Utility of proactive infliximab levels in paediatric Crohn's disease

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Received 5 March 2018
Revised 28 May 2018
Accepted 29 May 2018

ABSTRACT

Objective Infliximab (IFX) has an established role in Crohn's disease (CD), with serum trough levels of IFX (TLI) increasingly used to optimise dosing. We report the utility of routine, proactive TLI in children on combination therapy with immunosuppression (IS) from a single paediatric centre.

Methods This is a retrospective chart review of all children with CD receiving IFX therapy conducted betweenJanuary 2014–May 2017. Clinical phenotype, duration of therapy, TLI (µg/mL), drug antibodies, type of IS, biomarkers and changes in management were recorded.

Results 60 children (8–17 years; median 14.1 years) had 206 TLIs recorded. 56/60 (93%) were on IS, with 5/60 (8%) developing antidrug antibodies (ADAs). 63/206 TLIs were recorded duringan episode of relapse (median 3.0 µg/mL) vs 143/206 TLIs recorded in remission (median 5.2 µg/mL). For children with TLI <3 µg/mL, 31/63 (49%) were in relapse vs 30/143 (21%) in remission. For children with TLI >7 µg/mL, 7/63 (11%) were in relapse vs 46/143 (32%) in remission. Change in management resulted from 43/206 (21%) TLIs in 31/60 (52%) children: 21 dose escalations, 12 de-escalations and 10 changed to adalimumab. Of 31 postinduction TLIs, 15/17 (88%) children with TLI >7 µg/mL achieved clinical and biochemical remission for the duration of therapy (median 14 months), while 4/5 (80%) children with TLI <3 µg/mL required early dose escalation. Combination therapy with thiopurines (TP) (median TLI 4.9 µg/mL) versus methotrexate (MTX) (median TLI 5.2 µg/mL) achieved comparable levels with no difference in relapse frequency.

Conclusions Routine, proactive TLIs guide optimal management in children with CD. Postinduction and during maintenance, levels <3 µg/mL were associated with relapse and levels >7 µg/mL with sustained remission. Combination IS with TP and MTX appears to offer comparable TLI and ADA rates.

What is already known on this topic?

- Infliximab (IFX) has an established role in the treatment of Crohn's disease (CD), with serum trough levels of IFX increasingly used to optimise dosing.
- In children, increased disease severity and substantial interpatient variability in pharmacokinetic parameters drive an even greater need for therapeutic drug monitoring (TDM).

What this study adds?

- Proactive TDM performed at routine time points irrespective of clinical, biochemical and endoscopic markers has potential utility in helping guide management and optimise care in children with CD on IFX.
- Trough levels of IFX and clinical outcomes appear to be similar between children on dose-optimised thiopurine versus methotrexate combination therapy, with further research warranted.

INTRODUCTION

Crohn's disease (CD) is a chronic, debilitating intestinal disorder affecting nutrition, growth, quality of life and education, with approximately 8% of patients diagnosed before 17 years of age.[1 2] Paediatric-onset CD is a more severe phenotype, with many children proceeding to non-curative surgery within the first 5–10 years of diagnosis and significant morbidity of chronic disease commencing at a vulnerable period of psychosocial development.[1 3 4] Infliximab (IFX), a monoclonal antibody against tumour necrosis factor-alpha (TNFα), has an established role for induction and maintenance of remission in moderate to severe CD.[5] However, despite early clinical response rates of up to 80%, loss of response (LOR) occurs in 25%–40% of patients and may require dose intensification.[6 7] Therapeutic drug monitoring (TDM) of serum trough levels of IFX (TLI) and antidrug antibodies (ADAs) is increasingly used to optimise drug dosing, particularly in LOR, but also in helping clinicians better understand the relationship between disease activity, drug levels, antibody production and adjunctive therapy with immunosuppression (IS), and in defining treatment targets at different stages of the disease natural history.[8] In children, increased disease severity and distribution with likely increased inflammatory load and substantial interpatient variability in pharmacokinetic parameters at standard-dose therapy drive an even greater need for TDM and treatment optimisation.

IFX TDM has, to date, been performed empirically at the clinician's discretion based on the presence of gastrointestinal symptoms or surrogate biomarkers that suggest failure of initial response or LOR with recurrence of intestinal inflammation.[7] Alternatively, routine or proactive TDM is the measurement of a drug concentration at a

To cite: Burgess CJ, Reilly C, Steward-Harrison L, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2018-315100

prespecified time, irrespective of clinical, biochemical and endoscopic markers, followed by titration of the drug to a target range. Proactive monitoring of TLI has recently been demonstrated in adult studies to improve long-term IFX efficacy and safety,[9 10] potentially contributing to more optimal clinical outcomes, although additional data from large prospective studies are needed.

The role of IS as combination therapy for children being treated with IFX for CD remains uncertain. Previous studies have clearly demonstrated both higher TLI and decreased risk of immunogenicity in patients on dual therapy with both thiopurines (TP) and methotrexate (MTX), but failed to demonstrate a benefit in inducing or maintaining clinical remission.[11 12] The risk of serious adverse effects including malignancy, especially in combination with TP, continues to be a concern to both clinicians and families.[13] It remains to be demonstrated whether TP and MTX have the same profile with regard to TLI, response to therapy and relapse, or if one may be superior to the other.

The aim of this study was to investigate the real-world use of proactive TDM in children with CD on IFX and investigate its utility in helping guide management to optimise care. The secondary aims included a subgroup analysis of TLIs performed during induction to predict future response to therapy, and a comparison of patients on TP versus MTX to investigate whether these combination therapies have the same profile with regard to TLI and rate of relapse.

MATERIALS AND METHODS

Individual chart review was performed on patients receiving IFX for CD from January 2014 to May 2017 at the Lady Cilento Children's Hospital, an Australian tertiary paediatric gastroenterology centre. All patients <18 years with CD receiving IFX therapy had proactive levels recorded during this time and were therefore included, with TLIs analysed retrospectively to inform the value of levels on clinical practice. Standard induction therapy of 5 mg/kg IFX at 0, 2 and 6 weeks and standard maintenance therapy of 5 mg/kg IFX every 8 weeks were used, with no steroid or other medication routinely given around IFX infusion. There was no a priori plan for the management of TLI, rather all adjustments in dose or interval of IFX were at the clinician's discretion and based on multiple factors including clinical, biochemical and endoscopic features. TLIs were obtained immediately prior to every third infusion, therefore for patients on standard therapy at week 6 (immediately prior to the third induction dose) and then 6-monthly. All patients commenced on IFX prior to 16 February 2016 were on Remicade (11/60), with patients after this date commenced on the biosimilar Inflectra (49/60) in accordance with hospital regulations. There was no switching of brands for individual patients.

Clinical measures recorded for each patient included age, sex, disease phenotype, duration of IFX therapy, type of IS (TP or MTX), 6-thioguanine (6TG) level (pmol/8×10^8), TLI (μg/mL) and ADA (U/mL). Biomarkers recorded included the Paediatric Crohn's Disease Activity Index score (PCDAI) and C reactive protein (CRP) at the time of TLI monitoring, faecal calprotectin (FC) within 4 weeks of TLI, and endoscopy within 4 weeks of TLI. Any change in dose or interval of IFX infusions was recorded, and detailed chart review was performed to determine if this change was directly related to routine TLI monitoring as explicitly documented. At each TLI monitoring patients were recorded as being in remission or relapse; remission was defined as PCDAI ≤10, CRP ≤5, FC ≤200 and no active endoscopic disease, while relapse was defined as PCDAI >10 with supportive biomarker (CRP >5 and/or FC >200) and/or endoscopy.

Data were analysed using IBM SPSS Statistics V.22 for Windows. Non-parametric tests were required as data sets were not normally distributed; Mann-Whitney U test was used for continuous variables, Fisher's exact test for categorical data, and a p value <0.05 was considered significant. Different ELISA tests were used for the quantitative determination of serum TLI and ADA over the duration of this study due to a change in laboratory. Prior to October 2015 Matriks Biotek Enzyme Immunoassay (SHIKARI) was used, followed by Progenika Biopharma (Promonitor). TLI cut-offs consisted of a maximum of >14.4 μg/mL and a minimum of <0.1 μg/mL. All TLIs were undertaken using drug-sensitive assays; hence, antibodies were only looked for in the presence of very low levels or absence of drug.

Table 1 Patient demographics

Number of patients	60
Number of TLIs	206
Duration of therapy (months)	1.5–83 (median 22; IQR 11–34)
Age (years)	7–18 (median 14.1; IQR 12.2–15.7)
Sex (male:female)	43 (72%):17 (28%)
Phenotype (luminal:fistulising)	44 (73%):16 (27%)
Dual therapy (TP:MTX:none)	39 (65%):17 (28%):4 (7%)

MTX, methotrexate; TLI, trough level of infliximab; TP, thiopurines.

RESULTS

A total of 206 TLIs were recorded on 60 paediatric patients receiving IFX for CD (table 1). Patients ranged in age from 7 to 18 years, with a median age of 14.1 years (IQR 12.2–15.7 years). Of the 60 patients, 43 (72%) had luminal CD and 17 (28%) had fistulising CD. All patients were on IS at the time of commencement of IFX, and 56 (93%) of 60 patients remained on combination therapy with IS. Of 56 patients, 39 were on TPs, with 6TG level dose-optimised (median 215 pmol/8×10^8; IQR 132–309), and 17 were on standard-dose MTX. ADAs to IFX developed in 5 (8%) of 60 patients (1 of 5 on no IS) and all required a change of biologic within class. Four of five patients discontinued IFX therapy following a single recording of positive antibodies (135, 57, 35, 15 U/mL, respectively) with negligible IFX levels (≤0.1 μg/mL). One of five patients had a borderline antibody level (7.6 U/mL) but continued to have positive antibodies and negligible IFX levels (≤0.1 μg/mL) at the next TLI despite escalation of therapy, therefore also classified as LOR due to positive ADAs and IFX discontinued.

Sixty-three episodes of relapse at the time of TLI monitoring were recorded. Relapse was defined as PCDAI >10 with supporting biomarker (CRP >5 and/or FC >200) and/or active endoscopic disease. Thirteen patients had endoscopically confirmed relapse, and 50 patients had elevated PCDAI ≥15 with supporting biomarker. The median TLI for patients in relapse was 3.0 μg/mL. This was significantly lower than the median TLI for patients in remission, 5.2 μg/mL (p<0.001). TLI <3 μg/mL was seen in 31 (49%) of 63 in relapse vs 30 (21%) of 143 in remission (p<0.001). TLI >7 μg/mL was seen in 7 (11%) of 63 in relapse vs 46 (32%) of 143 in remission (p<0.001) (figure 1).

TLIs directly led to a change in management on 43 (21%) of 206 occasions in a total of 31 (52%) out of 60 children. There were 21 episodes of escalation of therapy directly related to proactive TLI monitoring, including escalations of infusion interval (14/21), dose (4/21) or both (3/21) at individual

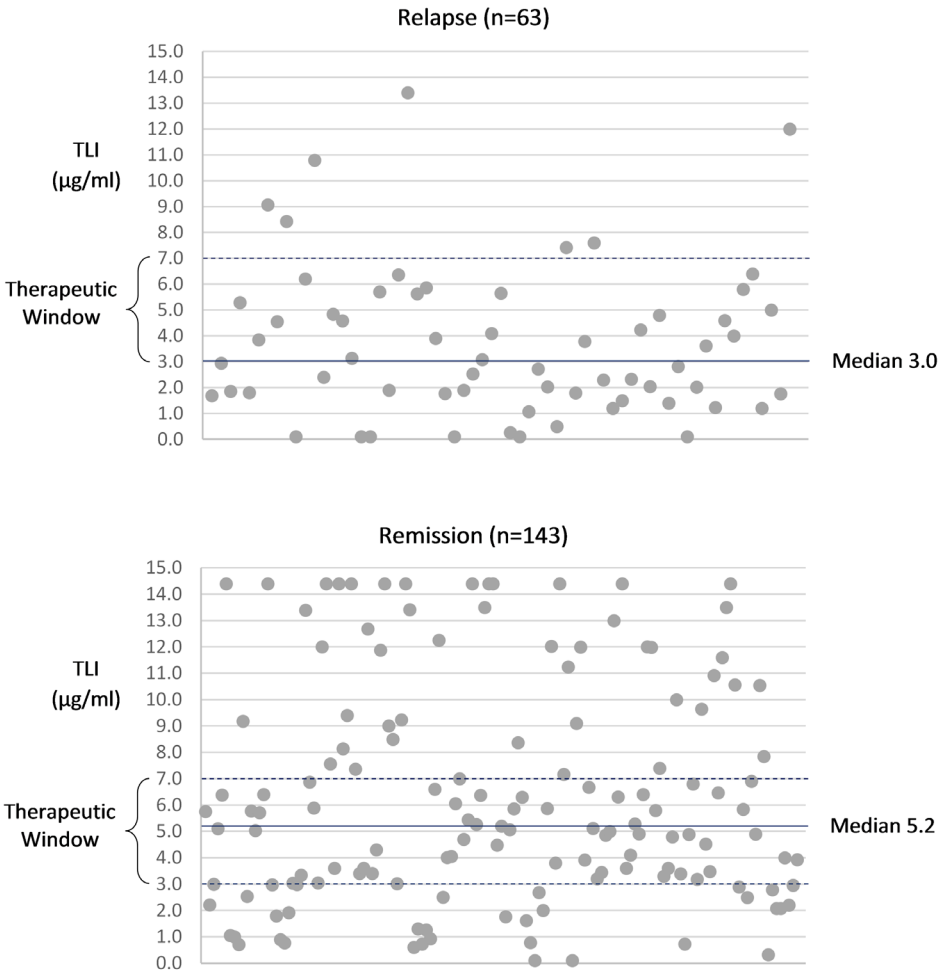

Figure 1 Scatterplot of all TLIs recorded during relapse versus remission. Relapse: PCDAI >10 with supportive CRP >5, FC >200 and/or endoscopy. Remission: PCDAI ≤10, CRP ≤5, FC ≤200 and no active endoscopic disease. CRP, C reactive protein; FC, faecal calprotectin; PCDAI, Paediatric Crohn's Disease Activity Index; TLI, trough level of infliximab.

clinician's discretion. Of the 21 escalations, 17 were for patients in relapse, with 7 obtaining complete clinical and biochemical improvement to normal at the time of the next TLI (median 2 months), and 85% of these demonstrating IFX levels which improved from subtherapeutic to therapeutic (>3 µg/mL). Of 17 patients, 5 had a partial improvement in PCDAI±biomarkers following escalation of therapy, with 40% increasing the IFX level to >3 µg/mL. Of these 17 patients, 5 had no clinical response, only 1 of whom had restoration of TLI to >3 µg/mL, with all eventually changed within class to adalimumab.

There were 12 episodes of de-escalation of therapy directly related to TLIs, all of which had decreased infusion interval. Of the 12 patients, 7 (58%) remained in complete clinical and biochemical remission, as well as maintained therapeutic TLI over the following 12 months. Two of the 12 patients maintained therapeutic TLI but had a flare of disease within 12 months of de-escalation, and the final 3 patients all had a subsequent disease flare (within a median of 8 months) as well as a TLI which fell to <3 µg/mL. Ten patients were changed within class to adalimumab and five of these due to the development of ADAs.

Subgroup analysis was performed on the cohort of patients (n=31) with documented TLI during induction therapy. Most postinduction TLIs were recorded at week 6 (78%), although some were recorded later between weeks 11 and 14. The median TLI for patients postinduction was 8.4 µg/mL (week 6 median=10.9 µg/mL; weeks 11–14 median 5.9 µg/mL), which was significantly higher than the median TLI of patients in maintenance therapy, 4.0 µg/mL (p<0.001). Supratherapeutic postinduction levels >7 µg/mL were recorded in 17 (55%) of 31 patients, and 15 (88%) of these 17 patients achieved clinical+biochemical remission postinduction and remained in this for the duration of their therapy (median follow-up 12 months, IQR 7–23 months). Of 31 patients, 5 (16%) had subtherapeutic postinduction levels <3 µg/mL. Two of these patients failed to demonstrate any clinical or biochemical improvement postinduction and all five required escalation of therapy within 6 months.

TLIs were assessed against combination therapy agent to determine any difference in TLI or rates of relapse between patients on TP versus MTX. Of the 60 children, 39 on combination with TP had a median TLI of 4.9 µg/mL, and recorded 42 of 142 episodes of relapse. Of the 60 children, 17 on MTX had a median TLI of 5.2 µg/mL (p=0.3), and recorded 20 of 52 episodes of relapse (p=0.3). Two patients within each group developed ADA, and one patient who was not on IS developed ADA. Within the TP subgroup serum 6TG levels were recorded where available at each measurement of TLI. Using standard recommended 6TG metabolite level of 235 pmol/8×10^8, there was no difference in TLI or rates of relapse using this cut-off. Forty-two TLIs

were recorded on children with documented 6TG level ≥235 pmol/8×10^8 (median 334, IQR 293–441); the median TLI was 5.0 µg/mL with 9 episodes of relapse recorded. Sixty-six TLIs were recorded on children with 6TG <235 pmol/8×10^8 (median 144, IQR 107–200); the median TLI was 4.9 µg/mL (p=0.8) with 21 episodes of relapse recorded (p=0.3).

DISCUSSION

In current paediatric practice TLIs are typically performed reactively, only when patients are losing response to treatment. We found that proactive TLIs have a high utility in helping guide management of therapy in children with CD on IFX. Almost a quarter of all levels performed in our cohort directly led to a change in clinical management, and this enabled optimisation of therapy in almost half of the patients. Routine, proactive monitoring of TLIs helps to predict response to treatment and can be used to prognosticate, counsel families, identify those patients who require closer monitoring and modify therapy. Strict definitions of relapse were used in this article to identify any patient who was not in deep remission and may therefore benefit from optimised IFX levels. At the time of sampling, TLI <3 µg/mL was associated with relapse and TLI >7 µg/mL was strongly associated with clinical and biochemical remission.

Similar results have been demonstrated in the TAXIT (Trough Level Adapted Infliximab Treatment) study, which prospectively optimised IFX dosing in adult patients with CD receiving maintenance therapy, demonstrating improved biochemical markers and disease activity indices with dose optimisation of TLI to a therapeutic range of 3–7 µg/mL.[14] More recently, the seminal CALM (effect of tight control management on Crohn's disease) study has demonstrated improved efficacy and cost-effectiveness of a tight control approach for disease management with adalimumab in patients with moderate to severe CD.[15] Significantly more tight control patients, using CRP, FC, Crohn's Disease Activity Index and prednisone use, achieved mucosal healing at week 48 (46%) compared with those with traditional symptom-driven care (30%) (p=0.01).[15] Although the philosophy behind our study and the CALM study is similar, examining potential effects of timely escalation and de-escalation of anti-TNF therapy based on both biomarkers and symptoms, the methodology of these studies is markedly different given that the multicentre, randomised, controlled phase III CALM study did not use anti-TNFα drug levels as a biomarker.

TLIs were also useful in patients immediately postinduction as a predictor of response to therapy. Postinduction TLI >7 predicted a sustained response to treatment, with 88% of these patients achieving clinical and biochemical remission which remained for the duration of their therapy (median 14 months), and TLI <3 predicted poor response or early relapse with 100% requiring escalation of therapy. To enable streamlined collection of proactive IFX blood samples and minimise missed samples, it was planned that TLI would be monitored prior to every third dose, therefore 6-monthly for patients on standard maintenance therapy. A by-product of this is that the majority of postinduction trough levels were taken immediately prior to dose 3 (week 6) which, although not standard practice, has recently shown to be useful in predicting treatment failure in an adult longitudinal cohort.[16] Unfortunately, given our small numbers, we were unable to analyse these week 6 vs 14 trough levels further. The results are also supported by a 2014 paediatric study which found TLI >3 µg/mL at week 14 was associated with a positive predictive value of persistent clinical remission at week 52 of 76%, increasing to 100% if the trough threshold was >7 µg/mL.[17]

In Australia, the publicly funded use of IFX is governed by the Pharmaceutical Benefits Scheme (PBS). Approved maintenance dosing is limited to 5 mg/kg 8-weekly, and proactive IFX levels may therefore provide useful supportive documentation in applying for compassionately funded medication due to LOR. Previous studies have clearly demonstrated that in patients with subtherapeutic TLI <3 µg/mL, dose escalation leads to a higher percentage with improved clinical response compared with switching within class (86% vs 33%).[18] PBS guidelines also stipulate that patients with luminal CD cannot be commenced on IFX unless they have failed standard induction therapy together with a minimum 3-month treatment with TP or MTX. For this reason, most of our patients are on combination therapy, likely accounting for the low ADA rate of 8%. With >80% of our patients on Inflectra, this study also adds to recently published literature on biosimilars in paediatrics demonstrating primary clinical effect and drug levels.[19]

Throughout the global paediatric inflammatory bowel disease community, there is ongoing concern regarding the concomitant use of TP with anti-TNF biologics due to the potential increased risk of malignancy in these patients, especially if Ebstein-Barr Virus (EBV) naïve.[13] Recent studies have suggested that rather than ceasing TPs, it may be more beneficial to decrease the target 6TG level aiming for ~125 pmol/8×10^8 to minimise toxicity while continuing to avoid the development of ADA.[20] Our cohort of patients with CD receiving combination therapy was fairly evenly split between TP and MTX, and these subgroups were further analysed to determine whether the type of IS affected the TLI or the outcomes. No significant difference in the median TLI or the number of patients relapsing on either therapy was noted, and there was no decrease in TLI or increased rates of relapse when patients on TP were maintained at lower 6TG levels (<235 pmol/8×10^8). We are unable to comment on the monotherapy group as all of these children were on IS at some time to meet the criteria for commencing IFX, and some patients were changed to monotherapy part way through therapy due to poor compliance, complications or perceived medication risk. Within this small, retrospective cohort, it appears that combination IS with TP and MTX gives comparable TLI and ADA rates, although further research using larger, prospective studies to decrease potential confounders is required.

Regular proactive IFX levels are cost-effective, with the average cost per patient year of only *$100* (€65) based on 6-monthly monitoring (every third infusion). The cost benefits of de-escalating therapy are obvious; however, the optimisation of IFX levels to prevent morbidity related to the lifelong nature of CD and the progressive disease burden of mucosal inflammation is likely more important. These cost benefits have been quantified in adult studies demonstrating that an individualised approach to IFX dosing can lead to a 56% cost reduction with similar clinical outcomes.[21 22] The de-escalation of therapy directly related to TLIs performed in our cohort saw 58% patients remain in complete biochemical and clinical remission, as well as maintain therapeutic TLI for the following 12 months. Further research into proactive monitoring of IFX levels for this group of patients will play a key role in allowing us to more readily individualise and most appropriately time this de-escalation of therapy to maximise safety and therapeutic benefit.

We recognise the inherent weaknesses associated with a single-centre retrospective study and within our methodology. Despite a decision to proactively monitor TLI for all children with CD on IFX, no *a priori* plan was created to formalise management

dependent on the level, which was left up to clinician judgement and based on multiple factors including clinical, biochemical and endoscopic features. The laboratory analysing the samples also changed once during the study observation period. Drug-sensitive assays were used in both instances, consistent with a recent post-hoc analysis of the TAXIT study demonstrating no significant long-term patient difference for drug-tolerant versus drug-sensitive assays.[23] Although levels are widely considered as comparable between these two ELISA assays, without formal calibration it remains a potential weakness of our study.

Routine, proactive TLIs have a high utility for guiding management of IFX in children, with 23% of TLIs in 44% of the patient cohort leading to dosing escalation, de-escalation or change of anti-TNF, with resulting optimisation of care. At the time of sampling, TLI <3 is associated with relapse and TLI >7 strongly associated with clinical and biochemical remission. Postinduction, TLI >7 predicts a favourable 6–12 months of sustained response and TLI <3 predicts poor response or early relapse. Although we recognise the inherent weaknesses of a retrospective study, a prospective intention-to-treat analysis using TLI to proactively adjust IFX dosing in a standardised fashion with long-term follow-up is yet to be performed in children. We believe that proactive TLIs have an important role in optimising use of biologic agents in children with CD.

Contributors CJB was involved in obtaining ethics approval, analysed the data, wrote the original and subsequent revisions of the manuscript, and agreed to the final manuscript. CR, LS-H and FB were involved in data collection, provided critical review and approved the final manuscript. PJL conceptualised this study, was involved in data collection and analyses, provided critical review of the original and subsequent manuscript drafts, and agreed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests PJL has received honoraria from both AbbVie and Janssen-Cilag.

Patient consent Not required.

Ethics approval This study was approved by the Human Research Ethics Committee of Children's Health Queensland, which is compliant with the Australian NHMRC guidelines and accepted international standards.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Medical data set only available to clinicians directly managing patient care.

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