Current Allergy and Asthma Reports (2022) 22:53–60
https://doi.org/10.1007/s11882-022-01031-4

PEDIATRIC ALLERGY AND IMMUNOLOGY (WK DOLEN, SECTION EDITOR)

# Multisystem Inflammatory Syndrome in Children (MIS-C)

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Accepted: 23 February 2022 / Published online: 22 March 2022


## Abstract

**Purpose of Review** The novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has developed into a pandemic. A unique challenge of this pandemic has been the emergence of multisystem inflammatory syndrome in children (MIS-C), a rare post-infectious hyperinflammatory disorder associated with SARS-CoV-2. This syndrome is characterized by overwhelming systemic inflammation, fever, hypotension, and cardiac dysfunction. This disorder may also have features overlapping with Kawasaki disease (KD), macrophage activation syndrome (MAS), and toxic shock syndrome (TSS). The goal of this review is to outline the presenting features, presumed immunopathogenesis, management, and outcomes of patients with MIS-C.

**Recent Findings** Patients with MIS-C present with characteristics that fall within a wide clinical spectrum. Main features include fever, gastrointestinal symptoms such as abdominal pain and diarrhea, and cardiac complications such as myocarditis and coronary artery aneurysms, although various other features have been reported. Younger children may present with features of Kawasaki-like disease, and older children are often admitted to the intensive care unit with cardiogenic shock. Current treatment guidelines recommend intravenous immunoglobulins (IVIG) and glucocorticoids, with utilization of biologics in refractory cases. Fortunately, the majority of patients recover, with resolution of the systemic inflammation and cardiac abnormalities. Mortality from MIS-C is rare.

**Summary** This review provides an overview of the presenting features, proposed pathogenesis, suggested therapies, and outcomes of MIS-C. Clinicians must have a high clinical suspicion for this disorder in children who have had recent COVID-19 infection or exposure and present with a significant inflammatory response. Understanding of this disorder continues to evolve, and prompt diagnosis and treatment allow for the best possible outcome for patients with MIS-C.

**Keywords** Multisystem inflammatory syndrome in children (MIS-C) · Pediatric inflammatory multisystem syndrome · COVID-19 · SARS-COV-2

## Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019. The disease was subsequently declared a pandemic in March 2020 by the World Health Organization (WHO). As of March 2022, this public health emergency has affected approximately 456 million people globally and resulted in more than 6 million deaths [1]. Compared to adults, the rate of hospitalization and death in children with acute COVID-19 is relatively low [2]. Children with COVID-19 can be asymptomatic or they may present with mild symptoms such as upper respiratory symptoms or fever. Young children (less than 1 year old) tend to have more severe disease [3, 4]. In the USA, pediatric COVID-19 cases account for approximately 19% of all cases and pediatric deaths account for approximately 0.26% of the country's over 900,000 deaths as of this publication. Of the states that have reported data, up to 0.01% of all pediatric COVID-19 cases resulted in death [5].

In April 2020, cases depicting a novel hyperinflammatory disorder associated with COVID-19 affecting children and adolescents were first reported in the UK and Italy [6•, 7•]. These patients presented with severe Kawasaki disease-like manifestations. Kawasaki disease is a pediatric systemic vasculitis that can manifest with various clinical features including

This article is part of the Topical Collection on *Pediatric Allergy and Immunology*

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coronary artery aneurysms [8]. Other countries quickly followed in reporting these unusual patient presentations. In May 2020, similar cases were first reported in the USA [9, 10]. Early in the pandemic, several terms were used to describe the disorder, such as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and multisystem inflammatory disorder in children and adolescents. Both the Center for Disease Control and Prevention (CDC) and the World Health Organization (WHO) developed case definitions (with slight variation), and the disorder has ultimately been named multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 (Box 1 and Box 2). Therefore, for the purposes of this review, this disorder will be referred to as MIS-C.

**BOX 1**

**Center for Disease Control and Prevention (CDC) Case-Definition of MIS-C [12]**

- Age <21 years old, fever >/=38.0 C for >/=24 hours, or report of subjective fever lasting >/=24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (>/=2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

**BOX 2**

**World Health Organization (WHO) Case-Definition of MIS-C [1]**

0–19 years of age

Fever >/=3 days

**AND** two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammatory signs (oral, hands or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
4. Evidence of coagulopathy (by prolonged PT, PTT, elevated D-dimers).
5. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain).

**AND**

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

**AND**

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

**AND**

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Of interest, it has been observed that patients with asymptomatic COVID-19 have been diagnosed with MIS-C in addition to patients who have had severe COVID-19 illness. It remains unclear which risk factors predispose some children to develop MIS-C after COVID-19 infection more than others. Children have presented to local health officials with a uniquely severe hyperinflammatory syndrome approximately 2–6 weeks after they have recovered from COVID-19 infection. These cases have also been frequently noted to occur a few weeks following peaks in community COVID-19 infection. The majority of patients with MIS-C have detectable antibodies against SARS-CoV-2 in contrast to exhibiting detectable virus via reverse-transcriptase polymerase chain reaction PCR [11]. This suggests that post-infectious immune dysregulation plays a significant role in the pathogenicity of MIS-C, rather than a process intrinsic to the acute viral infection.

As of March 2022, there were 7,459 MIS-C cases reported by the CDC and 63 children have died due to complications associated with MIS-C [12].

## Clinical Features and Outcomes

Children diagnosed with MIS-C can present with a wide spectrum of clinical features and disease severity. Dufort et al. reported on New York State's surveillance results of 99 confirmed MIS-C patients early in the pandemic [10]. The majority of patients were 6 to 12 years old and 54% of patients were male. Of 78 patients with reported race data, 40% were Black. Of 85 patients with reported ethnicity data, 36% were Hispanic. Obesity was the most common preexisting condition (29 out of 36 patients with comorbidity). Up to 80% of patients were admitted to the ICU, with 10% of patients requiring mechanical ventilation. Of 93 patients with echocardiograms, 52% showed abnormalities (particularly ventricular dysfunction), 32% had pericardial effusion, and 9% had coronary artery aneurysms. Seventy percent of patients were treated with IVIG, 64% received systemic glucocorticoids, and 48% received both IVIG and systemic glucocorticoids. Two patients died, neither of which received IVIG or glucocorticoids, although one had received extracorporeal membrane oxygenation.

Feldstein et al. reported on 186 patients defined as having MIS-C in surveillance data collected from pediatric health centers in 26 states [9]. The majority of patients were male, with major symptoms including gastrointestinal (92%), cardiovascular (80%), mucocutaneous (74%), and respiratory (70%). Eighty percent of patients received care in the intensive care unit with 20% requiring mechanical ventilation. Coronary aneurysms were found in 8% of patients, and 40% of patients presented with Kawasaki-like disease. The majority of patients were treated with IVIG (77%), systemic glucocorticoids (49%), and interleukin-1 receptor antagonist (IL-1Ra) or interleukin-6 (IL-6) inhibitor (20%). Four patients died, 2 of which had underlying comorbidities, and three patients had received extracorporeal membrane oxygenation. Feldstein et al. reported a mortality rate of approximately 2%. Similarly, Ahmed et al. reported a mortality rate of approximately 1.7% in 39 observational studies with 662 MIS-C patients [13].

Kaushik et al. reviewed 16 studies with 655 patients ranging from 3 months to 20 years old [2]. The median age was 8 years old, and 55% of patients were male. Many of the studies reviewed reported that the majority of patients were Black or Hispanic. Approximately 23% of participants had comorbidities, with obesity/overweight being the most common, followed by respiratory and cardiac disorders. Fever and gastrointestinal symptoms were the most common presenting manifestations. Cardiac involvement was found in 55% of patients, with the majority presenting with Kawasaki-like disease. Echocardiograms obtained in 73% of patients showed decreased left ventricular ejection fraction of < 55% in approximately 32% of these patients. However, it was noted that most patients recovered cardiac function at follow-up.

Bautista-Rodriguez et al. found that the majority of patients in an international series of 183 patients diagnosed with MIS-C fell within three clinical categories: shock, Kawasaki-like disease, and incomplete/atypical Kawasaki-like disease manifested by fever and systemic inflammation [14]. Patients admitted with shock tended to have thrombocytopenia, higher levels of C-reactive protein (CRP), ferritin, D-dimer, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). They also tended to develop cardiac involvement such as left ventricular dysfunction and valvulitis. These patients were more likely to require ventilator and inotropic support, and up to 55% of patients required ICU admission. The patients were older, predominantly Black (43.6%), and presented with predominantly gastrointestinal and neurological manifestations. Patients with Kawasaki-like disease were younger, had lower levels of inflammatory markers, and had shorter courses of hospitalization. The prominent type of cardiac involvement in these patients was coronary artery aneurysms. Patients with fever and inflammation also had much shorter recovery times, although they also exhibited increased risk of dilated coronaries on echocardiogram studies. Bautista-Rodriguez et al. found that an earlier requirement for hospital admission was a predictor of poor patient outcome, particularly associated with extracorporeal membrane oxygenation (ECMO) and/or death. Three patients died, one due to cerebral vascular accident while receiving extracorporeal membrane oxygenation and two as a result of cardiac arrest.

Gastrointestinal symptoms are a predominant clinical manifestation in MIS-C patients, and include abdominal pain, vomiting, and diarrhea. Viral illnesses causing these same symptoms are common in childhood, and MIS-C must be ruled out when there is a high clinical suspicion in a child who presents with recent COVID-19 infection or exposure, fever, and GI symptoms. CT or MRI obtained in evaluation of abdominal pain in MIS-C patients may reveal mesenteric lymphadenitis, hepatosplenomegaly, bowel wall thickening, and intestinal inflammation, particularly in the terminal ileum and colon [13, 15].

## Pathogenesis of MIS-C

The exact pathophysiology of MIS-C remains unknown. However, post-infectious immune dysregulation, particularly involving the innate immune system is implicated given that the majority of patients improve drastically with immunomodulatory agents. A "cytokine storm" plays an important role, with activation of the IL-1β pathway and elevation in levels of proinflammatory cytokines such as IL-6, IL-8, IL-18, tumor necrosis factor (TNF-α), and interferon γ (IFN-γ) having been reported in patients. This leads to the multi-organ involvement noted in MIS-C patients, with cardiac injury in particular [11]. Similarly, Carter et al. found elevated levels of IL-1β, IL-6, IL-8, IL-10, IL-17, and IFNγ, and decreased T and B cell subsets in the acute phase of MIS-C patients, with normalization of levels at follow-up visits [16]. Consiglio et al. found IL-6 and IL-17A levels to be elevated in patients with Kawasaki disease compared to patients with MIS-C, suggesting a different pathogenesis between the two disorders [17]. However, similar to Kawasaki disease, autoantibody-mediated immune complexes might lead to endothelial injury through compliment and Fc-γ receptor activation. The response of MIS-C patients to IVIG seems to be supportive of this thought. Upregulation of T cell activation also enhances the host immune response [18]. However, more studies are needed to better understand how SARS-CoV-2 disrupts host immune tolerance that leads to the multisystem involvement observed in MIS-C patients.

## Comparison of MIS-C with Kawasaki Disease

Kawasaki disease (KD) is a rare pediatric systemic vasculitis that typically affects medium-sized arteries, particularly the coronary arteries. The disorder was first described by pediatrician Tomisaku Kawasaki in Japan in 1967 [19]. In developed countries, Kawasaki disease is the leading cause of acquired heart disease. The cause of this disorder remains unknown, although most experts agree that a dysregulated immune response is responsible for the manifestations noted. To date, no specific infectious etiology has been able to be identified, although it is highly suspected that a viral agent is a trigger.

Untreated Kawasaki disease patients have an approximately 25% risk of developing coronary artery aneurysms; however, patients treated with IVIG and aspirin within the first 10 days of symptoms have a 5% risk of developing coronary artery abnormalities. Kawasaki disease is diagnosed in patients presenting with fever lasting 5 or more days, with four of the following clinical features: (1) cracking/erythema of lips, strawberry tongue; (2) bilateral bulbar conjunctival injection without exudates; (3) rash; (4) edema and erythema of hands and feet in the acute phase, and periungual desquamation in the subacute phase; and (5) cervical lymphadenopathy. Kawasaki disease is classified as incomplete if the patient has fever of at least 5 days, and 2–3 of clinical features, or an abnormal echocardiogram. Patients diagnosed with Kawasaki disease shock syndrome (KDSS) have Kawasaki disease clinical manifestations with signs of hypotension and shock [20].

Patients diagnosed with KDSS are more likely to have lab abnormalities similarly observed in MIS-C patients such as thrombocytopenia, coagulopathy, hyponatremia, hypoalbuminemia, and moderately elevated CRP. KDSS patients also present more commonly with abdominal symptoms, similar to MIS-C patients. MIS-C patients may also present with features that are often observed in Kawasaki disease patients such as conjunctivitis, oral mucosal changes, lymphadenopathy, and rash. Most patients affected with Kawasaki disease or MIS-C are predominantly male. The cardiac involvement seen in MIS-C, particularly coronary artery abnormalities and myocarditis, appears to resolve after treatment, similar to KDSS. Due to the similarities between MIS-C and Kawasaki disease as described above, it is important to continue consideration of Kawasaki disease in the differential diagnosis in children who seroconvert following COVID-19 infection.

While there is a certain degree of clinical overlap between MIS-C and Kawasaki disease, there are some important contrasting features that have been noted (Table 1). Approximately 5% of Kawasaki disease patients develop cardiovascular shock, necessitating inotropic support [8], compared to the approximate > 50% of MIS-C patients who develop cardiogenic shock requiring treatment in the ICU setting. In addition, the majority of MIS-C patients presenting with shock requiring vasopressor support tend to be older children and adolescents (mean age 10 years old) [21]. Approximately 80% of Kawasaki patients are < 5 years old, with most patients being less than 1 year old when diagnosed.

**Table 1** MIS-C and Kawasaki disease comparison

| | MIS-C | Kawasaki disease |
|---|---|---|
| Presenting age | ~10 years old | <5 years old |
| Race/ethnic predisposition | Black, Hispanic | Asian |
| Gender | Males > females | Males > females |
| ICU admission/inotrope support | >50% | ~5% |
| Presenting features | Fever, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) | Rash, conjunctivitis, oral mucosal changes |
| Cardiovascular involvement | Myocarditis, left ventricular dysfunction, coronary artery aneurysms (uncommon) | Coronary artery aneurysms |

Patients with MIS-C tend to have significantly higher levels of inflammatory markers than Kawasaki patients [11]. Ethnic and racial predominance also differs in Kawasaki disease and MIS-C, with higher rates of Blacks and Hispanics diagnosed with MIS-C, compared to higher rates of East Asians noted to be diagnosed with Kawasaki disease. MIS-C has also been only rarely reported in Asia, despite the prevalence of infections in Asian countries [21]. This may suggest a distinct genetic predisposition between MIS-C and Kawasaki disease. Although MIS-C patients can present with coronary artery aneurysms, they tend to present with lower rates of coronary artery abnormalities than Kawasaki disease patients (~8% and ~25%, respectively). MIS-C patients also tend to have lower ejection fractions compared to Kawasaki patients. These disparities suggest that MIS-C may be a distinct hyperinflammatory disorder from Kawasaki disease.

## Macrophage Activation Syndrome (MAS)

Macrophage activation syndrome (MAS) is a potentially fatal condition that may complicate infection, malignancy, and autoimmune disorders such as systemic lupus erythematosus, systemic juvenile idiopathic arthritis, and Kawasaki disease [22]. Untreated patients can deteriorate rapidly, and MAS may carry a mortality rate of up to 8% [22, 23]. MAS is characterized by persistent activation of T lymphocytes and macrophages which leads to a dysregulated immune response. Excessive production of proinflammatory cytokines results in a cytokine storm, leading to overwhelming inflammation and multi-organ damage. Most patients present with fever, lymphadenopathy, hepatosplenomegaly, encephalopathy, and disseminated intravascular coagulation (DIC). Common lab findings include hyperferritinemia, pancytopenias, hypertriglyceridemia, hypofibrinogenemia, coagulopathy, and transaminitis. Bone marrow aspirate typically reveals hemophagocytosis by activated macrophages. Treatment of MAS includes high-dose glucocorticoids and cyclosporine; however, many centers now are utilizing IL-1 receptor antagonist (recombinant human protein Anakinra) as first-line therapeutic agent. MAS has been observed in MIS-C patients; therefore, clinicians need to be aware of this potentially lethal complication and its presentation, as prompt recognition and treatment can decrease mortality and morbidity.

## Lab Findings

The majority of patients with MIS-C present with lab findings indicative of overwhelming systemic inflammation. Elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, ferritin, procalcitonin, and lactate dehydrogenase are commonly seen. Many patients also have lymphopenia, neutrophilia, thrombocytopenia, and hypoalbuminemia. Coagulopathy has been observed in some patients resulting in thrombosis, although the exact mechanism remains unclear. For those with cardiac involvement, it is not uncommon to observe significantly elevated troponin and NT-pro-BNP levels, indicating myocardial injury. As a personal observation, D-dimer and ferritin levels tend to fluctuate during the hospitalization course as other inflammatory markers normalize. However, the majority of patients have normal ferritin and D-dimer levels when labs are repeated at follow-up.

## Treatment

Due to the overlapping features commonly observed between MIS-C and Kawasaki disease, patients with MIS-C are currently treated empirically based on Kawasaki disease therapy protocols. The American College of Rheumatology has provided clinical practice guidelines for laboratory workup and management of patients with suspected MIS-C [24•]. Patients are recommended treatment with high-dose intravenous immunoglobulin (IVIG) at 2 gm/kg and glucocorticoids at ~2 mg/kg/day in divided doses. Glucocorticoids have been shown to have a favorable effect on the fever curve of MIS-C patients compared to IVIG monotherapy [25, 26]. Patients are also started on low-dose aspirin (3–5 mg/kg,

max 81 mg daily), unless there are contraindications such thrombocytopenia or active bleeding. For patients with significant left ventricular dysfunction evidenced by EF < 35%, anticoagulation with enoxaparin is usually commenced in consultation with pediatric hematology service. Patients with severe clinical presentation (ICU admission, significant cardiovascular involvement, evidence of macrophage activation syndrome) are treated with methylprednisolone pulses (30 mg/kg/day × 3 days) followed by glucocorticoids (~ 2 mg/kg/day in divided doses). Glucocorticoid therapy is tapered over 2–3 weeks in relatively uncomplicated cases, and tapered over 4–8 weeks in more complex cases.

### IL-1 Receptor Antagonist

Refractory MIS-C cases are often treated with IL-1 receptor antagonist (Anakinra). This biologic is often preferred over administration of a second IVIG dose due to increased risk of fluid shift that may result in pulmonary edema, particularly in older patients [24•]. IL-1α and IL-1β are key players in the cytokine storm in MIS-C. Cavalli et al. also showed Anakinra to be efficacious in dampening the hyperinflammatory response in acutely infected COVID-19 patients [27]. Similarly, Anakinra has been shown to be beneficial in treating refractory Kawasaki disease and decreasing the rate of developing coronary artery aneurysms [28]. Typical dosing of Anakinra is 2 mg/kg/day for inflammatory disorders such as systemic juvenile idiopathic arthritis and neonatal onset multisystem inflammatory disorder. However, due to the severe inflammation that occurs in MIS-C, higher doses of Anakinra (> 4 mg/kg/day up to 10 mg/kg/day in divided doses) are often used, particularly when there is evidence of macrophage activation syndrome [24•]. Anakinra has a favorable safety profile and a relatively short half-life (approximately 4–6 h), making it a desirable therapeutic agent, as it can be quickly stopped if side effects occur.

### TNF-α Blockade

Some institutions have used the TNF-α blocking agent infliximab to treat refractory MIS-C with variable results [15]. Infliximab is a chimeric human-mouse monoclonal antibody that binds to both circulating and cell surface TNF-α. It is noted that levels of TNF-α are elevated in Kawasaki disease, and infliximab is often used to treat refractory cases of Kawasaki disease.

### IL-6 Blockade

Tocilizumab is a humanized monoclonal antibody that binds to both circulating and cell surface IL-6 receptors. IL-6 is a proinflammatory marker that is noted to be elevated in Kawasaki disease and MIS-C. Consiglio et al. found IL-6 levels to be variable in MIS-C with some patients showing normal levels [17]. Several studies have assessed the safety and efficacy of tocilizumab in acute severe COVID-19 infection and related hyperinflammation, particularly in adults [29, 30]. However, clinical status and mortality rate did not improve when compared to the placebo group. Caution must also be taken when administering tocilizumab to MIS-C patients due to possible development of coronary artery aneurysm which has also been observed in refractory Kawasaki disease treated with tocilizumab [31]. More studies are needed in order to establish optimal treatment guidelines for MIS-C.

## Follow-up

Kaushik et al. noted a median of 7 days of hospitalization [2]. As per personal observation, hospitalization of the majority of admitted MIS-C patients range between a few days to up to 2–3 weeks. It is currently recommended that MIS-C patients are followed up closely after discharge as the long-term complications of the disorder are currently unknown, and the clinical course must therefore be carefully monitored. Patients are primarily followed by rheumatology and cardiology approximately 2 weeks post-discharge. For the time being, providers should consider following Kawasaki disease follow-up guidelines, with a repeat echocardiogram approximately 2 weeks after MIS-C diagnosis, and then at 4–6 weeks if the patient has had a stable course. However, it would be prudent to perform more frequent surveillance if the patient has had significant cardiac dysfunction or coronary artery aneurysms at presentation. The majority of MIS-C patients show complete recovery of cardiac abnormalities and normalization of labs at follow-up [2, 9, personal observation].

## Conclusions

MIS-C is a rare, recently recognized pediatric hyperinflammatory disorder affecting patients several weeks after infection with, or exposure to SARS-CoV-2 (COVID-19). Many patients present with features that overlap with Kawasaki disease, a pediatric vasculitis mainly affecting the coronary arteries, and shock. Significant differences in patients with MIS-C compared to those with Kawasaki disease include older age at onset, severe myocardial involvement, severe inflammation, and higher incidence among Blacks and Hispanics. Defining diagnostic criteria of MIS-C has remained a unique challenge. The current treatment paradigm for MIS-C patients typically parallels protocols for Kawasaki disease management. The majority of patients are treated with immunomodulators such as IVIG and glucocorticoids as first-line agents, and in refractory cases, biologics such as

IL-1 and TNFα blockers are often used. Prompt recognition of this disorder and initiating treatment is of upmost importance as lethal complications, such as macrophage activation syndrome, can occur. A multidisciplinary team approach, involving rheumatology, cardiology, hematology, and intensivists, is often necessary when caring for these patients. So far, favorable outcomes have been reported, with mortality rates of approximately 2%. However, the sequelae of MIS-C, particularly cardiovascular, in children and adolescents remain unknown. As such, long-term follow-up and more rigorous studies are needed to enhance our knowledge of this novel pediatric hyperinflammatory syndrome.

## Declarations

**Conflict of Interest** Julisa M. Patel declares that she has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

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