



Clinical practice guidelines in multisystem inflammatory syndrome (MIS-C) related to COVID-19: a critical review and recommendations

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Received: 21 August 2021 / Accepted: 5 December 2021 / Published online: 4 January 2022
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Abstract

Background Multisystem inflammatory syndrome in children (MIS-C) is a serious health condition that develops from and is linked to coronavirus disease 2019. MIS-C is considered a multi-organ dysfunction involving cardiac, renal, respiratory, hematologic, gastrointestinal and neurological symptoms and groups of signs and symptoms such as rash or bilateral non-purulent conjunctivitis, hypotension or shock and acute gastrointestinal problems, which require immediate therapeutic intervention to prevent the aggravation of the patient's health condition. MIS-C is relatively new in the field of evidence-based medicine; however, there are several clinical guidelines for good clinical practice. For every disorder, the guidelines have different suggestions. Hence, based on the current status of the evidence, recommendations have been combined to form a unified guideline for therapeutic management.

Methods This paper compares and evaluates the current MIS-C-specific clinical practice guidelines (namely, American Academy of Pediatrics, American College of Rheumatology, Helen DeVos Children's Hospital Foundation, Children's Hospital of The King's Daughters, and the Infectious Diseases Society of America). The compiled literature was then assessed by the authors separately, and an algorithm was proposed for each disorder, taking into consideration the various guidelines proposed for the management of the disorder.

Results The features of MIS-C patients are unified; this is very helpful in managing its symptoms and decreasing mortality rates. In addition, recommendations for pharmacological treatment for MIS-C symptoms are formulated after cross-comparison across five different guidelines.

Conclusions This study provides a general interpretation of the results in the context of other evidence and implications for future research. It proposes a unified guideline based on the current evidence, with the best potential to maintain suitable clinical standards in the Saudi Arabian Ministry of Health.

Keywords Coronavirus disease 2019 · Multisystem inflammatory syndrome · Pediatric multisystem inflammatory syndrome

Introduction

The pneumonia cases caused by the novel β -RNA coronavirus were named by the World Health Organization (WHO) coronavirus disease 2019 (COVID-19) [1]. Early in 2020,

the United Kingdom National Health Service observed a nationwide increase in a rare but serious health condition in children called multisystem inflammatory syndrome in children (MIS-C), which developed from and was linked to COVID-19 [2–4]. On April 7, 2020, the first MIS-C case of a 6-month-old infant in the USA was diagnosed with Kawasaki disease (KD) due to the similarities in the clinical features of MIS-C and KD [2–4]. A recent report by Riphagen et al. studied the clinical features of a group of children who had antibodies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and had a severe hyperinflammatory shock, which clustered at a rate of one or two children per week [5]. They found that the clinical presentations of these

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cases were closely related to the characteristics of KD and toxic shock syndrome [5]. A further study reported more cases that were broadly distributed and required immediate admission to intensive care units [6]. On May 1st, 2020, the UK Royal College of Paediatrics and Child Health published guidance on MIS-C [2]. Since then, several other worldwide health organizations have reported that MIS-C is temporally associated with COVID-19, with the development of symptoms two to six weeks after COVID-19 incidence [2–8]. However, the association between COVID-19 and MIS-C is not completely understood, which makes healthcare management more complicated. The first MIS-C case in Saudi Arabia of a 13-year-old female child, reported in September 2020, died despite critical care and management based on the Saudi Ministry of Health guidelines for COVID-19 management [7]. Currently, there are no MIS-C-specific clinical practice guidelines established by the Saudi Ministry of Health. According to the latest statistical update by the Centers for Disease Control and Prevention in the USA in early 2021, the total number of MIS-C cases increased to 1659 cases and 26 MIS-C deaths [9–11]. The median age of the patients ranged from seven to ten years, and more than 59% of all patients were male [8]. Data suggest that race has a strong association with MIS-C [2]. More than 70% of reported cases have occurred in children who are Hispanic or Latino [9]. The five main features of MIS-C, according to the WHO, are to be 0–19 years of age with a fever > 3 days and at least two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs, hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities, evidence of coagulopathy, and acute gastrointestinal problems, as well as elevation of the inflammatory markers with no other obvious microbial cause of inflammation plus either COVID-19 antigen test/serology positive or contact with COVID-19 patients [12].

Because some of the symptoms of MIS-C and KD are similar, it may be hard to tell the difference between them based on symptoms alone. MIS-C development after infection with COVID-19 is significant information to help confirm the diagnosis. Most of the available guidelines for good clinical practice are widely known and accepted, such as the American Academy of Pediatrics (AAP) guideline, updated on 17 November 2020 [1], the American College of Rheumatology (ACR) guideline, submitted to Arthritic Rheumatology on 15 February 2021 [2], and the HDVCH guideline by Spectrum Health Helen DeVos Children's Hospital, located in Grand Rapids, Michigan, United States on 10 January 2020 [3]. Children's Hospitals and Clinics of Minnesota is one of the largest freestanding pediatric health systems in the United States; it published MIS-C guidelines in January

2020 [4]. The pediatric intensive care unit (PICU) guidelines issued by Nature Research (which has principal offices around the world in London, New York, Berlin, Shanghai and Tokyo) were published online on 7 July 2020 [5]. The last CHKD (Children's Hospital of The King's Daughters) guideline was published on 31 May 2020) [6].

Many pharmacological therapies are used to manage the symptoms of MIS-C disease according to various guidelines available worldwide, as mentioned above [6, 7]. All the available clinical practice guidelines recommend the use of certain medications considered essential in managing MIS-C symptoms, including intravenous immunoglobulin (IVIG) at a dose of 2 g/kg/dose [6, 7]. In addition, due to the multi-inflammatory nature of the disease, therapies that have anti-inflammatory and immunosuppression activity must be used. The previously mentioned guidelines unanimously agree on the use of steroid medications such as methylprednisolone for this purpose, as well as biologics such as anakinra and remicade or interleukin-6 inhibitors. With follow-up, depending on clotting factors and risk factors, the use of low-dose aspirin as prophylaxis has been recommended, especially for patients who have developed KD-like features. For community-acquired shock, some guidelines such as AAP and Children's Hospitals and Clinics of Minnesota have recommended the use of antibiotics such as vancomycin, ceftriaxone and clindamycin along with other treatments [1, 5].

As in any other pediatric condition, clinicians need to follow the most reliable guidelines. MIS-C is assumed to be a critical condition with multiple serious complications that vary from patient to patient. Thus, clinicians must follow the safest and most effective treatment guidelines to minimize mortality and reduce the risk of long-term sequelae. Treatment for MIS-C aims to decrease systemic inflammation and restore organ function. Regarding the epidemiology, pathogenesis, clinical scope and long-term effects of MIS-C, much remains unknown.

Analysis of symptom, risk of death and quality of life based on each guideline and previous analysis to adopt the most accurate guideline with minimum harmful effect; this will help to decrease the risk of complications and mortality rate. As should be expected, all the above-mentioned guidelines need to be uniform and precise. However, as this review critique shows, there are several differences when these guidelines are compared. This paper, therefore, attempts to compare the treatment recommendations by the above-mentioned guidelines for MIS-C multi-symptoms and disorders and evaluates the differences among them. It also suggests a unified guideline, putting together common recommendations and available evidence from all the above.

Methods

A comprehensive literature search for published MIS-C practice management guidelines was conducted through many sources, such as ProQuest, Scopus, ScienceDirect, Wiley, Saudi Digital Library and PubMed. Google Scholar was used for additional relevant studies from 2020 to February 2021. The keyword searches were related to the main subject (e.g., “MIS-C or multisystem inflammatory syndrome”, “PMIS or pediatric multisystem inflammatory syndrome”, “COVID-19”) and the management domain (e.g., “antibiotic”, “antiviral”, “IVIG or immunoglobulin”, “anti-coagulant or heparin”, “antiplatelet or aspirin”, “biologic or anakinra or tocilizumab”). The most common guidelines, namely, the APA, ACR, HDVCH, Children Minnesota, PICU, CHKD and Infectious Diseases Society of America (IDSA), were also reviewed. The literature was then assessed by the authors separately and an algorithm was proposed for each disorder, taking into consideration the various guidelines proposed for the management of the specific disorder.

Results

Definition of multisystem inflammatory syndrome in children according to each guideline (Table 1)

Various guidelines show minor differences of opinion here, and hence the unified guideline recommending mostly the same criteria to define MIS-C cases.

Age

All the guidelines and the unified guideline recommend an age < 21 years. According to case series in the US and UK in 2020, the median age was 8–11 years (range 1–20 years). There have been rare reports of MIS-C disorder occurring in adults aged in the mid-20s where the patient met the other criteria, with the exception of age [14].

Fever

There are no differences of opinion among the guidelines in defining the fever, so the unified guideline is the best recommendation: the documented fever ≥ 38.0 °C (100.4 °F) for ≥ 24 hours or a report of subjective fever lasting ≥ 24 hours.

Laboratory evidence of inflammation

Several differences are apparent in the identification of laboratory markers of inflammation among the various

guidelines. The unified guideline recommends laboratory abnormalities noted in all guidelines based on the most frequent markers in critical case series [15–19]. All guidelines considered abnormal blood cell counts, including lymphocytopenia and thrombocytopenia; this is also supported by the unified guideline. In addition, almost all the guidelines recommend measuring inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin and ferritin] at the time of admission and then serially to monitor progression. With the exception of the HDVCH and CHKD guidelines, all others recommend the use of both CRP and ESR as routine inflammatory markers. The HDVCH and CHKD guidelines only recommend the use of CRP. Based on recent evidence, the ESR is not useful for serial monitoring because most patients with MIS-C are treated with IVIG, which can elevate the ESR. As in APA, HDVCH and CHKD, the unified guideline recommends monitoring of cardiac markers (troponin and brain natriuretic peptide). In contrast, the ACR and IDSA guidelines offer no specific recommendations for cardiac marker monitoring.

Multisystem involvement and Kawasaki disease-like symptoms

All the guidelines and the unified guideline recommend the involvement of two or more organ systems, KD-like symptoms and the development of MIS-C after COVID-19 infection by 4–6 weeks as required criteria to define MIS-C.

Management of multisystem inflammatory syndrome in children according to each guideline (Table 2)

As the vast majority of evidence supports the use of IVIG, all the guidelines and the unified guideline recommend the continued use of IVIG (1–2 gm/kg) and steroids as an anti-inflammatory. According to McArdle et al., in a surveillance study involving patients with MIS-C, primarily treated with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone, investigators found that the time until a reduction in disease severity was similar in the three groups [20]. Another study recently reported that initial treatment with a combination of IVIG plus glucocorticoids was associated with a lower risk of cardiovascular dysfunction than IVIG alone [21].

Immunosuppressants (prednisone, azathioprine) suppress the immune system action by curtailing the production of white blood cells (defensive cells), known as T-cells. Therefore, immunosuppressants curtail inflammation and cell damage, thereby minimizing symptoms. For example, the dosage for azathioprine (Rx) is 2–3 mg/kg once daily for the remission, maintenance and reduction of steroids. The lower dosage may be 100 mg/day and the length of the

Table 1 Definition of multisystem inflammatory syndrome in children according to each guideline [1–10]

Variables	AAP	WHO	CDC	ACR	HDVCH	CHKD	IDSa	Unified
Age (y)	<21	<21	<21	<21	<21	<21	<21	<21
Fever	>38 °C for ≥24 h	>38 °C	>38 °C for 24 h	>38 °C	>38.5 °C for ≥3 d	≥38.0 °C for ≥24 h	>38.0 °C for ≥24 h, or report of subjective fever lasting ≥24 h	≥38.0 °C for ≥24 h, or report of subjective fever lasting ≥24 h
Severe shock	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome	Toxic shock syndrome
Laboratory evidence of inflammation	Increase ESR/CRP Ferritin LDH Neutrophilia BNP or pro-BNP D-dimers	CRP > 6 mg ESR > 40 mm LDH Neutrophilia BNP D-dimers	↑ One or more of the following: CRP, LDH, D-dimer, procalcitonin, VBGw/lactate, neutrophils, BNP, ferritin	CRP ≥ 5 mg/dL ESR ≥ 40 mm/h At least one of: neutrophilia hyperalbuminemia	CRP > 10 mg/dL D-dimer > 1 mg/L High sensitivity Troponin > 30 pg/mL Ferritin > 350 ng/mL	↑ One or more of the following: CRP, ESR, LDH, fibrinogen, procalcitonin, D-dimer, IL-6, ESR, ferritin, lactic acid dehydrogenase, neutrophils, BNP, ferritin	One or more of the following: CRP, ESR, LDH, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, neutrophils Ferritin > 350 ng/mL [11, 13]	CRP ≥ 5 mg/dL ESR ≥ 40 mm/h LDH Neutrophilia BNP or pro-BNP D-dimers > 1 mg/L Troponin > 30 pg/mL Ferritin > 350 ng/mL [11, 13]
	Decrease	Platelets Albumin	Lymphocytes Albumin	ALC < 1000/ μ L Platelet count < 150,000/ μ L Na < 135 mmol/L	Lymphocyte count < 0.5 K/ μ L Albumin < 2 g/dL	Lymphocytes Albumin	Lymphocytes Albumin	Hyponatremia Lymphocyte count < 1000 cells/ μ L Platelet count < 150,000/ μ L Albumin [11, 13]
SARS-CoV-2 (COVID-19) infection	MIS-C develop after infection by 4 wk	MIS-C develop after infection by 4–6 wk	Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 wk prior to the onset of symptoms	MIS-C develop after infection by 4 wk	MIS-C develop after infection by 4–6 wk	Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 wk prior to the onset of symptoms	Positive for current or recent COVID-19 infection or COVID-19 exposure within the 4 wk prior to the onset of symptoms	MIS-C develop after infection by 4–6 wk

Table 1 (continued)

Variables	AAP	WHO	CDC	ACR	HDVCH	CHKD	IDSA	Unified
Multisystem involvement	> 2 organs	> 2 organs	> 2 organs	> 2 organs	> 2 organs	> 2 organs	> 2 organs	> 2 organs
Exclusion of other causes	No	No	No	No	No	No	No	Yes and exclusion of severe respiratory illness [11, 13]
KD-like features	Patient presenting with KD-like symptoms	Similarities to KD	KD features (complete or incomplete KD)	Patient presenting with KD-like symptoms	Patient presenting with KD-like symptoms	KD features (complete or incomplete KD)	Similarities to KD	Patient presenting with KD-like symptoms

MIS-C multisystem inflammatory syndrome in children, *AAP* American Academy of Pediatrics, *ACR* American College of Rheumatology, *HDVCH* Helen DeVos Children’s Hospital Foundation, *CHKD* Children’s Hospital of The King’s Daughters, *IDSA* Infectious Diseases Society of America, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *LDH* lactic acid dehydrogenase, *WHO* World Health Organization, *IL-6* interleukin 6, *BNP* brain natriuretic peptide, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *COVID-19* coronavirus disease 2019, *KD* Kawasaki disease

dosage is up to 84 months. Although Schoot et al. asserted that immunosuppressants are typically harmful in the initial COVID-19 treatment phase, the drugs are beneficial in the severe conditions of COVID-19 by repressing the overshooting of the immune responses [22]. At the same time, immunosuppressive indications confirm that they reduce the patient’s mechanical ventilation and mortality. Finally, early treatment with methylprednisolone is highly beneficial for a patient’s health under severe conditions [22].

According to Al-Ghafry et al., anticoagulants such as warfarin (Rx) or heparin tablets of 3–7 mg, twice a day for three or more months, as the dosages are considered based on the genotypes. The use of anticoagulants requires frequent monitoring until the patient’s health condition stabilizes. The primary use of anticoagulants is to curtail clot formation within the arterial and venous of patients with COVID-19. A reduction in blood clots after seven to twelve weeks without prolonged fatigue or any side effects from the patient indicates that the patient’s health status is stabilized [23].

Antiplatelet therapy, mainly aspirin, is commonly used in all the guidelines and recent reviews due to concerns about coronary artery involvement and the risk of blood clots [24]; hence, the unified guideline also recommends a low dose. According to Rizk et al., the use of 75 mg (low aspirin dose) for three months decreases cardiovascular diseases and lowers the risks of contracting COVID-19 by 29% [25]. Merzon et al. confirmed that the test results of COVID-19 patients who used aspirin shifted from positive to negative 3–4 days sooner than those who did not use aspirin, depending on their health conditions. Thus, the findings revealed that a low dosage of aspirin on COVID-19 infection seems to be a promising treatment [26].

Since no separate recommendations exist except for the IDSA guideline, the unified guideline recommends the use of an antiviral, remdesivir in particular, for patients known to have a presentation consistent with typical COVID-19. Only the AAP guideline has recommended antibiotic therapy for patients diagnosed and hospitalized with MIS-C. Recent evidence proposes the initial use of broad-spectrum antibiotics as the symptoms overlap with severe bacterial infections, which is also the recommendation of the unified guideline. With the exception of the CHKD and IDSA guidelines, all other guidelines recommend the use of anticoagulant therapy (enoxapanin) as a standard drug.

Discussion

Clinical guidelines have been formulated to improve clinical practice, optimize patient healthcare quality and safety and minimize variations in clinical practice [27, 28]. However, it has been shown that clinicians’ acceptance and

Table 2 Comparison of guidelines and unified guideline for the management of multisystem inflammatory syndrome in children [1–10]

Variables	AAP	ACR	HDVCH	CHKD	IDSa	Unified
Similarities	IVIG (1–2 g/kg) Steroid therapy (methylprednisolone 2–30 mg/kg/d)	IVIG (1–2 g/kg) Steroid therapy (glucocorticoids low-moderate dose, and high dose of patients with life-threatening complications)	IVIG (1–2 g/kg) Steroid therapy (methylprednisolone 1–2 mg/kg/d administered as IV/PO, over 2–4 wk)	IVIG (1–2 g/kg) Steroid therapy 2 mg/kg	IVIG (1–2 g/kg) Steroid therapy (corticosteroids)	IVIG (1–2 g/kg) Steroid therapy (2–3 mg/kg/d)
	Antiplatelet therapy (aspirin low-dose)	Antiplatelet therapy (aspirin low dose, 3–5 mg/kg/d; max 81 mg/d, avoided in patients with a platelet count \leq 80,000/ μ L) Patients with a Z score \geq 10.0 treated with low dose aspirin and anticoagulation with enoxaparin or warfarin	Antiplatelet therapy (aspirin 3–5 mg/kg/d, max = 81 mg orally)	Antiplatelet therapy (aspirin low dose)	Antiplatelet therapy (aspirin)	Antiplatelet therapy (aspirin low-dose)
Differences	No antiviral	No antibiotics	No antiviral	No antiviral	Antiviral	Antiviral: remdesivir 5 mg/kg load IV once (max dose 200 mg) on day 1, then 2.5 mg/kg (100 mg max dose) IV daily for 9 d
	Anticoagulant therapy (enoxaparin in patients with thrombosis)	Anticoagulant therapy (enoxaparin in patients with thrombosis or an ejection fraction $<$ 35% should receive until at least 2 wk after discharge from the hospital)	Anticoagulant therapy: (1) enoxaparin, prophylaxis dosing, $<$ 2 mon: 0.75 mg/kg/dose q12 h, \geq 2 mon: 0.5 mg/kg/dose q12 h; (2) enoxaparin, therapeutic dosing, $<$ 2 mon: 1.5 mg/kg/dose q12 h, \geq 2 mon: 1 mg/kg/dose q12 h	No anticoagulant therapy	No anticoagulant therapy	Anticoagulant therapy (enoxaparin; prophylaxis/therapeutic)
						Antibiotic therapy: (1) mild illness: ceftriaxone. If gastrointestinal symptoms are predominant add metronidazole; (2) severe illness or shock: vancomycin, clindamycin, and cefepime or vancomycin, meropenem, and gentamicin

AAP American Academy of Pediatrics, ACR American College of Rheumatology, HDVCH Helen DeVos Children's Hospital Foundation, CHKD Children's Hospital of The King's Daughters, IDSa Infectious Diseases Society of America, IVIG intravenous immune globulin, PO oral

implementation of guidelines are affected by the complexity of translating evidence-based medicine into clinical practice and pharmaceutical sponsorship [27]. In particular, the manipulation of recently established clinical guidelines for critical cases is relatively new to the scope of evidence-based medicine, such as MIS-C. Although there are some differences in the recommendations and evidence levels among the management guidelines established for MIS-C, a comparison of the current management guidelines has, to our knowledge, not been reported.

To improve clinicians' acceptance, an ideal guideline that would be derived from a comprehensive literature review is required. Such a guideline would make recommendations not only for the pharmacological management of children that fulfil the criteria for MIS-C but also for assessment and a multi-disciplinary team approach to interventions to decide the level of care, as the disease manifestations can be critically different. Hence, this study, for the first time, has attempted to comprehensively compare and evaluate the content quality of the five most-followed MIS-C guidelines: applicability and strength of evidence. Then it makes unified guideline recommendations for pharmacotherapy, which may be useful to clinicians and pharmacists.

In contrast to the definition of MIS-C according to each guideline, which was analogous to a fair level of specificity among the compared guidelines, recommendations for treatment were varied. Whereas in some pharmacotherapy fields, recommendations were quite similar among guidelines (e.g., IVIG, steroid therapy, antiplatelet therapy and low-dose aspirin), others differed widely (recommendations on antiviral, antibiotic and anticoagulant therapy). Such variations in recommendations make clinicians' decisions difficult to implement in their daily practice.

The unified guideline evaluates the guidelines' noteworthy recommendations and attempt to establish a broad initial approach to bridge the gap. A unified guideline suggested by Saudi health professionals, with the best potential to maintain the clinical standard, may help clear the confusion stemming from the use of different guidelines around the world. This guideline aims to provide simple, clear protocols for everyone involved in the care of MIS-C patients. Variations in the international guidelines, even simple variations, can affect patient outcomes and increase the risk of deterioration for unknown reasons. Therefore, greater consistency in pharmacotherapeutic recommendations is crucial. This study emphasized the need for continuing oversight of country-specific practices and periodic formal evidence-based inclusion of the guidelines to ensure better care.

McArdle et al. confirmed that the WHO recommendations for perfect criteria for antibody testing by researching SARS-CoV-2 require specificity that can inhibit asymptomatic common infection [20]. The WHO findings reveal

that MIS-C typically entails various illnesses for diagnostic test development. Thus, clinicians should be cautious in making treatment decisions during the occurrence of an inflammatory disease caused by SARS-CoV-2 infection. The WHO recommends the use of propensity score weighting to decrease bias by not integrating additional treatments during the primary treatment.

In conclusion, MIS-C is a novel disease for which children with COVID-19 are at high risk. Although there have been an increasing number of case reports and case series, the association between COVID-19 and MIS-C remains unclear. Various guidelines are used for the treatment of MIS-C, such as AAP and IDSA; however, there are no unified guidelines for the treatment of MIS-C. This study compared and evaluated the five most-followed MIS-C guidelines. Based on the management strategies found in the AAP and IDSA guidelines, it is important to know the features of the disease in every patient to determine the appropriate treatment, manage the symptoms and decrease the mortality rate.

Author contributions AAS contributed to study conception, design, supervision, methodology, data curation, and formal analysis. ANM, KNZ, ARA, ARS, and ASH contributed to data collection, analysis, interpretation of results and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or profit sectors.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Ethical approval Not need.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. The authors have no conflict of interest to declare.

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