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Perceptions of Methotrexate Intolerance and Its Impact on Daily Life in School-Age Children with Juvenile Idiopathic Arthritis

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ABSTRACT

Purpose: Methotrexate (MTX) is a disease modifying anti-rheumatic drug commonly used to treat children with Juvenile Idiopathic Arthritis (JIA). Unfortunately, half of children taking MTX will experience MTX intolerance, which includes distressing gastrointestinal and behavioural symptoms associated with weekly MTX treatment. This qualitative study aimed to explore the perceptions of school-age children with JIA experiencing MTX intolerance, how they managed MTX intolerance, and how it impacted their daily life.

Design and methods: An interpretive descriptive design was used. Twelve children participated in one individual 30-minute semi-structured interview using a storyboard technique to elicit their perceptions through storytelling. Interview transcripts and observational data collected during the interviews were analyzed using inductive content analysis.

Results: Children described MTX intolerance as extremely challenging. Three themes emerged from the data: (1) "No kid likes taking MTX". This theme was comprised of two subthemes related to: (a) associative MTX intolerance; namely, "Talking about it sometimes makes me feel sick"; and (b) anticipatory MTX intolerance, "Before [I take it], I have a little stomach ache". Other themes included: (2) The importance of strategies and routines; and (3) Working hard to live with MTX intolerance.

Conclusions: This study sheds new light on MTX intolerance as perceived by school-aged children with JIA. Results highlight the importance of providing families and healthcare professionals with the necessary information for early recognition of MTX intolerance and optimizing care through the development of early intervention strategies.

Practice implications: Study findings highlight the importance of prioritizing early identification and prevention of MTX intolerance.

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common childhood rheumatic disease, causing both physical disability and reduced quality of life (Len, Silva, & Terreri, 2014). Methotrexate (MTX) is a commonly used disease modifying anti-rheumatic drug for treating JIA (Takken, van der Net, & Helders, 2001). Approximately half of children taking MTX experience 'MTX intolerance,' which includes distressing physical and behavioural symptoms associated with weekly MTX treatment (Bulatović et al., 2011). Some common symptoms children experience include nausea, vomiting, and fear and anxiety in anticipation of taking MTX. There have been no studies to-date focused on school-age children's perceptions of the challenges they face in relation to MTX intolerance, despite the potential effects on their emotional and physical well-being and day-to-day activities. This study aimed to elicit school-aged children's perceptions of MTX intolerance, the strategies they used to manage it, and its impact on their daily life.

JIA and MTX treatment

JIA is defined as the presence of arthritis in one or more joints for a duration of at least six weeks in children less than 16 years of age (Petty, Laxer, & Wedderburn, 2016). This condition is characterized by joint stiffness, swelling, pain and limited range of motion resulting in loss of function, as well as periods of flare up and remission throughout the disease course (Espinosa & Gottlieb, 2012; Gowdie & Tse, 2012). Although there is currently no cure for JIA, pharmacotherapy and a

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multidisciplinary approach to treatment have improved prognosis and outcomes for children living with this chronic condition. If appropriate treatment is not started early, significant morbidity such as leg-length discrepancy, joint contractures, and permanent joint destruction can occur (Hashkes & Laxer, 2005; Petty et al., 2016).

Approximately 25% to 33% of patients with JIA achieve adequate disease control with first line treatment of non-steroidal anti-inflammatory drugs (Petty et al., 2016). The remainder requires more aggressive second-line pharmacotherapies such as MTX which is the first choice of disease modifying anti-rheumatic drug for the treatment of JIA. MTX is shown to effectively induce disease remission in over 70% of children with JIA by significantly reducing joint swelling, tenderness, stiffness, and pain and limitation of motion (Petty et al., 2016). While effective, there is a notably high prevalence of MTX intolerance in children with JIA (Bulatović et al., 2011). This intolerance is of concern as it can affect physical well-being (e.g. nausea, vomiting), emotional well-being (e.g. fear of injections), and day-to-day activities (e.g. school absenteeism) (Bechard et al., 2014; Bulatović Ćalasan & Wulffraat, 2014).

MTX intolerance

In 2011, Bulatović et al. coined the term 'MTX intolerance' to better describe physical and behavioural symptoms that occur in children taking MTX. Symptoms occur simultaneously and include nausea, vomiting, abdominal pain, and diarrhea, as well as crying, restlessness, and aversion to therapy. This combination of symptoms can occur prior to taking MTX (anticipatory symptoms), can be triggered when thinking about factors related to taking MTX, such as medication colour or day of treatment (associative symptoms), or after taking MTX. Bulatovic et al. developed the MTX Intolerance Severity Score (MISS) questionnaire for children with JIA (n = 297, ages 2–18 years), and found a high proportion of their sample (50.5%, n = 150) experienced MTX intolerance (Bulatović et al., 2011). While the MISS provides a numerical intolerance symptom score, it does not provide information on how MTX intolerance affects the child's daily life.

Clinicians have attempted to minimize the symptoms related to MTX intolerance by prescribing anti-emetics and changing the route of drug administration (Espinosa & Gottlieb, 2012); however, these strategies are not effective for all children. Patil et al. (2014) found that 73% of adolescents (n = 36/49) self-reported MTX induced nausea and vomiting, and while 22% (n = 11) of those were on anti-emetics, 55% reported little to no benefit.

Children's experiences taking MTX

MTX intolerance places a significant burden on children and their families (Bechard et al., 2014; van Dijkhuizen et al., 2015). Mothers (n = 171) in one descriptive-exploratory study noted that while the severity of their children's side effects was worse than expected, they valued MTX as a treatment and gave it a positive rating overall (Mulligan et al., 2013).There is evidence to suggest that taking MTX can negatively impact children's health-related quality of life (HRQoL). Mulligan et al. administered the Pediatric Quality of Life Inventory (PedsQL) to children aged 8 to 16 years (n = 116) on MTX and found those who reported difficulty taking MTX had poorer scores in the physical domains of the PedsQL (Mulligan, Wedderburn, & Newman, 2015).

While information provided by parents regarding their children's experiences is valuable, discrepancies between parent and child reports of pain and disability related to JIA have been identified (Palermo, Zebracki, Cox, Newman, & Singer, 2004). It has been suggested that eliciting children's perspectives directly would provide first-hand insight into their experiences and identify what is most important to them (Söderbäck, Coyne, & Harder, 2011). Although parents have been useful proxies in exploring methotrexate intolerance, it is important to understand the child's point of view. Studies have shown that when asked developmentally appropriate questions and with gentle probing, school-age children can provide reliable self-reports on their health-related experiences (Riley, 2004). They have been found to successfully and consistently communicate their symptoms and needs in clinical settings (Riley, 2004). The child's perspective can often guide clinical practice and lead to better outcomes (Söderbäck et al., 2011).

The purpose of this study was to explore school-age children's perceptions of MTX intolerance by addressing the following research questions: How do school-age children with JIA experience MTX intolerance? How do children with JIA manage MTX intolerance? How does MTX intolerance impact their daily lives? Ultimately, this study aimed to enhance our depth of knowledge regarding children's perceptions of MTX intolerance to inform the development of clinical practice strategies to manage intolerance.

Materials and methods

Study design and participants

An interpretive descriptive design was used to gain a deeper understanding of children's subjective perceptions of MTX intolerance. Interpretive description seeks to develop a coherent conceptual description that taps into the thematic patterns and commonalities that characterise the phenomenon under study (Thorne, 2008; Thorne, Kirkham, & MacDonald-Emes, 1997; Thorne, Kirkham, & O'Flynn-Magee, 2004). It was essential that a child-centred, participatory approach be used to engage participants; thus, we adopted a storyboard technique to encourage children to describe their experiences. Through the discovery of associations, relationships, and patterns in the children's descriptions, themes and patterns were identified in the data yielding implications for clinical practice (Thorne, 2008; Thorne et al., 1997; Thorne et al., 2004).

Purposive sampling was used to recruit 9 girls and 3 boys (n = 12) diagnosed with JIA and experiencing MTX intolerance from the rheumatology clinic of one Canadian, quaternary care pediatric hospital. One child who was approached refused to participate as he did not want to talk about MTX. Children ranged in age from 6 to 12 years; spoke English or French; and had been receiving oral (PO; n = 4) or subcutaneous (SC; n = 8) MTX at home with the assistance of their parents, for periods of time ranging from 11 months to 7.5 years (Table 1). The higher number of girls in the sample was representative of the higher incidence of JIA in females (Espinosa & Gottlieb, 2012). The greater number of children receiving SC MTX was representative of medical practice in the study setting. Data were collected until no new information was generated and redundancy, or data saturation, was achieved (Guest, Bunce, & Johnson, 2006; Polit & Beck, 2013).

Procedure

The study was approved by the hospital's Institutional Review Board. All children who agreed to participate provided verbal assent, and their parents provided written consent. A storyboard technique was used to conduct one semi-structured interview with each participant (Table 2). Interviews lasted an average of 30 min. At the beginning of the interview, the child was shown a storyboard consisting of a large square board covered in felt material and representing four rooms of a house. Children were provided with a variety of felt pieces depicting family members, pets, toys and household furniture. Medical play items were provided, including a syringe, a pill container and an alcohol swab. Using the felt pieces and medical play items, participants were asked to tell us about their experience with MTX by visually setting up and talking about their MTX administration routine. The use of the storyboard in combination with semi-structured interview questions fostered a sense of engagement and encouraged children to describe their MTX intolerance, how they managed it, and its impact on their daily lives. Parents were invited to be present during the interview if they/their child wished, and all decided to remain in the room. To

Table 1
Characteristics of the study sample.

Participant number	Gender	Age (years)	Time since diagnosis (years)	JIA classification	Active joints	MTX treatment duration in (years)	MTX administration dose (route)	Antiemetic (frequency)
P01	Female	7	6.1	Oligoarthritis extended	0	4.3	15 mg (PO)	Dimenhydrinate; 3 doses (1 pre and 2 post treatment)
P02	Female	10	2.8	Oligoarthritis	0	1.3	17.5 mg (SC)	Dimenhydrinate, ondansetron (not currently used)
P03	Female	7	2.2	Oligoarthritis	0	1.7	20 mg (SC)	N/A
P04	Female	8	6.7	Undifferentiated JIA	1	6.3 (on and off)	20 mg (SC)	Ondansetron (not currently used)
P05	Female	11	8	Oligoarthritis extended	0	7	12.5 mg (SC)	Ginger lozenges (PRN)
P06	Male	9	4.3	Systemic JIA	1	3.4	20 mg (SC)	Ondansetron and Dimenhydrinate (currently not used)
P07	Female	11	3.3	Polyarticular JIA	1	3.3	25 mg (SC)	Odansetron (pre treatment)
P09	Male	9	7.6	Systemic JIA	0	7.4	17.5 mg (PO)	N/A
P10	Female	9	2.6	Polyarticular JIA	0	2.5	15 mg (PO)	N/A
P11	Female	6	2.8	Undifferentiated JIA	0	0.8	15 mg (SC)	Ondansetron (pre and post)
P12	Female	10	0.8	Polyarticular JIA	6	0.8	25 mg (SC)	Ondansetron (pre)
P13	Male	12	1.9	Polyarticular JIA	0	1.8	10 mg, (PO)	N/A

Route of MTX administration per os (PO) or subcutaneously (SC), anti-emetic as needed (PRN), not applicable (N/A).

minimize distraction and maximize engagement with the child, parents were seated with a Nurse Clinician in an area located behind the child and out of their visual range, and were asked not to interrupt the interview. Children remained engaged throughout the interview and did not interact with their parents. Interviews were audio-recorded and subsequently transcribed. Observational data were collected in the form of field notes (e.g., nonverbal behavior, tone of voice), and inserted into the transcripts to complement the interview data and facilitate analysis.

Table 2
Interview guide.

Interview question	Probes
Can you show and tell me about how you take your MTX (Use child's preferred name for MTX).	Who is in your family? Who helps with MTX? What room do you take your MTX in, time of day, routine after MTX administration?
How do you feel when you take your MTX?	When does the feeling happen? How long does it last? What do you do that makes it better? What do you do that makes it worse? Is there anything anyone else does that makes it better?
Do you ever worry about taking the MTX?	What do you worry about? When do you worry? How long does it last? Is there something that makes you worry less? Is there something that makes you worry more?
You said you feel like X (X = feeling/symptom/other stated by the child) when you take your MTX, what are some other things that make you feel like X?	What reminds you of MTX? Are there things other than the needle/pill that remind you of MTX?
Is it ever hard to do activities the day of or the day after taking MTX?	For example, is it difficult to play with your friends? To do sports? To do family activities (e.g. watching a movie, playing outside, etc.)? To do your chores at home? To do your homework? What makes it easier to do "Y" activity (Y = playing with friends, sports, family activities, or anything else the child might speak to)? Is there anything that makes it harder to do "Y" activity?
What would you like to tell other children who take MTX?	What would you tell them that makes it better when you take MTX? What would you tell them that makes it worse when you take MTX?

Trustworthiness

The trustworthiness of the data was ensured by establishing its credibility, confirmability, dependability and transferability (Polit & Beck, 2013). Credibility and confirmability were established through investigator triangulation and peer debriefing. Member checking was conducted with participants throughout the interviews to validate investigators' understanding of children's experiences. An audit trail of research activities was kept ensuring data dependability, and a thorough description of the participants and analytical process was recorded to facilitate transferability of study findings (Polit & Beck, 2013).

Data analysis

Data analysis took place after each set of interview data was collected. This allowed each interview to inform subsequent interviews, and facilitated an inductive approach to content analysis. Two of the investigators (JM, SK) independently read and re-read each transcript to get a sense of the interview as a whole and immerse themselves in the data (Granheim & Lundman, 2004; Sandelowski, 1995). They then conducted open-coding by reviewing the transcripts line-by-line and assigning a code that described each segment of text (Polit & Beck, 2012). The investigative team met weekly to review the codes and resolve any discrepancies in the coding process. An inductive content analysis was conducted, in which the research team drew connections between codes and identified broader data categories across interviews (Elo & Kyngäs, 2008; Polit & Beck, 2013). Concept maps were created to visualize the categories, draw connections between and across them and to identify overarching themes (Burnard, 1991; Burnard, Gill, Stewart, Treasure, & Chadwick, 2008). The observational data supported the verbal data and provided a deeper understanding of the child's experience.

Results

Three overarching themes emerged from the data. The first was, 'No kid likes taking MTX', and it included two sub-themes related to children's experiences with associative and anticipatory intolerance: (a) "Talking about it sometimes makes me feel sick", and (b) "Before I [take MTX], I have a little stomach ache." The second theme, 'The importance of strategies and routines,' captured the ways in which children managed MTX intolerance. The third theme, 'Working hard to live with MTX intolerance,' described children's struggle with MTX

intolerance beyond the day of administration, and how it affected other parts of their lives.

Theme 1: "no kid likes taking MTX"

Children expressed in simple, straightforward terms that they did not like MTX, stating "I don't like it" (P02, P04, P06, P07, P10) and "no kid likes taking MTX" (P02). They described experiencing negative physical and behavioural symptoms before, during and after MTX administration. Physical symptoms included nausea (P01, P02, P05-P07, P09-P13), vomiting (P01, P04-P07, P09-P13), stomach ache (P02, P04, P05, P07, P09, P13), fatigue (P05, P06, P13), increased salivation and spitting (P07, P10), gagging (P02), and loss of appetite (P04). Children expressed fear, worry and anxiety, and described behaviours including crying, protesting and shaking (P02, P07, P09, P10). Their dislike of MTX was also expressed through changes in body language observed during the interviews. Participants were animated and smiling while setting up their storyboard; whereas, their facial expressions became serious and their voices became quiet when talking about MTX (P01, P03, P04, P06, P07, P11).

"Talking about it sometimes makes me feel sick"

Associative MTX intolerance was triggered by sensory cues (visual, olfactory, somatosensory and taste). For example, one child said when she saw the sharps disposal container in her house, "I can see all the needles that I took, it just reminds me of, uh, how I felt those times" (P02). Another said, "I freak out," referring to when his mom took the injection out of the fridge. He explained that "freak out" meant "Like [pause], like I could die, like I'm gonna be sick [pause] and I could die" (P09). Another child shared that her "tummy feels weird when mommy puts the [lidocaine] cream on [my arm]" (P04), prior to her injection.

All children set up their felt storyboard with enthusiasm; however, when discussing MTX they were observed to become quiet, withdrawn and sad (P01, P04, P06, P11). Half of the participants (P03, P04, P06, P07, P11, P13) described feeling nauseous during their interviews. One child requested a drink of water to relieve his nausea (P06), while another (P04) said, "I wanna stop talking about that [MTX]". All who became nauseated were asked if they would like to discontinue the interview: Two decided to stop (P03, P04), while the rest chose to continue.

"Before [taking it] I have a little stomach ache"

For some children, the sensory cues associated with MTX intolerance provoked anticipatory symptoms. One child explained that when she went down to the basement and was about to receive her MTX, "I'm shaking and full of fear" (P02). The room in which she took her MTX became an environmental trigger, contributing to anticipatory MTX intolerance. Children clearly expressed their symptoms of anticipatory intolerance, describing nausea (P02, P13), and worry (P05, P07, P09, P10) prior to receiving MTX. Children also exhibited behavioural changes and expressed emotions such as feeling "scared of [MTX]" (P04) prior to its administration.

Theme 2: the importance of strategies and routines

Children described strategies to manage MTX intolerance that were established through a 'trial and error' process. Strategies were developed by the children themselves or with the help of family members and clinicians. Children reported various distraction techniques to manage MTX intolerance, such as watching TV during their injection (P02, P04, P06). Some relied on comfort measures like having their parents present to support them through the MTX administration process (P01, P02, P04, P06, P07, P09, P10, P12, P13). Others used self-talk strategies to manage their anxiety (P07, P10, P12), such as one child who told herself on the day of her injection, "it's not right now, it's later today" (P10). Going to sleep after receiving a MTX injection (P02, P06, P07, P09, P12) or having an injection done while they were asleep (P05, P11) was an effective way of managing intolerance for some children.

Having a consistent routine in place to manage MTX intolerance was important (P05, P09, P12, P13). All children described the administration routine in detail, including the day of the week and time of day they received MTX, the room of their house they received it in, and who prepared and gave them their medication. Deviations from that routine could result in negative outcomes, such as "feeling less confident" in their ability to manage intolerance (P13).

While some children attempted to "buy some time" by going to the washroom or picking out a stuffed toy to delay receiving their MTX (P02, P07, P10), this strategy was often accompanied by anxiety, worry and fear. One child described going to the basement on the day of her MTX injection: "I just [go down the stairs] in slow motion. [...] I never want to go there" (P02). In addition, management strategies could lose their effectiveness over time and become negatively associated with MTX. For example, one child played games on his computer tablet as a distraction strategy while his mom administered the MTX injection (P13). He said, "it helped keep my mind off of it, so I didn't feel as nauseous. But some of the video games I would play, when I played them without having the injection, would remind me of it and so I would feel nauseous."

Clinicians contributed to the management of MTX intolerance in a number of ways. For some children, pharmacological strategies such as taking an antiemetic (e.g. ginger lozenges, dimenhydrinate, ondansetron) before or after taking MTX were suggested and used (P05, P07, P09, P13). For others, changing the route of administration (e.g. PO to SC, or vice versa) was helpful in managing MTX intolerance (P05, P10, P13).

Theme 3: working hard to live with MTX intolerance

Children struggled with MTX intolerance beyond the day of administration, as it affected other parts of their lives. One child said, "well, for every minute of the day [after receiving MTX] I feel like I'm about to throw up." She went on to explain that the day after MTX administration, "it takes a little bit longer for me to do my homework… I lose my, uhh, like, focus" (P05). Symptoms slowed children down and made it difficult to focus on homework or play sports (P05, P12, P13). One child explained that the day after MTX administration "I feel a little weaker when I play [hockey], and when I skate fast I get nausea" (P13). Efforts were made to minimize the impact of MTX intolerance on extracurricular activities, (P05, P07, P12, P13). For one child, "when I would sing [at choir] on Sunday, I would ask to do it [MTX injection] on Friday because it would be easier for me." She elaborated on the reason for changing the day of her injection, saying "just in case I feel sick, even if I don't feel sick, just in case" (P05). Substantial trial and effort went into establishing a routine that did not interfere in other important parts of the child's life.

Some children found themselves thinking about MTX during the week. One child said she sometimes thought of MTX during recess at school on the day of her MTX administration (P10). Children appeared to compartmentalize the MTX administration process as they went on with their daily lives; however, MTX administration and intolerance remained an ongoing burden. Some children engaged in avoidant behaviours when faced with things they associated with MTX (i.e. alcohol swabs, apple juice) during the rest of the week (P02, P07, P10). One child described making a conscious effort to "just try to avoid it" (P02), in referring to associative reminders. These comments reflect the lengths that children went to, to cope with the effects of MTX intolerance on their lives.

Children in this study were all exposed to numerous and ongoing invasive procedures as part of their treatment, but were able to distinguish between their SC MTX injections and other, seemingly more invasive procedures, such as blood tests (P02, P04, P05, P06, P09, P10,

P12, P13) and intravenous infusions (P06, P09). They expressed how much harder it was to receive MTX injections, and voiced little to no issues with other invasive procedures. Once child explained, "Well, for my MTX sometimes I feel sick after, but for the blood test it just hurts a little when you put [the needle] in and you take it out" (P05). Another participant went as far as saying "needles are not in blood tests" (P04). Children explained that MTX administration differed from the other interventions because of MTX intolerance (P02, P05, P06, P10, P12, P13). One child explained what bothered her was: "the way I feel after [receiving MTX]" (P02). This contrast between SC MTX injections and other invasive procedures was striking.

Discussion

Using a child-centered, participatory research approach allowed us to capture school-age children's voices and gain a comprehensive understanding of their experiences with MTX intolerance. Study results shed new light on children's emotional and behavioural responses to MTX intolerance, the management strategies they use to cope with it, and how hard they work to live with MTX intolerance. Consistent with previous literature, physical symptoms, particularly nausea and vomiting, were found to be extremely challenging (Bulatović et al., 2011; Mulligan et al., 2013; Mulligan et al., 2015). This discussion will focus on the development of anticipatory nausea and vomiting in these children and the potential importance of anti-emetics at the initiation of MTX treatment. We will also examine the challenges experienced by these children in managing MTX intolerance, and implications for clinical practice.

Children provided detailed information regarding the anticipatory nausea and vomiting they experienced resulting from MTX intolerance. Theme 1 of our results, "Talking about it sometimes makes me feel sick," is an example of anticipatory nausea and vomiting which has been studied extensively in pediatric cancer patients. It has been described as a classic Pavlovian conditioned response resulting from chemotherapy treatment and its associated environmental triggers (Dupuis et al., 2014; Roscoe, Morrow, Hickok, & Stern, 2000; Tyc, Mulhern, & Bieberich, 1997). Participants in our study described a wide variety of associations that provoked MTX intolerance, including the smell of alcohol swabs used to clean their skin, the sight of their MTX injection and the taste of apple juice, when they took with their MTX. Typically, anti-emetics were started after the child developed anticipatory nausea and vomiting; however, despite use of pharmacological treatment, children expressed limited relief of their physical symptoms. For some participants, the anti-emetic became one of the conditioned stimuli triggering their anticipatory and associative nausea and vomiting. Once a conditioned response develops, it is challenging for clinicians to effectively treat anticipatory symptoms, as they are strongly associated with sensory stimuli (Dupuis et al., 2014; Roscoe et al., 2000). For pediatric patients at risk of developing anticipatory and associative nausea, treatment should be aimed at preventing this conditioned response.

Children with Crohn's disease and irritable bowel syndrome (IBS) undergoing MTX treatment regimens similar to those with JIA also experience anticipatory nausea and vomiting, as described in Theme 1 of our findings (Dupont-Lucas et al., 2017; Kempiska et al., 2011; Van der Meer et al., 2007). A retrospective study compared children with Crohn's disease who were premedicated with ondansetron 30 to 60 min before taking MTX at initiation of their treatment regimen ($n = 50$), with those who were not premedicated ($n = 10$) (Kempiska et al., 2011). Only 2% ($n = 1/50$) of premedicated children experienced nausea within the first 3 months of treatment, compared to 60% ($n = 6/10$) of those who were not premedicated, highlighting the importance of examining the efficacy of premedication with anti-emetics at initiation of MTX treatment in children with JIA. In contrast, in a study involving children with inflammatory bowel disease treated with MTX, the MISS questionnaire was used to identify risk factors for MTX intolerance (Dupont-Lucas et al., 2017). They found that the use of anti-emetics at initiation of treatment was not significant in preventing symptoms of MTX intolerance. The investigators suggested that noncompliance with the anti-emetic may have been a limitation (Dupont-Lucas et al., 2017). Considering opposing findings in these two studies regarding the success in preventing MTX intolerance with use of anti-emetics at initiation of MTX treatment, further research is required prior to making recommendations for premedication with anti-emetics at initiation of MTX treatment for children with JIA.

Children with chronic illness face many challenges in learning to manage their disease and the numerous elements of care that it involves (Boekaerts & Roder, 1999). While children in our study expressed discomfort and worry about receiving MTX injections, they reported that undergoing arguably more invasive procedures, such as blood tests and intravenous infusions, was not difficult. In Theme 2 of our results regarding the importance of routines and strategies, children described implementing numerous strategies to manage MTX intolerance. Despite their efforts these strategies were not always effective, leaving them to manage a considerable emotional burden as described in Theme 3 of our results "working hard to live with MTX intolerance". The stress and coping literature suggests that emotional reactions and behavioural responses to a stressor are determined by one's cognitive appraisal of the stressor and their available coping resources to address it (Boekaerts & Roder, 1999; Lazarus & Folkman, 1984). Children may have appraised blood tests and intravenous infusions as easier to endure because they had the resources to manage them whereas this was not the case with MTX intolerance. In fact, they identified their struggles with MTX intolerance as the most challenging and distressing difference between venipuncture and MTX injections. The interference of MTX intolerance with children's regular daily activities suggests they lacked much-needed resources to manage it.

Practice implications

Study findings highlight the importance of prioritizing early identification and prevention of MTX intolerance. At the initiation of MTX treatment, it is crucial to inform parents of the physical symptoms, behaviours and emotions children may experience. Questions regarding the child's behaviour (e.g. avoidance, crying, protesting) before, during and after MTX administration can be asked during follow-up visits to identify subtle cues that may indicate early signs of anticipatory and associative MTX intolerance. Assessing these signs and symptoms is necessary for clinicians and families to better detect and manage MTX intolerance. Child-appropriate assessment methods are needed in the clinical setting to elicit the child's direct thoughts and feelings. Finally, the development of clinical guidelines to track MTX intolerance in children with JIA may help identify those at risk and promote early intervention.

Limitations

To maximize participant comfort during the interview, parents were invited to remain with their child, and all agreed to do so. Although parents sat behind their child in the interview room and did not participate, children may nevertheless have expressed themselves differently or revealed additional details regarding their experiences if their parents had not been physically present. In addition, while steps were taken to maximize the transferability of study findings, children with JIA who are followed in other clinics may receive different treatment protocols that could influence their experience with MTX intolerance. Collecting data from multiple sites would provide a broader context for understanding children's experiences, potentially adding a new perspective to our findings.

Conclusion

This study sheds new light on the experiences of school-age children with JIA who develop MTX intolerance. Participants were able to

express their thoughts and feelings clearly using a child-centred, storyboard interview technique. The weekly experience of receiving MTX was found to be distressing and challenging for children. Once anticipatory and associative nausea and vomiting had developed, it was especially difficult to implement strategies to manage MTX intolerance. Health care interventions are needed to provide optimal and accessible support for these children to prevent and manage MTX intolerance.

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Institution where work performed

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CRediT authorship contribution statement

Sarah Khan: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jacqueline Mancini:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Charlene Hopper:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Resources, Writing - review & editing. **Janet E. Rennick:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Resources, Writing - review & editing.

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