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Patient preferences for prophylactic regimens requiring regular injections in children and adolescents: a systematic review and thematic analysis

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ABSTRACT

Background At present, limited literature exists exploring patient preferences for prophylactic treatment of acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Given low treatment completion rates to this treatment in Australia, where the burden of disease predominantly affects Aboriginal and Torres Strait Islander people, an improved understanding of factors driving patient preference is required to improve outcomes. Due to limited available literature, this review sought to explore treatment preferences for conditions for which the findings might be generalisable to the ARF/RHD context.

Objective Explore treatment preferences of patients, parents/caregivers and healthcare providers towards regular injection regimens in paediatric and adolescent populations for any chronic condition. Findings will be applied to the development of benzathine penicillin G (BPG) prophylactic regimens that are informed by treatment preferences of patients and their caregivers. This in turn should contribute to optimisation of successful BPG delivery.

Methods A systematic review of databases (Medline, Embase and Global Health) was conducted using a search strategy developed with expert librarian input. Studies were selected using a two-stage process: (1) title and abstract screen and (2) full text review. Data were extracted using a reviewer-developed template and appraised using the JBI Critical Appraisal tool. Data were synthesised according to a thematic analytical framework.

Results 1725 papers were identified by the database search, conducted between 12 February 2022 and 8 April 2022, and 25 were included in the review. Line-by-line coding to search for concepts generated 20 descriptive themes. From these, five overarching analytical themes were derived inductively: (1) ease of use, (2) tolerability of injection, (3) impact on daily life, (4) patient/caregiver agency and (5) home/healthcare interface.

Conclusions The findings of this review may be used to inform the development of preference-led regular injection regimens for paediatric and adolescent patient cohorts—specifically for BPG administration in ARF/RHD secondary prophylaxis.

Trial registration number Patient, parent and health personnel preferences towards regular injection regimes in paediatric and adolescent populations—a protocol for a systematic review. PROSPERO 2021 CRD42021284375.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Currently, there are low rates of successful delivery of benzathine penicillin G (BPG) for secondary prophylaxis of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in Australia. There is a lack of research exploring patient preferences for regular BPG delivery for secondary ARF/RHD prophylaxis. This review explores patient preferences for regular injection delivery in a paediatric and adolescent patient cohort.

WHAT THIS STUDY ADDS

⇒ This review outlined five analytical themes pertaining to patient preference for regular injection delivery: ease of use, tolerability of injection, impact on daily life, patient/caregiver agency and home/healthcare interface. These themes may be applied to the optimisation of successful BPG delivery in a paediatric/adolescent cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this review contribute to a larger body of existing and ongoing qualitative research to establish best-practice care for secondary prophylaxis of ARF/RHD. This review promotes measures such as improving ease of use, focusing on care engagement and working with patients and their families to improve coping mechanisms to promote successful BPG delivery.

Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021284375.

INTRODUCTION

Rheumatic heart disease (RHD) is an end-stage cardiac condition developing in childhood or adolescence from extensive valvular damage following recurrent episodes of acute rheumatic fever (ARF) caused by *Streptococcus pyogenes* (group A *Streptococcus*, Strep A) infections. In Australia and other high-income countries, this condition disproportionately

affects First Nations peoples and represents the major driver of cardiovascular inequity.[1] At present, the standard of practice for the treatment and prevention of ARF and RHD is secondary prophylaxis with monthly intramuscular injections of benzathine penicillin G (BPG) to prevent further Strep A throat or skin infections.[2] Successful delivery of >80% of planned injections reduces ARF recurrences and RHD progression.[3]

Having to attend a medical practice every 3–4 weeks for a minimum of 5 years or until the age of 21 (depending on which is longest) to receive the injections is difficult for patients, who are typically from rural or remote populations. Furthermore, patients also report that the injections are especially painful, providing an additional obstacle to effective treatment.[1 2] As a result, BPG intramuscular injections for patients with ARF/RHD in Australia remain limited in their effectiveness as a prophylactic measure. A 10-year study of a Far North Queensland paediatric population showed that only 4% of patients received >50% of BPG within the 28-day timeframe required to optimise prophylaxis, and none of the patients within the cohort received the recommended dose of >80%.[4]

Consideration of treatment preferences may provide an insight into ways to improve successful delivery of regular injection regimens in vulnerable paediatric populations. Patient preference is defined as 'the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions'.[5] Furthermore, they are an aggregate of diverse attributes that combine to define an individual preference, such as age, gender, socioeconomic status and community and cultural considerations. Understanding the complexities of patient preferences has direct relevance to clinical decision-making and 'may reveal critical determinants of the decisional processing of patients and […] detect crucial factors to explain and predict health-related decisions'.[5] Understanding patient preferences and offering flexible options are likely to be critical to improving successful delivery of BPG as secondary prophylaxis for ARF/RHD.

Initially, this review aimed to explore preferences of patients, caregivers and healthcare providers (HCPs) regarding BPG administration specifically in the context of ARF/RHD. An initial scoping review did not identify a body of literature available for BPG treatment preferences. Therefore, the scope of the review was expanded to explore treatment preferences for any regular injectable medications for children and adolescents to capture sufficient data which were generalisable to the ARF/RHD context. Furthermore, preferences of patients, parents/caregivers and HCPs were all addressed, as family and HCP input are a vital component of health decision-making within a paediatric context.[6] The overarching aim was to inform the development of more patient-centric and culturally secure BPG regimens, which might improve secondary prophylaxis programmes.

METHODS

This review was developed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist criteria.[7] The protocol was registered with PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=284375.

Study eligibility and inclusion criteria

The inclusion criteria for eligible studies were framed around the Population, Intervention, Comparison and Outcomes framework[7] and focused on (1) ensuring the age of patient cohort, (2) elicitation of preferences and (3) generalisability of preference findings to best comply with the review objectives. Studies were excluded if they did not include children or adolescents as distinct study groups, did not elicit or explore preferences, explored preference in the context of symptomatic or efficacy outcomes relevant to another condition (meaning that findings were not generalisable), did not investigate regular injection regimens (such as vaccinations or acute parenteral treatments) or were secondary literature.

Search strategy

The search strategy (online supplemental appendix A) was applied to the following databases: Ovid MEDLINE(R) ALL (OVID), Embase (OVID) and Global Health (OVID). Contact with subject matter experts and bibliography searches were also used to supplement these searches and mitigate the risk of publication bias.

Screening and data extraction

Relevant studies were selected by means of a two-stage strategy, starting with title and abstract, to determine if the publication met specified inclusion criteria. Following this, studies were appraised at full length against the inclusion criteria. The search strategy occurred between 12 February 2022 and 8 April 2022. This was conducted by a lead reviewer (JI) with further evaluation by a second reviewer (RT). A third reviewer (HW) was available to adjudicate in the case of discordant assessments.

The data extraction process of the included studies was performed according to the predetermined Data Extraction Template (online supplemental appendix B). The data collected for each study were compiled in the template and compared prior to synthesis. The Data Extraction Template was developed under the guidance of the Cochrane Handbook Data Collection Checklist[8] and research team input. Critical appraisal of each study using the JBI critical appraisal tool was included in the Data Extraction process.

Data synthesis

Given the qualitative nature of the available data, a thematic analysis of the data was conducted. A thematic analysis involves the initial identification of line-by-line 'codes' which are then collated across the literature and grouped into descriptive themes. These descriptive themes are then synthesised into analytical themes. An

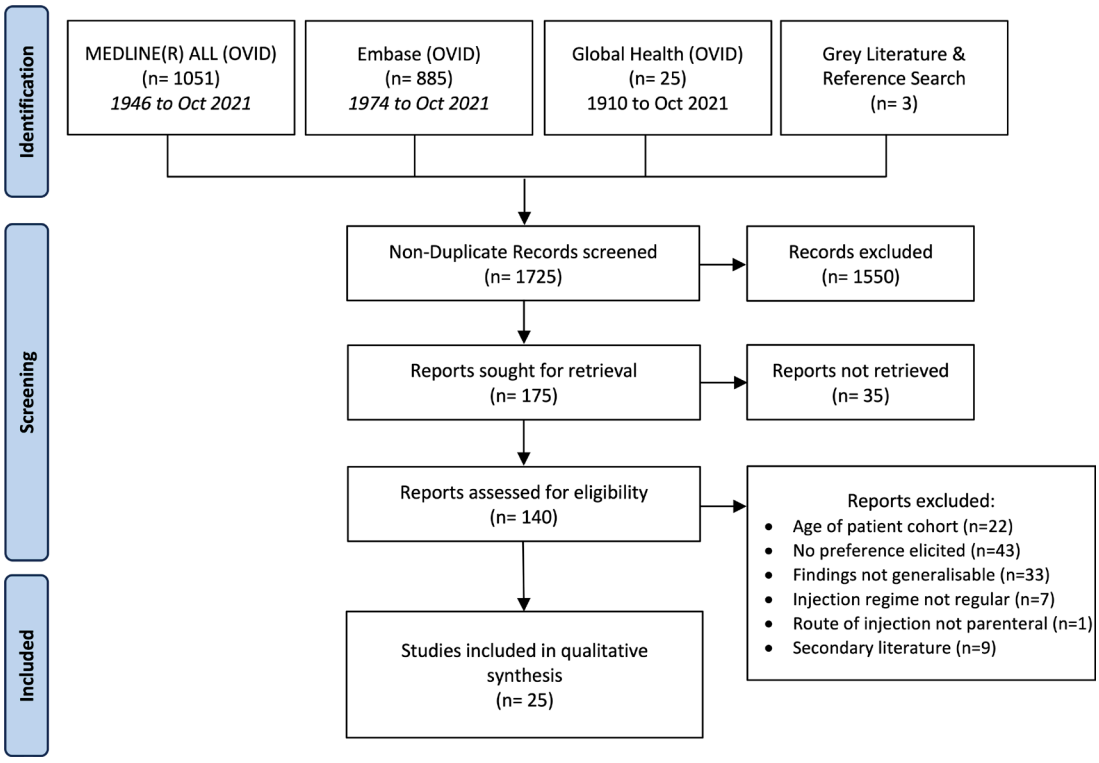

Figure 1 PRISMA flow diagram of eligible studies available for data synthesis.

exploratory approach to analysis was taken, meaning codes and themes were content driven, rather than predetermined.[9] Themes were tabulated and analysed more closely to allow for discussion of review findings. Quantitative data were also described within the thematic analytical framework.

RESULTS

Summary of included studies

1961 papers were identified across the initial database searches, with three additional papers arising from contact with subject matter experts and bibliography searches. Following deduplication, 1725 papers were screened according to title and abstract. This process was duplicated by two reviewers (JI/RT) independently. After discussion and resolution of any discrepancies in selection, it was determined that 175 studies were to be reviewed in full. 140 full texts were retrieved for full-text review, and 25 of these studies were included in the final review as per the prespecified inclusion criteria.[10–34] A PRISMA flow diagram summarising the study selection process is shown (figure 1). The characteristics of the studies included in the review are described below (table 1). The condition seen most frequently across the included studies was growth hormone deficiency (GHD) (n=11) or any condition requiring treatment with recombinant human growth hormone (r-hGH), with the remaining studies exploring treatment preferences of paediatric rheumatological disease (n=4), type 1 diabetes mellitus (n=2) and malignancy (n=2). The remaining conditions (n=6) (classified as 'Other' in table 1) included thrombosis, primary immunodeficiency, HIV, allergic airway disease and chronic paediatric disease more broadly. There was one study of preferences in RHD.

Most studies were conducted in Europe, with some from North America, Oceania (New Zealand and Australia only) and Asia, sometimes spanning several regions. Overall, the review was marked by an absence of studies in low-income and middle-income countries, which may have implications for the generalisability of findings beyond high-income settings. The study setting was most commonly in outpatient paediatric clinics.

The preferences most widely elicited were those of patients. Preferences of parents were often explored in the context of the child-caregiver 'dyad',[18] and typically, multiple preferences were explored per study.

Data were also collected regarding the age of the subject patient cohort; however, given the discrepancies in the reporting age across the studies, it was not analysed. Overall, four studies separately classified children and adolescents/teenagers, each giving different age ranges for the two groups. One study had a patient cohort of <12 months.[26] All remaining studies captured an age range, typically spanning from early childhood (1–5 years of age) to adolescence (17–18 years of age), as indicated either by provided age ranges or by median age. Revisions to the age requirement of inclusion criteria were made to accommodate for several studies which included patients up to the age of 26 years in the 'young adult' category. Two studies[24 30] also included adult cohorts, but separated data by age group were available and the findings relevant

Table 1 Baseline characteristics of studies reporting preferences for children and young people receiving regular injectable medications

Study characteristic		Number of studies (n)
Condition	Growth hormone deficiency	11
	Paediatric rheumatological disease	4
	T1DM	2
	Malignancy	2
	Other	6
Region	Europe	15
	Northern America	6
	Oceania	4
	Western Asia	2
	Eastern Asia	1
Setting	Paediatric specialist clinic	11
	Focus group	4
	Computer based	3
	Home	2
	Inpatient	1
	Other/not specified	5
Preference elicited	Patient	18
	Caregiver	14
	Patient-caregiver dyad	4
	Healthcare provider	4

T1DM, type 1 diabetes mellitus.

to adult patients were not included. Several studies did not explicitly state age ranges, rather classifying patients solely as 'paediatric'. These were still included in the review (table 1). The characteristics of findings from individual studies for hGH and other injectable medications are provided (tables 2 and 3, respectively).

Thematic analysis

The application of a thematic analytical framework generated an initial 20 descriptive subthemes across the included studies. Extraction of 'key concepts' from these subthemes saw five analytical themes emerge: ease of use (n=18), impact on daily life (n=9), patient/caregiver agency (n=9), home/healthcare interface (n=6) and tolerability of injection (n=10; figure 2). There is significant overlap within the subthemes that comprise these overarching thematic frameworks, which are discussed in greater depth below. These analytical themes were elicited by the primary reviewer (JI) and discussed with a secondary reviewer (RT) to ensure consistency of interpretation.

Ease of use

This theme emerged most consistently across all included studies, with 18 studies generating relevant subthemes. Preferences for ease of preparation of injection, injection administration, convenience, storage and route of administration from patients, caregivers and HCPs alike were the most prevalent subthemes contributing to this analytical theme. Device features were found to drive preference when they ensured that '[a] treatment plan [was] easier to follow'.[29] Another study found that the 'highest value was placed on device features associated with ease of use'.[21] Attributes reflecting convenience, ease of preparation and storage, such as 'no mixing required', 'room temperature stable' and 'confirmation of dose delivery', were rated most highly by parents in the study, while the lowest ranked feature was 'electronic vs manual operation'.[25] Autoinjectors and prefilled devices were consistently preferred over devices requiring manual loading or mixing, particularly in the context of parent/caregiver or self-administration.[10 11 13 17–25 27–29 31 33 34]

There was also a significant interplay between ease of use and themes of patient/caregiver agency and reduction of conflict at the home/healthcare interface—with studies finding that devices that were more intuitive to use conferred greater confidence and a sense of control of health outcomes, particularly in parents/caregivers and adolescents.[10 17 19 22 28] The quality of instructions and convenience and comfort of use were 'far more likely to result in self-administration' in patients 10 years or older.[17] Similar findings were noted where a much higher proportion (32% vs 5% and 47% vs 18% of children in the 10–12 and 12+ years of age categories, respectively) were able to prepare their injection unassisted using a novel device compared with an older version. These findings corresponded with "[feeling] that ease of use was much greater" with the novel device and preferred by patients.[22]

The need for training was also a driver of physician preference for a device or regimen.[10] Ease of use was also found to be a driver of physician preference for regular injection regimes in a clinical setting, second only to standard/institutional protocol.[13]

Tolerability of injection

Tolerability was identified from subthemes including device features, pain, fear/anxiety and reliability of device. Device features were a central subtheme where studies explored preferences for novel treatment devices compared with older models. These studies largely showed that device attributes improving tolerability of injection/overall procedure increased satisfaction. For example, the ability to adjust needle visibility was rated highly by parents and mitigated injection anxiety.[11 14 22 23 25 27 30 32–34]

Pain also comprised a significant component of device feature preferences. Features associated with lower levels of pain, as perceived by both patients and caregivers, were consistently preferred.[11 27 30 33] Minimisation of site reaction, such as bruising or rashes, had a significant effect on the acceptability of treatment in some[11 32] but was not universal,[22] perhaps suggesting the variability in tolerability across different study cohorts. The notion of

Table 2 Key characteristics summary of included human growth hormone (hGH) deficiency studies

Method studied/ reference	Country	Participant characteristics	Outcomes accessed	Preferred treatment characteristics	Associated analytical theme
Family choice of injection devices for GH therapy [11]	UK	Children and their parents attending a paediatric endocrine clinic (n=56). Median age of 13 years	Key attributes associated with utility levels using computer-based interviews	▶ Lack of bruising, autoinjection (device feature) and lack of pain. ▶ Least important factor was home delivery of drugs and nurse support at home	▶ Ease of use ▶ Tolerability of injection ▶ Home/ healthcare interface
Evaluation of a pen injector for GH[17]	New Zealand	Children and parents of children on hGH treatment (n=77)	Via questionnaires, subjects perception of associated benefits, adequacy of instructions, satisfaction of information and response to treatment	▶ Preference for pen due to: self-administration, device characteristics (convenience and comfort) and instruction quality	▶ Ease of use ▶ Patient/ caregiver agency
Disposable self-injector pen vs reusable pen for administration of hGH [18]	USA	Children and their caregivers (n=91 boys, 45 girls). Mean age of 12.3 years	Injection Pen Assessment Questionnaire (IPAQ), accessed ease of use, convenience, education and preference	▶ Preference for disposable pen was due to: preparation ease, ease of use and administration characteristics	▶ Ease of use
Comparison of three injection devices: Norditropin FlexPro Pen (FP), Genotropin GoQuick (GQ), Norditropin NordiFlex (NF) [21]	Germany	Subjects diagnosed with GHD, TS or short stature (n=64). Age range: >10 to <18 years old	Subjects device preferences regarding device features, overall ease of learning, ease of use and preference using a series of questionnaires	▶ FP was easier to use and learn	▶ Ease of use
Needle-free device with a lower injection volume[22]	The Netherlands	Subjects who had been prescribed standard GHT and standard care (n=73). Mean age 10 years (SD 3.6 years)	Satisfaction, ease and frequency of reconstitution, painful sensations/bruising during administration and preference were measured through a questionnaire and diary	▶ New device preference due to ease of use, lower pain/bruises and self-administration	▶ Ease of use ▶ Tolerability of injection
Treatment experience of NordiFlex device[23]	South Korea	Patients who previously used NordiLet/other devices and had used another GH device (n=94). Age range 4 to ≤18 years	Three-part survey to access GH device preference and ease of use, self-efficacy, positive feeling about injection and minimal disruption to daily life	▶ Usability, minimal disruption to daily life and self-efficacy	▶ Ease of use ▶ Tolerability of injection ▶ Impact on daily life ▶ Patient/ caregiver agency
Factors driving patient preferences for GHD injection regimen and injection device features[24]	USA	Child, adolescent and adult patients with a clinically confirmed diagnosis of GHD (n=224). Age range: paediatric 3–17 years (and caregivers) and adults (>25 years)	Evaluation of factors driving preferences for r-hGH injection regimen and device features via DCE administered online questionnaire	▶ Device characteristics (autoinjector), ease of preparation and injection schedule	▶ Ease of use ▶ Impact on daily life

Continued

Table 2 Continued

Method studied/ reference	Country	Participant characteristics	Outcomes accessed	Preferred treatment characteristics	Associated analytical theme
Preferred features of GH injection devices[25]	Switzerland	Parents who had children (1–18 years) without GHD (n=192). Average age of respondents was 40.2 years	Closed-design, web-based questionnaire measuring preferences and willingness to pay for specific attribute	► Storage and preparation convenience, device features and improved parent confidence	► Ease of use ► Tolerability of injection ► Patient/ caregiver agency
Preferred attributes of r-hGH administration[28]	France, Germany, Italy, UK and USA	Individuals with experience in r-hGH administration (parents (with children <14 years old), teenage patients (13–15 years old) and physicians and nurses) (n=67)	Through a questionnaire, 19 attributes were assessed to evaluate the importance of ergonomics, functionality and the psychological impact of device	► Reliability, ease of use, lack of pain, safety, storage requirements and number of steps in preparation prior to use	► Ease of use
Attitudes towards a reusable self-injection system (SurePal)[29]	France, Germany and the UK	Paediatric patients with GH deficiency, turner syndrome (TS), small gestational age, Prader-Willi syndrome, chronic renal failure (n=550). Mean age 10.8 years	Questionnaire measured attitudes on, attractiveness of device, training received, the low drug-wastage system and experience compared with other devices	► Ease of preparation and administration	► Ease of use ► Impact on daily life
Needle-free device for GH[31]	USA	Children (aged 4–10 years) with type 1 diabetes mellitus (n=50)	A survey compared characteristics of a needle-free device to subjects morning insulin needle injection	► Pan, easier preparation and administration	► Ease of use

DCE, discrete choice experiment; GHD, growth hormone deficiency; GHT, growth hormone treatment; r-hGH, recombinant human growth hormone.

variability in what constitutes tolerability was highlighted by the finding that patients with a longer course of disease or from an older age group had a reduced preference for sedation during intra-articular corticosteroid injections in juvenile idiopathic arthritis (JIA).[14] Similarly, patients with a longer course of disease and their caregivers considering a novel r-hGH device 'may be more sensitive to device features that improve treatment experience'.[23]

Safety profile and efficacy of treatments are also widely cited as central to preference for a novel treatment or alternative regime.[30 32] Although this was specifically not included in the review given the lack of capacity to generalise these findings, preferences elicited by patients or their caregivers for alternative injection regimes are developed on the basis that the change in regime will not alter health outcomes for the patient.

Impact on daily life

Impact on daily life overlapped with other analytical themes. Injection frequency was an important component of preference and adherence; 'less frequency',[30] 'injection schedule'[24] and 'minimal disruption of daily life'[23] were each separately shown to be highly scoring factors driving preference for device/regimen attributes. In particular, adolescents showed a greater desire to switch to a less frequent injection schedule.[12 15 23 24 29 30 32–34]

Adolescents also cited reasons such as 'feeling ashamed' and 'being reminded of disease throughout the day' by a device that remains in situ.[15] This sentiment was echoed in patients suggesting that adherence may be improved by 'removing (the) constant daily reminder' when using a long-acting treatment option[32] and expressing satisfaction with 'life quality, school success and reduced school absenteeism' with less frequent dosing.[12] These findings highlight the importance of a treatment schedule that promotes normalcy and privacy for patients with chronic disease.

The routine of regular injections may paradoxically enhance successful delivery. For children experiencing regular methotrexate injections for JIA, blood tests were reported as more painful than the regular subcutaneous injections, due to 'the firm routines families had established at home. Children did not have to worry about variations in everyday injection procedures, while blood tests could be performed in unpredictable ways'.[33] Routine was also considered as an enabler for adherence by HCPs and patients in a study exploring the acceptability of a

Table 3 Key characteristics summary of included studies (excluding hGH papers)

Method studied/ reference	Country	Participant characteristics	Outcomes assessed	Preferred treatment characteristics	Associated analytical theme
Insulin pen-NovoPen Echo[10]	Canada, Finland, Israel and Sweden	Participants diagnosed with type 1 diabetes (n=315). Aged 2–18 years	Rating effects of memory function in paediatric insulin devices	► Preference for NovoPen: ease of preparation, administration and improved confidence	► Ease of use ► Patient/caregiver agency
Effect of subcutaneous tocilizumab (TCZ) administration on patient satisfaction and disease control[12]	Turkey	Paediatric patients diagnosed with juvenile idiopathic arthritis (JIA) (n=39) who were switched from TCZ-IV to TCZ-SC (n=9). Age range 8.6–13.5 years	Questionnaire evaluating improvement in school performance, happiness with the drug and general satisfaction	► Improved quality of life, school success and improved school attendance	► Impact on daily life
Intravenous and intramuscular administration of asparaginase[13]	USA	Paediatric medical professionals who treat patients with acute lymphoblastic leukaemia (ALL) (n=74)	Online survey accessing practices and attitudes of physicians	► Intravenous preferences due to the ease of administration, patient preference and convenience	► Ease of use
Patient and parent preference of sedation vs no sedation for intra-articular corticosteroid injections (IACI)[14]	Bolivia	Patients and their parents who had received IACI with and without sedation (n=45). Median age 10.6 years	Preference for anaesthesiologist-controlled deep sedation with sevoflurane vs no sedation and associated characteristics	► Most children prefer to receive IACI under sedation due to pain, whereas parents tended to prefer avoiding the risk	► Tolerability of injection
Insuflon device (ID) for the administration of [15]	The Netherlands	Children receiving chemotherapy or requiring stem cell mobilisation (n=29). Median age of 3 years	Patient preferences for benefits, side effects and form of administration for ID	► Preferred characteristics of ID was due to usability, reliability and safety in the care of children	► Impact on daily life
Intravenous IgG (IVIg) treatment vs home treatment with subcutaneous IgG (SCIg)[16]	Sweden	Children aged >1–<18 years with documented PID requiring IgG replacement therapy (n=12). Median age 10.9 years	Questionnaires assessed quality of life and healthcare resource utilisation following treatment change	► Preference of SCIg treatment: increased independence, freedom, reduced healthcare utilisation and improved quality of life	► Home/ healthcare interface
Preference and usability of the NovoTwist insulin pen needle vs conventional screw thread needles[19]	UK	Children and adolescents with type 1 diabetes being treated with insulin (n=30). Age range 6–17 years	Preference and perception of ease of learning, ease of attachment and detachment of needle, and ease of disposal	► Preferred characteristics of NovoTwist included ease of attachment/ detachment and ease of use	► Ease of use

Continued

Table 3 Continued

Method studied/ reference	Country	Participant characteristics	Outcomes assessed	Preferred treatment characteristics	Associated analytical theme
Perspectives and knowledge around allergen-specific immunotherapy (ASI) of parents[20]	Turkey	Parents whose children were diagnosed with asthma and/or allergic rhinitis with positive skin prick test (n=198)	Survey evaluating the demographical and sociocultural characteristics of parents, knowledge levels and perspectives of parents	► Parents prefer sublingual ASI due to ease of use and lower risk of severe side effects	► Ease of use
Experience of parents who have given their infant enoxaparin[26]	Australia	Parents/caregivers of children <12 months (n=11)	Experiences and educational needs of parents/caregivers	► Parents felt overwhelmed by experience of managing treatment and high importance on education	► Patient/caregiver agency ► Home/ healthcare interface
Prefilled pen vs prefilled syringe of methotrexate (MTX) subcutaneous injection[27]	Poland	Children diagnosed with JIA with ongoing subcutaneous MTX therapy (n=23). Median age 11.7 years	Preference for the MTX prefilled pen vs prefilled syringe after 1 month of treatment and comparison of experiences	► MTX preference due to pain, ease of preparation and higher confidence	► Ease of use ► Tolerability of injection
BPG reformulation preferences towards a new penicillin treatment[30]	New Zealand	Children (n=50) (age range 10–21 years) receiving regular BPG injections for ARF/RHD, their family members (n=40) and health professionals (n=43)	Explored factors included experiences, preferences and drug characteristics for a new penicillin prevention and barriers and enablers to treatment	► Pain, provide alternative route of administration, reduce frequency, remove injections	► Tolerability of injection ► Impact on daily life ► Patient/caregiver agency ► Home/ healthcare interface
Acceptability of long-acting injectable antiretroviral treatment (LAI-ART)[32]	USA	Experienced HIV care providers (n=7), persons living with HIV (PLWH) (n=31) and parents of children living with HIV (n=5)	Semistructured focus group discussions to examine acceptability of LAI-ART, initial perception and desired attributes was examined	► Fear of needles, preference for clinic administration (avoid self-administration), cost and reduced injection frequency	► Tolerability of injection ► Impact on daily life ► Patient/caregiver agency ► Home/ healthcare interface
Effects of regular needle injections on children and their parents' daily living[33]	Norway	Children with rheumatic disease (RD) aged 6–17 years (n=16) and their parents (n=16) who recently started needle injection treatment	Individual interviews and focus groups evaluated the effects of regular needle injections on daily living	► Difficulties incorporating injections into lives, pain, fear, lack of confidence from parents	► Ease of use ► Tolerability of injection ► Patient/caregiver agency ► Home/ healthcare interface
Barriers to administering non-oral medicines to children with chronic conditions[34]	UK	Children and their parents with chronic conditions (n=90). Age range 0–17 years	Semistructured interviews examined 88 barriers to administering non-oral medication	► Barriers: difficult preparation, injection administration, disruption to life	► Ease of use ► Tolerability of injection ► Impact on daily life

ARF, acute rheumatic fever; BPG, benzathine penicillin G; JIA, juvenile idiopathic arthritis; RHD, rheumatic heart disease.

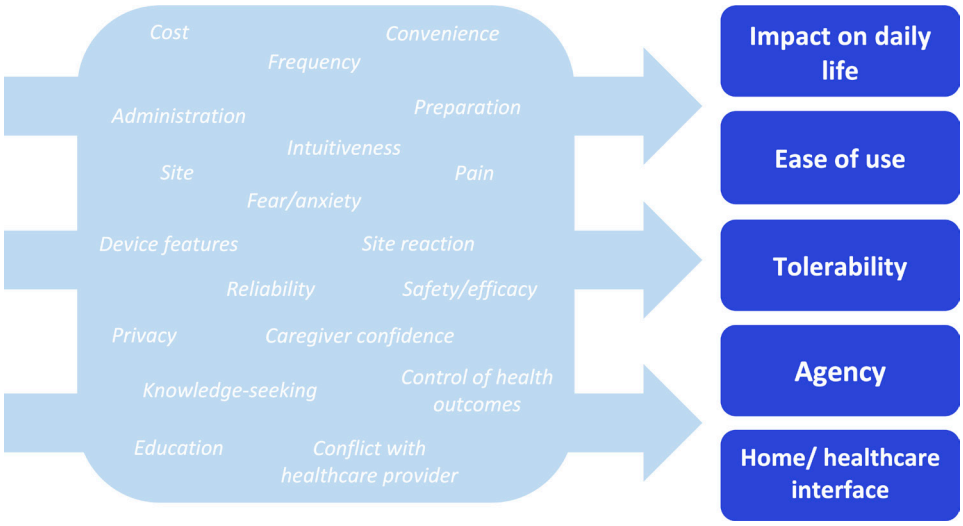

Figure 2 Depiction of the data synthesis process, identified descriptive subthemes corresponding to overarching analytical themes.

long-acting antiretroviral treatment in HIV, citing provider concerns about adherence for dosing intervals greater than weekly due to 'lack of consistent routine (causing) decreased care engagement'. The same study found that multiple injections per dose were deemed intolerable by patients, even at the cost of reduced frequency of visits.[32] These findings elucidate the interplay between perceived ease of treatment due to minimised impact on daily life and preferences for actual outcomes.

Patient/caregiver agency

Despite the use of an inductive approach to thematic analysis, there were several predicted areas of discussion prior to synthesis. This theme emerged unanticipated. Street *et al*[35] described patient agency as a way of describing engagement and motivation, requiring skills across the spectrum of participation of care. In this review, the theme of patient/caregiver agency developed from descriptive subthemes of knowledge-seeking behaviour, seeking control of health outcomes, education and caregiver confidence as factors driving preference.[10 15 17 23 25 26 30 32 33]

Notably, control of health outcomes emerged in preferences expressed by adolescent patients. For example, one study found that 8 out of 29 patients preferred subcutaneous daily injections over the use of an Insuflon device (requiring weekly changes) for the administration of granulocyte colony-stimulating factor in paediatric patients with cancer.[15] While the median age of the study was 3 years, the median age of patients preferring subcutaneous daily injections was 13 years. Older children reported that 'the feeling of control over their life and disease was improved by administering the daily injections by themselves'.[15] A further study emphasised the 'children's need to participate in healthcare decision making', finding self-administration and/or participation in the implementation of needle procedures a motivational factor for patients.[33] A perception of control was even found to be the preferred coping strategy over distraction.[23]

Caregiver confidence also emerged as a significant subtheme. Studies exploring ease of use found that device intuitiveness corresponded with caregiver confidence.[28 31] Caregiver confidence was also dictated by education and available support. Several studies cited patient and caregiver education needs being unmet in clinical settings and translating to poorer caregiver confidence and fear/anxiety for patients. In one study, parents administering enoxaparin to infant children overwhelmingly found the process 'difficult and confronting'.[26] Parents with access to a specialised nurse described the support and capacity to contact someone with an understanding of their situation as 'hugely helpful'. Suggestions for other improvements from a caregiver perspective included '(1) a structured information session, (2) an opportunity to practice and (3) written information they could refer to at home". Furthermore, most parents felt insecure when taking over the responsibility for their children's injections on discharge from a hospital, reporting that 'handling of injections at home was hardly ever explored at regular follow-up consultations' and noting a 'lack of psychological advice' from HCPs.[33]

Home/healthcare interface

Once again, there was a significant interplay between relevant subthemes for patient/caregiver agency and the home/healthcare interface. However, the subthemes of conflict and administration setting prompted the categorisation of home/healthcare interface as a separate analytical theme.[11 16 26 30 32 33]

Conflict at the home/healthcare interface is closely linked to the theme of education and caregiver confidence. Poor communication at the home/healthcare interface drove conflict between caregivers and HCPs. Poorly communicated discharge planning and mixed messages left parents 'in the deep end' and unable

to appropriately prepare for an ongoing injection regimen.[26]

In regard to the setting of treatment, one study found that 'significant improvements were seen […] for the mental health and family activities concepts' due to 'increased independence, freedom and flexibility' when a home-based treatment regimen of subcutaneous human Ig was compared with hospital-based intravenous administration.[16] The switch to home-based treatment was also associated with reduced healthcare utilisation costs. In the only study of BPG, the 'family home' was the most preferred setting of treatment for both children and family members, citing 'privacy issues' for other locations, such as school or friends' homes. Interestingly, however, self-administration was a less preferred option, with administration by a nurse most preferred across all cohorts.[30] Similarly, another study evaluating long-acting injectable antiretroviral treatment acceptability for patients with HIV found that several young adult patients preferred clinic administration to avoid self-administration, for increased privacy and for ongoing professional care input. However, patient context did factor into preferences towards the setting of treatment, with parents living further away describing an increased preference for home administration to avoid concerns about time involved with clinic-administered injections.[32]

DISCUSSION

Application to ideal regimen characteristics

In accordance with the growing recognition of treatment preference as a contributing factor to successful delivery and clinical decision-making, it is imperative to incorporate preference-led findings into treatment regimens for any patient. This becomes even more important when exploring best methods of therapeutic protection for vulnerable and heterogenous populations. The present systematic review and thematic synthesis of paediatric treatment preference studies demonstrates five key themes that should inform the ideal characteristics of regular paediatric regimens for injectable medications.

The most significant finding of the review was the preference for ease of use in any paediatric treatment regimen across all cohorts. Discussion of ease of use emerged in multiple contexts, such as improving convenience of administration (eg, comparing a prefilled syringe against an autoinjector device) or simplifying preparation and storage requirements. Many of these discussions revolved around device features that similarly contributed to findings surrounding the tolerability of injection. Devices that minimised pain, site reaction and fear/anxiety in patients were consistently preferred by patient, caregiver and HCP cohorts. Although these two themes were generated by differing subthemes, they are undeniably interwoven in their implications for application to regimen characteristics. An easier-to-use regimen with greater tolerability of injections is a clearly preferable outcome for patients, caregivers and HCPs alike. Improvements to regimen ease and tolerability as derived from the findings of the review may include incorporating device features that require minimal prior preparation, uncomplicated storage requirements, minimised physiochemical constraints (eg, reduced viscosity for easier administration), adjustable needle visibility and improved ergonomics (eg, low weight and easy-grip features).

A preferred regimen consisting of greater flexibility, ease of use and tolerability of injection will minimise impacts on daily life. Key features highlighted prior may include ease of preparation and administration, dose confirmation, reduced frequency, greater privacy and increased sense of normalcy. For patients requiring more frequent dosing or families located far from clinical sites, a facility for self-administration in the home would be advantageous but not at the cost of care engagement.

Overall, for the management of conditions affecting paediatric and adolescent patients, it is important to reflect the heterogeneity of patient values and attitudes across this age range and incorporate flexibility to accommodate individual preferences. Injectable regimens should reflect suitability for the person tasked with delivering the injection, promoting confidence in caregivers administering injections for younger patients and promoting agency and control of health outcomes for adolescent patients practising self-administration. Incorporating ease-of-use considerations and focusing on tailoring education efforts to the target population may suffice but should remain flexible and provide a suitable spectrum of support for all potential users.

Adapting regimens to reflect the suitability of the patient population applies within a clinical setting as well. Patients and caregivers demonstrate knowledge-seeking behaviours in this setting, which is often daunting and foreign, particularly for patients with reduced health literacy. For HCPs, educational strategies informed by both way learning and codesign should be an integral component of any regular injection regimen. This may take the form of comprehensive discharge planning, family meetings and linking families in with ongoing support through allied health/external networks to ensure they are coping with the demands of chronic disease and minimise conflict at the home/healthcare interface.

Application to ARF/RHD context

The findings of this review were not all directly applicable to the specific context of secondary prophylaxis to prevent ARF/RHD. Many of the included studies specifically explored preferences for device features rather than for complete treatment regimens. Furthermore, the heterogeneity of conditions limited generalisability. Diverse conditions such as GHD, diabetes and immunodeficiency require daily injections, while at present, BPG is administered at monthly intervals, so many of the findings of the review do not apply to the current BPG treatment regimen. Due to the need for daily dosing,

the reviewed studies explore preferences for devices and regimens suitable for self-administration or caregiver administration, whereas BPG is typically administered in a clinical setting. However, as BPG reformulation efforts progress, self-administration may become an option for families, particularly given the largely rural and remote locations with limited healthcare availability within affected communities in Australia. In this case, the findings from this review regarding developing device features amenable to ease of use in the context of self-administration or caregiver administration may become more relevant.

Another factor limiting the applicability of the findings of this review is that many of these conditions are being treated by regular injection regimens, whereas monthly BPG injections function prophylactically. This means that patients do not experience relief from symptoms with the injections, which may impact agency and acceptability. For this reason, incorporation of the findings relevant to patient/caregiver agency plays a large role in improving the delivery of secondary prophylaxis, such as education and perceived control of health outcomes for patients and caregivers. Poor acceptability and as well as health service constraints were major contributing factors to low levels of prophylaxis delivery. Allowing patients and families to participate in healthcare decisions was also shown to improve engagement, removing this sense of 'othering' and increasing acceptability of healthcare. Further research in this area is likely required to improve the understanding of cultural considerations required for optimal patient and HCP education and care within affected First Nations communities.

Key aspects of care engagement identified in the review were routine and frequency. This is particularly relevant to the BPG context, where socially determined factors such as inconvenience, uncertainty about dosing timing and mobility between communities all contribute to ineffective programmes.[36] Efforts to establish culturally safe research are an important component of the literature surrounding effective BPG delivery. For example, the Full Moon Strategy, developed by a team in the Northern Territory, launched a patient and healthcare worker education and media campaign with promotional materials to encourage patients to use the moon cycle as a memory aid for monthly injections, which showed an improvement in adherence.[36] Continued implementation of these culturally relevant practices and ongoing research in the area will serve to mitigate socially determined drivers of suboptimal delivery of therapy.

Another significant component of poor adherence to BPG regimens is pain. Adhering regularly to very painful injections presents a significant barrier to a younger patient cohort and their caregivers. The findings of this review suggest overwhelming preference for reduced pain; however, there are no concrete findings to suggest what might reduce pain for patients. Pain aversion is also shown to predominate in younger patients with a shorter course of disease, illustrating the importance of coping strategies which older patients often develop through experience. Incorporating early coping strategies into the clinical setting for BPG administration to minimise fear and anxiety regarding the injection will be an important component of improving adherence. Current injection methods are intramuscular administration at the dorsogluteal, ventrogluteal or vastus lateralis site. Patient preference studies in adults suggest that subcutaneous routes of administration are often preferred by patients and find that adherence is greater with a subcutaneous regimen.[37] Subcutaneous administration is also preferred by HCPs due to the reduced level of discomfort they cause patients as opposed to intramuscular.[37] Recent findings from BPG reformulation studies that are currently underway suggest that penicillin profiles following BPG injection are improved with subcutaneous administration.[38 39] This research is still ongoing, and more information is required to consolidate these findings; however, a transition to a subcutaneous injection regimen for patients with ARF/RHD that hurts less and lasts longer is a tangible goal.

CONCLUSION

This review of treatment preferences for regular injection regimens in paediatric and adolescent patients found the following five key themes: ease of use, tolerability of injection, impact on daily life, patient/caregiver agency and home/healthcare interface. These themes can be used to develop characteristics of treatment regimens that promote adherence and care engagement. This may include the incorporation of novel device features that improve convenience of preparation and administration, promoting ease of use, reliability and tolerability of injection, reduced frequency requirements to minimise impact on daily life, ensuring sufficient education to enable patient and caregiver control of health outcomes, reducing conflict at home/healthcare interface and consideration of privacy of treatment regimen for patients and families.

Application of these findings to the administration of BPG in the ARF/RHD context may take the form of improving ease of use, focusing on care engagement and working with patients and their families to improve coping mechanisms. Findings of this review contribute to a larger body of existing and ongoing qualitative research surrounding eliminating RHD and improving outcomes for Indigenous Australians[40] and should be implemented in conjunction with this relevant qualitative research to establish best-practice care. Further research both generally and specifically in the RHD context is required to improve understanding of social drivers of adherence and to reduce the pain of injections.

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