



This is a repository copy of *Colchicine for children with pericarditis: systematic review of clinical studies*.

White Rose Research Online URL for this paper:  
<http://eprints.whiterose.ac.uk/100800/>

Version: Accepted Version

---

**Article:**

Alabed, S. [orcid.org/0000-0002-9960-7587](https://orcid.org/0000-0002-9960-7587), Pérez-Gaxiola, G. and Burls, A. (2016) Colchicine for children with pericarditis: systematic review of clinical studies. *Archives of Disease in Childhood*, 101 (10). pp. 953-956. ISSN 0003-9888

<https://doi.org/10.1136/archdischild-2015-310287>

---

**Reuse**

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

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

Samer Alabed<sup>a</sup>, MD MSc, Giordano Pérez-Gaxiola<sup>b</sup>, MD, Amanda Burls<sup>c</sup>, BA MSc MBBS  
FFPH

**Affiliations:** <sup>a</sup>Academic Radiology Registrar at Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; <sup>b</sup>Cochrane México, Hospital Pediátrico de Sinaloa, Culiacán, México; Professor of Public Health, City University London, United Kingdom

**Address correspondence to:** Giordano Pérez-Gaxiola, Hospital Pediátrico de Sinaloa, Blvd. Constitución s/n, Col. Almada. 80200, Culiacán, Sinaloa, 80200, Mexico.  
[giordano@sinestetoscopio.com](mailto:giordano@sinestetoscopio.com).

**Keywords:** colchicine, pericarditis, children, systematic review

**Funding Source:** No external funding for this manuscript.

**Financial Disclosure:** The authors have no financial relationships relevant to this article to disclose.

**Potential Conflicts of Interest:** The authors have no conflicts of interest relevant to this article to disclose.

**Review Registration:** PROSPERO 2015:CRD42015024647 Available from  
[http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015024647](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024647)

**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 as 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](http://clinicaltrials.gov).

### 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).

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 reduce 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.

**"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

## References:

1. Dudzinski, D. M., Mak, G. S. & Hung, J. W. Pericardial diseases. *Curr. Probl. Cardiol.* **37**, 75–118 (2012).
2. Zayas, R. et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. *Am. J. Cardiol.* **75**, 378–82 (1995).
3. Miller, R. H., Horneffer, P. J., Gardner, T. J., Rykiel, M. F. & Pearson, T. A. The epidemiology of the postpericardiotomy syndrome: a common complication of cardiac surgery. *Am. Heart J.* **116**, 1323–9 (1988).
4. Yazigi, A. & Abou-Charaf, L. C. Colchicine for recurrent pericarditis in children. *Acta Paediatr.* **87**, 603–4 (1998).
5. Soler-Soler, J., Sagrista-Sauleda, J. & Permanyer-Miralda, G. Relapsing pericarditis. *Heart* **90**, 1364–1368 (2004).
6. Alabed, S. et al. Colchicine for pericarditis. *Cochrane database Syst. Rev.* **8**, CD010652 (2014).
7. Imazio, M. et al. Efficacy and safety of colchicine for pericarditis prevention. Systematic review and meta-analysis. *Heart* **98**, 1078–82 (2012).
8. Imazio, M. et al. Meta-analysis of randomized trials focusing on prevention of the postpericardiotomy syndrome. *Am. J. Cardiol.* **108**, 575–9 (2011).
9. Lotrionte, M. et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for acute pericarditis and its recurrences. *Am. Heart J.* **160**, 662–70 (2010).
10. Shakti, D., Hehn, R., Gauvreau, K., Sundel, R. P. & Newburger, J. W. Idiopathic pericarditis and pericardial effusion in children: contemporary epidemiology and management. *J. Am. Heart Assoc.* **3**, e001483 (2014).
11. Alabed, S., Guul, A. & Gaxiola, Giordano Pérez Burls, A. Colchicine for children with pericarditis: a systematic review of case-series and case-reports. PROSPERO 2015 CRD42015024647
12. Sterne, J., Higgins, J. & Reeves, B. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI). Version 1.0.0 at <<http://www.riskofbias.info>>
13. Raatikka, M., Pelkonen, P. M., Karjalainen, J. & Jokinen, E. V. Recurrent pericarditis in children and adolescents: report of 15 cases. *J. Am. Coll. Cardiol.* **42**, 759–764 (2003).
14. Brucato, A. et al. Recurrent Pericarditis In Children and Adolescents: Etiology, Presentation, Therapies, and Outcomes In a Multicenter Retrospective Cohort Of 100 Patients. [abstract]. *Arthritis Rheum.* **65**, 365 (2013).
15. Adler, Y. et al. Colchicine for large pericardial effusion. *Clin. Cardiol.* **21**, 143–144 (1998).
16. Brucato, A., Cimaz, R. & Balla, E. Prevention of recurrences of corticosteroid-dependent idiopathic pericarditis by colchicine in an adolescent patient. *Pediatr. Cardiol.* **21**, 395–6
17. Jurko, A., Pokorny, Farska, Z. & Sparcova, A. Colchicine in atypical forms of pericarditis

- in children. (2002).
18. Picco, P. et al. Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1beta receptor antagonist (anakinra): an unrecognized autoinflammatory disease? *Arthritis Rheum.* **60**, 264–8 (2009).
  19. Scardapane, A., Brucato, A., Chiarelli, F. & Breda, L. Efficacy of an interleukin-1β receptor antagonist (anakinra) in idiopathic recurrent pericarditis. *Pediatr. Cardiol.* **34**, 1989–91 (2013).
  20. Betrián Blasco, P. & del Alcázar Muñoz, R. Pericarditis recurrente, colchicina y dolor pericardítico sin patología objetivable. *An. Pediatría* **65**, 273–274 (2006).
  21. del Fresno, M. R. et al. Intravenous immunoglobulin therapy for refractory recurrent pericarditis. *Pediatrics* **134**, e1441–6 (2014).
  22. Peterlana, D. et al. Efficacy of intravenous immunoglobulin in chronic idiopathic pericarditis: report of four cases. *Clin. Rheumatol.* **24**, 18–21 (2005).
  23. Adler, Y. et al. Colchicine treatment for recurrent pericarditis. A decade of experience. *Circulation* **97**, 2183–2185 (1998).
  24. Imazio, M. et al. COPE: Colchicine in addition to conventional therapy for acute pericarditis: results of the COLchicine for acute PERicarditis (COPE) trial. *Circulation* **112**, 2012–6 (2005).
  25. Imazio, M. et al. CORE: Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COLchicine for REcurrent pericarditis) trial. *Arch. Intern. Med.* **165**, 1987–91 (2005).
  26. Imazio, M., Cecchi, E., Ierna, S. & Trincherio, R. CORP (COLchicine for Recurrent Pericarditis) and CORP-2 trials--two randomized placebo-controlled trials evaluating the clinical benefits of colchicine as adjunct to conventional therapy in the treatment and prevention of recurrent pericarditis: study des. *J. Cardiovasc. Med. (Hagerstown)*. **8**, 830–4 (2007).
  27. Imazio, M. et al. A randomized trial of colchicine for acute pericarditis. *N. Engl. J. Med.* **369**, 1522–8 (2013).
  28. Imazio, M., Cecchi, E. & Trincherio, R. Colchicine for the prevention of the postpericardiotomy syndrome: the COPPS trial. *International journal of cardiology* **121**, 198–199 (2007).
  29. Imazio, M. et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet* **383**, 2232–7 (2014).
  30. Authors/Task Force Members et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. *Eur. Heart J.* ehv318 (2015). doi:10.1093/eurheartj/ehv318
  31. Alabed, S., Cabello, J. B. & Burls, A. Cochrane corner: colchicine for pericarditis. *Heart* (2015). doi:10.1136/heartjnl-2015-307780



	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*