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Clinical Burden and Unmet Need in Recurrent Pericarditis: A Systematic Literature Review

Allan Klein, MD, CM, FACC, Paul Cremer, MD,* Apostolos Kontzias, MD,† Muhammad Furqan, MBBS,* Anna Forsythe, MS, MBA, PharmD,‡ Christopher Crotty, PhD,‡ Michelle Lim-Watson, MPH, MBA,§ and Matthew Magestro, MS, MBA§*

Abstract: Inflammation of the pericardium (pericarditis) is characterized by excruciating chest pain. This systematic literature review summarizes clinical, humanistic, and economic burdens in acute, especially recurrent, pericarditis, with a secondary aim of understanding United States treatment patterns and outcomes. Short-term clinical burden is well characterized, but long-term data are limited. Some studies report healthcare resource utilization and economic impact; none measure health-related quality-of-life. Pericarditis is associated with infrequent but potentially life-threatening complications, including cardiac tamponade (weighted average: 12.7% across 10 studies), constrictive pericarditis (1.84%; 9 studies), and pericardial effusion (54.7%; 16 studies). There are no approved pericarditis treatments; treatment guidelines, when available, are inconsistent on treatment course or duration. Most recommend first-line use of conventional treatments, for example, nonsteroidal anti-inflammatory drugs with or without colchicine; however, 15–30% of patients experience recurrence. Second-line therapy may involve conventional therapies plus long-term utilization of corticosteroids, despite safety issues and the difficulty of tapering or discontinuation. Other exploratory therapies (eg, azathioprine, immunoglobulin, methotrexate, anakinra) present steroid-sparing options, but none are supported by robust clinical evidence, and some present tolerability challenges that may impact adherence. Pericardiectomy is occasionally pursued in treatment-refractory patients, although data are limited. This lack of an evidence-based treatment pathway for patients with recurrent disease is reflected in readmission rates, for example, 12.2% at 30 days in 1 US study. Patients with continued recurrence and inadequate treatment response need approved, safe, accessible treatments to resolve pericarditis symptoms and reduce recurrence risk without excessive treatment burden.

From the *Department of Cardiovascular Medicine, Center for the Diagnosis and Treatment of Pericardial Diseases, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, OH; †Department of Medicine, Division of Rheumatology, Allergy and Immunology, Center of Autoinflammatory Diseases, State University of New York Stonybrook, New York, NY; ‡Purple Squirrel Economics, New York, NY; §Value and Access, Kiniksa Pharmaceuticals Corp., Lexington, MA.

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Correspondence: Allan Klein, MD, CM, FACC, Department of Cardiovascular Medicine, Center for the Diagnosis and Treatment of Pericardial Diseases, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Mail Code J1-5, 9500 Euclid Ave, Cleveland, OH 44195. E-mail kleina@ccf.org.

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Pericarditis refers to inflammation and fibrotic thickening of the pericardium.[1] The most common (85–90%) and self-evident symptom of pericarditis is excruciating chest pain, typically sharp and pleuritic, worse with inhalation and exhalation, and when lying down, improved by sitting up and leaning forward.[2,3]

Acute pericarditis (AP) is the most common condition affecting the pericardium, and the majority (66–90%) of cases in the United States and the developed world are of viral or idiopathic origin.[2,3] While healthcare resource utilization data are limited, AP leads to emergency department visits and, in some cases, hospitalizations; 1 large study in Italy estimated an incidence of 27.7 new cases per 100,000 population per year.[4] While studies vary, in general, over half of AP cases occur in males, with a mean age of approximately 50 years.[5,6]

Most pericarditis episodes manifest as a single event and resolve without complication. Recurrent pericarditis (RP), by contrast, is diagnosed when an index acute episode is followed by a symptom-free period of at least 4–6 weeks, followed by a subsequent episode.[2] RP has been reported to occur in 15–30% of pericarditis patients, some of whom go on to experience multiple recurrences.[7] Pericarditis is considered incessant when symptoms persist for over 1 month and chronic when symptoms persist beyond 3 months.[2,8] These timeframes reported in the literature are variable, and RP may develop into incessant (symptoms not resolving, or recurring upon attempts to taper treatment) or intermittent (symptoms recurring after disease-free intervals) chronic disease without adequate management (Figure 1).[3,9]

In addition to recurrent, incessant, and chronic pericarditis, clinical evidence demonstrates that pericarditis is associated with serious and potentially life-threatening complications, such as cardiac tamponade and constrictive pericarditis (CP).[3] Both cardiac tamponade and CP are relatively rare among patients with acute idiopathic etiology but more common in patients with a defined etiology such as malignancy or tuberculosis.[10] However, some studies have reported conventional treatment—or poor response to conventional treatment—as a risk factor for complications such as cardiac tamponade and CP.[3] Early use of corticosteroids (CS) is considered a risk factor for the development of complications.[3] One prospective cohort study identified failure of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) as a risk factor for complications following AP (hazard ratio, 5.50; 95% confidence interval [CI], 3.56–8.51).[11] Procedures such as pericardiocentesis or pericardial window may be performed to decompress the pericardium and thereby reduce the risk of progression to these complications.[10]

There are no US Food and Drug Administration-approved treatments for acute or recurrent pericarditis, nor are there US treatment guidelines. The painful nature of AP episodes coupled with the lack of evidence-based treatment options suggests that the clinical,

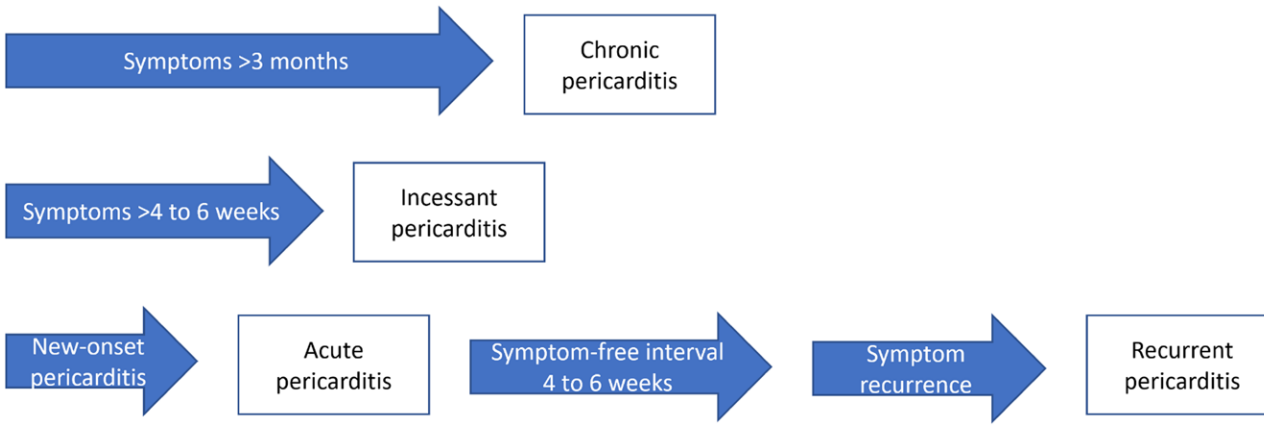

FIGURE 1. Acute, incessant, chronic, and recurrent pericarditis.[8]

health-related quality-of-life (HRQOL), and economic burden and unmet need in RP could be substantial.

The aim of this systematic literature review (SLR) was to identify and summarize publications on the clinical, HRQOL, and economic burden of pericarditis, focusing on recurrent and complicated disease. As many of the studies underpinning the recommendations in the European Society of Cardiology (ESC) Guidelines were carried out in Italy, we were mindful of obtaining data, perspective, and context from US studies where possible. Furthermore, this review aims to summarize the evidence and outcomes associated with the various treatment options for recurrences, to better understand the unmet medical needs in RP.

METHODS

Eligibility Criteria

Two analysts independently screened all studies in the initial literature search based on previously established inclusion/exclusion criteria that were built using the Population, Intervention, Comparator, Outcome, Study type statement. Studies published from January 1, 2003, to January 31, 2020, were included if they evaluated patients with AP or RP, including those refractory or intolerant to treatment or dependent on CS. Studies were excluded if they were preclinical/nonhuman, involved patients under 12 years of age, involved known causes of pericarditis (eg, tuberculosis, cancer, trauma), or were case reports/series or other lower levels of evidence such as letters or editorials (Table 1). A review protocol was developed. However, as this review was not supporting a metaanalysis, the protocol was not publicly published.

Systematic Literature Search

A SLR was conducted through the Ovid platform covering publications (English language only) from January 1, 2003, through October 1, 2018, and was updated with a search for January 1, 2005, through January 29, 2020: 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), and Econlit database. Congress proceedings were not searched, but conference abstracts were included if they were indexed in the databases that were searched, or if they came up in bibliography searches. The bibliographies of SLRs, metaanalyses, and selected studies identified through database searches were also reviewed. This process ensured that relevant publications not identified in the searches would be included. The methodology followed principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions,[12] University of York Centre for Reviews and Dissemination Guidance for Undertaking Reviews in Health Care,[13] and Methods for the Development of NICE Public Health Guidance,[14] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15] Search terms on interventions, outcomes, and the burden of acute, recurrent, and treatment-refractory pericarditis (Appendix, Supplemental Digital Content A, http://links.lww.com/CIR/A27) were used to index all possible literature for subsequent screening by reviewers. The initial list of interventions was based on treatment guidelines from the ESC.[2] The date range for the first search was chosen to cover a 15-year period in which all currently used treatments were available and used in RP. The updated search had several years overlapping with the first search to ensure no records were missed due to indexing variations, and all selected studies were crosschecked to ensure that there were no duplicates.

Both the initial and updated search included 2 additional separate searches, 1 for HRQOL evidence, and 1 for economic evidence.

Study Selection and Data Collection

All publications (titles/abstracts, followed by full text) were independently reviewed by 2 SLR-trained, doctoral-level analysts (with a third, senior, independent reviewer for discrepancies) against the criteria. All publications selected for full-text review were retained for data extraction using Microsoft Excel (Office 365 Version). Data included study sample demographics, methodology, as well as reported rates and clinical outcomes of RP (eg, baseline pain score, C-reactive protein [CRP] level, occurrence of pericardial effusion, previous recurrences of pericarditis, prior therapy, recurrence rate, time to flare, safety, HRQOL). While case reports were not selected based on inclusion criteria, they were consulted for supplemental information regarding treatments used in different geographical locations.

RESULTS

The initial search identified a total of 5744 records, of which 54 were selected for data extraction: 8 clinical studies, 32 real-world-evidence (RWE) studies, 14 SLRs/metaanalyses. The remainder were excluded due to not meeting inclusion/exclusion criteria (Figure 2). The updated search yielded 6 additional records for data extraction, for an updated total of 8 clinical studies, 35 RWE studies, and 17 SLRs/metaanalyses (see Selected Records, Supplemental Digital Content 1, for the list of included records http://links.lww.com/CIR/A28). While an objective of the research was to identify HRQOL evidence, no papers covering patient-reported HRQOL

TABLE 1. Study Eligibility Criteria

Category	Inclusion Criteria	Exclusion Criteria
Patient population	• Patients diagnosed with AP or RP (according to ESC Guidelines) • Recurrent corticosteroid-dependent, colchicine-resistant, or intolerant pericarditis • Treatment-refractory RP	• Nonhuman • Patients with a mean age <12 yr • Tuberculous, neoplastic, purulent, or radiation etiology, postthoracic blunt trauma (eg, motor vehicle accident), myocarditis, or systemic autoimmune diseases, uremic pericarditis • Not fulfilling inclusion criteria
Intervention and comparators	• Aspirin or NSAIDs, colchicine, corticosteroids • Third-line treatments: anakinra, intravenous immunoglobulin, azathioprine • Pericardiectomy	• Studies not including at least 1 of the interventions listed in the inclusion criteria
Outcomes measures	• Clinical outcomes: ◦ Pericarditis recurrence, rate of recurrence, time to recurrence ◦ Treatment patterns: use of colchicine, corticosteroids, third-line treatments, treatment duration ◦ Symptom burden: chest pain, elevated C-reactive protein, fever, pericardial effusion, ST-segment elevation, pericardial friction rub ◦ Severe complications: cardiac tamponade, constrictive pericarditis • Humanistic burden ◦ Health-related quality-of-life ◦ Utilities/disutilities (decrease in utility due to disease or adverse effects of treatment)/ quality-adjusted life years for health states or adverse events • Economic burden • Cost effectiveness or cost utility of treatments, costs, healthcare resource use, productivity loss	• Studies not including at least 1 of the interventions listed in the inclusion criteria
Study design	• Interventional studies: randomized or single-arm clinical trials • Noninterventional studies ◦ Large-scale relevant prospective observational studies or retrospective studies ◦ Database analyses, registries, chart reviews ◦ Surveys • Economic studies ◦ Budget impact analyses ◦ Resource use studies, cost/economic burden of illness studies ◦ Cost-benefit analyses, cost-effectiveness analyses, cost-minimization analyses, cost-utility analyses, cost analyses • Systematic reviews and meta analyses (to be used for reference cross-checking only)	• Case reports • Case series (sample size <3) • Nonhuman/preclinical studies • Notes/Comments/Letters • Reviews/Editorials • News/Newspaper article
Restrictions	• English language • Year limitation: January 1, 2003, to October 1, 2018, for initial search; January 1, 2005, to January 29, 2020, for updated search	• Non-English language studies • Published prior to 2003

AP indicates acute pericarditis; ESC, European Society of Cardiology; NSAIDs, nonsteroidal antiinflammatory drugs; RP, recurrent pericarditis.

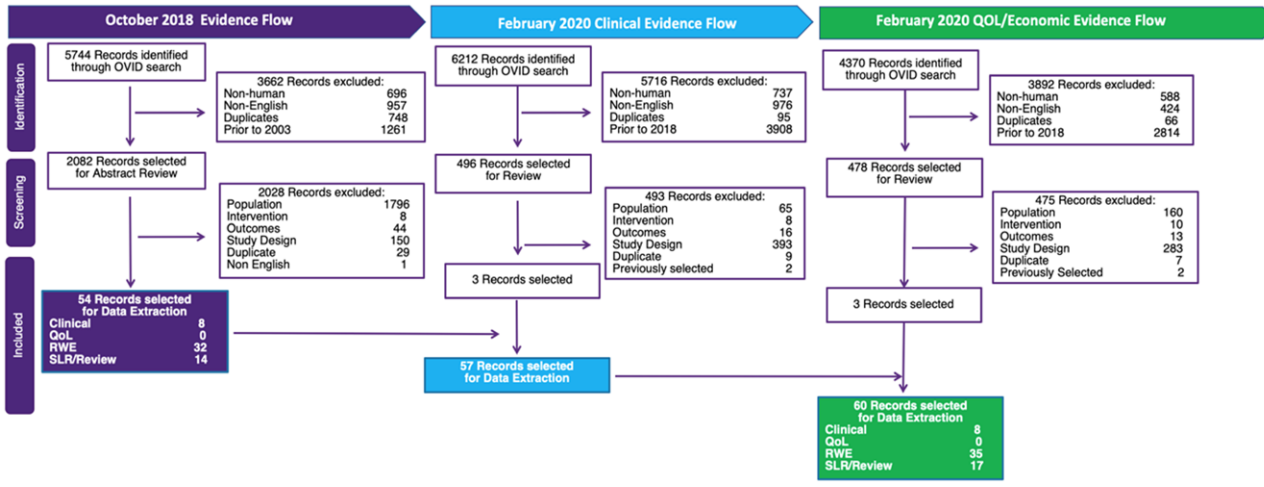

FIGURE 2. PRISMA Flow Diagram: burden of illness studies. QoL indicates quality-of-life; RWE, real-world evidence; SLR, systematic literature review.

TABLE 2. Levels of Evidence

Level	Description	Results
1A	Systematic review of RCTs	Two reviews with metaanalysis were identified: • One on effect of anakinra on colchicine-resistant and steroid-dependent RP • One on impact of colchicine on pericarditis and postpericardiotomy syndrome[17,18]
1B	RCTs	Six placebo-controlled RCTs were identified: • Three compared colchicine with placebo[19–21] • Two compared colchicine + aspirin with aspirin alone[22,23] • One was a randomized withdrawal study with anakinra[24]
2A	Systematic review of cohort studies	An initial reporting of the results of this SLR described clinical burden and healthcare resource utilization in RP[25]
2B/2C	Single-arm trials or RWE studies	One nonrandomized single-center observational study compared colchicine with noncolchicine treatment,[26] One single-arm prospective open-label study investigated anakinra in patients resistant and intolerant to previous treatment with aspirin and NSAIDs, colchicine, and CS[27] RWE studies: • Four pediatric (weighted mean age = 13.2 yr)[28–31] • Eight in adult pericarditis patients with information on prescribed first- or second-line treatments (weighted mean age when reported = 50.9 yr)[26,32–38] • Three retrospective studies evaluating second-line CS treatment, typically coadministered with colchicine and NSAIDs[30,33–35] • Nine RWE studies with third-line treatment: 7 with anakinra,[37,39–43] 2 with azathioprine,[44,45] and 1 with IVIG[46] • Ten studies with some information about health care resource use (eg, frequency and duration of hospitalizations, procedures, and readmissions),[5,6,28,29,47–52] including 4 US-focused studies, 2 of which are studies of US commercial claims databases with extensive details regarding resource use and costs,[6,48] 1 of which is a study of a US commercial claims database with extensive details on RP epidemiology,[51] and 1 of which analyzes US readmission data after acute pericarditis[49] • Two studies evaluating long-term outcomes (morbidity and mortality) following an episode of acute pericarditis[53,54]

CS indicates corticosteroid; IVIG: intravenous immunoglobulin; NSAID: nonsteroidal antiinflammatory drug; RCT: randomized controlled trial; RP: recurrent pericarditis; RWE: real-world evidence; SLR: systematic literature review; US: United States

outcomes were identified. The studies were further evaluated by level of evidence (Table 2).[16–54]

Clinical Burden of Illness

The studies that were reviewed reported on several key complications of acute and/or recurrent pericarditis. Pericardial effusion was reported in 16 of the studies reviewed, with a mean prevalence of 54.7% (standard deviation [SD] 32.6%). Among the 16 studies, about half were restricted to recurrent pericarditis patients, while the other half included a broader AP population. Cardiac tamponade (CT) occurred in a weighted average of 12.7% of patients across 10 real-world studies; this figure was consistent for the US-only studies, given that the weighted average was driven heavily by 1 large US study of hospitalized patients[6] (Figure 3). In a prospective cohort study of patients with AP (excluding specific etiology other than connective tissue diseases or pericardial injury syndromes), significantly higher rates of CT were found in patients who went on to have a recurrence (16.4%) versus those who did not experience recurrence (2.5%; $P < 0.001$).[35]

With regard to CP, a number of publications identified in this SLR referred to related complications of pericarditis, such as "transient constriction,"[30] "effusive-constrictive pericarditis,"[31] "constrictive physiology,"[39,55] and "pericardial constriction;"[35,42] the reported prevalence of these was 1.8–14.3% among patients with pericarditis.

The weighted average CP rate was 1.84% across 9 RWE studies (Figure 4), with higher prevalence in certain populations. In a retrospective single-institution study of pediatric patients (<21 years of age) selected to undergo cardiac magnetic resonance imaging (between 2005 and 2014) for pericardial pathology (including pericarditis, CP, recurrent pericarditis, and pericardial effusion), 3 of 21 patients (14.3%) had CP and underwent pericardial resection.[31] In a prospective study conducted from 1996 to 2001, patients with AP who were considered at lower risk of complications were treated with high-dose aspirin in an outpatient setting with a mean follow-up of 38 months. In this study, 9.1% of patients (3 of 33) not responsive to aspirin treatment developed CP compared with 0.5% (1 of 221; $P = 0.004$) of patients with response to aspirin, which may be suggestive of a lower CP rate in patients who experienced resolution of inflammation.[32] The association between CP and specific attributed pericarditis etiology was investigated in a prospective cohort study of 500 patients with a first episode of AP with mean follow-up of 60 months.[56] In patients with specific etiology for AP (including autoimmune and neoplastic causes, tuberculosis, and purulent bacterial infection), 8.3% (7 of 84) developed chronic CP versus 0.5% of patients with idiopathic AP. While rates of CP can be higher in certain selected populations, CP is quite rare in other populations. In 1 observational single-center study of adult RP patients, all of whom were treated with CS at 1 point, no cases of CP were reported during a mean follow-up of 8.3 years,[26] and CP in pediatric patients with RP followed for a median of 60 months was 2.5%.[30]

We examined the literature for evidence regarding risk factors for developing recurrent or treatment-refractory pericarditis, potentially with complications. Poor prognostic indicators were identified in 1 early study as predictive of short-term complications or specific etiology; they include fever, sub-acute onset, immunodepression, trauma, oral anticoagulant therapy, myopericarditis, large (>20 mm echo-free space) pericardial effusion, and cardiac tamponade.[32] Incomplete response to NSAIDs and elevated high-sensitivity CRP have been identified as risks for developing complicated pericarditis following an acute attack, while pericardial effusion, younger age, and sex are not thought to be associated.[3]

Economic Burden of Illness

Ten studies that presented evidence on healthcare resource utilization and economic burden of AP and RP were identified. Table 3 presents evidence from the 2 economic and epidemiologic studies of pericarditis patients most directly comparable, including patients

Reference	Population	n/N	Context
Imazio 2005 (35)	adults w/ RP followed up mean 74 months	9/55	1st attack (recurred)
Imazio 2016 (30)	pediatrics w/ RP followed up median 60 months	15/110	1st attack
Kumar 2016 (6)	≥ 16 years old hospital admissions w/ diagnosis of pericarditis	17,914/135,710	during hospitalization
Sud 2018 (49)	adults w/ AP and readmitted within 30 days	62/487	during readmission
Moretti 2013 (46)	adult refractory RP	1/9	history of tamponade
Brucato 2006 (26)	adult refractory RP	4/61	1st attack
Klein 2019 (51)	adult acute pericarditis	35/682	during follow-up
Ratnapalan 2011 (28)	pediatrics presenting to ED with isolated AP	1/22	1st attack
Imazio 2005 (35)	adults w/ AP followed up mean 72 months—no RP	6/239	1st attack (no recurrence)
Shakti 2014 (29)	<21 years old in hospital records with pericarditis and PE	11/543	during hospitalization
Imazio 2011 (56)	adults w/ viral/idiopathic AP followed-up mean 60 months	5/416	during follow-up

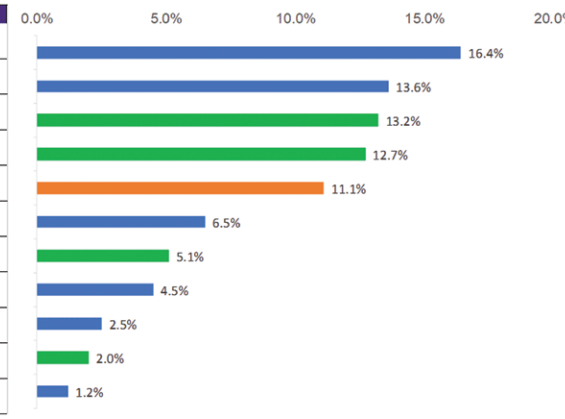

FIGURE 3. Prevalence of cardiac tamponade in pericarditis. Gray bar indicates treatment with a third-line therapy (IVIG); Black bars indicate US studies. AP indicates acute pericarditis; ED, emergency department; RP, recurrent pericarditis.

Short reference	Population	n/N	Context
Baskar 2018 (31)	pediatrics w/ pericarditis who underwent cardiac MRI	3/21	CP at index CMR
Imazio 2004 (32)	adults w/ pericarditis who did not respond to aspirin	3/33	developed CP during follow-up
Imazio 2011 (56)	patients w/ specific etiology AP followed-up mean 72 months	7/84	chronic CP during follow-up
Alraies 2015 (38)	adults w/ RP all treated w/ colchicine and NSAIDs	17/507	CP during follow-up
Imazio 2016 (30)	pediatrics w/ RP followed up median 60 months	3/118	transient CP during follow-up
Klein 2019 (51)	adults with acute pericarditis	129/7502	CP during follow-up
Imazio 2004 (32)	adults w/ pericarditis who did respond to aspirin	1/221	developed CP during follow-up [(p=0.004) comapred w/ no response to aspirin]
Imazio 2011 (56)	patients w/ viral/idiopathic AP followed-up mean 72 months	2/416	chronic CP
Brucato 2006 (26)	adults w/ RP followed mean 8.3 years	0/61	no CP during follow-up

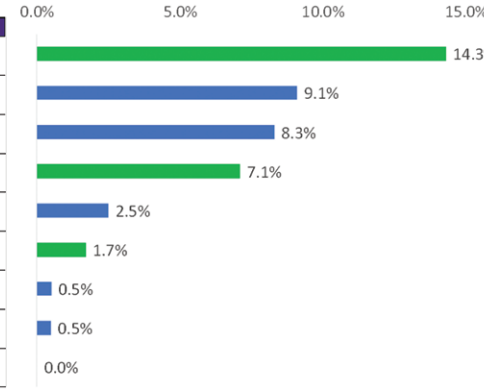

FIGURE 4. Prevalence of constrictive pericarditis. Black bars indicate US studies. ANA indicates anakinra; AP, acute pericarditis; CMR, cardiac magnetic resonance; CP, constrictive pericarditis; MRI, magnetic resonance imaging; NSAID, nonsteroidal antiinflammatory drug; RP, recurrent pericarditis.

with a single pericarditis episode in addition to recurrent cases.[6,48] Both of these US studies were conducted in the inpatient setting and thus likely skew toward more severe pericarditis cases, as patients with less severe pericarditis may be managed as outpatients. One study using the Nationwide Inpatient Sample (NIS) reported a significant decrease of 18.0% in hospitalizations for AP from 2003 to 2012 ($P \leq 0.001$), as well as a significant decrease of 14.6% during the same period in mean length of stay (LOS) ($P \leq 0.001$).[6] In contrast, among Medicare beneficiaries in the United States from 1999 to 2012, hospitalization rates were stable at 26 per 100,000 person-years, while mean LOS trended downward (nonsignificantly) in this population.[48] The mean cost/stay was substantially higher in the NIS study compared with the Medicare study, presumably due to different data sources and methodologies, but in both populations, mean cost/stay for pericarditis increased significantly over time.

Another US RWE study specifically examined readmission after hospitalization for AP.[49] Using data from the 2014 National Readmission Database, it was found that there were 3995 admissions with a primary AP diagnosis in 2014; of these, there were 487 readmissions within 30 days (12.2%), with a mean LOS of 3.7 days. The most common reason for readmission was recurrent pericardial disease; other reasons included arrhythmias, pleural effusion, and sepsis, and 17.2% of readmitted patients required pericardial drainage.

Treatment Paradigm

To date, there are no FDA-approved treatments for pericarditis (acute or recurrent) or US treatment guidelines. There are no European Medicines Agency-approved therapies either, but there is a general treatment paradigm as outlined in Table 4.[2] The treatment paradigm recommends NSAIDs and colchicine for the first 2 acute episodes but provides less clear guidance for the second or later recurrence. Options at that later stage include CS, with the recommendation to taper when feasible.

Efficacy and Safety of First-line Therapy

NSAIDs or aspirin and colchicine are mainstays in the first-line approach in AP, often at high doses (necessitating consideration of gastric protection therapy). The response is typically assessed by resolution of presenting symptoms but also can be evaluated by CRP levels, which reflect inflammation. Three to six months of colchicine therapy are recommended in addition to standard antiinflammatory therapy.[2] Current ESC guidelines were informed by 5 randomized controlled trials (RCTs) published between 2005 and 2014.[19–23] Treatment duration was 3 months in the studies that enrolled patients

TABLE 3. Incidence, Length of Stay and Average Costs of Pericarditis Hospitalizations in the United States

	NIS, 2003–2012[6]			Medicare, 1999–2012[48]		
	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 (d)	4.8	4.1	–14.6%*	5.8	5.5	–
Mean cost/stay	$31,242	$38,947	+24.7%*	$8404	$9982	+18.8%*
Demographics	Mean age: 53.5 ± 18.5 yr Female: 40.5% of patients			Mean age: 76.3 ± 7.7 yr Female: 54.4% of patients		

*Statistically significant $P \leq 0.001$.
NIS indicates nationwide inpatient sample.

with acute index pericarditis only,[20,23] 6 months in the studies that enrolled patients with 1 previous recurrence,[19,22] and 6 months in the study that enrolled patients with ≥2 recurrences (Figure 5).[21]

Across the 5 studies, antiinflammatory therapy with NSAIDs/aspirin plus colchicine reduced, by approximately half, the risk of recurrence during follow-up. Despite this improvement, 12–23% of colchicine-treated patients experienced subsequent recurrence during the observation period. Mean time elapsed between the index episode and the first recurrence was 6.35 months in 1 study[19] and 5.45 months in another.[22] Several studies showed an association between colchicine treatment and longer recurrence-free intervals. In the Imazio et al[22] study, a modest benefit was seen: patients received 6 months of therapy, and the median time to first recurrence (10th–90th percentile) was 1 month (0–5.5) for placebo and 2.5 months (0–19.1) for colchicine ($P < 0.001$). A larger benefit was seen in Imazio et al[22] median symptom-free intervals were longer for colchicine-treated patients versus the placebo group (17.2 vs 10.6 months, $P = 0.007$), extending well beyond the 6-month treatment period. The totality of data demonstrates that many patients experienced recurrence within the time that they were undergoing treatment, and yet the recurrence-free interval was extended well beyond the treatment period for some treated patients.

In these 5 RCTs, gastrointestinal intolerance to colchicine was the main adverse event (2.2–9.2%). Gastrointestinal effects of colchicine, including diarrhea (often dose-limiting), nausea, cramping, abdominal pain, and vomiting, are a major cause of dose reduction or discontinuation.[21,35] Colchicine toxicities may be severely exacerbated when combined with P-gp or strong CYP3A4 inhibitors, such as several statin therapies, in patients with renal or hepatic impairment. Of note, the long historical use of colchicine means that it has not undergone the same registrational trials as most contemporary drugs, so information on safety is less standardized than with most drugs.[57]

The results of the 5 RCTs discussed in the ESC guidelines are consistent with the findings of a 2019 SLR and metaanalysis of the efficacy and safety of colchicine in pericarditis and postpericardiotomy syndrome.[18] The metaanalysis included 10 prospective RCTs enrolling 1981 patients, with AP or RP, with a mean follow-up of 13.6 months. Recurrence rate was lower in pericarditis patients receiving colchicine versus placebo (risk ratio [RR], 0.57; 95% CI, 0.44–0.74). The rehospitalization rate (RR, 0.33; 95% CI, 0.18–0.60) and symptom duration after 72 hours (RR, 0.43; 95% CI, 0.34–0.54) were also lower with colchicine versus placebo. The number needed to treat was 3–5 for the prevention of RP, that is, 3–5 patients would need to be treated with colchicine to prevent a single recurrence. Adverse events, particularly gastrointestinal effects, were higher in patients receiving colchicine relative to placebo. An important limitation to this study was that the follow-up time ranged widely among included studies, from 1 to 24 months. A 2020 metaanalysis of the safety of colchicine in various indications included 7 pericarditis and related (eg, postpericardiotomy syndrome) studies and found a risk ratio of 1.32 (95% CI, 0.95–1.83) for experiencing any adverse event while taking colchicine versus comparator.[57] Overall, across indications, a significant increase was seen only for diarrhea and gastrointestinal adverse events relative to comparator.

Efficacy and Safety of CS Therapy

Although the antiinflammatory effects of CS can provide symptomatic relief in some patients with RP, there are numerous challenges associated with their use, including adverse effects with both short-term and cumulative exposure, contraindications for use in patients with certain comorbidities, and high recurrence rates, leading to difficulty in tapering patients off of the treatment. Therefore, CS are recommended only in AP or RP patients with contraindications or treatment failure of first-line NSAIDs/aspirin with colchicine.[2] If it is necessary to use CS, doses should be low to moderate, with slow tapering to maintain symptom relief and attempt to prevent recurrence. This type of slow taper prolongs total duration

TABLE 4. Current Treatment Paradigm[3]

Stage of Pericarditis	Acute	First Recurrence	Multiple Recurrences	Colchicine-resistant or Steroid-dependent	Constrictive
Imaging	Echocardiogram for pericardial effusion, myocardial involvement, constriction	Echocardiogram for constriction CMR in select cases for pericardial inflammation or constriction	Same as for "first recurrence"	Same as for "first recurrence"	Same as for "first recurrence" Plus possible computed tomography for extent of calcification and preoperative planning
Treatment	NSAIDs (wk) Colchicine (3 mo)	NSAIDs (wk to mo) Colchicine (≥6 mo)	NSAIDs + colchicine + prednisone (>6 mo, taper steroid as tolerated) Consider steroid-sparing agent (warrants further study)	NSAIDs + colchicine + prednisone + steroid-sparing agent (6–12 mo, taper steroid as tolerated) Consider pericardiectomy (warrants further study)	Intensify medical therapy if inflamed Pericardiectomy if "burnt out"

All patients with acute pericarditis should have an echocardiogram for short-term risk stratification, and subsequent echocardiograms can be performed if there is concern for constrictive pericarditis. In recurrent pericarditis, cardiac magnetic resonance imaging has an emerging role to assess for pericardial inflammation if the clinical evaluation is equivocal and to assess for constrictive pathophysiology if the echocardiogram is indeterminate. Computed tomography is primarily employed to assess pericardial calcification and for preoperative planning. The mainstay of treatment is NSAIDs and colchicine with the addition of low-dose corticosteroids in patients with multiple recurrences. Steroid-sparing agents can be added in refractory cases. Early use of steroid-sparing agents and pericardiectomy for recurrent pericarditis may be beneficial and warrants further study.
NSAIDs indicates nonsteroidal antiinflammatory drugs.

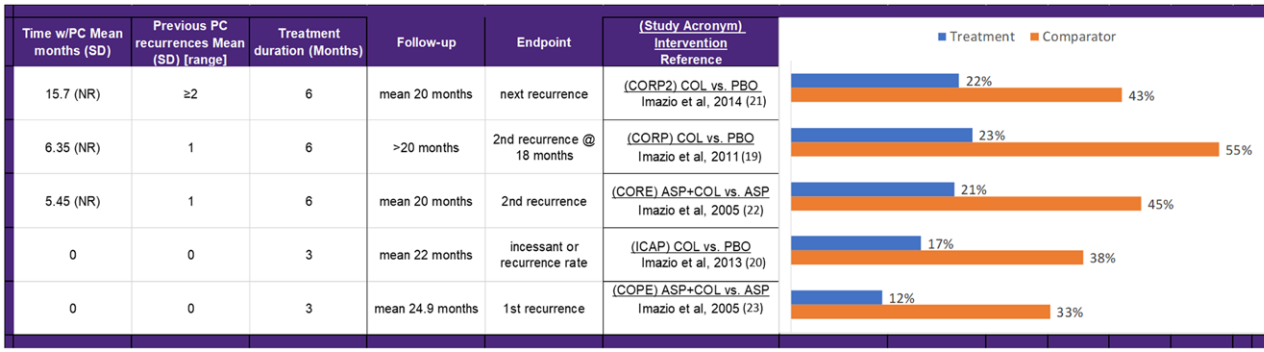

FIGURE 5. Colchicine significantly reduces the rate of recurrence in both acute and recurrent pericarditis RCTs. ASP, aspirin; COL, colchicine; Colchicine for Recurrent Pericarditis (CORP); NR, not reported; PBO, placebo; PC, pericarditis; SD, standard deviation.

of exposure to CS and thus magnifies the potential adverse consequences of steroid use. In addition, prolonged exposure to higher doses of CS (1–1.5 mg/kg/d compared with 0.2–0.5 mg/kg/d) was associated with higher rates of severe adverse effects and higher rates of minor adverse effects.[33]

CS therapy is associated with high recurrence rates in RP. Available evidence comes from RWE studies. In 1 international, multicenter retrospective review of RP patient data (all of whom had been treated with colchicine), recurrence was significantly associated with prior CS treatment (OR, 6.68; 95% CI, 1.65–27.0; $P=0.008$).[34] In a multicenter retrospective review of pediatric patients with RP, recurrence rates were twice as high in patients treated with CS (5.84 ± 4.86) versus no CS (2.76 ± 1.36) ($P<0.001$).[30] A retrospective review of adults treated with CS for RP evaluated patients who had received high-dose prednisone (1.0 mg/kg/d) or low-dose prednisone (0.2–0.5 mg/kg/d); while baseline disease severity and recurrence history were similar, recurrence rates after a mean follow-up of 55.8 months were significantly higher in the high-dose group (64.7% of patients) compared with the low-dose group (32.6%; $P=0.005$).[33] An earlier prospective cohort study by the same group also established that previous use of CS was associated with an increased rate of recurrence (odds ratio [OR], 10.35; 95% CI, 4.46–23.99; $P<0.001$).[35] The studies demonstrating higher rates of recurrence among patients treated with CS do not show causality because of likely differences in the patient populations: patients who require CS treatment may have more persistent underlying disease.[35]

Efficacy and Safety of Exploratory Steroid-sparing Therapies

Azathioprine (AZA), intravenous immunoglobulin (IVIG), and anakinra (ANA) are referenced in the ESC guidelines as steroid-sparing options for patients in whom prior treatments were ineffective or not well-tolerated. There is, however, limited evidence to support the efficacy or safety in pericarditis. Evidence is particularly sparse for AZA and IVIG (Table 5).[17,24,27,37,39–46]

AZA

One study reported on effectiveness of AZA in 46 cases of treatment-resistant RP retrospectively reviewed from clinical records:[45]

- In 40 patients with idiopathic RP, there were moderate reductions in recurrence while on treatment (ie, mean 3.5 recurrences/patient before AZA and 2.4 recurrences/patient while on AZA, with a mean treatment duration of 13.6 months).
- Discontinuation of AZA without recurrence was possible in 27 of 46 (58.6%) treatment-resistant RP patients (treatment duration, 14.6 months; mean follow-up 60.9 ± 27.8 months).

Lowered rates of recurrence following AZA were also reported in a retrospective chart review study of 13 patients with RP (10/13 idiopathic or postviral, 3/13 postmyocardial injury), all of whom had ≥5 months of continuous prednisone use (mean of 21 mg/d) with an average of 3 recurrences/patient in the 6 months before AZA:[44]

- Mean daily prednisone dose was reduced to 13 mg (38% reduction; $P=0.003$) during months 3–6 (accounting for 3-month onset of AZA activity) after starting AZA, with a reduction to 0.3 recurrences/patient during this 3-month interval.
- Three patients were not able to lower prednisone on AZA (2 were on AZA dose <1.5 mg/kg/d).
- This study had some limitations due to the continued use of CS in patients receiving AZA; it is unclear if the patients experienced a benefit from CS, AZA, or the combination.

IVIG

Evidence on IVIG treatment in RP was reviewed in 1 SLR[58] that identified 13 single case studies, 3 case series with ≤4 patients, and 1 retrospective analysis of 9 idiopathic RP patients with index episodes occurring from 1994 to 2010, with varying treatment courses and differing concomitant medication.[46] The patients in the retrospective analysis experienced a mean of 5 relapses during a mean period of 11 months subsequent to their first recurrence before the first IVIG treatment. High-dose IVIG was added to ongoing NSAIDs, CS, or colchicine treatment, with varying tapering and withdrawal over 3–6 months (mean follow-up, 57 months). Four patients had complete remission after 1 IVIG course (5 consecutive days of IVIG), and 4 patients showed complete remission after either a second IVIG course (n = 2) or NSAID treatment (n = 2), while 1 patient underwent pericardial window and long-term immunosuppressive therapy following unsuccessful IVIG. Pericarditis recurred in 26.6% of patients following 1 IVIG cycle, and 22 of 30 patients (73.4%) included were recurrence-free (mean follow-up of 33.1 months).

Anakinra

Some of the challenges associated with the use of anakinra in RP include a limited evidence base, difficulty in discontinuation due to recurrence, high rates of adverse events, including injection-site

TABLE 5. Summary of Studies of Exploratory Steroid-Sparing Therapies

Treatment	Reference and Evidence	N (Mean Age, yr)	Results
AZA	Vianello et al[45] RWE	46 (39.7)	Moderate (31.4%) decrease in recurrence while on treatment in 40 idiopathic RP patients AZA d/c was possible in 58.6% of 46 patients
	Brown et al[44] RWE	13 (NR)	Effective recurrent event reduction subsequent to AZA, but patients remained on CS (38% mean lower dose, 3/13 unable to lower CS)
IVIG	Moretti et al[46] RWE	9 (37.6)	Complete remission in 4/9 patients following 1 IVIG cycle; 4/9 recurred, requiring either NSAIDs (2/4) or additional IVIG (2/4) 1/9 required pericardial window and long-term immunosuppression
	Imazio et al[24] SLR	30 (19.7 excluding Moretti 2013)	Recurrence occurred in 26.6% after 1 IVIG cycle 22 of 30 patients (73.4%) included were recurrence-free (mean follow-up of 33.1 mo)
ANA	Brucato et al[24] RCT (AIRTRIP)	21 (45.4)	All tapered off CS during open-label part 1 (60 d) Recurrence occurred in 9/10 randomized to PBO (6/9 occurred within 60 d of ANA d/c) and 2/11 randomized to ANA
	Vassilopoulos et al[27] SACT	10 (42)	All on CS at baseline (n = 8) d/c CS 5/7 (70%) that d/c ANA relapsed (mean 18 ± 9 d)
	Lazaros et al[37]; Antonatou et al[43]		57% were not able to stop ANA 4/5 were restarted on ANA; 1 was treated with NSAID + colchicine
	Jain et al[39] RWE	13 (50.9)	73% tapered off CS 71% that d/c ANA had recurrence 85% were not able to stop ANA
	Finetti et al[40] RWE	15 (16.4)	All tapered off CS 33% that d/c ANA had recurrence 69% were not able to stop ANA
	Imazio et al[41] RWE (IRAP)	50 (41.4)	55% tapered off CS ANA led to recurrence drop from 6/patient to 0.9/patient 36% not able to taper off ANA at 28 mo mean follow-up
	Mendel et al[42] RWE	7 (NR)	CS were d/c after mean of 4 mo 4 patients were able to taper ANA to <7 d/wk No patient was able to stop ANA
	Furqan et al[17], metaanalysis	65 (NR)	Pericarditis recurrence at day 60 of ANA treatment was 7.4% ($P < 0.001$; 95% CI, 2.7–18.2%) Recurrence at day 180 was 11% ($P < 0.001$; 95% CI, 4.6–24%) Patients on ANA were able to decrease (92.3%; $P < 0.001$; 95% CI, 81.0–97.1%) and discontinue (89.3%; $P < 0.001$; 95% CI, 76.5–95.6%) CS therapy

AIRTRIP indicates, Anakinra in Recurrent Pericarditis; ANA, anakinra; AZA, azathioprine; CI, confidence interval; CS, corticosteroid; d/c, discontinued or discontinuation; IRAP, International Registry of Anakinra for Pericarditis; IRRP, idiopathic recurrent refractory pericarditis; IVIG, intravenous immunoglobulin; NR, not reported; NSAIDs, nonsteroidal antiinflammatory drugs; PBO, placebo; RRP, recurrent refractory pericarditis; RWE, real-world evidence; SACT, single-arm clinical trial; SLR, systematic literature review.

reactions that contribute to treatment burden. The short half-life of anakinra necessitates daily self-injections. Anakinra has been studied in only 2 investigator-initiated trials (n = 31 patients).[24,27,37,43] In a placebo-controlled randomized withdrawal Anakinra Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP; N = 21; mean 6.8 recurrences, 27.8 months with pericarditis, all on CS at baseline, all on colchicine at enrollment or previously) study, anakinra provided fast onset of symptom relief. All patients were judged to have had a complete response by day 8 and were successfully tapered off CS by week 6.[24] Following randomization, recurrence occurred in 90% (9/10) of patients in the placebo arm compared with 18% (2/11) of patients randomized to remain on anakinra. Colchicine was discontinued in 9 patients (4 placebo, 5 anakinra), but the use or continuation of colchicine did not significantly affect recurrence rates. The majority of recurrence events in placebo-treated patients (6/9, 66.7%) occurred within 30 days after discontinuing anakinra treatment, with a range from 3 to 90 days for recurrence. In a long-term follow-up (median 35 months), with 1 additional patient included, 3 of the 11 total patients (27%) discontinued anakinra and remained recurrence-free, while 8 (73%) remained on anakinra (3 on full dose, 5 on reduced dose). This demonstrates that most patients needed to stay on anakinra for several years.

In a single-arm trial[27,37,43] (N = 10; baseline mean 8 ± 3.7 recurrences, 37 ± 22 months with pericarditis), anakinra provided rapid resolution of symptoms, normalization of CRP, and no recurrences while on treatment (mean follow-up 24 ± 16 months). Of 7 patients who discontinued anakinra, 5 (70%) relapsed within a month (mean time of 18 ± 9 days); 4 of the 5 were restarted on anakinra, and 1 was treated with NSAIDs and colchicine. In all cases, treatment resulted in clinical remission. The rapid relapse followed by response to further treatment suggests that anakinra treatment initially may have been too short in duration.

Evidence on anakinra efficacy is also available from 4 RWE studies. Anakinra has shown some efficacy as a steroid-sparing agent; 2 studies reported that all patients were able to taper off of CS,[40,42] while 2 reported less success, 1 in which 73% of 13 patients were tapered off CS,[39] and 1 (the International Registry of Anakinra for Pericarditis [IRAP] study) in which 55% of 49 patients were able to taper CS.[41] RWE studies suggests that while anakinra appears effective and fast-acting in resolving pericarditis symptoms and preventing recurrent events, treatment tapering, or discontinuation led to reported recurrence rates of 33–71%, and between 36% and 100% of patients treated with anakinra were not able to stop treatment.

An SLR and metaanalysis also investigated the efficacy of anakinra in colchicine-resistant and CS-dependent RP.[17] Eight studies involving a total of 65 patients underwent a pooled analysis; the evidence was low level due to the lack of RCT evidence. In the pooled analysis, pericarditis recurrence at day 60 of anakinra treatment was 7.4% ($P < 0.001$; 95% CI, 2.7–18.2%). Recurrence at day 180 was 11% ($P < 0.001$; 95% CI, 4.6–24%.) The majority of patients on anakinra were able to decrease (92.3%; $P < 0.001$; 95% CI, 81.0–97.1%) and discontinue (89.3%; $P < 0.001$; 95% CI ,76.5–95.6%) their CS therapy, although many did not discontinue anakinra therapy.

In the AIRTRIP trial, adverse events during anakinra treatment included transient local skin reactions (20/21; 95.2%), herpes zoster (1/21; 4.8%), transaminase elevation (3/21; 14.3%), and ischemic optic neuropathy (1/21; 4.8%).[24] Six patients (60%) in the single-arm trial[27,37,43] experienced mild injection-site skin reactions, and 1 patient discontinued anakinra due to transient elevation of aminotransferases. Adverse events in the RWE studies included transient, mildly painful, blotchy red injection-site reaction (31–48%),[39–41] arthralgia (16%), transaminase elevation (6%), and leukopenia (4%).[41] The frequency of injection-site reactions with anakinra has been reported to range up to 71% in randomized controlled trials of rheumatoid arthritis.[59]

EFFICACY AND SAFETY OF PERICARDIECTOMY

ESC guidelines describe pericardiectomy as a "last resort," considered only after a thorough trial of unsuccessful medical therapy.[2] While patients may undergo pericardiectomy with the goal of definitive treatment to address ongoing symptoms, this procedure is often performed on patients whose comorbidities may limit the success of the outcomes. The risks of pericardiectomy may outweigh the benefits, particularly in patients with advanced CP.[60]

Limited data on pericardiectomy are available for AP and RP, and several of the studies focus only on pediatric patients.[29,47] The largest study to date reported on 13,593 patients identified from the US NIS who underwent pericardiectomy between 1998 and 2008.[60] Mean LOS for all pericardiectomy patients during this period was 11.2 ± 11 days. AP was the indication for pericardiectomy in 1790 (13.2%) of cases or an average of 163 cases/yr. CP secondary to AP or idiopathic pericarditis was the most common etiology in this survey, with 3851 cases (28.3%), and in-hospital mortality was lower for CP (7.2%) than for AP (8.4%; $P < 0.001$). Another retrospective study on pericardiectomy over 20 years at a single US institution found low morbidity and mortality among patients with RP or constriction.[61]

DISCUSSION

This SLR identified studies reporting RWE incidence of clinical complications associated with RP, including pericardial effusion, and the less frequent CT and CP. Recurrence itself can also be considered a complication. Most literature on AP and RP allude to the high HRQOL and healthcare resource utilization burden of RP. This SLR identified evidence for the healthcare resource utilization associated with RP but did not find studies reporting on HRQOL outcomes in RP. The literature shows that there are no published evidence-based US guidelines for the treatment of RP, but that the ESC has published a treatment paradigm. There is, however, limited evidence supporting several of the treatments recommended in the ESC treatment paradigm, and much of this evidence is Level 2 RWE rather than Level 1 RCTs.

While the clinical burden of recurrent pericarditis on the patient is evident, the HRQOL and economic impact are not well documented. ICD-10 codes do not distinguish between AP and RP; hence, the large-scale US studies identified in this SLR that reported on costs did not provide data on rates of recurrence and additional economic burden attributable to RP. One relevant feature of the patients identified in third-line RWE studies is their age: mean weighted average age of these patients was 36.2 years. These patients are therefore in prime earning potential years, with many likely having ongoing financial and family responsibilities that may be impacted by unresolved RP.

While first-line treatments (NSAIDs and colchicine) do not vary widely by country and are generally effective at resolving symptoms in AP, in an estimated 15–30% of patients, pericarditis recurs after treatment; some patients fail to respond sufficiently to treatment, while others may have had treatment discontinued prematurely.[2,3] One US-based study found that 28% of patients with AP experience at least 1 recurrence, with nearly half of these patients experiencing another recurrence, and a small subset of patients going on to have persistent recurrences for several years.[51] Another US-based study found that 12.2% of patients are readmitted following a hospitalization for AP.[49] These recurrence and readmission rates suggest that first-line therapy is inadequate for some patients, and these patients are not well managed on later-line treatments. Upon failure of first-line therapy, treatment patterns are more variable by geography, with little consensus on the best course for these difficult-to-treat patients. The lack of clear second- and later-line treatment options likely stems from the limited and generally low-quality evidence supporting any existing treatment option.

CS should be limited to cases of first-line treatment failure or intolerance to NSAIDs/aspirin and colchicine, as it is well understood to be problematic. While low-dose CS may provide rapid control of symptoms in some patients, they have broad immunosuppressive activity rather than targeting autoinflammation that is primarily implicated in patients with RP. Among patients who require long-term treatment with CS, discontinuing treatment becomes problematic, and there is evidence that CS can be associated with a higher risk for recurrence.[30,33,34] Since the RWE studies that highlight risk of recurrence with CS are not free from bias, it remains unresolved whether the observed higher recurrence risk is due to selection of patients with more persistent underlying disease features, or if CS treatment tends to provoke a physiological response predisposing the patient to recurrence.[3] For patients who are ready to discontinue CS therapy, current European pericardial disease guidelines recommend slow tapering, which must be reconciled with the risk of CS toxicity due to cumulative exposure. Given the established safety concerns with the use of CS, this class is not an ideal second-line option for many patients, and the latest ESC guidelines recommend considering steroid-sparing third-line options (ie, IVIG, ANA, and AZA).[2]

We identified a small number of studies evaluating these CS-sparing options. Patients included in these studies were uniformly treatment-refractory and requiring long-term CS treatment, usually with multiple bouts of recurrence and typically at least a few years with RP. These are patients referred to in a recent review as "complicated pericarditis," along with cases of potentially fatal complications, CT, and pericardial constriction.[3] The pattern that emerges from limited RWE studies with anakinra indicates efficacy in preventing recurrence in these refractory RP patients. Attempts to taper or discontinue anakinra, however, led to recurrence in many cases, suggesting that treatment may have been discontinued prematurely; 31–48% of patients receiving anakinra for RP also experience injection-site reactions, with the proportion ranging even higher in rheumatoid arthritis, and anakinra must be self-injected daily. IVIG seemed to provide reasonable efficacy, although data are very limited and mainly consist of case studies with 1 patient, and only 1 study with more than 4 patients.[46,58] Azathioprine is associated with moderate reductions in recurrence, but the key issue that remains unresolved in studies with azathioprine and IVIG relates to extent and duration of concomitant use of CS. As with anakinra, there is no evidence to help clinicians determine the optimum treatment duration to minimize the likelihood of recurrence upon treatment discontinuation of azathioprine. There clearly is an urgency to identify effective, safe, and fast-acting treatment options for patients who present with RP.

A better understanding of the pathophysiology of treatment-refractory RP is required to be able to predict which patients are at higher risk, to inform treatment, and to develop and test novel compounds. The inflammatory responses of the innate immune system are increasingly being looked at to try to gain productive insights into

RP pathophysiology. Picco et al[62] first reported on the effectiveness of anakinra, a recombinant, human interleukin-1 (IL-1) receptor antagonist (IL-1Ra). The mechanistic basis for relieving symptoms in autoinflammatory diseases is beginning to be more well understood in terms of the role of inflammasomes (particularly NLRP3 and pyrin) in mediating response, and the role of the proinflammatory cytokine IL-1 as one of the more downstream elements of inflammasome activation that can be targeted pharmacologically.[3,63] Targeting specific inflammatory cytokines, such as IL-1, may be a more appropriate approach to treating recurrent pericarditis, compared with more generalized antiinflammatory treatments such as CS, that may add considerably to the adverse event burden of patients who may already have comorbidities.

LIMITATIONS

The limitations of this SLR relate to the paucity of data pertaining to complicated pericarditis. The limited number of studies reporting on CT and CP hamper attempts to carry out metaanalyses; the data are therefore presented in a summarized form with no further analysis beyond simple weighted averages. Separating incident cases of acute as opposed to further recurrences was not possible in many studies, due to imprecision in the ICD-9 and ICD-10 codes. The inclusion and exclusion criteria for the SLR could, in principle, have caused the exclusion of relevant studies, because the only included procedure was pericardiectomy. There was, however, only 1 study excluded based on the intervention criteria, as it assessed devices for percutaneous therapy of pericardial effusions; thus, the selection criteria did not cause relevant studies to be excluded.

From the perspective of seeking to understand the burden and unmet need of RP in the United States, we found relatively few US-focused studies. Not only are there no US treatment guidelines for RP, but many of the RWE studies, particularly relating to the outcomes of specific treatments, are also based on ex-US evidence. It would therefore be beneficial to conduct more studies to define current treatment patterns, resource utilization, and long-term outcomes among US patients.

CONCLUSIONS

Beyond the debilitating chest pain associated with pericarditis events, this inflammation-driven disease is also associated with rare but serious complications such as CT and CP. Particularly in patients with a high recurrence burden, the impact on patients' lives is likely high, including treatment-related morbidity with CS and other comorbid conditions, and surgery-related mortality with pericardiectomy, but the HRQOL impact has not yet been studied. Tolerability, toxicity, and treatment burden are challenges associated with current exploratory therapies, all of which are off-label, that likely contribute to adherence challenges. For patients with continued recurrence and inadequate response to current treatments, there is a high unmet need for FDA-approved, safe, accessible treatments that resolve recurrent events and reduce recurrence risk without posing excessive treatment burden to patients. Novel therapies targeting autoinflammatory pathways implicated in pericardial inflammation warrant further evaluation in clinical trials.

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