International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

Acute pericarditis: moderniz.

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Date of Submission: 20-11-2024 Date of Acceptance: 30-11-2024

ABSTRACT:
Ongoing research has improved our current understanding of acute pericarditis since the publication of ESC guidelines on pericardial diseases in 1915. This review provides information on the most recent advancements in this area. Auto inflammation has been added to the list of causative mechanisms for recurrent acute pericarditis, which helps to clarify the previously vague diagnoses of "idiopathic" pericarditis. Cardiac magnetic resonance can help direct treatment in challenging patients by identifying current pericardial inflammation. Creating risk scores could help pinpoint patients with complex pericarditis who require close monitoring and aggressive treatment. The efficacy of IL-1 inhibitors in recurrent cases has been demonstrated, showing a favorable safety profile. Recently, there has been a growing interest in acute pericarditis due to its occurrence as a possible side effect after COVID-19 vaccination and its potential complication in SARS-CoV-2 infection. Advances in acute pericarditis have led to an improved comprehension of the illness, enabling a personalized approach for each patient. Nevertheless, there are still unresolved queries that necessitate additional investigation.

I. INTRODUCTION:

Acute pericarditis is the most frequently seen inflammatory heart condition, surpassing acute myocarditis and infective endocarditis. In the Western society, around 27.7 cases of acute pericarditis per 100,000 people occur each year, with a hospital admission rate of 3.32 cases per 100,000 person-years. Pericarditis, like myocarditis, is more prevalent in younger males. Sex hormones, particularly testosterone, seem to influence the varying susceptibility of pericarditis in males and females .

Acute pericarditis is a typically harmless and self-limiting condition. Nevertheless, complications can arise in certain cases, either shortly after the procedure (like cardiac tamponade, a severe and potentially life-threatening issue if not quickly identified and addressed), during the middle term (reoccurring pericarditis), or in the long term (lasting constrictive pericarditis). Complications rates are mainly influenced by the cause of the condition (more common in secondary forms), specific patient traits (age and gender), and treatment decisions (like using glucocorticoids). Acute pericarditis can manifest as a standalone condition or as part of a systemic illness. In the second scenario, a multidisciplinary approach is crucial for a positive result. In idiopathic forms of heart conditions, presumed to be caused by viruses, cardiologists handle patient care, while collaboration between cardiologists and other medical specialties like rheumatologists and oncologists is necessary in secondary forms. Unlike initial cases of acute pericarditis, recurrent pericarditis can be challenging to manage and is often resistant to treatment. Following an initial episode of acute pericarditis, the percentage of cases experiencing a first recurrence is estimated to be between 15-30% . It is worth mentioning that 25-50% of patients who experience a first recurrence will also have a second recurrence, and 20-40% will have a third recurrence. In rare instances (around 5–10%), patients may experience further recurrences that negatively affect their quality of life, caused by frequent visits to the emergency department or hospital and complications from medical treatment . Therefore, glucocorticoid-dependent, colchicine-resistant recurrent pericarditis presents a significant challenge for modern cardiology, leading to intense research on its pathophysiology, timely identification of affected patients, and the most effective treatment options.

Etiology:

The cause of pericarditis involves both infectious and non-infectious types . Viral pericarditis is the predominant form of infectious pericarditis, representing around 80–85% of all cases . Approximately 40% of patients with acute inflammation of the pericardium have been found to have recently experienced a viral infection, either in the upper respiratory tract or through gastroenteritis. During pericarditis diagnosis, it is not possible to confirm viral infection through serology antibody testing because IgM antibodies are usually not detectable. Utilizing molecular

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

methods (such as polymerase chain reaction) on pericardial fluid or tissue post-pericardiocentesis and pericardial biopsy could potentially detect the infectious organism, yet this invasive and not advised for a generally harmless condition.

Based on the current guidelines, routinely identifying the virus causing an infection is not typically recommended, except for hepatitis C virus and HIV, as it doesn't impact treatment choices or outcomes . Based on the clues mentioned earlier, in today's literature, viral and idiopathic pericarditis are viewed as interchangeable terms, with idiopathic being assumed to possibly have a viral cause . It is emphasized that when investigating the cause of acute pericarditis, it is important to always take into account the local epidemiological data. In developing countries, tuberculous pericarditis is the predominant type, accounting for around 70–80% of cases, rising to 90% in HIV-positive individuals.

Most common etiology of acute pericarditis

A. Infectious (80–85%)	B. Non-infectious (15–20%)
Viral (most common):	**Autoimmune (up to 10%):**
• Coxsackievirus	• Post-cardiac injury syndromes
echovirus	• Systemic autoimmune and autoinflammatory diseases
• Herpes viruses	**Neoplastic pericarditis (5–7%):**
• Influenza	• Rarely primary and most often secondary tumors
• Adenovirus	**Metabolic:**
• HCV	
• HIV	
• Parvovirus B19	
• SARS-CoV-2, etc	

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As previously stated, determining the root cause is crucial for creating a personalized treatment strategy. It is highly advised to identify patients who likely have pericarditis within the framework of a systemic disorder in this particular situation. summarizes the characteristics hinting at a secondary (specific) cause. Patients who have any of those symptoms should be admitted to the hospital for monitoring of complications (especially cardiac tamponade) and undergo a thorough diagnostic evaluation, including blood tests and additional imaging to identify possible underlying causes. Approximately 15% of all individuals with acute pericarditis are estimated to have at least one high-risk criterion among them. In addition to the commonly known causes of acute pericarditis, two significant new causes have been identified in the past 2 years.

The initial one is contagious, known as SARS-CoV-2, while the other is not contagious, being the COVID-19 vaccine, particularly the mRNA vaccine technologies. With these two new causes, pericarditis and myocarditis have become the main focus. During COVID-19 infection, data from real-life situations indicated that 1.5% of cases experienced newly-developed pericarditis. In patients with pericarditis, the 6-month all-cause mortality was 15.5%, compared to 6.7% in matched controls with COVID-19 but no pericarditis . In a different extensive research, the ratio of pericarditis incidence 1-28 days after a positive SARS-CoV-2 test was reported as 2.79. Regarding COVID-19 vaccination, a recent study showed that out of 38,615,491 adults who received at least one dose, only 0.001% were hospitalized for pericarditis in the 1-28 days following vaccination with any COVID-19 vaccine. Another study, which involved 2,000,287 individuals who had received at least one vaccination dose, produced comparable results. In 37 cases, pericarditis occurred mostly after the second immunization, approximately 60% of the time, with a median onset of 20 days (IQR, 6.0–41.0 days) following the latest vaccination. Unlike acute myocarditis, pericarditis was found to be more prevalent in older patients. The data above clearly show that the advantages of COVID-19 vaccination outweigh any worries about the extremely uncommon cases of vaccine-related pericarditis and inflammatory heart disease

Diagnosis:

Without a particular biomarker, like troponins for myocardial necrosis, acute pericarditis diagnosis (first episode or recurrences) relies on clinical and imaging findings. As per the 2015 ESC guidelines for diagnosing and managing pericardial diseases, a diagnosis is confirmed by meeting a minimum of 2 out of the 4 criteria outlined in Table Table22 and Supplemental Fig. 1 [1]. Most frequently experienced is pleuritic chest pain, which usually aggravates with breathing in and is alleviated when sitting or leaning forward. In around 90-95% of cases, the second most common finding is the presence of pericardial rubs during auscultation. Despite being a telltale sign of acute pericarditis, they are found in about 30% of patients. Nonetheless, identifying this issue sporadically necessitates specialized knowledge [1, 22]. Pericardial effusion is present in 60-80% of cases and should be considered if it initially appears or worsens throughout the illness [1, 14, 23]. Approximately 80% of the time, the effusion is of a small size, while it is less common for it to be moderate (10%) or large (10%) with or without signs of cardiac tamponade [14]. It is important to highlight that the effusion size is assessed semi-quantitatively using transthoracic echocardiography, measuring the largest diameter in end-diastole. The effusion is seen as a space without echoes between the layers of the pericardium, being classified as small if under 1 cm, moderate if 1-2 cm, and large if over 2 cm.

Computed tomography and cardiovascular magnetic resonance can be used to quantitatively evaluate pericardial fluid with specific software. An electrocardiogram is an important tool in identifying acute pericarditis and ruling out other possible causes of chest pain. Traditionally, it is said that there are 4 phases, each lasting about 1 week. Nevertheless, the length of each stage differs significantly among individuals and is influenced by the timing of commencing medical therapy, its efficacy, and the potential development of complications [1, 21]. Common discoveries consist of widespread concave elevation of the ST segment with no specific distribution in coronary artery territories, PR segment depression (which is the most distinctive discovery in acute pericarditis), absence of reciprocal ST segment depression, ST segment depression in lead aVR and sometimes in lead V1, and notably, absence of Q wave formation. During the second stage, the ST and PR segments become isoelectric, the third stage shows T wave inversion, and the electrocardiogram normalizes in the final phase (although sometimes this last phase may be delayed). Regrettably, this common sequence of events is seen in 50-60% of instances and in some patients, the ECG shows non-specific results.

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Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

In addition to the criteria mentioned before, the individual patient might experience other less specific symptoms like fever, cough, and difficulty breathing. These additional findings could indicate a secondary form such as arthritis, skin rash, and swollen lymph nodes. As per the ESC guidelines, markers of inflammation and signs of myocardial inflammation through imaging (CT, CMR) are considered as supportive indicators and are currently not part of the primary diagnostic criteria [1]. Limited availability and cost are the primary factors leading to exclusion in CMR. Concerning C-reactive protein, in addition to being not very specific (as it increases in any inflammatory condition), another issue is that it is within normal levels at the time of presentation in around 22% of cases [24]. This is a result of CRP synthesis rate dynamics.

When evaluating a patient for suspected acute pericarditis, it is important to take into account their age and gender. For example, research has demonstrated that older women with acute pericarditis may experience difficulty breathing instead of chest discomfort, lack rubs and fever, and show non-specific results on the electrocardiogram, making it difficult to diagnose pericarditis using the usual criteria.

Diagnostic work up:

For a patient suspected of having their first episode of acute pericarditis, following ESC guidelines, the initial diagnostic assessment should consist of thorough medical history, physical exam focusing on heart sounds, chest X-ray, ECG, echocardiography, and basic blood tests such as CRP, troponin, and thyroid hormones. If one or more high-risk criteria are present, a more thorough evaluation should be conducted because secondary conditions are more common in these patients [1]. The statement also applies to patients who have recurrent acute pericarditis, where secondary conditions are also commonly found. If a secondary condition is suspected, a comprehensive blood test should be conducted which includes autoimmune disease markers, thyroid hormones, QuantiFERON-TB Gold, and tumor markers. CCT or cardiac MRI are considered second-level investigations and should be utilized if initial testing is inadequate for diagnosis.

CCT provides the benefit of enhanced spatial resolution. It is the most precise method of imaging to measure the thickness of the pericardium and assess pericardial calcifications (both their presence and extent), especially useful for surgical planning of pericardiectomy. On the other hand, inflammatory pericardial conditions are not included in the evaluation [26]. Cardiac MRI provides invaluable information about treatment guidance in addition to diagnostic clues, thanks to its tissue characterization capabilities [10, 26, 27••]. In fact, the identification of pericardial edema in T2 sequences and late gadolinium enhancement is used to assess the disease stage and treatment effectiveness, particularly for recurring cases. Particularly, in the acute stage of pericarditis, both swelling and late gadolinium enhancement (LGE) are present. The presence of LGE alongside resolving edema indicates a subacute/chronic stage of the illness, while the absence of both signals healing [1, 10, 26, 27••]. Cardiac MRI is useful for evaluating effusive-constrictive pericarditis, a rare condition characterized by both pericardial effusion causing tamponade and thickened visceral pericardium causing constriction, usually detected after draining the pericardium. The indication of pericardial edema and LDH seen on MRI hints at the potential for the condition to improve with anti-inflammatory therapy.

Tumor markers, PET-CT, and pericardial biopsy may be carried out in a personalized manner. It is important to note that patients with difficult-to-treat cases of recurrent "idiopathic" pericarditis should be regularly evaluated to rule out the possibility of developing a secondary condition, as this diagnosis is not necessarily permanent. Within this specific category of patients, studies have demonstrated that around 10% of individuals may develop a hidden additional condition, typically an autoimmune disorder like Sjögren syndrome or rheumatoid arthritis as seen in a significant case study.

Differential diagnosis:

The range of possible diagnoses for sudden chest pain includes myocardial ischemia/infarction, pulmonary embolism, aortic dissection, inflammatory chest conditions like pneumonia, and less serious issues like gastroesophageal reflux and musculoskeletal pain [1, 21, 22]. Typically, by conducting initial tests like electrocardiography, chest X-ray, echocardiography, routine blood work, CRP, and troponin, an accurate diagnosis for pericarditis can usually be achieved. However, additional tests such as D-dimer measurement and chest CT may be required in each patient [1]. It is important to note that it can be difficult to rule out a heart attack in some medical situations. Although diagnosing acute pericarditis is usually easy in a young male with chest pain and ST segment elevation but no

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

risk factors for coronary artery disease, the same cannot be said for an older man with a history of coronary artery disease and a similar electrocardiogram. In this particular situation, it may be necessary to exclude coronary artery obstruction with coronary arteriography. In a research study, around 17% of patients who were ultimately diagnosed with acute pericarditis underwent coronary arteriography [29]. Approximately 25% had an elevated ST segment among those who were observed. This percentage determines the diagnostic difficulties in cases of suspected acute pericarditis in routine medical practice.

Individuals displaying symptoms of acute pericarditis along with raised troponin levels, but no signs of decreased left ventricular ejection fraction or abnormalities in left ventricular wall motion, are being identified as having myopericarditis. However, individuals who experience pleuritic chest pain, regardless of the presence of pericardial effusion, but show signs of left or biventricular function issues, are diagnosed with perimyocarditis and treated similarly to individuals with pure myocarditis. The subset of myopericarditis patients receives treatment identical to that of individuals with "pure" acute pericarditis. Nonetheless, as per the ESC recommendations, it is advised to use the minimal effective dose of NSAIDs for the shortest duration possible as studies in animal models suggest that NSAIDs could potentially worsen inflammation and raise mortality rates. Additionally, there is not enough current data to support recommending the use of colchicine in this situation. From a clinical point of view, these patients don't appear to have a more negative outlook in comparison to those with acute pericarditis. Surprisingly, they experience fewer recurrences (11% compared to 32%) following the initial episode. Nonetheless, it is logical to conduct cardiac CMR in patients with myopericarditis to evaluate the presence and level of myocardial participation.

Treatment:

The principles for treating acute pericarditis are illustrated in Figure 1. Exercise limitation is advised during the initial phase until symptoms improve and CRP levels return to normal. Competitive sports can be resumed 3 months after the acute attack in simple cases, but should be delayed to 6 months in cases of myopericarditis. The timing of limiting exercise, particularly with recurring cases, is a topic of discussion and typically, intense physical activity should likely be postponed further [31].

The primary treatment options for acute pericarditis consist of NSAIDS, colchicine, and proton pump inhibitors to protect the stomach. Ibuprofen (600–800 mg three times daily), aspirin (1 gram three times daily), naproxen (500 mg twice daily), and indomethacin (50 mg three times daily) are the NSAIDs most frequently used in clinical settings. Aspirin is recommended for patients who are already taking it for a different reason, such as coronary or peripheral artery disease. Despite its reliable anti-inflammatory properties, the use of indomethacin is restricted due to concerns about side effects, particularly gastrointestinal issues, especially in elderly patients and those with coronary artery disease. NSAID dosage reduction, while lacking strong evidence, is recommended by the majority of experts [1, 7, 21]. Based on the latest guidelines, it is advised to administer the complete dosage for 7-10 days, then gradually decrease over 3-4 weeks in a personalized approach (250-500 mg for aspirin and 200-400 mg for ibuprofen every 1-2 weeks). Prior to reducing the dosage, it is important for the CRP levels to return to normal. If not, there is a risk of the patient experiencing a recurrence of symptoms. A longer period of NSAID treatment is frequently necessary in instances of recurring pericarditis. In a recent study, it was found that adding beta-blockers to standard anti-inflammatory treatments can help improve symptom control by reducing heart rate and decreasing friction between pericardial layers. Colchicine is considered the primary medication for all cases of pericarditis, including first episodes and recurrences. It is the sole treatment proven to cut in half the occurrence of initial and subsequent flare-ups, making it the most effective medication in preventing recurrences. It is given in addition to anti-inflammatory drugs such as NSAIDs or corticosteroids. The suggested amount is 0.5–0.6 mg to be taken two times a day [1, 34]. It is a secure treatment with the most frequent side effects being gastrointestinal issues (especially diarrhea) in around 10% of instances [1, 7, 21, 34]. Due to its narrow therapeutic index, colchicine's potential interactions with other medications may cause concern [7, 34, 35]. Still, this is quite uncommon when following the recommended dosages for pericarditis. Consider initiating treatment with a half dose for patients over 70 years old and weighing less than 70 kg to prevent side effects that may result in stopping the medication. In addition, it is important to make changes to the dosage when dealing with chronic kidney disease based on both

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

creatinine clearance and liver function [1]. Colchicine needs to be given for a period of 3 months for initial cases of acute pericarditis, and for a minimum of 6 months for cases that occur repeatedly. In cases that are hard to manage, the possibility of longer treatment periods should be assessed on a case-by-case basis [1]. Currently, colchicine is not advised as sole treatment for any pericardial condition and does not appear to be helpful without obvious inflammation, particularly with normal CRP levels [1, 33]. A recent study has raised doubts about the effectiveness of colchicine in preventing recurrences in low-risk cases (patients experiencing their first episode without receiving glucocorticoids), but this does not warrant a change in the current practice of using colchicine for all patients with acute pericarditis.

In the treatment plan for pericarditis, glucocorticoids are considered as a secondary choice for treatment [1, 36]. They are given for genuine allergy or intolerance to NSAIDs, recent gastric ulcer, use of anticoagulants with high bleeding risk, chronic kidney disease (NSAIDs are not recommended with creatinine clearance under 30 ml/min and should be used carefully with clearance between 30 and 50 ml/min), pregnancy after 20 weeks, systemic inflammatory conditions, and potentially post-cardiac syndromes where they show greater effectiveness. Glucocorticoids are highly efficient in quickly alleviating symptoms. Nonetheless, they might prefer side effects, and their safety profile is worrisome when used for extended periods of time [7]. It is advised to take 0.2–0.5 mg of prednisone or a similar dose of another steroid after ruling out bacterial infections, including tuberculosis [1]. Following the full dose administration until symptoms improve and CRP levels return to normal (typically within 1-2 weeks), the dosage should be gradually reduced based on the initial dose as per ESC guidelines. Particularly, it is important to decrease the dose gradually in stubborn recurring cases, particularly if the dose given is near the patient's threshold for recurrence. It is recommended to use calcium and vitamin D supplements in all scenarios, along with bisphosphonates in men and women after menopause, to address calcium imbalance and bone loss, particularly for extended treatment periods.

The subset of individuals with refractory pericarditis who rely on glucocorticoids are receiving a lot of attention and are the focus of extensive research. This population is highly challenging, typically having a disease duration of approximately 4.7 years, and requiring a personalized treatment plan based on the individual patient's clinical presentation. A comprehensive analysis of this subgroup is beyond the scope of this brief update. Briefly, possible treatments involve using a combination of NSAIDs, colchicine, and glucocorticoids [36]. NSAIDs are typically included when flare-ups occur while reducing glucocorticoids, aiming to stop the cycle of relying on steroids. Additional choices consist of immunomodulatory, immunosuppressant, and biological medications like IV human immunoglobulins, azathioprine, hydroxychloroquine, anakinra, and rilonacept [1, 38, 39]. Nevertheless, there is reliable data for the two biological agents mentioned [40, 41, 42••, 43•]. The reason behind adding anakinra and rilonacept to the treatment of refractory pericarditis is the new idea that repeated cases of pericarditis may be part of autoinflammatory disorders like familial Mediterranean fever. In these conditions, an irregular activation of the innate immune system and IL-1 plays a key part in the symptoms of the disease [44]. Anakinra and rilonacept both block IL-1α and β, and have shown great effectiveness in treating difficult cases of pericarditis, leading to fast and lasting improvements in the disease while maintaining a good safety record [40, 41, 42••, 43•]. IL-1 inhibition is especially suggested for instances with a substantial inflammatory load, as indicated by elevated CRP levels and recurring fevers [37•]. On the other hand, for a non-inflammatory phenotype, particularly when an autoimmune disease is present, intravenous immunoglobulins and azathioprine could be helpful [22, 37•]. A matter that requires specific focus is that even though IL-1 inhibition is a significant advancement

During the COVID-19 pandemic, the current treatments like colchicine, glucocorticoids, and anakinra are deemed appropriate for pericarditis [46]. There is no solid scientific evidence supporting concerns about the impact of NSAIDs on the worsening of COVID-19.

Prognosis:

The outcome of acute pericarditis is mainly determined by the underlying cause [1]. It works well for idiopathic pericarditis but is concerning for malignant pericardial involvement (primary or metastatic tumor). In a Finnish database, 1.1% of patients admitted with acute pericarditis died [3]. In an Italian study with a 60-month follow-up, complications observed post initial acute pericarditis episode were cardiac tamponade (1.2%), constrictive pericarditis (0.48%), and recurrent pericarditis (25%). The rates

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 6 Nov - Dec 2024, pp: 541-550 www.ijprajournal.com ISSN: 2456-4494

mentioned in additional documents are 20.2% (primarily due to neoplastic pericarditis), 8.3%, and 57.1% correspondingly [5]. Recently, continuous pericarditis has shown a connection with constrictive pericarditis [11]. In 4.3% of instances, arrhythmias, mainly atrial fibrillation/flutter, arise and the choice for long-term anticoagulation should be determined by the CHA2DS2-VASc score [47]. As previously noted, it is essential to regularly assess the patient, particularly when new symptoms arise, to discover any previously unidentified specific reasons and adjust medical care.

The identification of patients at risk for recurring episodes is a significant hurdle in the management of acute pericarditis. It is advisable to treat these patients aggressively by giving them the highest possible dose of anti-inflammatory medication, colchicine, monitoring CRP levels regularly before reducing the dosage, and seeking guidance from CMR for treatment decisions, including considering new therapies like anti-IL-1 agents. Factors linked to recurrences include glucocorticoid usage (particularly high doses with rapid tapering), absence of colchicine use, and tapering of anti-inflammatory treatment before CRP levels normalize [6•, 10]. A new risk score ranging from 0 to 22 points has been created at our hospital to predict the likelihood of recurrence in patients admitted with their first episode of acute pericarditis [6•]. The risk score comprises 6 factors correlated with relapses, including age.

II. CONCLUSION :

Recent advancements in the understanding of pathophysiological issues and treatments, particularly for difficult cases, have brought increased focus to acute pericarditis. The public and media are focusing more on pericardial syndromes due to the COVID-19 pandemic, as pericarditis can occur with COVID-19 or post-vaccination, potentially impacting trust in vaccines.

While progress has been made in understanding and managing acute pericarditis, there is still a need for additional research. For this purpose, the recent development of animal models for pericarditis is crucial for understanding recurrent pericarditis and potentially identifying patients at risk of relapses, a significant issue in the study of pericarditis. Recently, medications like colchicine and anti-IL-1 drugs have been created to target the pathophysiology, specifically inhibiting NLRP3 inflammasome formation [50, 51]. In this scenario, additional drugs that can lead to prolonged and definite remissions even after stopping treatment are highly desired. While the latest ESC guidelines provide more information on pericardial syndromes, they still have a high proportion of recommendations with a level of evidence C (~ 75%). Therefore, more research is needed to gather evidence-based information for the best possible management of pericardial syndromes.

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