

Unmet Needs & Burden Of Recurrent Pericarditis (RP): Results Of A Systematic Literature Review (SLR)

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BACKGROUND

- Pericarditis, a condition of inflammation of the sac surrounding the heart, is characterized by chest pain that can be debilitating.
- Typically pericarditis manifests as a single event and resolves without complication. However, some cases are associated with serious complications, such as cardiac tamponade and constrictive pericarditis, that can be life-threatening.
- Recurrent pericarditis, defined by the recurrence of signs and symptoms of pericarditis at least 4-6 weeks after the original acute event has resolved, occurs in 15-30% of pericarditis patients, some of whom go on to experience multiple recurrences.

METHODOLOGY

Search Strategy

- The search strategy focused on epidemiology, interventions, outcomes and the burden of acute and recurrent pericarditis, with a particular focus on evidence in patients with relapsing/refractory pericarditis. All published evidence from randomized clinical trials (RCTs) was included. The initial list of interventions was based on treatment guidelines from the European Society of Cardiology (Adler 2015).

Databases and Guidelines

- The following databases were searched through the OVID platform covering publications from January 2003 through October 2018:
- Medical Literature Analysis and Retrieval System Online [MEDLINE®] and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions®
- Excerpta Medica database [Embase®]
- Cochrane database (Collaboration databases)
- Econlit database
- The methodology followed principles outlined in the following:
 - Cochrane Handbook for Systematic Reviews of Interventions, (Higgins and Green 2011)
 - University of York Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Health Care (CRD 2009)
 - Methods for the Development of NICE Public Health Guidance (National Institute for Health and Care Excellence 2012)

RESULTS

Search Results

The 55 records that were extracted included: eight clinical studies, 33 real-world evidence (RWE) studies, and fourteen systematic literature reviews / meta-analyses (Figure 1)

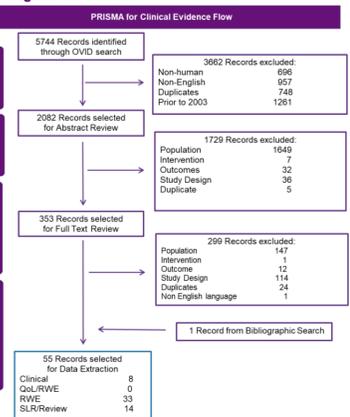
Clinical Trials and Studies:

- Six randomized placebo-controlled trials (three compared colchicine with placebo, two compared colchicine + aspirin with aspirin alone and one randomized withdrawal study with anakinra)
- One non-randomized single-center observational study compared colchicine with non-colchicine treatment
- One single-arm prospective open-label study investigated anakinra in patients resistant and/or intolerant to previous treatment with aspirin and/or NSAIDs, colchicine and corticosteroids

Real World Studies:

- Four pediatric studies (weighted mean age = 13.2 years)
- Fifteen studies in adults prescribed first or second line treatments (weighted mean age when reported = 53.5 years)
- Three retrospective studies of second-line corticosteroid treatment, typically co-administered with colchicine and NSAIDs
- Nine studies with third-line treatments (six anakinra, two azathioprine and one IVIG) (weighted mean age when reported = 39.6 years)
- Eight studies contained some information about health care resource use, of which two extensively discussed resource use and costs

Figure 1: PRISMA



OBJECTIVES

A systematic literature review (SLR) was conducted in October 2018 to identify and summarize publications that provide the current understanding of symptom burden, quality of life and economic burden in patients with pericarditis focusing prominently on patients with recurrent disease. Further, this study aimed to summarize the evidence and outcomes associated with the various treatment options to understand unmet medical needs.

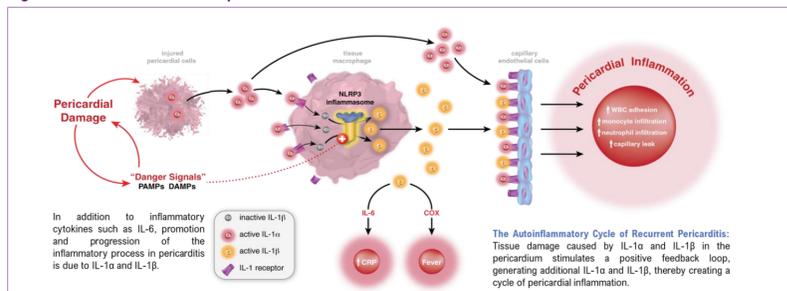
Inclusion and Exclusion Criteria

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines were followed using the below listed PICOS (Population, Intervention, Comparators, Outcomes and Study Design) criteria to define record inclusion / exclusion for data extraction.

- Population:** Patients diagnosed with acute or recurrent pericarditis with focus on recurrent, treatment-refractory pericarditis.
- Interventions & Comparators:** anti-inflammatory treatments, colchicine, corticosteroids, anakinra, intravenous immune globulin (IVIG), azathioprine, pericardiectomy
- Outcomes:** Clinical Outcomes: pericarditis recurrence, rate of recurrence, time to recurrence; Treatment Patterns: use list interventions; Symptom burden: chest pain, elevated C-reactive protein (CRP), fever, pericardial effusion, ST-segment elevation, pericardial friction rub; Severe Complications: cardiac tamponade, constrictive pericarditis; Humanistic Burden: Health-Related Quality of Life (HRQL), utilities /dis-utilities, health states, Quality-Adjusted Life Years (QALYs), adverse events; Economic burden: health care resource use, productivity loss
- Study Design:** Interventional studies: randomized clinical trials, single-arm clinical trials; Non-interventional Studies: prospective and retrospective observational studies, database analyses, registries, chart reviews, surveys; Economic Studies: cost analysis, budget impact analysis, cost-benefit/effectiveness/minimization/utility analysis; Systematic Reviews and Meta-analyses: for reference cross-checking; Case series, case studies, and case reports with less than 3 subjects were excluded.

Disease Pathway

Figure 2: Role of IL-1 α and IL-1 β in Recurrent Pericarditis



PAMPs pathogen associated molecular patterns
DAMPs damage associated molecular patterns

Pathophysiology

- In Western Europe and the United States, the majority of pericarditis episodes (80%-90%) are considered idiopathic and presumed to be post-viral in nature (Cremer 2016).
- While the underlying cause of recurrent pericarditis is often unknown, recent evidence suggests involvement of an autoinflammatory pathway driven by interleukin-1 (IL-1) that leads to pericardial inflammation, elevated CRP and fever (Brucato 2018).

Epidemiology

Published assumptions support a US recurrent pericarditis prevalence ranging from 31K-61K

- Annually, approximately 18-35K patients experience recurrence, approximately 50% of these patients go on to have multiple recurrences over time (8-15% of the total pericarditis population)
- Of the prevalent population, a range of 13-26K patients have 'Complicated Pericarditis' defined as: >2 recurrences, or <2 recurrences with chronic or incessant pericarditis, or serious complication such as cardiac tamponade or constrictive pericarditis.

Figure 3: Epidemiology of Recurrent and Complicated Pericarditis

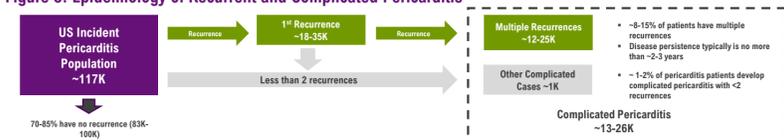


Figure 4: Prevalence of Cardiac Tamponade in Pericarditis

Short Reference	Population	n/N	Context	Prevalence
Imazio_CIRC_2011	adults w/ specific etiology AP followed-up mean 60 months	1784	during follow-up	20.2%
Imazio_AJC_2005	adults w/ RP followed-up mean 74 months	955	1st attack (recurred)	16.4%
Imazio_JCVMED_2016	pediatrics w/ RP followed-up median 60 months	15110	1st attack	13.6%
Kumar_CARD_2016	≥ 16 years old hospital admissions w/ diagnosis of pericarditis	17,914/135,710	during hospitalization	13.2%
Sud_ACC_2018_ConfAb	adults w/ AP and readmitted within 30 days	62487	during readmission	12.7%
Moretti_AJC_2013	adult refractory RP	119	history of tamponade	11.1%
Brucato_AJC_2006	adult refractory RP	461	1st attack	6.5%
Ratnaparkhi_PEC_2011	pediatrics presenting to ED with isolated AP	122	1st attack	4.5%
Imazio_AJC_2005	adults w/ AP followed-up mean 72 months—no RP	6/239	1st attack (no recurrence)	2.5%
Shakti_AJHA_2014	<21 years old in hospital records with pericarditis and PE	11543	during hospitalization	2.0%
Imazio_CIRC_2011	adults w/ viral/idiopathic AP followed-up mean 60 months	5416	during follow-up	3.1%

Cardiac tamponade (CT) is a rare but severe life-threatening complication of pericarditis where the accumulation of fluid in the pericardium compromises the ability of the heart to pump.

- Kumar (2016) and Sud (2018) reported rates of CT in hospitalized pericarditis patients of 13.2% and 12.7%, respectively.
- Shakti (2014) reported a hospitalized CT rate of 2.0%, however 16.5% underwent a drainage procedure, likely preventing CT.
- Imazio (2011) reported CT prevalence of 20.2% in pericarditis patients with specific etiology vs. 1.2% in patients with idiopathic/post-viral AP
- Imazio (2005) reported CT prevalence of 16.4% in AP patients who went on to have a recurrence vs 2.5% in patients who were recurrence-free.

Clinical Burden Of Illness

Figure 5: Prevalence of Constrictive Pericarditis

Short reference	Population	n/N	Context	Prevalence
Baskar_PPC_2018	pediatrics w/ pericarditis who underwent cardiac MRI	3/21	CP at index CMR	14.3%
Imazio_JACC_2004	adults w/ pericarditis who did not respond to aspirin	3/33	developed CP during follow-up	9.1%
Imazio_CIRC_2011	patients w/ specific etiology AP followed-up mean 72 months	7/84	chronic CP during follow-up	8.3%
Imazio_JCVMED_2016	pediatrics w/ RP followed-up median 60 months	3/118	developed CP during follow-up	2.5%
Imazio_JACC_2004	adults w/ pericarditis who did respond to aspirin	1/221	transient CP during follow-up (p<0.004) compared w/ no response to aspirin)	0.5%
Imazio_CIRC_2011	patients w/ viral/idiopathic AP followed-up mean 72 months	2/416	chronic CP	0.5%
Brucato_AJC_2006	adults w/ RP followed-up mean 8.3 years	0/61	no CP during follow-up	0.0%

ANA=anakinra; AP=acute pericarditis; CP=constrictive pericarditis; MRI=magnetic resonance imaging; RP=recurrent pericarditis; TEC=transthoracic echocardiography

Constrictive pericarditis (CP) is a rare but severe complication in recurrent pericarditis, where thickening, scarring and calcification of the pericardium is implicated in impaired cardiac functioning.

- CP prevalence was not reported to be associated with recurrence.
- Idiopathic/post-viral and response to aspirin was associated with low (<1%) CP prevalence.
- Higher CP prevalence (>8%) was reported in more selected populations (i.e. pediatric patients selected for MRI, AP patients not responding to aspirin, specific etiology such as autoimmune disease, bacterial infection.)

Evidence on the economic burden is from two real-world studies of pericarditis patients, including patients with a single event and also recurrent cases. Both were conducted in the inpatient setting and thus likely skew toward more severe cases.

- Kumar (2016) reported pericarditis hospitalizations using the US Nationwide Inpatient Sample (NIS) database from 2003 – 2012. Mean age 53.5 ± 18.5 years; 40.5% women
- Mody (2018) reported pericarditis hospitalizations among Medicare beneficiaries in the US from 1999 – 2012. Mean age 76.3 ± 7.7 years; 54.4% women

Overall hospitalization rates were found to decline, though Mody (2018) reported stable incidence in the Medicare population. Despite both studies reporting decreases in average length of stay, statistically significant increases in average costs were found. Substantial cost differences between the NIS and Medicare studies are likely attributable to different data sources and methodologies.

Economic Burden Of Illness

Table 1: Incidence, length of stay and average costs of pericarditis hospitalizations in the US

	US NIS (Kumar 2016)			US Medicare (Mody 2018)		
	2003	2012	Change	1999-2000	2011-2012	Change
Cases / 100,000 Person-years	6.6	5.4	-18.0%*	26	26	—
Mean Length of Stay (days)	4.8	4.1	-14.6%*	5.8	5.5	—
Mean Cost / Stay	\$31,242	\$38,947	+24.7%*	\$8,404	\$9,882	+18.8%*

* Statistically significant p ≤ 0.001

Humanistic Burden of Illness

Although there is agreement in the published literature that Recurrent Pericarditis has a severe impact on patient HRQoL, to date there are no systematically derived data addressing this topic.

Current Treatment Paradigm

- While there are no FDA or EMA-approved treatments for pericarditis or US treatment guidelines, the European Society of Cardiology (ESC) issued recommendations for managing patients with recurrent pericarditis (Adler 2015).
- Cremer and colleagues (2016) incorporated these recommendations into a stratification framework

Table 2: Clinical Stages of Pericarditis and Treatment Considerations (Adapted from Cremer 2016)

Stage of pericarditis	Acute	First recurrence	Multiple recurrences	Colchicine-resistant or steroid dependent	Constrictive
Treatment	• NSAIDs (weeks) • Colchicine (3 months)	• NSAIDs (weeks) • Colchicine (>6 months)	• NSAIDs • Colchicine • Prednisone (>6 months, taper steroid as tolerated) • Consider steroid sparing agent (warrants further study)	• NSAIDs • Colchicine • Prednisone • Steroid sparing agent (>6-12 months, taper steroid as tolerated) • Consider pericardiectomy (warrants further study)	• Intensify medical therapy • Pericardiectomy if "burnt out"

1st Line Therapy

Five randomized, controlled clinical trials show that NSAIDs / aspirin + colchicine are effective for most patients in treating flares and decreasing the risk of recurrence. However 12-23% of patients had another episode during follow-up.

- Treatment duration varied between 3-6 months.
- Gastrointestinal intolerance to colchicine was the main adverse event (2.2% - 9.2%)

2nd Line Therapy

Clinical trials have not been conducted evaluating corticosteroids in pericarditis; available evidence comes from three real-world studies in patients intolerant or refractory to first line therapy.

- Artom (2005) reported a 2.5-fold increase in recurrence among patients treated with corticosteroids who received prior colchicine therapy (OR: 6.68; 95%CI: 1.65-27.0; P=0.008).
- Imazio (2008) showed recurrence was twice as high in patients with high-dose vs. low-dose corticosteroids (P=0.002).
- Imazio (2016) showed a 36% reduction in recurrences in patients treated with corticosteroids vs a 53% reduction with no corticosteroid exposure.

While ESC guidelines summarize that corticosteroids provide rapid control of symptoms but favor chronicity, more recurrences and side effects, it is difficult to determine if the noted recurrence is due to selection of patients with persistent underlying disease, or some mechanistic feature of corticosteroid treatment.

The safety profile of corticosteroids has been studied in other patient populations. In particular, high-dose and long-term corticosteroid use is associated with the following side effects which in some cases are irreversible (Rhen 2005):

- Osteoporosis
- Easy bruising
- Slow wound healing
- Increased susceptibility to infection
- Avascular necrosis
- High blood pressure
- High blood pressure
- Peripheral edema
- Diabetes
- Cataracts and glaucoma
- Psychological changes

CONCLUSIONS

- The prevalent US recurrent pericarditis population ranges from 31,000 – 61,000 patients, of which about 40% suffer from multiple recurrences due to inadequate response to currently used, off-label treatments and persistent disease.
- While the clinical burden of recurrent pericarditis is evident, its economic and humanistic impact is not well-documented. Beyond the intense pain of pericarditis flares, the disease is also associated with serious, but rare complications such as cardiac tamponade and constrictive pericarditis. Particularly in patients with high recurrence burden, the impact of disease on patients' lives is likely high, including the treatment-related morbidity. Improved understanding of the clinical, economic and humanistic burden of illness can help support the evaluation of therapeutic options by clinicians and budget holders.
- For patients with continued recurrence and inadequate response to current treatments, there is a high unmet need for licensed, safe treatments that resolve flares and reduce recurrence risk. Tolerability, toxicity, and treatment burden (e.g. daily injection) are challenges associated with current off-label therapies. Treatment with IL-1 blockers targeting the autoinflammatory pathway warrants further evaluation in clinical trials.

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Disclosures

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Acronyms

AP=acute pericarditis; CP=constrictive pericarditis; ED=emergency department; MRI=magnetic resonance imaging; NR=not reported; RP=recurrent pericarditis