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Review

Kounis syndrome: A case report and literature review of pre-hospital treatment

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Abstract

Introduction
Kounis syndrome is an uncommon clinical presentation of acute coronary syndrome secondary to an allergic or hypersensitivity reaction, especially anaphylaxis. It results when inflammatory mediators are released following mast cell activation, some of these mediators cause coronary artery vasospasm and may initiate thrombus formation in susceptible individuals. Although Kounis syndrome is becoming more widely known, many clinicians are still unaware of its existence. We present a case report and a literature review of the pre-hospital treatment of Kounis syndrome by emergency medical services.

Methods
A literature search of the EMBASE, MEDLINE and PubMed electronic medical databases was conducted using the terms 'Kounis syndrome', 'allergic acute coronary syndrome' and 'allergic myocardial infarction'. The purpose of the literature search was to identify the pre-hospital treatment of Kounis syndrome by emergency medical services. We included case reports of Kounis syndrome that described the medical treatment provided by emergency medical services, published any time up to October, 2017.

Results
Anaphylaxis is the most commonly treated component of Kounis syndrome by emergency medical services (66% of reported cases). Both components of Kounis syndrome, anaphylaxis and acute coronary syndrome, were treated in 16% of reported cases. No specific treatment was provided for either component of Kounis syndrome in 16% of reported cases.

Conclusion
The pre-hospital treatment of Kounis syndrome by emergency medical services is infrequently reported in the literature. Kounis syndrome involves two distinct clinical conditions, both of which should be considered during treatment.

Keywords:
Kounis syndrome; allergic acute coronary syndrome; allergic myocardial infarction; pre-hospital; EMS

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Introduction

Kounis syndrome (KS) was first described in detail in 1991, however the first reported case of acute myocardial infarction (MI) secondary to an allergic reaction occurred in 1950 (1,2). Kounis syndrome is defined as the concurrent presentation of an allergic or hypersensitivity reaction (mostly, but not exclusively anaphylaxis) and acute coronary syndrome (ACS), which may range from unstable angina to ST-elevation MI, and occurs as a result of the inflammatory mediators released during mast cell activation (3). The main pathophysiologic mechanism proposed is coronary artery vasospasm (4).

There are three reported variants of KS. Type I occurs in subjects with normal or near-normal coronary arteries due to coronary artery vasospasm. Type II occurs in subjects with pre-existing atherosclerotic disease due to coronary artery vasospasm with or without plaque disruption and thrombosis. Type III includes subjects with drug-eluting stent thrombosis. The cardiac enzymes and troponins may be normal or indicate acute MI (3,4).

Although KS is currently under-recognised, as clinician awareness increases the number of cases reported in the literature is growing exponentially (3). Owing to its unpredictability, the opportunity to study KS predominantly comes from the reporting of individual cases. We present the case of a man, 69 years of age, who developed ACS following penicillin-induced anaphylaxis as well as a literature review of the pre-hospital treatment of Kounis syndrome by emergency medical services (EMS).

Case report

A male, 69 years of age, suffering for several days with fever and right-sided neck pain, was seen at his house by a locum general practitioner. The patient was prescribed oral penicillin for a tonsillar abscess, which the patient self-administered shortly after the doctor had departed. Approximately 5 minutes after ingestion the patient developed an erythematous and pruritic abdominal rash associated with nausea, vomiting and dyspnoea. An ambulance was called immediately. Ambulance Victoria (AV) operates a two-tiered emergency ambulance service; initially Advanced Life Support (ALS) paramedics responded as the sole resource. An intensive care paramedic was requested from the scene by ALS paramedics following an abnormal 6-lead electrocardiogram (ECG).

The patient's past medical history included type 2 diabetes, hypertension, dyslipidaemia and previous coronary artery bypass graft surgery. Notably, the patient had no known pre-existing allergies.

On examination, the patient was alert with a blood pressure of 120/85 mmHg and a heart rate of 124 beats/minute. The initial 6-lead ECG showed sinus tachycardia with ST segment elevation with Q waves in leads III and aVF as well as reciprocal ST segment depression in leads I and aVL, indicating acute inferior MI (Figure 1). Before treatment, a 12-lead ECG was attempted but not possible due to artefact caused by severe rigors as the patient was febrile with a temperature of 39.2°C. Pulse oximetry demonstrated an oxygen saturation (SpO2) of 84% on supplemental oxygen via nasal cannulae, applied by ALS paramedics. Chest auscultation revealed clear lung fields with no adventitious sounds. The patient didn't complain of chest pain at any point during ambulance attendance.

The patient was treated with aspirin 300 mg and ondansetron 4 mg orally by the ALS paramedics. A non-rebreather mask with oxygen flow at 10 L/min improved SpO2 to 99%. Adrenaline 300 mcg was administered intramuscularly, one further dose of intramuscular adrenaline 300 mcg was required 5 minutes after the first dose. The patient also received dexamethasone 8 mg intravenously. Normal saline 0.9% was attached to keep vein open with a total volume of 250 mL administered.

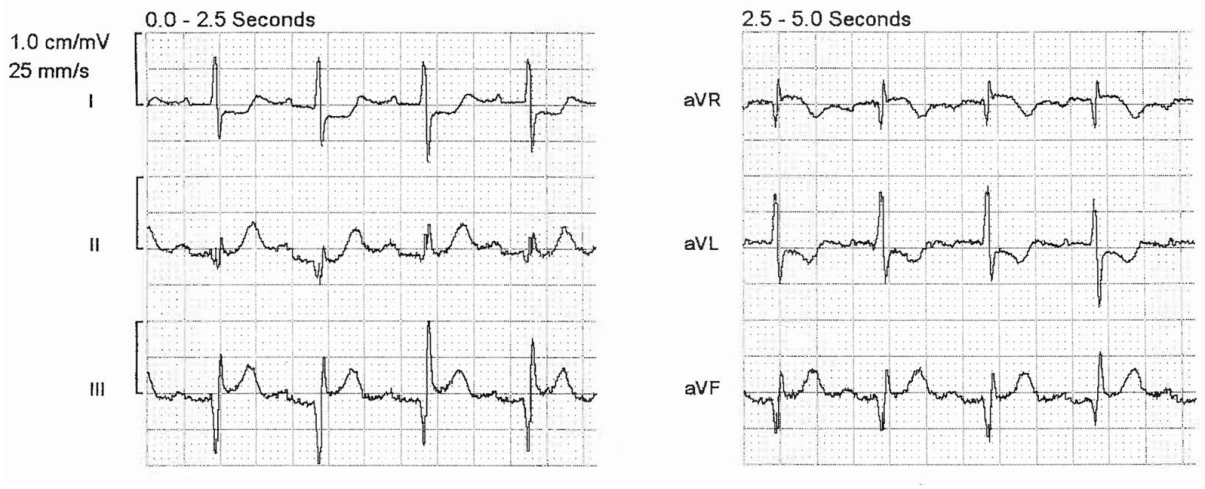

Figure 1. Initial 6-lead ECG showing ST segment elevation with Q waves in leads III and aVF, and ST segment depression in leads I and aVL

Following treatment a 12-lead ECG was performed before arrival at the emergency department (Figure 2).

The treatment resolved the patient's pruritus, nausea, vomiting and dyspnoea; only a small patch of erythema remained. In the emergency department (ED) subsequent ECGs showed resolution of the ST segment abnormalities. An echocardiogram wasn't performed in the ED. Bloods showed a troponin peak of 0.34 mcg/L (N<0.05) and evidence of sepsis with a peak CRP of 107 mg/L. The patient was treated with intravenous ceftriaxone and metronidazole and was discharged home on day four of admission following an uncomplicated hospital stay with no further evidence of acute ECG abnormalities. Angiography wasn't performed during the patient's hospital admission. An outpatient stress echocardiogram demonstrated no evidence of inducible ischaemia at moderate workload and the patient has remained asymptomatic from a cardiac point of view.

Methods of literature review

A literature search of the EMBASE, MEDLINE and PubMed electronic medical databases was conducted using the terms 'Kounis syndrome', 'allergic acute coronary syndrome' and 'allergic myocardial infarction'. The purpose of the literature search was to identify the pre-hospital treatment of Kounis syndrome by EMS. We included case reports of Kounis syndrome that described the medical treatment provided by EMS, published any time up to October, 2017. Articles not in the English language were excluded.

Globally, EMS are not all staffed in the same manner; some ambulances are staffed solely by paramedics whereas others are staffed with doctors alongside paramedics. In this literature review all reports were included, regardless of whether the treatment was provided by a doctor or a paramedic.

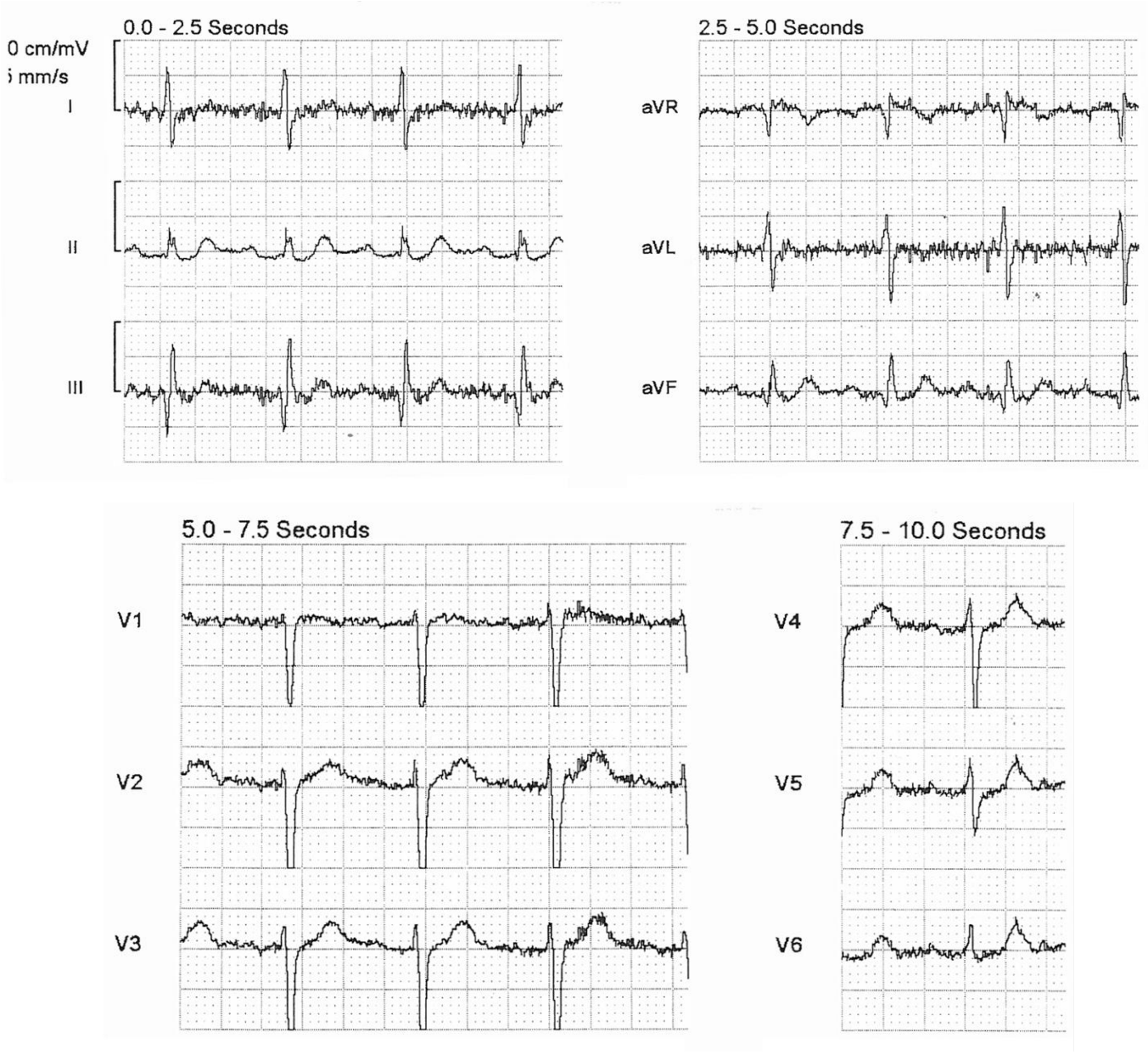

Figure 2. 12-lead ECG following treatment by paramedics

Where a report specifically stated treatment was provided by a doctor this was recorded, otherwise it was assumed that a paramedic provided treatment.

Results

The search identified a total of 3273 articles, after exclusion of duplicates and articles not in the English language, 12 articles met the inclusion criteria (Table 1). Of the 12 articles identified, three identified a doctor as the treating clinician.

Eight patients (66%) were treated for anaphylaxis, making it the most commonly treated component of KS by EMS. Three patients (25%) were treated for ACS. In two patients (16%), both components of KS were treated by EMS. One of these patients was treated by a doctor and the other patient was treated by a paramedic. Two patients (16%) received no specific treatment for either anaphylaxis or ACS.

Discussion

Anaphylaxis and ACS are two clinical presentations that EMS are familiar with, however they usually present separately.

When patients present with evidence of anaphylaxis as well as findings of acute myocardial ischaemia, KS should be suspected. Kounis syndrome causes coronary artery vasospasm and may occur in combination with plaque disruption in susceptible individuals with pre-existing atherosclerosis. The diagnosis of anaphylaxis is based on clinical signs and symptoms that emphasise multi-system involvement (17). The diagnosis of ACS is based on clinical signs and symptoms as well as electrocardiographic, laboratory, echocardiographic and angiographic findings (18).

The incidence of KS is unknown, largely because KS goes unrecognised and/or undiagnosed by clinicians and is infrequently reported in the literature. The only prospective study into the incidence of KS found that among patients admitted to the emergency department, the incidence of KS in all admissions and among allergy patients were 19.4 per 100,000 and 3.4%, respectively (19). Other non-prospective studies place the incidence of KS between 2% and 12.9% (20-22). In 2017, a review by Abdelghany et al reported the incidence of each KS variant in the literature: of all reported cases of KS, the type I variant is the most common accounting for 72.6% of cases, type II accounts for 22.3% of cases and type III accounts for 5.1% of cases (23).

Table 1. Pre-hospital treatment of Kounis syndrome

Author	Clinician	Treatment		
		Acute coronary syndrome	Anaphylaxis	Non-specific
Antonelli (5)	Paramedic	-	Hydrocortisone Promethazine	-
De Groot et al (6)	Paramedic	-	-	IV fluid (not specified)
Gosselin and Gross (7)	Paramedic	-	-	Dopamine
Ihdayhid and Rankin (8)	Paramedic	Glyceryl trinitrate Fentanyl	-	-
Licitra et al (9)	Paramedic	-	Adrenaline Hydrocortisone	IV fluid (not specified)
Memon et al (10)	Paramedic	Heparin	Diphenhydramine Methylprednisolone Salbutamol	IV fluid (not specified)
Mirijello et al (11)	Doctor	-	Chlorphenamine Hydrocortisone	Crystalloid solution
Nittner-Marszalska et al (12)	Doctor	-	Adrenaline Hydrocortisone Clemastine	Colloid solution
Regis et al (13)	Paramedic	-	Diphenhydramine Salbutamol	Normal saline
Rekik et al (14)	Doctor	Aspirin Clopidogrel	Diphenhydramine Methylprednisolone	-
Scherbak et al (15)	Paramedic	-	Adrenaline Methylprednisolone	-
Wada et al (16)	Paramedic	-	-	Normal saline

The patient described in this case report had several signs and symptoms that can be attributed to anaphylaxis. The World Allergy Organization provides a detailed list of signs and symptoms of anaphylaxis, including the sudden onset of urticaria, pruritus, erythema, oedema of the oral structures (eg. lips, tongue), dyspnoea, wheeze, stridor, cough, nausea, vomiting, abdominal pain, syncope and hypotension (17).

Signs and symptoms of myocardial ischaemia include various combinations of: chest, upper extremity, mandibular or epigastric discomfort, dyspnoea, fatigue, diaphoresis, nausea, vomiting, syncope and palpitations. Special patient groups including women, the elderly and diabetics may present with atypical symptoms (18). In this case, the patient's diabetic history may be a possible explanation for the absence of any chest pain.

The patient presented with several acute ECG abnormalities that corrected with treatment. The initial ECG (Figure 1) shows ST segment elevation and Q waves in leads III and aVF along with reciprocal ST segment depression in leads I and aVL indicating acute inferior MI. The post-treatment ECG (Figure 2), along with ECGs performed in the ED, show that the Q waves persist in lead III and completely resolve in lead aVF. The Q waves in lead III persist but reduce in depth across serial ECGs taken in the ED. The Q waves most likely represent a previous MI, however they may be transient and normalising or they may be a normal finding in this patient (18). The 12-lead ECG comprehensively examines the heart to identify ischaemic changes, it may be considered for all cases of anaphylaxis to help identify KS. The presence of cardiac biomarker changes (preferably cardiac troponin) indicates myocardial necrosis and is designated as MI (18). Presumably, the patient's ECG changes as well as the troponin rise were due to coronary artery vasospasm progressing to acute MI.

Fever is a common feature in acute MI; it can develop within 4–8 hours and usually resolves by the fourth to fifth day. The presence of fever is an independent predictor of adverse clinical outcomes and a larger infarct area in patients with STEMI. In this case, the timeframe from antibiotic ingestion to ambulance arrival indicates that the origin of the fever can be attributed solely to the tonsillar abscess (24).

Kounis syndrome can be caused by medications, insect bites and food. Antibiotics are among many known medications that cause KS, others include: nonsteroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, contrast media, glucocorticoids, anti-neoplastics, anaesthetics, analgesics, skin disinfectants, thrombolytics, anticoagulants and proton pump inhibitors (3). Antibiotics and insect bites are reported to be the most common causes of KS (23). Kounis syndrome secondary to penicillin has been reported previously, and was the cause of the first ever reported case of acute MI secondary to an allergic reaction in 1950 (2).

Mast cells are the main inflammatory cells implicated in the development of KS, along with their interactions with macrophages and T-cells (3). Mast cell activation is mediated by either immunologic or non-immunologic mechanisms in response to a range of stimuli (25). The activation of mast cells leads to both the release of pre-formed mediators as well as the release of de novo synthesised mediators, which comprise of a heterogeneous group of molecules with diverse but interlinked biological effects that act both locally and systemically (26). A number of these mediators are capable of inducing coronary artery vasospasm, the main pathophysiologic mechanism responsible for KS. Histamine, platelet-activating factor (PAF), thromboxane, serotonin, prostaglandin D2, and leukotriene C4 released during mast cell activation are all capable of inducing vasospasm in coronary arteries (27). Additionally, mast cells found in coronary arteries secrete the neural proteases chymase, cathepsin D and cathepsin G (28). Chymase, cathepsin D and cathepsin G are able to convert angiotensin I to angiotensin II, a potent vasoconstrictor (3,29). Along with vasospasm, patients with type II KS may experience atherosclerotic plaque disruption with resulting intraluminal thrombosis, which may be occlusive or non-occlusive (3,4,18). Several mediators released during mast cell activation can potentially cause plaque disruption and initiate thrombus formation, these include: histamine, PAF, tryptase, chymase, cathepsin D, cathepsin G, thromboxane and tumour necrosis factor-α (3). Finally, coronary artery vasospasm itself may cause plaque disruption in type II KS.

The majority of cases of ACS result from coronary artery thrombosis secondary to atherosclerotic plaque disruption following the rupture, ulceration, fissuring or erosion of the fibrous cap and may occur with or without coronary artery vasospasm (18,30). Although ACS is not usually associated with an acute allergic or hypersensitivity reaction, the role that inflammation plays in the long-term progression and ultimate disruption of atherosclerotic plaques in ACS is well established (30,31). Mast cells, macrophages and T-cells are found in advanced atherosclerotic plaques and many exhibit signs of activation long before plaque disruption and thrombosis (31,32). Activated mast cells, macrophages and T-cells produce mediators that may contribute to plaque disruption through a number of mechanisms (30). Many of the mediators found in patients with advanced atherosclerosis and ACS are the same as those released during an episode of KS. This pathophysiological parallel points toward a possible common pathway between KS and cases of ACS not associated with allergy or hypersensitivity (3,30). Despite the knowledge that mast cells and their mediators play a key role in the progression of atherosclerosis, this understanding has failed to translate into novel detection methods or therapeutic options to avert plaque disruption in patients with stable coronary artery disease (CAD) and other manifestations of atherosclerosis. It is known that serum tryptase level, a substance released during mast cell activation, is elevated in patients with stable CAD (33-35).

The levels of several other mast cell-derived molecules such as histamine, chymase, thromboxane, leukotrienes and interleukin-6 are all elevated in stable CAD and ACS (3). Anti-inflammatory medications that stabilise the mast cell membrane may play a future role in the management of atherosclerosis.

The treatment of KS is complex because of the need to manage two separate conditions and the medications normally given for one condition can adversely affect the other (3). In 2016, Fassio et al proposed the first treatment algorithm for KS. It contains two treatment arms: one for the allergic or hypersensitivity reaction and one for the ACS (36). Treating the allergic or hypersensitivity reaction may abolish symptoms in type I KS, but type II KS requires treatment directed at ACS as well (3).

Adrenaline administration for KS is recommended to resolve symptoms of anaphylaxis, but its use comes with several pros and cons. The administration of adrenaline in KS may provoke unwanted cardiovascular effects. Adrenaline in KS may worsen coronary artery vasospasm, exacerbate myocardial ischaemia or trigger arrhythmia. These adverse effects are more likely when adrenaline is administered intravenously and the intramuscular route is considered a safer alternative (17). The potential for adverse effects should be balanced against the beneficial actions of adrenaline. In doses used in anaphylaxis, adrenaline causes vasoconstriction by acting on alpha-1 adrenoceptors, which is particularly helpful in correcting hypotension. Adrenaline, through its action on beta-1 adrenoceptors, increases the inotropic and chronotropic properties of the heart. Adrenaline's action on beta-2 adrenoceptors includes bronchodilation as well as rapid stabilisation of mast cells (37). Mast cell stabilisation decreases mediator release and terminates the allergic or hypersensitivity reaction that underlies KS. The case described above illustrates the efficacy and beneficial effects of adrenaline administered intramuscularly in KS. In this patient, adrenaline administration resulted in almost complete resolution of the signs and symptoms of anaphylaxis, in combination with the rapid resolution of the ECG signs of transmural ischaemia.

Treatment of chest pain with morphine may be problematic in KS owing to its ability to induce mast cell degranulation. Fentanyl use may prove to be a sensible alternative in this respect (3). In the case presented here, pain was never reported.

Conclusion

The pre-hospital treatment of KS by EMS is infrequently reported in the literature. Kounis syndrome is an under-recognised and under-diagnosed presentation and should be suspected when symptoms of anaphylaxis and ACS occur concurrently. The treatment of KS is incomplete without acknowledging the presence of both pathological processes, although careful consideration should be given to each therapeutic option, as with any other treatment plan.

Conflict of interest

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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