*Cardiology in the Young*

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# Colchicine in post-operative Fontan patients

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## Original Article

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## Abstract

*Background:* Prolonged effusions post-Fontan procedure are associated with morbidity. Fontan patients have higher pro-inflammatory cytokines in chest tube drainage compared to controls. Colchicine, an anti-inflammatory medication, decreases effusions in adults after cardiac surgery. We hypothesised that patients post-Fontan treated with colchicine would have decreased pro-inflammatory cytokine levels and shorter duration of chest tube drainage. *Methods:* This pilot clinical trial enrolled nine patients (intention to treat); five completed the protocol (per protocol). Post-operative Fontan patients 20 months to 5 years receiving colchicine were compared to a previously published control cohort (n = 25). Per protocol patients received 0.6 mg colchicine daily starting post-operative day 2, ending 1 day after chest tube removal. Chest tube samples were taken on days 1–4, 7 and 10, or until removal and analysed with a 17-cytokine Bio-Plex Assay. Descriptive statistics and basic univariate comparisons were made. *Results:* There was no difference in duration of chest tube drainage or length of stay between intention to treat patients and controls. Per protocol patients had shorter duration of chest tube drainage compared to controls (6 days [interquartile range 4.7–7], versus 10 days [7–11], p = 0.007) and shorter length of stay (7 days [5.5–9] versus 9 days [9–13], p = 0.005). Pro-inflammatory cytokines trended lower in per protocol patients. *Conclusions:* In this pilot cohort, patients who completed the colchicine protocol post-Fontan procedure had shortened duration of chest tube drainage and length of stay. A decrease of pro-inflammatory cytokines may contribute to the mechanism of this change.

ClinicalTrials.gov: Colchicine in Postoperative Fontan Patients (CPFP); NCT03575572; https://clinicaltrials.gov/ct2/show/NCT03575572.

Post-operative pleural effusions in Fontan patients are common, with prolonged effusions seen in 20–45% of patients.[1–3] Pleural effusions remain a significant source of morbidity associated with increased post-operative intensive care and hospital length of stay[4]. Fontan patients also have an exaggerated systemic inflammatory response to cardiopulmonary bypass, and this activation of the inflammatory cascade can cause vascular capillary leak to promote the development of effusions.[1,5–8] Post-operative Fontan patients have a higher concentration of pro-inflammatory cytokines localised to the pleural space in comparison to similar-aged controls after bypass suggesting an ongoing local inflammatory process.[9] Colchicine, a widely recognised anti-inflammatory medication, has been used to treat recurrent pericarditis and to reduce post-operative pericardial and pleural effusions, thereby shortening post-operative hospital stays after cardiac surgeries in adults.[10–15]

The aetiology for prolonged pleural drainage in a Fontan patient is not known, but thought likely to be multifactorial from causes such as elevation of central venous pressure, the inadvertent surgical disruption of lymphatic channels during the Fontan surgery, or abnormalities of the lymphatic channels themselves.[16] Current treatments aimed at the above aetiologies are lacking in efficacy or not widely available.[17,18] Although many Fontan patients have prolonged effusions and longer chest tube drainage with or without the diagnosis of chylothorax, treatment strategies are similar. Our aim was to determine if there is an association between empiric colchicine treatment in post-operative Fontan patients and a decrease in chest tube duration, possibly due to a decreased level of inflammatory cytokines in the pleural space.

## Materials and methods

This prospective pilot clinical trial enrolled nine patients who underwent Fontan palliation at a single centre. These patients were compared to a published historical control of 25 Fontan patients undergoing similar sampling protocol in 2016 without intervention at the same institution.[9] This study received institutional review board approval and the use of colchicine was

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given an IND exemption from the FDA due to its off-label use in children under the age of 4 years in this study. The study is listed in ClinicalTrials.gov. All consecutive patients undergoing the Fontan procedure between the ages of 20 months and 6 years at the University of Michigan between August 2018 and July 2019 were screened and approached for consent if eligible. Further patients were not able to be enrolled due to study termination dictated by the COVID-19 pandemic. Patients were excluded if they had received an investigational drug within 3 months, were taking a medication which would interact with colchicine, had pre-existing myelosuppression, renal, or liver disease, or were under 10 kg. Informed consent from parents or guardians was obtained for all patients included in the study.

Chest tube fluid samples were taken in sterile fashion on post-operative days 1–4, 7, and 10, until chest tubes were removed. Chest tubes were removed based on a decision by the clinical team; standard removal criteria at this institution were output at ≤1 mL/kg/8 hours for two consecutive 8 hour shifts. Management of Fontan patients was similar at the institution between the time of enrolment of the cases and the historical controls, and Fontan patients were excluded from any "early chest tube removal" initiatives or studies during both study timeframes. Samples were not collected after additional procedures in the chest. Blood samples were collected for safety monitoring. Colchicine was given enterally once daily at 0.6 mg starting on post-operative day 2 and continued until 24 hours after chest tubes were removed. The dose was standard for all study patients and pre-determined based on efficacious and safely reported uses in young children.[19–27]

Pleural fluid was assayed for 17 inflammatory cytokines using the Bio-rad Bio-Plex ProHuman Cytokine 17-plex Assay (#M5000031YV) on the Bio-Rad MAGPIX Multiplex Reader.[28,29] Assay values below the limit of detection for a given cytokine were set to 0.01 pg/mL below the limit of detection value for that cytokine. Though all 17 cytokines were analysed in both current and historical cohorts, the four pertinent cytokines from the historical report (IL-8, IL-10, MIP-1β, and TNF-α) were of particular interest and are the only cytokines included in the current analysis.[9]

Clinical information gathered included patient demographics, pre-operative heart catheterisation data, and pre-operative echocardiogram findings. Intraoperative data collected included the surgical procedure (i.e. lateral tunnel versus extracardiac or additional procedures including tricuspid valve repair/replacement), cardiopulmonary bypass, cross clamp, deep hypothermic arrest times, and use of intra- or peri-operative steroids. Post-operative data included total daily pleural fluid output, total chest tube days, use of non-steroidal anti-inflammatory drugs, and presence of chyle as judged by the clinical team. Per institutional consensus, chyle was defined as an increase in chest tube output with milky appearance after initiation of post-operative feeds and was further aided by higher pleural triglyceride levels as compared to serum. Post-operative mechanical ventilation, hospital length of stay, and maximum vasoactive inotropic score within 2 hours and 24 hours of operation were recorded.[30] Complications including extracorporeal membrane oxygenation, renal replacement therapy, infection, unplanned surgical procedure or catheterisation, cardiopulmonary resuscitation, and death were recorded. Treatment for prolonged pleural drainage was documented including need for periods of nil per os with total parenteral nutrition, octreotide infusion, thoracic duct ligation, and pleurodesis. Standard care for Fontan patients at this institution included early extubation, typically in the operating room if deemed safe by the surgeon and anaesthesiologist, followed by simple nasal cannula oxygen which was weaned as tolerated to room air for oxygen saturations >85%. Milrinone was started in the operating room as clinically indicated by the surgeon but was not standard for all Fontan patients. There was no empiric use of vasopressin or phosphodiesterase inhibitors unless clinically indicated at this institution.

### Statistical design

Data are reported using mean ± standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables, and frequency (%) for categorical variables. Demographics and clinical characteristics are described. Univariate analyses comparing outcomes and cytokines are described in those who were treated (intention to treat group) compared to controls, and those who completed the protocol (per protocol group) and controls. Univariate comparisons were made comparing patient characteristics, peri-operative characteristics, and total cytokine mass in control versus intention to treat patients or per protocol patients using Student's t-test, Mann–Whitney test, or Wilcoxon rank sum test, as appropriate. All analyses were performed using GraphPad Prism.

## Results

Of the 24 consecutive eligible patients, 12 parents/guardians declined enrolment, 3 patients were excluded (one for myelosuppression, one for weight < 10 kg, and one for requiring a reintervention on post-operative day 0), and 9 patients were enrolled in this study. Of the nine patients enrolled, five patients completed the protocol and four were withdrawn. Of the patients withdrawn, one was due to an increase in creatinine in the setting of dehydration, one was due to an increase in transaminases in the setting of dehydration, and two were due to parental request. The demographics of patients enrolled are described in Table 1.

### Clinical characteristics

Nearly all (89%) patients underwent a hemi-Fontan procedure for superior cavopulmonary anastomosis followed by a lateral tunnel, fenestrated Fontan palliation, which reflects the institutional preference. The one patient who underwent bidirectional Glenn who required extracardiac Fontan was due to the prior operation occurring at a different institution. None of the 9 intention to treat patients had a prolonged effusion (> 2 weeks) after their first stage operation(s), and one patient had a prolonged effusion after their second stage operation. This patient had a cumulative 39 days of chest tube drainage after their second stage operation. This patient completed the colchicine protocol, and the duration of their chest tube drainage was only 7 days after the Fontan operation while being treated with empiric colchicine. When comparing the pre-operative haemodynamic data, the control group had lower median end diastolic pressure and higher median transpulmonary pressure than either per protocol or intention to treat groups (Table 2). As part of routine clinical practice, all patients in the intention to treat group received post-operative non-steroidal anti-inflammatory medications (100%), and two of the five patients in the per protocol group received peri-operative steroids (40%), whereas all but two patients in the control group received non-steroidal anti-inflammatory medications (92%) and only one received peri-operative steroids (4%). Both ketorolac (1–4 days post-operatively) and ibuprofen (4–26 days following ketorolac, given as needed) were used in all intention to treat patients. Of note, steroids are not standard of care in peri- or post-operative

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**Table 1.** Patient demographics.

| Characteristics | Per protocol (n = 5) | Intention to treat (n = 9) | Controls (n = 25) |
|---|---|---|---|
| Female sex | 2 (40) | 5 (56) | 7 (28) |
| Weight, kg | 11.7 (10.9–15.0) | 13.7 (11.1–15.4) | 12.4 (11–13.9) |
| Caucasian race | 2 (40) | 6 (67) | 22 (88) |
| Chromosomal abnormality | 2 (40) | 2 (22) | 1 (4) |
| Other organ abnormality | 3 (60) | 6 (67) | 15 (60) |
| Age, years | 2.7 (2.2–3.6) | 2.7 (2.1–4.3) | 2.5 (2.1–2.9) |
| Primary diagnosis | | | |
| HLHS | 3 (60) | 6 (67) | 14 (56) |
| Not HLHS | 2 (40) | 3 (33) | 11 (44) |

**Table 2.** Clinical characteristics.

| *Pre-operative and operative characteristics* | Per protocol (n = 5) | Intention to treat (n = 9) | Controls (n = 25) | p-value[a] | p-value[b] |
|---|---|---|---|---|---|
| CPB time, minutes | 46 (42–67) | 51 (45.5–75.5) | 57 (51.5–73.5) | 0.15 | 0.39 |
| Cross clamp time, minutes | 21 (17.5–38.5) | 25 (17.5–29.5) | 25 (16.5–30) | 0.92 | 0.78 |
| MPI | 0.48 (0.39–0.59) | 0.49 (0.39–0.59) | 0.41 (0.32–0.52) | 0.20 | 0.18 |
| Systemic ventricle EDP, mmHg | 10 (8–11) | 10 (8–11) | 6.5 (5–8) | 0.01 | 0.001 |
| SVC pressure, mmHg | 12 (9.5–13.5) | 12 (11–13) | 11 (10.25–12) | 0.73 | 0.52 |
| Transpulmonary gradient, mmHg | 3 (2.5–4.5) | 3 (2–4) | 5 (4–5) | 0.02 | 0.002 |
| PA pressure, mmHg | 12 (9.5–14) | 12 (11–12.5) | 11 (10–12) | 0.36 | 0.31 |
| AV valve regurgitation | | | | 1 | 1 |
| None/trivial/mild | 5 (100) | 8 (89) | 22 (88) | | |
| Moderate or greater | 0 (0) | 1 (11) | 3 (12) | | |
| *Post-operative characteristics and complications* | | | | | |
| Mechanical ventilation required | 2 (40) | 2 (22) | 4 (16) | 0.25 | 0.64 |
| Infection | 0 (0) | 0 (0) | 0 (0) | | |
| Unplanned surgical procedure or catheterisation | 0 (0) | 0 (0) | 4 (16) | 1 | 0.55 |
| Diaphragm plication | 0 (0) | 0 (0) | 3 (12) | 1 | 0.55 |
| Chylous effusion | 0 (0) | 0 (0) | 3 (12) | 1 | 0.55 |
| Treatment for pleural drainage | | | | 1 | 1 |
| Low-fat diet | 0 (0) | 0 (0) | 1 (4) | | |
| NPO | 0 (0) | 0 (0) | 1 (4) | | |
| Octreotide | 0 (0) | 0 (0) | 1 (4) | | |
| Thoracic duct ligation/pleurodesis | 0 (0) | 0 (0) | 0 (0) | | |
| Highest VIS in 1st 2 hours post-operatively | 5 (1.5–15) | 4 (1.5–8) | 3 (0–11.5) | 0.59 | 0.85 |
| Highest VIS in 1st 24 hours post-operatively | 7 (1.5–15) | 5 (2.5–11.5) | 5 (0–13) | 0.71 | 0.78 |
| ECMO/RRT/CPR/death | 0 (0) | 0 (0) | 0 (0) | | |

Abbreviations: AV = atrioventricular; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; EDP = end diastolic pressure; MPI = myocardial performance index; mmHg = millimetres of mercury; NPO = nil per os; PA = pulmonary artery; RRT = renal replacement therapy; SVC = superior vena cava; VIS = vasoactive inotropic score.
Data are presented as n (100%) or median (interquartile range).
[a]p-value compares per protocol and control patients from Mann–Whitney U-test or Fisher's exact test.
[b]p-value compares intention to treat and control patients from Mann–Whitney U-test.

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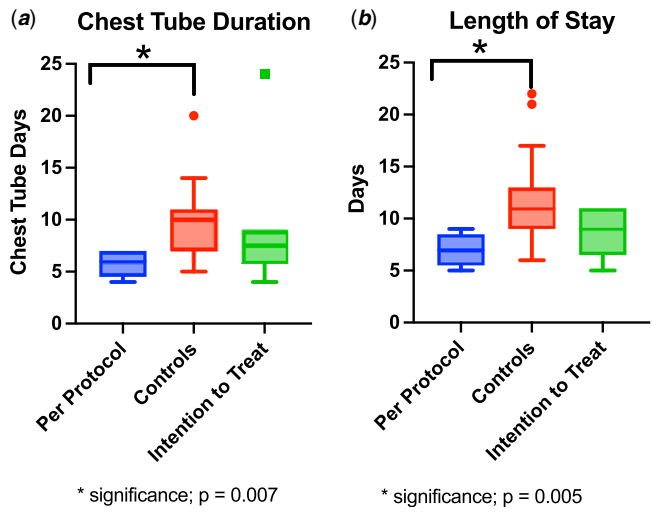



**Fig. 1.** Comparison of chest tube drainage (a) and length of stay (b). a. Chest tube duration is shorter in per protocol patients (6 days, Interquartile Range [IQR] 4.5 – 7 days) as compared to controls (10 days, IQR 7 – 11 days, *p = 0.007). There is no difference between intention to treat patients (7.5 days, IQR 5.8 – 9) and controls (p = 0.17) b. Per protocol patients had shorter hospital length of stay (7 days, IQR 5.5 – 9 days) as compared with control patients (9 days, IQR 9 – 13 days, *p = 0.005). There is no difference between intention to treat patients (9 days, IQR 6.5 – 11) and controls (p = 0.13). The symbol ● represents outliers.

cardiopulmonary bypass patients at the institution. One patient in the intention to treat cohort was on dopamine for the first post-operative night, one patient in the per protocol cohort was on vasopressin for the first post-operative night, and four of the nine intention to treat patients (three of the five per protocol patients) were on milrinone for the first post-operative night. None of the intention to treat patients were treated with phosphodiesterase inhibitors.

Per protocol patients had a shorter duration of chest tube drainage and a shorter hospital length of stay than controls ($p = 0.007$ and 0.005, respectively). Intention to treat patients had no difference in duration of chest tube drainage or hospital length of stay compared to controls ($p = 0.17$ and 0.13, respectively, Fig 1). Median volume of chest tube drainage per kilogram per day was compared on each of the first seven post-operative days. Median volume per kilogram per day was lower in both the intention to treat and the per protocol groups when compared to controls on each of the first seven post-operative days ($p = 0.04$ and 0.008, respectively). When comparing only those patients who were withdrawn from the protocol to controls, there was no difference in volume per kilogram per day ($p = 0.64$, Supplemental Figure S1). Furthermore, those who were withdrawn from the protocol had an increase in volume of output following discontinuation of colchicine (Supplemental Figure S2).

### *Cytokine data*

A comparison of the levels of specific cytokines in the chest tube drainage is shown in Fig. 2. There appears to be a trend towards lower total amount of certain pro-inflammatory cytokines in the chest tube drainage of those in the per protocol group when compared to the control group, with no such trend in the intention to treat group. Median total IL-8 and TNF-α mass digress on post-operative day 7 in the per protocol group. MIP-1β trends down to nearly zero by post-operative day 7 in the per protocol group but remains constant to mildly elevated in both the controls and intention to treat group. The anti-inflammatory cytokine, IL-10, follows nearly the same course over time in all groups.

### *Adverse effects*

The most common adverse effect recorded for all patients receiving colchicine was gastrointestinal. One patient had abdominal pain, two patients had diarrhoea or loose stools, and five patients (55%) had nausea and vomiting. The rate in the historical controls of nausea and vomiting was similar at 67%. One patient had an elevation in transaminases; one patient had an elevation in creatinine. Both of these were reviewed to be more likely related to clinical dehydration and were reversed with rehydration and reduction of diuretics.

## Discussion

This pilot study suggests a significant decrease in duration of chest tube drainage from 10 days to 5 days in Fontan patients who complete a protocol with empiric treatment with colchicine and a shortened hospital length of stay from 9 days to 7 days. Per protocol treatment with colchicine was also associated with decreased volume of chest tube drainage per kilogram per day, with a subsequent increase in those patients who stopped treatment. There are trends towards decreasing pro-inflammatory cytokines within the chest tube drainage in the per protocol colchicine-treated patients, suggesting this may be involved with the mechanism behind colchicine's effect.

Currently, treatment methods for prolonged chest tube drainage include aggressive diuresis, fluid restriction, low-fat diet, parenteral nutrition, Fontan fenestration, and time. Octreotide administration, thoracic duct ligation, and pleurodesis are reserved for refractory drainage with variable results.[17,18,31,32] No treatment methods have ideal results and patients requiring treatment often continue to drain. Fontan patients have longer duration of chest tube drainage (10–15 days), longer baseline hospital lengths of stay with related higher hospitalisation costs than other post-operative cohorts,[32,33] and reducing this burden has long been an objective in our field.[17,34] Post-operative Fontan patients who have drainage longer than 2 weeks are at increased risk of protein losing enteropathy, plastic bronchitis, and have diminished short- and long-term survival.[34–36] This pilot study suggests that colchicine may be efficacious in decreasing duration of chest tube drainage.

Patients undergoing the Fontan procedure have increased post-operative plasma levels of inflammatory cytokine and complement production compared to pre-operative levels.[5] In addition, cytokine and complement levels are reported to be higher in patients who have the Fontan procedure with cardiopulmonary bypass compared to patients who undergo the Fontan procedure off pump.[6] Limited studies of post-operative fluid drainage in non-cardiac surgeries have demonstrated increased localised cytokine production.[37,38] In particular as shown in the prior study, the pro-inflammatory cytokines IL-8, MIP-1β, and TNF-α are elevated in post-operative Fontan chest tube drainage, and they increase over time as compared to an age-matched control cohort.[9] Though not statistically significant, this study suggests a trend of decreasing pro-inflammatory cytokines, particularly MIP-1β, in the per protocol patients over time when compared to controls and intention to treat patients.

The cytokines analysed have clinical and physiologic correlations that could impact chest tube drainage. IL-8 is a chemoattractant for immune cells with increased plasma levels during

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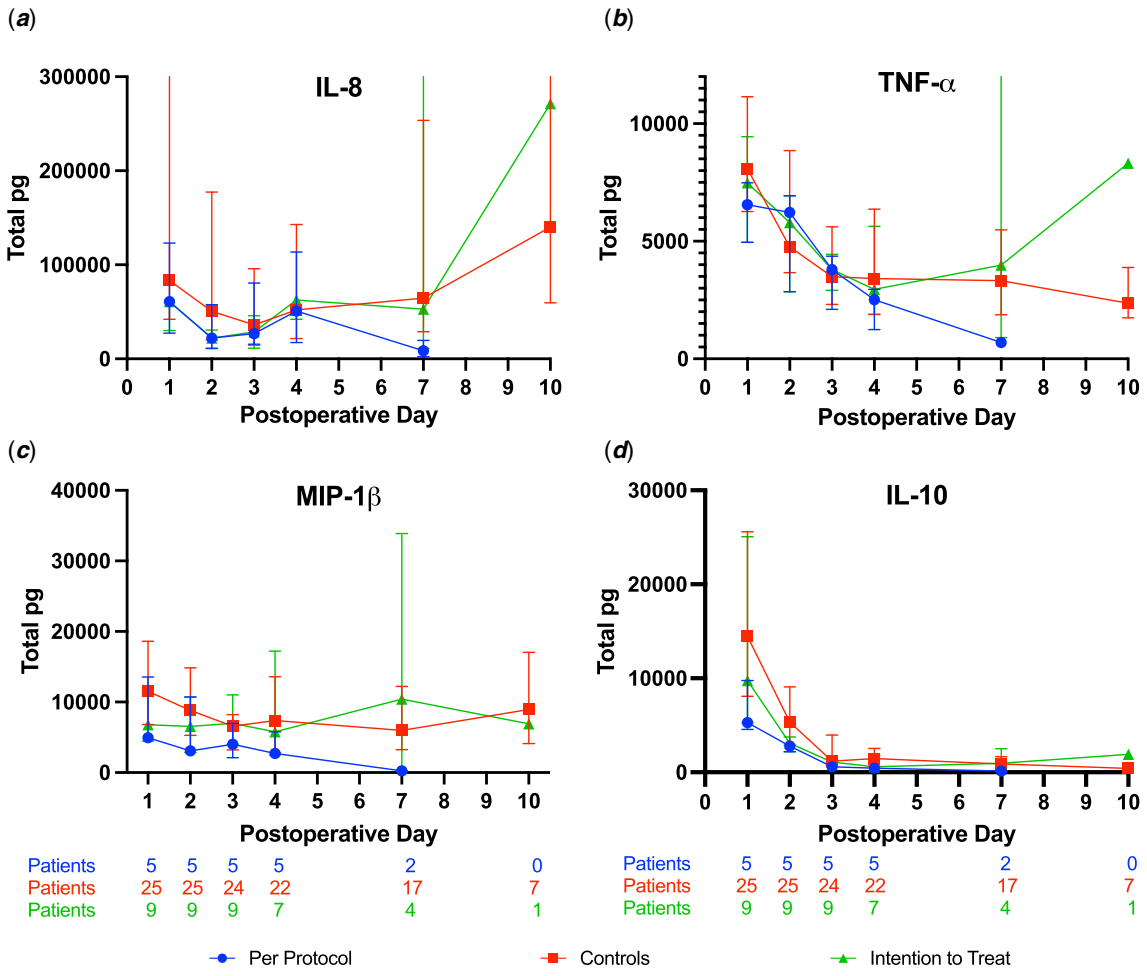



**Fig. 2.** Total cytokine mass over time. Trend for total cytokine mass (in picograms) in chest tube drainage over time for (a) IL-8, (b) TNF-α, (c) MIP-1β , and (d) IL-10 comparing per protocol patients (blue), intention to treat patients (green), and control patients (red). IL = interleukin; MIP-1β = macrophage inflammatory protein beta; TNF-α = tumor necrosis factor alpha. Patients affected are represented beneath the x-axis.

inflammatory disease. MIP-1β is a chemokine produced by macrophages which activates granulocytes leading to neutrophilic inflammation and induces the synthesis and release of other pro-inflammatory cytokines (IL-1, IL-6, and TNF-α).[39] TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation.[40] IL-10 is an anti-inflammatory cytokine, which inhibits expression of multiple pro-inflammatory cytokines and chemokines.[28] Thus, targeting these inflammatory pathways may break the cycle of localised inflammation post-Fontan operation and could lead to shorter duration of chest tube drainage.

Colchicine has a mechanism of action that likely targets these cytokines. Colchicine is used in multiple inflammatory conditions[19,41–43] and has wide ranging anti-inflammatory effects by modulating multiple pro-inflammatory pathways. It prevents microtubule assembly, thereby disrupting inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes, cytokines, and phagocytosis.[44] Colchicine also impairs neutrophil function by impacting inflammatory pathways and mediators of neutrophil activation and decreases levels of the pro-inflammatory cytokines including IL-1β, INF-γ, IL-18, and IL-6. In addition, colchicine blunts TNF-α induced activation of macrophages and reduces the number of TNF-α receptors on the surface of macrophages and endothelial cells.[44] Colchicine was also shown to acutely suppress local cardiac production of inflammatory cytokines in patients with acute coronary syndrome.[45] These previously observed effects of colchicine on inflammation may explain, at least in part, the shortened duration of chest tube drainage seen in the per protocol colchicine-treated post-operative Fontan patients. Clinically, colchicine has been shown to shorten duration of pleural and pericardial effusions and to reduce post-pericardiotomy syndrome after adult cardiac surgery,[14,15,46,47] congruent with the results we saw here.

While the association with prolonged chest tube drainage and the development of protein losing enteropathy and plastic bronchitis are hypothesised to be associated with lymphatic abnormalities, the lymph fluid itself is immunomodulatory. Cytokines cause lymphatic endothelial cells to express interleukins, tumour necrosis factors, and adhesion molecules.[48–50] Cytokine blockade can decrease lymphatic branching, decrease formation of abnormal valve-less lymph vessels, and has been shown to improve the drainage of ascites.[51] Thus, if further studies show colchicine does in fact decrease the duration of chest tube drainage via the disruption of pro-inflammatory cytokine cascades, it is plausible that this may in turn lead to decreased development of these abnormal pathways and thus improved long-term outcomes in the Fontan population.

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Colchicine itself, in combination with other therapies, or for longer duration of therapy in this population is an area ripe for further investigation.

This study is limited by its small sample size. This pilot analysis did not have enough power to find significant differences in the total cytokine masses nor to analyse commonly described clinical risk factors for prolonged pleural drainage such as elevated venous pressures, elevated end diastolic pressures, atrioventricular valve regurgitation, or poor ventricular function. There was also a relatively high rate of removal from the protocol (4 out of 9). The two cases of parental preference for withdrawal were predominantly due to their child complaining of nausea or abdominal discomfort, a common symptom after the Fontan surgery but a possible side effect of colchicine as well. The other two patients were removed from the protocol due to elevated creatinine from baseline (1) and elevated liver function tests from baseline (1), but both were in the context of clinical over-diuresis and both laboratory values improved after clinical rehydration. The use of steroids in 2 of the 5 per protocol group could be confounding the results, as only 1 of the 25 control patients was treated with steroids. When analysing cytokines in patients who received steroids compared to those who did not in the per protocol group, the cytokine trends were similar (data not shown). The cytokine data should be interpreted with caution as the decreased level of cytokines did not reach significance and the trends described may be due to chance. Finally, this study was not blinded, so it is possible that the clinical team was biased to remove chest tubes from this cohort of patients earlier. Though this is possible, it is unlikely due to long-standing and well-practiced chest tube removal criteria at this institution.

In summary, Fontan patients are known to have prolonged length of stay and chest tube duration as compared to other post-operative cohorts. Inflammation may be contributing to these effusions. This pilot study shows a shortened duration of chest tube drainage and a shorter hospital length of stay when post-operative Fontan patients are given an empiric protocol of daily colchicine, a well-known anti-inflammatory drug with minimal side effects. While limited by our sample size, if further studies with a larger cohort confirmed this result, colchicine treatment could become common post-operative management for this population to shorten chest tube drainage and length of stay, thus also decreasing cost of hospitalisation.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/S104795112200186X.

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**Conflicts of interest.** None.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Title 45 of the Code of Federal Regulations) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees (the University of Michigan Institutional Review Board).

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