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## Colchicine for children with pericarditis: systematic review of clinical studies

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**Abbreviations:** Cochrane risk of bias tool for non-randomized trials (ACROBAT-NRSI), C-reactive protein (CRP), electrocardiography (ECG), erythrocyte sedimentation rate (ESR), intravenous immunoglobulin (IVIG), non-steroidal anti-inflammatory drugs (NSAID), prospectively registered systematic reviews in health and social care (PROSPERO),

**Contributors' Statement:**

Dr Alabed conceptualized and designed the review protocol, undertook data extraction and drafted the initial manuscript. He approved the final manuscript as submitted.

Dr. Pérez-Gaxiola reviewed search strategy, undertook data extraction and gave comments on the draft manuscript. He approved the final manuscript as submitted.

Dr. Burls checked the protocol, double checked the process and format of the review, and provided advice and feedback on the draft manuscript. She approved the final manuscript as submitted.

## **Abstract**

### **Objective**

To review the evidence for the efficacy and safety of colchicine in children with pericarditis.

### **Design**

Systematic review

### **Search strategy**

The following databases were searched for studies about colchicine in children with pericarditis (June 2015): Cochrane Central, Medline, EMBASE and LILACS.

### **Eligibility criteria**

All observational and experimental studies on humans with any length of follow-up and no limitations on language or publication status were included. The outcomes studied were recurrences of pericarditis and adverse events.

### **Data extraction**

Two authors extracted data and assessed quality of included studies using the Cochrane risk of bias tool for non-randomized trials.

### **Results**

Two case series and nine case reports reported the use of colchicine in a total of 86 children with pericarditis. Five articles including 74 paediatric patients were in favour of colchicine in preventing further pericarditis recurrences. Six studies including 12 patients showed that colchicine did not prevent recurrences of pericarditis.

### **Limitations**

No randomised controlled trials were found.

### **Conclusion**

Although colchicine is an established treatment for pericarditis in adults, it is not routinely used in children. There is not enough evidence to support or discourage the use of colchicine in children with pericarditis. Further research in the form of large double-blind randomised controlled trials is needed to establish the efficacy of colchicine in children with pericarditis.

## **INTRODUCTION**

Pericarditis is the inflammation of the pericardium, the membranous sac surrounding the heart. Pericarditis is idiopathic in 80% of cases, however it is presumed to be viral in origin <sup>1</sup>. Other causes of pericarditis include post-pericardiotomy syndrome, tuberculosis or bacterial and neoplastic diseases <sup>2</sup>. Post-pericardiotomy syndrome is a more common cause in children than in adults <sup>3</sup>.

The incidence of pericarditis is 2-3 in every 1000 hospitalised children <sup>4</sup>. Symptoms include chest pain and fever which can present as recurrent episodes in up to 15% - 30%. Recurrent pericarditis severely impairs quality of life and can be disabling<sup>5</sup>.

The diagnosis of pericarditis can be challenging. The most common signs include a pericardial rub or effusion<sup>1</sup> and electrocardiography (ECG) changes such a widespread ST-segment elevation might be present. Raised inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) with chest pain might be the only signs<sup>1</sup>.

Colchicine has been shown to be effective in preventing recurrent episodes in adults <sup>6-9</sup>, however it is not routinely used in children <sup>10</sup>. The objective of this systematic review was to identify the efficacy and safety of colchicine in children.

## **METHODS**

This systematic review was registered in the international database of prospectively registered systematic reviews in health and social care (PROSPERO) on the 20th July 2015 (registration number: CRD42015024647) <sup>11</sup>.

### **Data Sources**

The following databases were searched (from their start to June 2015): Cochrane Central, Medline, EMBASE and LILACS. The search did not include any language or time restriction. The search strategy was designed for maximum sensitivity using the Boolean operator AND to combine all synonyms for colchicine with all possible ways of referring to pericarditis. (See

appendix 1 for full details.) In addition, bibliographic references of identified articles were reviewed. We searched [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for on-going trials on 14th February 2016.

### **Eligibility Criteria**

Although randomised controlled trials (RCT) are the best way to test treatments, we anticipated that we would not find many. Therefore our eligibility criteria were any study design of pericarditis in children treated with colchicine. There was no limitation on length of follow-up, language or publication status.

### **Outcomes**

- 1) Efficacy of colchicine in treating children with pericarditis, defined as prevention of recurrences or symptom relief.
- 2) Adverse effects and tolerability of colchicine in children.

### **Data extraction and analysis**

Two authors independently screened titles and abstracts for inclusion. The opinion of a third author was sought when an agreement could not be reached. Full-text publications were obtained for included studies or where eligibility was unclear from the title and abstract. Two authors extracted data and assessed quality of included studies using a pre-defined data collection form. We adopted the Cochrane risk of bias tool for non-randomized trials (ACROBAT-NRSI) to assess the quality of included studies<sup>12</sup>. The tool assesses domains of confounding, selection of participants, outcome measurement, missing data and follow-up.

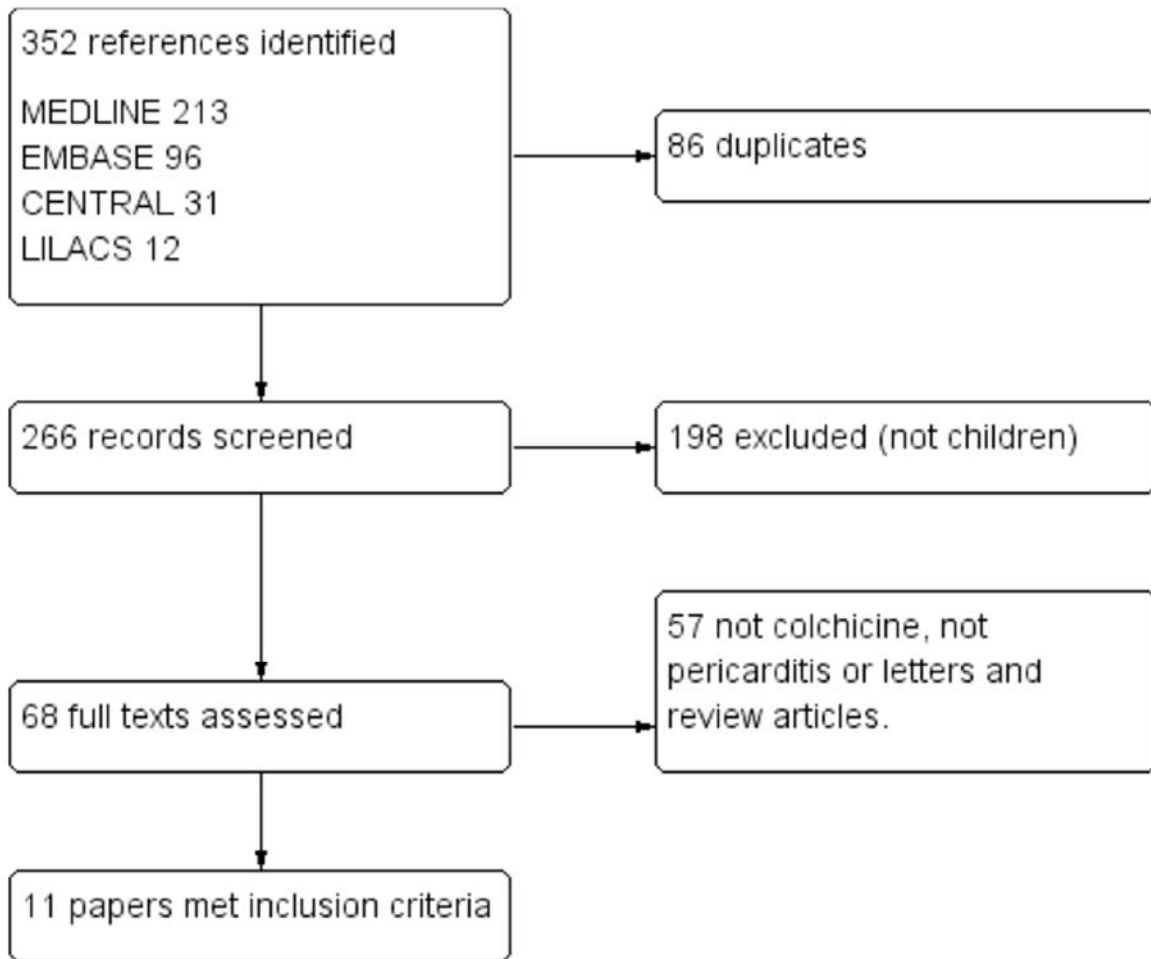
### **Subgroup analysis**

We planned to analyse dose regimens used and duration of treatment.

## RESULTS

A total of 352 records were identified. Removal of duplicates left 266 articles for screening. A total of 68 full texts were assessed for eligibility and 11 articles met the inclusion criteria (Figure 1). No additional study was found through the manual search of bibliographic references of the retrieved papers. No ongoing clinical trials were found on clinicaltrials.gov.

**Figure 1 Study Flow Diagram**



### Study Characteristics

Two case series<sup>13,14</sup> and nine case reports<sup>4,15-19</sup> reported the use of colchicine in a total of 86 children with pericarditis. Studies reported children with different severities of pericarditis. Three studies (two case reports and one case series) were in children with post-pericardiotomy syndrome<sup>13,20,21</sup>. The study characteristics are given in table 1.



## **Quality of included studies**

### 1) Selection of participants

Two case series were included. Consecutive inclusion of patients was reported in one of the studies <sup>14</sup>, while we could not tell if all consecutively patients were included in the other case series <sup>13</sup>.

### 2) Risk of bias of confounding.

No included study pre-specified a list of potential confounders of pericarditis therapy. No study carried out statistical modelling for confounding factors or adjusted for time-varying confounding.

We could not tell from the included reports if confounding factors such as indication of treatment, additional therapies, type of pericarditis and age of children, affected the effect of colchicine.

### 3) Outcome measurement and assessment

Methods for collecting data were poorly reported and we could not tell if any of the studies used more than one outcome assessor to repeat the analysis to ensure reliability.

None of the included studies had control groups. Findings were reported as recurrence free period after colchicine. Two studies reported pre- and post- colchicine recurrence rate <sup>13,14</sup>.

### 4) Missing data

The included papers did not report incomplete or missing data. We could not tell if this because of lack of reporting or absence of missing data. However, the included case reports had appropriate follow up of 6 – 24 months (Table 1).

	Study Type	Children on Colchicine	Type of Pericarditis	Age (years)	Gender	Follow up (months)	Colchicine Dose	Response to colchicine
<b>Adler 1998</b>	Case report	1	Idiopathic	2	female	6	1 mg/day for 6 months	No recurrences
<b>Blasco 2006</b>	Case report	1	Post-pericardiectomy	12	male	24	1 mg/day	Further recurrences
<b>Brucato 2000</b>	Case report	1	Idiopathic	14	male	29	1 mg/day for 6 months	No recurrences
<b>Brucato 2013</b>	Case series	67	87% idiopathic and 9% post-pericardiectomy	13 (range 1 - 17)	62% male	60 (6 - 360)	0.5- 1.5 mg/day	Reduced Recurrences
<b>Del Fresno 2013</b>	Case reports	2	Post-pericardiectomy	4	male and female	24	0.5mg/day for 4 months	Further recurrences
<b>Jurko 2002</b>	Case reports	2	Idiopathic	not reported	not reported	9 and 12	not reported	No recurrences
<b>Peterlana 2005</b>	Case report	1	Idiopathic	11	male	60	1 mg/day	Further recurrences
<b>Picco 2009</b>	Case reports	3	Idiopathic	12, 13 and 14	1 male, 2 female	6	1 mg/day for 6 months	Further recurrences
<b>Raatikka 2003</b>	Case-series	4	Post-pericardiectomy	8, 9, 12 and 15	3 males, 1 female	96p (48 - 192)	0.5- 2 mg/day for 6 months	Further recurrences
<b>Scardapane 2012</b>	Case report	1	Idiopathic	11	male	24	1 mg/day for 6 months	Further recurrences
<b>Yazigi 1998</b>	Case reports	3	Idiopathic	4, 5 and 14	male	17 - 24	0.25 - 0.5 mg/day for 6 months	No recurrences

**Table 1 Study Characteristics**

Two articles were only available as conference abstracts <sup>14,17</sup> which limited the amount of data available.

### **Efficacy of colchicine or pericarditis in children**

Included studies were heterogeneous in populations, study designs and outcome reporting; we therefore did not pool data in a meta-analysis. The findings of the included studies are described below. Two types of pericarditis were studied: idiopathic pericarditis and post-pericardiotomy syndrome.

A detailed data extraction of all included studies is given in Appendix 2.

#### **Idiopathic Pericarditis**

Seven case reports <sup>4,15-19,22</sup> and one case series <sup>14</sup> reported the use of colchicine in children with idiopathic pericarditis.

The case reports included 12 children with a median age of 11.5 (range 2-14) and 70% male gender distribution. All children had multiple recurrences of pericarditis while treated with NSAIDs and steroids. When colchicine was added, 7 out of 12 children (58%) had no further recurrences, while the other 5 (42%) continued to have recurrences. The median follow up was 12 months (range 6 – 60). The included articles did not report the exact number of pericarditis recurrences pre and post colchicine treatment.

The case series was only available as an abstract and included 100 children with a median age of 13 (range 1 – 17) and 62% male gender distribution. Colchicine was added to NSAIDs or steroids in 67 patients (67%). The median follow up was 60 months (range 6 – 360 months). The number of pericarditis recurrences per year was 3.8 before colchicine was given and 1.6 afterwards.

#### **Post-pericardiotomy syndrome**

One case series <sup>13</sup> and two case reports <sup>20,21</sup> reported the use of colchicine in children with post-pericardiotomy syndrome.

The case series studied 15 children with at least two recurrences of pericarditis post open heart surgery. Four patients were treated with NSAIDs and eleven with steroids. Colchicine was added to four patients on steroid treatment. The four patients on colchicine had a median age of 12.5 years (range 8 to 16 years). All children treated with colchicine had further recurrences of pericarditis. The mean number of recurrence while on steroids only was 2.4 recurrences per year and increased to 4.8 recurrences per year after colchicine was started. The mean number of recurrences in the NSAIDs group were 1.2 recurrences per year. The authors concluded that colchicine was not effective in preventing pericarditis recurrences. However, colchicine was only used in the more severe steroid-resistant group.

The two case reports included 3 children, one girl aged 4 and two boys aged 4 and 12. The children had recurrent episodes of pericarditis following cardiac surgery. The pericarditis episodes were not controlled with NSAIDs or steroids. The three children continued to have recurrences during their 24 months follow up after colchicine was added.

### **Adverse effects of colchicine in children**

Severe adverse events were not reported in the included studies. Adverse effects included abdominal symptoms such as nausea and diarrhoea <sup>4,17,23</sup>.

### **Colchicine dose and treatment regime**

Yaazigi 1998 and Del Fresno 2013 used a colchicine dose of 0.25 - 0.5 mg/day for 4 - 6 months. Colchicine 1 mg/day was used by (Adler 1998, Brucato 2000, Scardapane 2012 and Picco 2014, Peterlana 2005, Blasco 2006) for 6 months. Scardapane 2012 and Brucato 2013 used 1mg - 1.5 mg/day. Brucato 2013 also used 0.5mg / day for children less than 5 years. Raatika 2003 used a colchicine dose of up to 2 mg/day.

## **DISCUSSION**

Colchicine is an established treatment for pericarditis in adults <sup>6-9</sup>. It's efficacy to reduces recurrences and help relieving symptoms has been proven in a number of RCTs <sup>24-29</sup>. However, no RCT has been carried out in children <sup>30</sup> and there are no ongoing trials. We estimate that a

RCT with 82 children is needed to detect the same pericarditis recurrence risk reduction as in adults (for 5% significance level and 80% power).

This systematic review shows that the evidence on colchicine in children is scarce, of poor quality and contradictory. The largest case series from 2013<sup>14</sup> has still not been published as a full text. One case series<sup>14</sup> and four case-reports<sup>4,15-17</sup> including 74 children were in favour of using colchicine to prevent further pericarditis recurrences. These children had mainly an idiopathic pericarditis. On the other hand, one case series<sup>13</sup> and five case reports<sup>18-22</sup> including 12 children showed that colchicine did not prevent recurrences. Three of these studies were in children with post-pericardiotomy syndrome<sup>13,20,21</sup>. Two studies<sup>18,19</sup> reported children with pericarditis resistant to colchicine but responded to the use of interleukin-1b receptor antagonist (anakinra).

Studies reported that colchicine was well tolerated in children although the small number of included children might not be representative. It is noted that colchicine is not licensed in either the USA or Europe for the use in pericarditis<sup>31</sup>.

## **LIMITATIONS**

Very little is reported on the use of colchicine in children in the medical literature. Included studies are case series and case reports only, therefore the conclusions of this review are based on low quality evidence. Two articles were only available as abstracts<sup>14,17</sup>.

Nine of the twelve included studies were reported from centres in the Mediterranean region (Italy, Spain, Lebanon and Israel)<sup>4,14-16,18-22</sup>. This is similar to the situation in adult studies where all randomized controlled trials of colchicine in pericarditis were done in Italy<sup>31</sup>. It is possible that the findings may not apply to groups from other climates or geographical locations. Two studies reported pre- and post- colchicine recurrence rate to report colchicine efficacy in preventing recurrences<sup>13,14</sup>. However, this conclusion is not appropriate as there was no control group and it was not possible to tell what the recurrence rate in the same population would have been without colchicine.

## **CONCLUSIONS**

The available literature suggests that colchicine might be effective in preventing recurrences in children with idiopathic pericarditis, however the quality of evidence is very low.

Taking into account that colchicine is cheap to produce and effective in adults, it is important that its efficacy in children with pericarditis is tested further in the form of large double-blind randomised controlled trials.

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**"What is already known on this topic"**

Two in every thousand hospitalized children experience episodes of pericarditis. Recurrent episodes can occur in up to 30% of the affected children, severely impairing their quality of life. Colchicine has been shown to be effective in adults.

**"What this study adds"**

There is need for large double-blind randomised controlled trials is needed to establish the efficacy of colchicine in children with pericarditis

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## **Appendix 1**

### **Search Strategy**

#### **CENTRAL**

#1 MeSH descriptor: [Pericarditis] explode all trees

#2 MeSH descriptor: [Pericardium] this term only

#3 pericard\*

#4 #1 or #2 or #3

#5 MeSH descriptor: [Colchicine] explode all trees

#6 colchi\*

#7 colchysat or colcine or colcrys or colgout or goutichine or goutnil or kolkicin or "nsc 757" or

tolchicine

#8 #5 or #6 or #7

#9 #4 and #8

#### **OVID (MEDLINE and EMBASE)**

1. exp Pericarditis/

2. Pericardium/

3. pericard\*.tw.

4. or/1-3

5. exp Colchicine/

6. colchicin\*.tw.

7. colchin.tw.

8. colchicum\*.tw.

9. colchily.tw.

10. colchimedio.tw.

11. colchiquim.tw.
12. colchisol.tw.
13. colchysat.tw.
14. colcine.tw.
15. colcrys.tw.
16. colgout.tw.
17. goutichine.tw.
18. goutnil.tw.
19. kolkicin.tw.
20. nsc 757.tw.
21. tolchicine.tw.
22. colchichin\*.tw.
23. or/5-22
24. 4 and 23

## **Appendix 2**

### **Data Extraction of included studies**

#### Idiopathic pericarditis

**Adler 1998**<sup>15</sup> described a 26 year old man and a 2-year-old girl with idiopathic pericarditis and large pericardial effusions. The girl did not respond to non-steroidal anti-inflammatory drugs (NSAID), corticosteroids or pericardiocentesis. She was then given colchicine (1 mg/day) for 6 months. Response to colchicine was described as immediate and dramatic with the resolving of the pericardial effusion. No recurrences of pericarditis were observed in a 6 month follow up period.

**Yazigi 1998**<sup>4</sup> included 3 children aged 4, 6 and 14 years with multiple recurrent pericarditis and pericardial effusion. They did not respond to NSAIDs (salicylates or diclofenac). In addition, prednisone was tried in one patient and pericardiocentesis in two patients. However, pericarditis recurrences occurred and the patients were then started on colchicine. Colchicine was given 0.25 - 0.5 mg/d for 6 months and follow up continued for 12 to 18 months after colchicine was stopped. No pericarditis relapses occurred throughout the treatment or follow-up period.

**Brucato 2000**<sup>16</sup> describes a 14 year old boy who experienced multiple remittent–intermittent recurrences of pericarditis and pleural effusion despite being treated with indomethacin and methylprednisolone. He was then started on colchicine 1 mg/day for one year and had no further pericarditis recurrences for the follow up period of 29 months. No adverse effects of colchicine were noted.

**Jurko 2002**<sup>17</sup> [ENREF 6](#) is an abstract of a study which included 2 children with a severe form of idiopathic recurrent pericarditis. Both were dependent on corticosteroids and one became cushingoid. Both then received colchicine instead of a steroid and did not have any further relapses during a follow up period of 12 months.

**Peterlana 2005**<sup>22</sup> describes four patients with pericarditis. One of the patients was an 11 year old boy with pericarditis that was only responsive to high dose (50mg) prednisone. On attempts to reduce the dose of prednisone to 15-20mg he experienced multiple (15) recurrences of pericarditis. To reduce the steroid dose, colchicine 1 mg/day was added, however without effect. The same patient did not respond to other medications such as methotrexate, cyclosporine, azathioprine or intra-venous immunoglobulin (IVIG). The authors concluded that colchicine was ineffective in preventing recurrences in resistant pericarditis and suggested

using IVIG in such cases.

**Picco 2009**<sup>18</sup> reports 3 children aged 12, 13 and 14 years with recurrent pericarditis and pleural effusions. These patients represent all consecutive cases of recurrent idiopathic pericarditis between 2005 and 2008. The patients were treated with high dose prednisone (1 - 2 mg/kg/day) with or without NSAIDs. In addition, one patient had a pericardiectomy and another pericardiocentesis. Pericarditis recurrences occurred once prednisone dose was tapered down to (0.5 mg/kg/day). All three patients were started on colchicine 1 mg/day in a bid to reduce steroid dose. The patients developed further pericarditis episodes within 2 months of starting colchicine and had further recurrences later. The patients' symptoms eventually settled after starting interleukin-1b receptor antagonist (anakinra). However, they had recurrences of pericarditis soon after anakinra was discontinued. No adverse effects of colchicine were reported.

**Scardapane 2012**<sup>19</sup> reports an 11 year old boy with recurrent episodes of pericarditis and pericardial effusion. He was initially treated with ibuprofen (35 mg/kg/day) and prednisone (1 mg/kg/day). Three months later a further pericarditis episode required hospitalisation and colchicine (1 mg/day) was added to ibuprofen and the tapering steroid. The boy was symptom free for 20 months while on colchicine. The steroid was tapered down to 0.15 mg/kg/day after which the boy had a further pericarditis recurrence. Colchicine dose was increased to 1.5 mg/day and ibuprofen was substituted with indomethacin (2 mg/kg/day), while continuing on prednisone 0.15 mg/kg/day. After a 6 months recurrence free period, the boy was readmitted with a new recurrence. Colchicine and indomethacin were stopped and anakinra was given after which symptoms resolved and the patient had no further recurrences for 12 months. No adverse

effects of colchicine were reported. The authors concluded that anakinra is an effective alternative to colchicine and NSAIDs or for those who experience adverse effects with steroids. **Brucato 2013**<sup>14</sup> is an abstract of a retrospective case series of 100 consecutive cases of children with pericarditis recruited from 7 centres in Italy. All included children had at least two recurrences of pericarditis prior to recruitment. The aetiology of pericarditis was 88% idiopathic and 10% post-pericardiotomy and 2% familial Mediterranean fever. The mean age of included patients was 13 (range 1 – 17) with a 62% male gender distribution. Colchicine (0.5mg – 1.5mg) was added to NSAIDs or steroids in 67 patients (67%). The participants were followed up for a median of 73 months (range 3 – 312 months). The included patients had on average 1.6 pericarditis recurrences / year compared to 3.8 recurrences / year before colchicine was started. Based on the reduction of the number of pericarditis recurrences before and after taking colchicine, the authors concluded that colchicine halved the number of recurrences in their study population.

### **Post-pericardiotomy syndrome**

**Raatikka 2003**<sup>13</sup> studied 15 children with recurrent pericarditis post open heart surgery. Patients were included if they had at least two recurrences of pericarditis after the initial attack. Four patients were treated with NSAIDs and eleven with steroids. Four patients had further recurrences despite steroid treatment and were given colchicine. The four patients on colchicine were aged 7 to 17 years. Colchicine dose given was 0.5- 2 mg/day and follow-up was for 4 - 16 years (mean 8 years). All children treated with colchicine had further recurrences of pericarditis. The number of recurrences while on steroids plus colchicine ranged from 3 – 10 recurrences (mean 5.8) during a follow up period of 6 - 27 months (mean 13.3 months). The number of recurrences while on steroids only and before colchicine was started was 4 - 15 recurrences

(mean 7.5) during a follow up period of 10 to 71 months (mean 35 months). This equates to a mean of 0.4 recurrences/month with colchicine and a mean of 0.2 recurrences/month before colchicine. The total mean of recurrences of pericarditis in patients who were treated with steroids (with or without colchicine) was 8.3 and ranged from 2 to 26 recurrences during a follow-up of 48 months or 0.17 recurrences/month. The mean recurrences of pericarditis in the NSAIDs group was 4.6 (range 2 to 6) or 0.1 recurrences/month. Total remission over 4 years was reported in 5 (45%) of the patients treated with steroids and 2 (50%) of the patients treated with NSAIDs. The authors concluded that colchicine was not effective in preventing pericarditis recurrences. Colchicine was only used in the more severe steroid-resistant group, therefore we could not compare it to the steroid or NSAID responsive group.

**Blasco 2006**<sup>20</sup> reports a 12 year old boy who developed a recurrent episodes of pericarditis 2 months post-cardiac surgery (atrial septal defect closure). The patient was started on NSAIDs and improved. NSAIDs were stopped after two months. Two weeks later the patient had recurrence of his symptoms. He was restarted on NSAIDs with additional colchicine (1 mg/day) and had a rapid resolution of symptoms. Two months later, the patient had another relapse when the NSAID dose was tapered while still on colchicine. NSAID dose was increased again and treatment with NSAID and colchicine continued for another 6 months and then stopped. One month after stopping treatment he had another recurrence of pericarditis. Treatment with NSAID and colchicine was restarted. NSAID was given for 2 months and colchicine continued until his follow-up. . On follow up, 10 months later, he remained symptom free while still being treated with colchicine. The authors concluded that post-pericardiotomy pericarditis showed a partial response to colchicine. No adverse effects of colchicine are reported.

**Del Fresno 2013**<sup>21</sup> reports two 4 year-old children with recurrent pericarditis due to post-pericardiotomy syndrome. The first patient was a girl who had corrective surgery for tetralogy of Fallot. She developed pericarditis and pleural effusion that initially responded to prednisone (2 mg/kg/day). Prednisone was tapered down and eventually stopped after 11 weeks and the patient developed a recurrent episode of pericarditis and pleural effusion three weeks afterwards. Prednisone 1 mg/kg/day was restarted and in addition to colchicine 0.5mg/day for 4 months. The patient did not improve and developed pericardial effusions. Her symptoms were controlled after adding IVIG to her therapy. She remained recurrence free for 13 months afterwards.

The second patient was a boy who had cardiac surgery for hypertrophic obstructive cardiomyopathy. After surgery he developed pericarditis and pleural effusion. He was treated with ibuprofen, prednisone 2mg/kg/day and colchicine 0.75 mg/day for 2 years. His pleural effusion worsened three months later and methotrexate and IVIG were added to control his pericarditis and pericardial effusion.

The authors concluded that colchicine was not effective in resistant pericarditis and suggested IVIG as alternative therapy.