various doses of anthracycline. Next, we separated the patients into, 1) patients who received dexrazoxane as well as anthracy-

cline (<150mg/m^2, 150-250mg/m^2 or >250mg/m^2) and 2) those who received anthracycline only (<150mg/m^2, 150-250mg/m^2 or >250mg/m^2) to isolate whether patients receiving dexrazoxane experienced significantly more toxic effects than those who did not.

All graphs were made using GraphPad Prism 4 Software or Excel. In all cases where toxicity is analyzed between two or more groups a Kruskal-Wallis ANOVA test with a Dunn's post hoc test was used. To analyze whether patients diagnosed with LR-ALL and HR-ALL exposed to dexrazoxane experienced significantly more treatment delays than dexrazoxane naïve patients, a one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts. Stars indicate the strength of the relationship ($p<0.05$*, $p<0.01$**, $p<0.001$***).

Results

The patients included in this study total 178, with a M:F ratio of 41:48. The average age at diagnosis between patients who received dexrazoxane, and those who did not was similar at 7.9 and 7.6 years, respectively. Most patients included in this study were diagnosed with either high-risk or low-risk acute lymphocytic leukemia (HR-ALL, LR-ALL) (Table 1).

We analyzed the efficacy and toxicity of dexrazoxane for patients who received: 1) less than 150mg/m^2, 2) between 150-250mg/m^2 and 3) more than 250mg/m^2 of anthracycline. For statistical strength, multiple diagnoses were included in each group. For example, most patients who received between 150-250mg/m^2 of anthracycline were diagnosed with HR-ALL, lymphoma, neuroblastoma, or a Wilms tumor. Of all the patients included, 45% received dexrazoxane and 55% did not. Most patients who received dexrazoxane were treated with either 150-250mg/m^2, or more than 250mg/m^2 of anthracycline whereas patients who did not receive dexrazoxane were mostly treated with <150mg/m^2 of anthracycline.

To analyze the cardioprotective-related efficacy of dexrazoxane, the cumulative amount of anthracycline per patient was obtained and plotted against the following cardiac parameters: 1) LVEF, 2) LVFS, 3) LVIDd/s, 4) LVPWD, and 5) LV mass. All efficacy readouts were recorded during follow-up appointments which occurred 2.4 years, and 3.4 years in the dexrazoxane-naive and dexrazoxane treated patients, respectively (Table 1). We expected to see better long-term cardiac outcomes in patients who received dexrazoxane but found no significant relationships regarding cardiac function in the dexrazoxane-naive and dexrazoxane treated groups (Figure 1).

To analyze the toxicity of dexrazoxane administration, we monitored 1) platelet counts, 2) neutrophil counts, 3) development of febrile neutropenia, and 4) development of infection during each patient's chemotherapy regimen. Based on the cumulative anthracycline dose received, we found no significant difference regarding neutrophil counts, the development of either febrile neutropenia or infection between patients who received dexrazoxane and those who did not (Figure 3). We did, however, find regardless of whether a patient has received dexrazoxane, as the dose of anthracycline increases, there are more platelet delays (Figure 2Ai). Whether this was an effect of anthracycline or dexrazoxane remained unclear. Therefore, we analyzed these groups separately. Patients who received both anthracycline and dexrazoxane had significantly more platelet delays (Figure 2Aii). This relationship did not hold true for patients who received solely anthracycline suggesting that dexrazoxane could be the cause of platelet delays (Figure 2Aiii). These results also show that there are significantly more platelet delays between patients who received 150-250mg/m^2 and those who received >250mg/m2 when dexrazoxane is administered (Figure 2Aii). However, this relationship does not exist when patients are treated with anthracycline alone (Figure

Table 1. Patient Demographics.

	Treated with Dexrazoxane (n=79)	Untreated with Dexrazoxane (n=99)
Female	44/96 (46%)	52/96 (54%)
Male	35/82 (43%)	47/82 (57%)
Average Age at Diagnosis	7.9 years	7.6 years
Average Follow Up Time	2.4 years	3.4 years
Diagnosis:		
HR-ALL	26/48 (54%)	22/48 (46%)
LR-ALL	12/48 (25%)	36/48 (75%)
AML	4/11 (36%)	7/11 (63%)
NHL/HL	6/31 (19%)	25/31 (81%)
Neuroblastoma/WILMS	6/14 (43%)	8/14 (57%)
Sarcoma	25/26 (96%)	1/26 (4%)

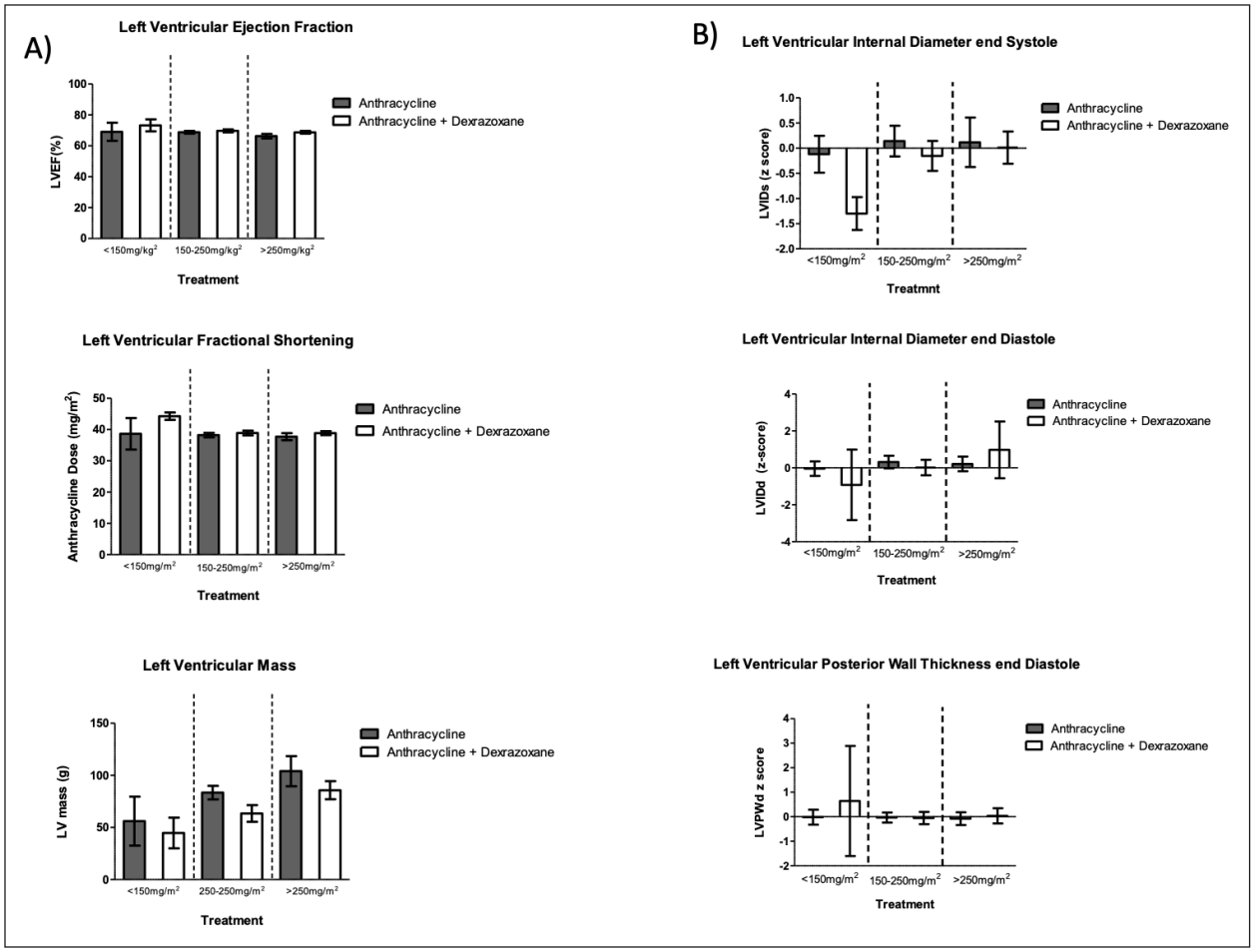

Figure 1. Pediatric patients who receive dexrazoxane do not have better long-term cardiac outcomes compared to patients who did not regardless of total anthracycline dose. (A) Left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS) and left ventricular mass values were recorded from patient charts over time. Patients were stratified into groups based on total anthracycline received. The average LVFS, LVEF and LV mass were plotted (ntotal=136; n<150=39, n150-250=56, n>250=41). (B) Left ventricular internal dimension at end systole (LVIDs), left ventricular internal dimension at end diastole (LVIDd) and left ventricular posterior wall thickness at end diastole (LVWPD) were recorded before and monitored overtime post-treatment. Z-scores were plotted against the total dose of anthracycline received (ntotal=136; n<150=39, n150-250=56, n>250=41).

2Aiii). We also found that patients receiving >250mg/m^2 anthracycline as well as dexrazoxane have significantly more cases of thrombocytopenia leading to treatment delays than their untreated counterparts (Figure 2B).

We also analyzed toxicity read outs based on diagnosis. The most common diagnoses in this patient cohort were LR-ALL (n=48) and HR-ALL (n=48). Of all patients in the LR-ALL group that were treated with anthracycline and dexrazoxane, 83% and 75% of patients experienced a treatment delay due to low ANC and the development of FN, respectively (Table 2). In the HR-ALL group, we find similar results where 84% and 80% of patients treated with anthracycline and dexrazoxane experienced treatment delay due to low ANC or the development of FN, respectively (Table 3).

Discussion and Conclusion

Anthracyclines have been shown to increase the risk of congestive heart failure and dilated cardiomyopathy in pediatric patients[10,24,25]. Despite this, they remain the drug of choice for many cancer types due to their efficacy[26]. Due to an increase in the number of children expected to live decades post-anthracycline exposure, there has been an emphasis on developing methods to reduce and/or prevent anthracycline-induced cardiotoxicity[27,28].

To date, dexrazoxane is the only cardioprotective agent that has been shown to protect against long-term anthracycline induced cardiotoxicity[29]. In children, dexrazoxane was contraindicated mainly due to concerns regarding the development of second primary malignancies which was refuted in 2017[30,31]. Currently, it is suggested that children aged 0-18 expected to

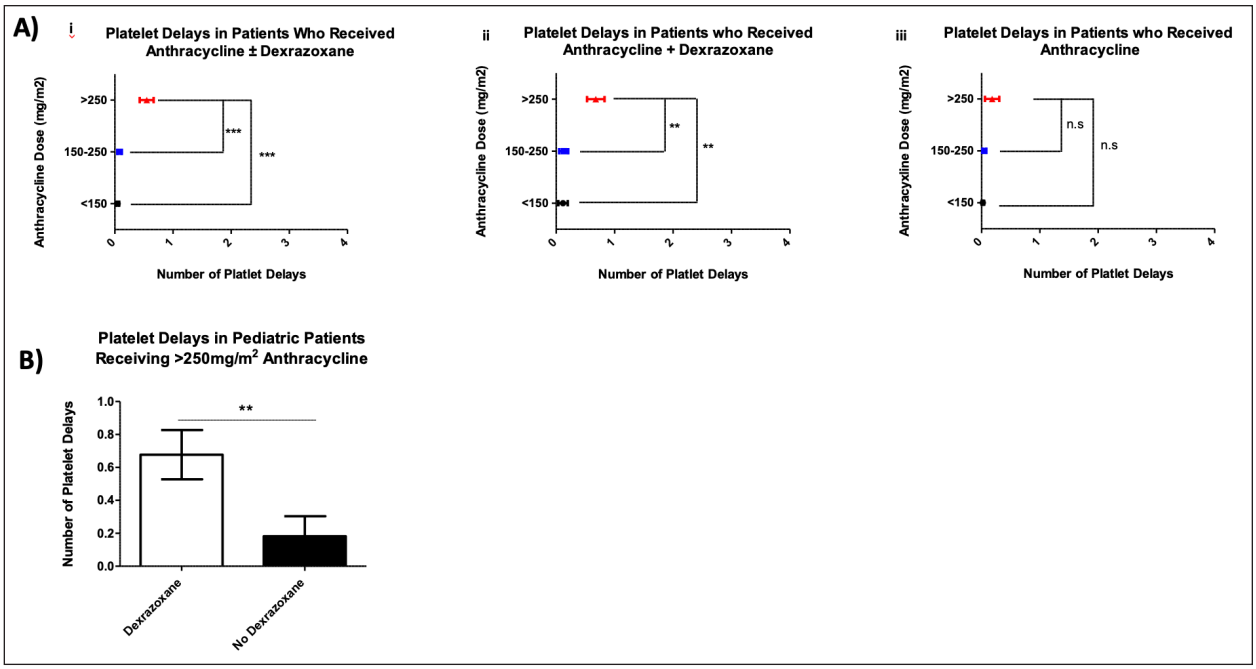

Figure 2. Pediatric patients who receive dexrazoxane are more likely to experience platelet delays compared to their untreated counterparts. (Ai) Platelet counts were recorded from patients receiving anthracyclines with or without dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). (Aii) Platelet counts were recorded solely from patients receiving anthracycline with dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). (Aiii) Platelet counts were recorded from patients receiving anthracycline only. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11). (B) The number of platelet delays experienced by patients receiving >250mg/m2 anthracycline who did and did not receive dexrazoxane (ndex=31; nnodex=11). Platelet delays were defined as counts < 75,000, p<0.05=*, p<0.01=**, p<0.001=***.

receive a cumulative dose of anthracycline >300mg/m^2 should receive dexrazoxane. There is limited long-term data regarding the impact of dexrazoxane on cardiac and non-cardiac function with many arguing for its use in children and the minority cautioning it[19,20,22,23,32–38]. In this study, we focused specifically on the efficacy and toxicity of dexrazoxane use in pediatric cancer patients at the IWK Health Centre.

Dexrazoxane has been shown to be cardioprotective when administered in conjunction with >300mg/m^2 cumulative anthracycline in adults with breast, non-small cell lung cancer, and sarcomas[39–42]. We found no significant differences in cardiac function (measured by LVEF and LVFS) between dexrazoxane treated and dexrazoxane-naïve patients despite the cumulative dose of anthracycline received. Lipshutz et al. 2015 showed that the use of dexrazoxane in addition to doxorubicin in ALL patients resulted in a more normal end-systolic dimension and end diastolic thickness-to-dimension at 2- and 3-year follow-up respectively. Although not significant due to the number of patients analyzed, we found that end-systolic and diastolic dimension may be improved using dexrazoxane in patients who receive <150mg/m^2 of anthracycline but not in those receiving more. Like Lipshutz et al. 2015 we found no significant differences regarding LV mass or LVFS.

Studies regarding non-cardiac toxicities of dexrazoxane have focused on the risk of hepatotoxicity, myelosuppression and pulmonary fibrosis[43]. Furthermore, a phase II trial studying dexrazoxane in children suggests that studies looking at the cardioprotective effects of dexrazoxane use much lower doses than the maximum tolerated dose which is often given depending on the institution and clinical context. Therefore, non-cardiac toxicities may be underreported.

We add to this literature showing that pediatric patients who receive dexrazoxane and >250mg/m^2 of anthracycline are more likely to experience severe thrombocytopenia. This finding can be supported by the BC Cancer Agency which states that approximately 10% of patients treated with dexrazoxane will experience severe thrombocytopenia[44]. Toxicities often effect the timing of treatment administration. Our study shows the toxicity associated with dexrazoxane use impacts the timing of chemotherapy administration. Children who receive dexrazoxane are more likely to have a treatment delay due to thrombocytopenia induced by dexrazoxane. In patients diagnosed specifically with LR and HR-ALL we show that the use of dexrazoxane may lead to a higher risk of developing febrile neutropenia as well as low ANC counts leading to delays in treatment.

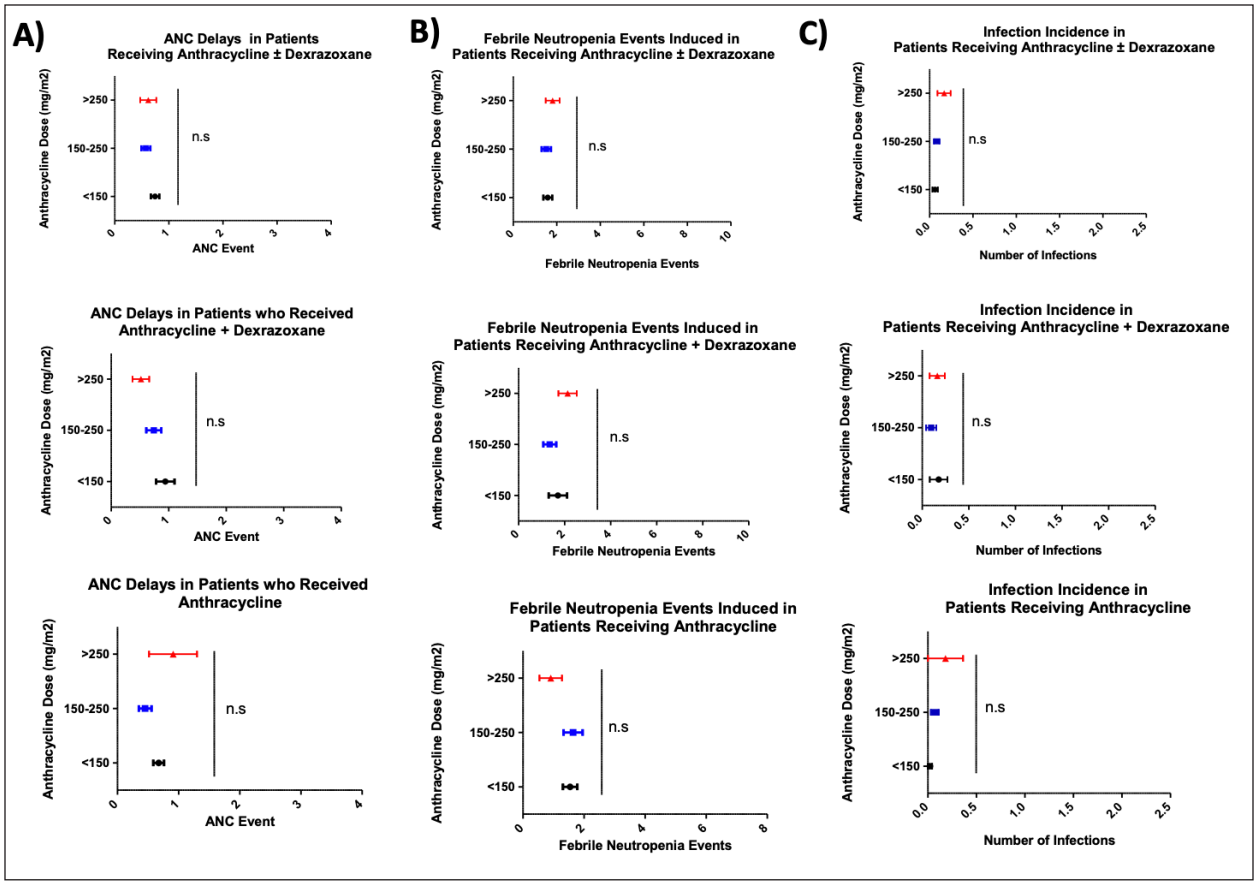

Figure 3. Pediatric patients who receive dexrazoxane are more likely to experience platelet delays compared to their untreated counterparts. (Ai) Platelet coPatients receiving dexrazoxane and anthracycline did not experience more treatment delays due to low ANC, FN or infection. (A) Neutrophil counts were recorded from patients receiving anthracyclines with or without dexrazoxane. Neutrophil delays were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). Platelet/Neutrophil counts were recorded solely from patients receiving anthracycline with dexrazoxane. Platelet delays were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). Platelet/Neutrophil counts were recorded from patients receiving anthracycline only. Neutrophil delays were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11). Neutrophil delays were defined as <100, 000. (B/C) The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients receiving anthracycline with or without dexrazoxane. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=178; n<150=63, n150-250=73, n>250=42). The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients solely receiving anthracycline with dexrazoxane. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=79; n<150=17, n150-250=31, n>250=31). The number of times a patient experienced febrile neutropenia/got an infection were recorded from patients solely receiving anthracycline. The number of febrile neutropenia events/infections were then plotted based on cumulative anthracycline dose, (ntotal=98; n<150=46, n150-250=41, n>250=11), p<0.05=*, p<0.01=**, p<0.001=***.

Table 2. Patients diagnosed with LR-ALL and treated with dexrazoxane experience more delays in treatment due to low ANC count and the development of FN.

	Delay	No Delay	p-value
Platelet	1/12 (8%)	11/12 (92%)	0.3388
ANC	10/12 (83%)	2/12 (17%)	<0.0001
FN	9/12 (75%)	3/12 (25%)	0.02
Infection	2/12 (17%)	10/12 (83%)	0.1661

A one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts, <0.05=*, p<0.01=**, p<0.001=***.

Table 3. Patients diagnosed with HR-ALL and treated with dexrazoxane experience more delays in treatment due to low ANC count and the development of FN.

	Delay	No Delay	p-value
Platelet	5/25 (20%)	20/25 (80%)	0.03
ANC	21/25 (84%)	4/25 (16%)	<0.0001
FN	20/25 (80%)	5/25 (20%)	<0.0001
Infection	2/25 (8%)	23/25 (92%)	0.1615

A one-sample Wilcoxon signed rank t test was conducted comparing the number of patients who experienced delays against the null hypothesis which states patients who are treated with dexrazoxane do not experience more treatment delays compared to their untreated counterparts, <0.05=*, p<0.01=**, p<0.001=***.

In conclusion, we argue that 1) the benefits of dexrazoxane administration need to be more clearly elucidated depending on the cumulative dose of anthracycline received and 2) more follow up studies should be done in patients who experienced a treatment delay due to dexrazoxane toxicity to assess long term outcomes. In this study however, we suggest that the use of dexrazoxane should be cautioned in pediatric oncology patients especially those receiving >250mg/m^2 of cumulative anthracycline.

Limitations

A limitation of this study is the use of echocardiogram (ECHO) which shows subjective changes and is reliant on the reporter. Nonetheless, ECHO remains the best method of measuring cardiac dysfunction. LVEF and LVFS are currently used in clinical practice to modify doses of anthracyclines and as such were the parameters that were captured in this study. In addition to this, the heterogeneity of anthracycline choice was not taken into consideration here. Much of the literature supporting the use of dexrazoxane in children focuses on the use of dexrazoxane when administered with doxorubicin. In addition, we only assessed cardiac outcomes 2-3 years post-anthracycline administration. For this reason, it is possible that we are missing patients who ultimately will experience late cardiotoxicity.

Other limitations of this study are that we did not capture concomitant therapies such as chest radiation and cardiac toxic chemotherapy, the study included subjective reporting of patient chart/database information based on the completeness of the available files and due to small sample size, we were unable to capture the effects of dexrazoxane use on solid tumors. We also note that there are multiple variables that limit our ability to make conclusions such as the wide range of patients included. However, we feel that we have contributed to literature that questions the use of dexrazoxane in children with cancer.

Appendix A

Anthracycline dosing of all patients divided by diagnosis. Patients diagnosed with LR-ALL (n=48), HR-ALL (n=48), AML (n=11), lymphoma (n=31), neuroblastoma/Wilms (n=14) and sarcoma (n=25) received differing doses of anthracycline.

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