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Advancing in the understanding of coagulopathy during hemorrhagic shock: From the triad to the deadly pentad

Avanzando en el entendimiento de la coagulopatía durante el choque hemorrágico: de la tríada a la pentada mortal

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Abstract

The deadly triad concept represented a dogma in the definition of poor outcomes and death associated with major bleeding in trauma. This model of end-stage disease was then rapidly transferred to other major bleeding scenarios. However, and notwithstanding the fact that it represented a severe scenario, the original triad fails to establish a sequence, which would be relevant when defining the objectives during the initial treatment of severe bleeding. Likewise, this model admits only one scenario where all the conditions shall co-exist, knowing that each one of them contributes with a different risk burden. Based on a structured review, we propose a pentad model that includes a natural pattern of events occurring with hypoxemia as the main trigger for the development of hypocalcemia, hyperglycemia, acidosis and hypothermia, as surrogates of multi-organ impairment. This severity model of major bleeding considers coagulopathy as a result of the failure to restore the initial components of damage.

Key words: Coagulation disorders; Hemorrhage; Acidosis; Hypothermia; Calcium; Hyperglycemia; Anesthesiology.

Resumen

El concepto de la tríada mortal significó un dogma en la definición de malos desenlaces y muerte asociados al sangrado mayor en trauma. Este modelo de afectación terminal fue luego rápidamente trasladado a otros escenarios de sangrado mayor. Sin embargo y a pesar de significar un escenario de gravedad, la tríada original falla en adjudicar una secuencialidad, lo cual sería importante a la hora de definir los objetivos durante el tratamiento inicial de la hemorragia grave. De igual forma, solo admite un único escenario en donde deben coexistir todas las condiciones, cuando se sabe que cada una atribuye una carga diferencial de riesgo. A partir de una revisión estructurada proponemos un modelo de pentada que incluye un patrón natural de eventos que se implantan sobre la hipoxemia como principal detonante para el desarrollo de hipocalcemia, hiperglucemia, acidosis e hipotermia como representantes del deterioro en múltiples sistemas. Este modelo de gravedad del sangrado mayor culmina con la coagulopatía como resultante de la falla en la resolución de los demás componentes previos.

Palabras clave: Trastornos de la coagulación; Hemorragia; Acidosis; Hipotermia; Calcio; Hiperglucemia; Anestesiología.

BASIC HEMOSTASIS FOCUSED ON THE CELL-BASED MODEL

Pro-hemostatic response requires physical-chemical, biological and mechano-electric processes in response to different stimuli associated with vascular lesion. Its primary objective is to ensure the efficient generation of fibrin-rich clots from optimal fibrinogen concentrations. (1) The cell-based coagulation model highlights the participation of the endothelium, platelets, and thrombin generation as essential elements of coagulation. (2,3) This interaction is not established as a sequence (4), but rather as basically overlapping phases that include an "initiation" characterized by the exposure of the subendothelial tissue factor (TF) and the generation of the first thrombin pulse (factor IIa [FIIa]) which shall stimulate the first platelets; a massive platelet and coagulation factors "amplification" which induces a favorable environment for a massive production of FIIa and the "propagation" of large amounts of FIIa on the platelet surface responsible for the cleavage of fibrinogen into fibrin for its subsequent polymerization.

The concept of mortal triad emerged as a description of terminal events associated with high risk of death in the context of trauma bleeding, which then expanded into non-trauma bleeding scenarios (gynecologic, digestive, perioperative, neurological). The original triad described coagulopathy, hypothermia and metabolic acidosis as predictive conditions of death. (5,6)

This new concept proposal is based on the currently accepted causes, pathophysiological components and potential targets of severe hemorrhagic shock, to conclude in a causal pattern of mortality during major bleeding, under the premise that this phenomenon is not exclusive of trauma. This particular scenario shall only be approached when absolutely necessary.

METHODS

This explanatory model was developed on a structured search of systematic reviews, clinical trials and observational studies reported in MEDLINE, Embase and Cochrane including the following terms: (((("Hemorrhage"[Mesh]) AND "Shock, Hemorrhagic" [Mesh]) AND "Shock, Hemorrhagic/mortality"[Mesh]) AND ("Shock, Hemorrhagic/diagnosis"[Mesh] OR). (((("Calcium/analysis"[Mesh]) AND "Acidosis/analysis"[Mesh]) AND "Hypothermia"[Mesh]) AND ("Hyperglycemia/analysis"[Mesh] OR "Hyperglycemia/blood"[Mesh])), until July 2021. Studies including adults with bleeding or critical hemorrhage were taken into consideration.

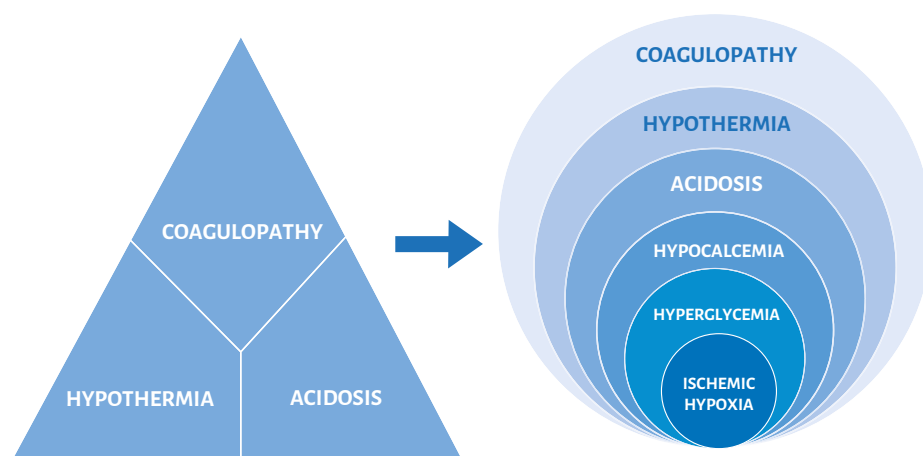
DEVELOPMENT OF PENTAD

In 2014, Quintana et al. suggested that hypoxia and hyperglycemia were independent factors that should be added to the deadly triad. (7) They suggested an inaccurate concept with potential for improvement due to the existence of underlying overlapping mechanisms, where coagulopathy may be considered as an epiphenomenon derived from broadly described modifiable factors. Some of

these remain inconspicuous or irrelevant in the current therapeutic context. Along this pathway, tissue hypoxia is the underlying cause of metabolic dysfunction (represented by hyperglycemia and hypokalemia as markers of severity). Tissue debt promotes endothelial dysfunction, metabolic acidosis, and hypothermia, resulting in refractory coagulopathy. Hence, the concept of severity is no longer a triad of "distant" components but rather a concentric process of pathophysiological dependency, where the extent of the hypoxic compromise shall define the severity of the other phenomena on which the end-stage hemostatic disorder is based (Figure 1).

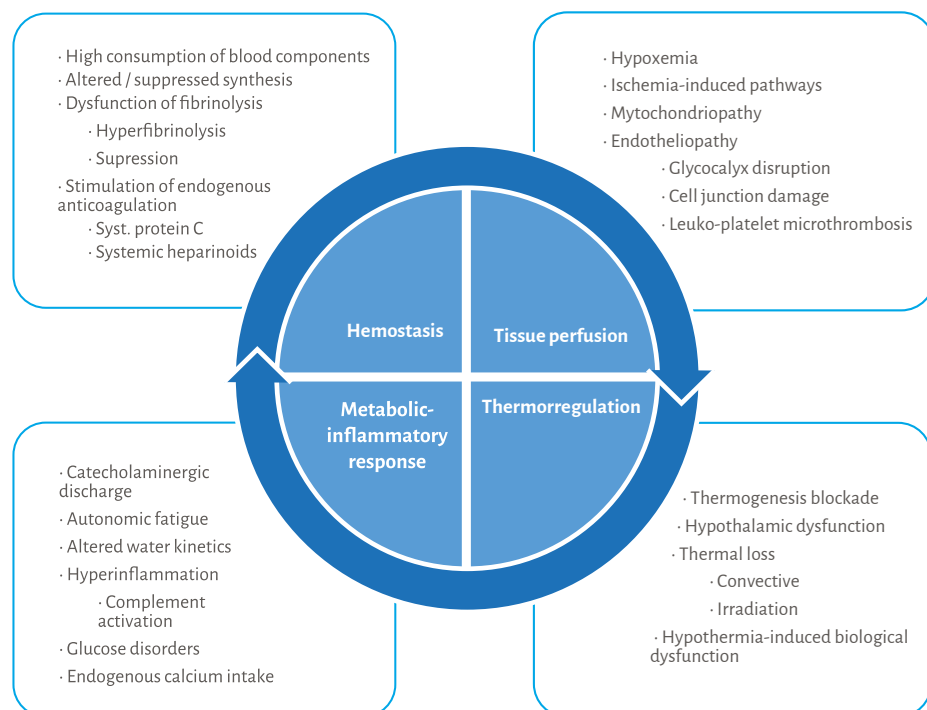
During massive exsanguination, the oxygen delivery to the tissues is insufficient to meet the demand. A forced transition to anaerobic metabolism (characterized by the generation of lactic acid, inorganic phosphates and oxygen radicals) occurs, leading to injury and/or cell death. Hypoxia and derivated tissue derangements triggered by the decrease of adenosine triphosphate (ATP), finally promote disruption of mitochondrial and cell membranes, apoptosis or necroptosis. (8) These events derived from hypoxia due to hypovolemia or reactive vasoconstriction led to progressive multiorgan failure. Lethal cases of brain and myocardial hypoperfusion could cause cerebral

Figure 1. Transition from the concept of triad to the coagulopathy-associated pentad.



Source: Authors.

Figure 2. Pathophysiological components of coagulopathy and interaction among hemostasis, tissue perfusion, metabolic/inflammatory response, and thermoregulation.



Source: Authors.

anoxia and fatal arrhythmias in a matter of minutes. (8) In addition to multiple organ failure, during hemorrhagic shock, induced endothelial activation and damage, is expressed as distributive shock. (8)

The massive release of catecholamines is a catalyst of endothelial cell injury and destruction of the glycocalyx (8) (Figure 2).

MICROCIRCULATORY DEFICIT, ACIDOSIS, AND COAGULOPATHY

Coagulation factors are pro-enzymes synthesized by liver and endothelium that become activated thanks to its specific affinity for other proteases. Such affinity results in pro-enzyme cleaving and generation of bi-enzymatic complexes that are able to further and even more efficient cleavage of other zymogens. The proteins involved in this prohemostatic activation are affected by pH. Deviations from the usual blood pH ranges may promote conformational and stoichiometric

changes of these protein complexes, which may negatively impact on homeostasis. (9) pH values < 7.3 are related to a negative impact on the production of FIIa and inhibition of the fibrinolysis modulators. A pH value 7.1 was associated with an increase in the fibrinogen degradation rate of up to 1.8 fold as compared to the controls. (10) This imbalance between consumption and production of fibrinogen during major bleeding, supports the supplementation of fibrinogen as a cornerstone of hemostatic resuscitation.

In a study published by Endo et al. (6), the predictors of mortality in trauma patients were assessed retrospectively. The authors concluded that fibrinogen degradation products ($\geq 90 \mu\text{g/mL}$), base deficit ($\leq -3 \text{ mmol/L}$) and temperature ($\leq 36^\circ\text{C}$) had the best predictive power for this event. However, the influence of these three variables on the primary outcome was not equally distributed. The predictive value of hyperfibrinolysis and acidosis as independent markers for mortality,

was approximately three and two-fold greater than central body temperature, respectively.

HYPERGLYCEMIA

Hyperglycemia has been defined as a predictor of worse prognosis, particularly in patients with traumatic brain injury (11). In a study published by Kassam et al. (12), blood glucose levels at admission worked as predictors of mortality, extended hospital and ICU stay in trauma affected patients. A blood glucose level of $\geq 200 \text{ mg/dL}$ was established as the cut-point for poor outcomes, based on in vitro data extrapolated to the clinical setting.

Hyperglycemia during tissue stress has been attributed to an increase in glucagon associated with massive secretion of catecholamines and insulin inhibition. (13) The mechanisms whereby hyperglycemia generates toxicity-associated tissue injury include the induction of oxygen-reactive species, oxidative stress, disruption of nitrogen species and downregulation of Bcl-2 (14), all of them associated with the promotion of apoptosis. (15) Hyperglycemia in trauma patients independently defines a greater risk of death. In the study published by Yendamuri et al., the increase of glucosa levels (mild > 135 mg/dL or moderate > 200 mg/dL), was associated with longer hospital stay and mortality. (16,17)

The retrospective study published by Alexiou et al. have found an association between hyperglycemia and worse prognosis in patients with traumatic brain injury. (18) These analyses, which included subjects recruited over four years, concluded that coagulopathy (identified in 23 % of the subjects) was significantly associated with low levels of hemoglobin, increased INR, and hyperglycemia levels at admission. Patients with more severe traumatic brain injury presented with significantly higher blood serum glucose levels than patients with minor injuries. A threshold value of 151 mg/dL was suggested to differentiate those patients who developed coagulopathy.

Hyperglycemia is associated with an increase of TF (19), which facilitates microvascular thrombosis. This late injury pattern is associated with platelet and leukocyte hyperreactivity that leads to the production of non-soluble macroaggregates, responsible for persistent tissue ischemia and organ failure. It is not unusual that coagulopathy and hypercoagulability coexist on the same individual with severe shock simulating disseminated intravascular coagulation. (16) Microthrombosis, ischemic lesions and focalized neurological damage have been described in subjects with hyperglycemia-associated coagulopathy. (20)

DYSREGULATED FIBRINOLYSIS

Impairment of normal fibrinolysis associated with trauma were described for the first time by Morgagni in 1769. These observations were later confirmed by John Hunter (1794), who associated them with hemorrhagic events and disruption of coagulation in violent death subjects. Biggs and MacFarlane described adrenaline release as an event associated with increased fibrinolysis.

A higher proportion of deaths related to severe trauma occurs over the first 24 hours. Uncontrolled massive bleeding and severe brain injuries are the most frequent causes. (21) Various phenotypes of fibrinolytic lesions have been described in these subjects. In an observational study of 180 patients, Moore et al. (22) showed dynamic mortality patterns in trauma, related to increased fibrinolysis, a finding subsequently confirmed in a larger multicenter trial including 2,540 patients. Different phenotypes of fibrinolysis were described, but the most frequent one was fibrinolysis “shutdown” in 46 % of the subjects, followed by physiological fibrinolysis in 36 % and hyperfibrinolysis in 18 %. From all, hyperfibrinolytic phenotype was mostly associated with mortality (34 %), followed by suppressed fibrinolysis (22 %). (23) These findings remained

unchanged after model adjustment by age, severity score, cause of death, and blood pressure. Traumatic brain injury was the most frequent cause of death, followed by hemorrhage and organ failure.

Identification of disturbed fibrinolytic phenotypes is important for the approach of trauma patients. Multiple clinical trials suggest the benefit of antifibrinolytic therapy. The CRASH-2 (24) trial reported a reduced mortality (14.5 % versus 16 % in controls) and a lower percentage of fatal bleeding episodes (4.9 % versus 5.7 %). Optimal benefit in survival from the use of tranexamic acid was obtained when it was administered early (first 3 hours after the event), despite the fact that the fibrinolytic activity of the subjects included was not studied. The MATTERS trial (25) reported similar results in military trauma patients. However, the benefit associated with antifibrinolytic therapy apparently is not applicable to all trauma patients, making it mandatory to understand the individual fibrinolytic response, both on early and later stages, in order to implementing measures intended to optimize extremely disruptive fibrinolytic events.

HYPocalcemia

Hemorrhagic shock and some of the interventions during its management, directly impact the availability of calcium needed for the activation and optimization of vital compensatory response. (26) Some of these are—but are not limited to—platelet reactivity, clotting factor activity, vascular function, and myocardial contractility. It has been suggested that hypocalcemia during hemorrhagic shock may result from altered intracellular flow secondary to ischemic and reperfusion events. (27,28) Major bleeding is also a significant cause of loss of plasma components, including calcium (27), contributing to the deterioration of homeostasis and the increase of sympathetic activity, which in turn is responsible for its massive use and

consumption. Hypocalcemia is a common characteristic in multiple types of shock and critical end-stage disease.

Ionized calcium derangement has been sufficiently described in critical patients as a very frequent metabolic disorder (incidence reported between 62-97.3 %). (29) Zhang et al. showed that early moderate to severe hypocalcemia was an event particularly related with severe disease and poor survival in critical patients, with a strong discriminative power (area under the curve [AUC]; receptor operating characteristic [ROC] 0.78) (30), while calcium supplementation have a protective effect against mortality. Multiple studies have shown an association among hypocalcemia, high mortality, and massive transfusion, even after controlling for some confounding factors. (31) A significant association has also been described between hypocalcemia and coagulopathy (odds ratio [OR] 2.9; 95 % CI [1.01-8.3]). A recent systematic review concluded that in trauma patients, hypocalcemia at admission ($iCa < 1.0$ mmol/L) was significantly associated with a high probability of overall and early mortality (26.4 % vs. 16.7 %). (32)

HYPOTHERMIA

The thermogenic compromise resulting from tissue ischemia, drug-induced immobility, and radiation losses during hemorrhagic shock, is associated with large amount of fluids, transfusions, and worse outcomes. (33,34) In a retrospective study of 38,000 patients, Wang et al. (35) found that hypothermia was independently associated with an increased probability of death (OR 3.03; 95 % CI [2.62 - 3.51]). Spontaneous hypothermia is an indicator of energy depletion and disruption of cellular homeostasis which is correlated with severe lesions. (36,37) A body core temperature <35 °C at admission was independently associated with increased mortality in two retrospective trials that

stratified their results by the severity of the lesion. (5,6) Consequently, hypothermia represents a powerful dual factor occurring as a consequence of ischemic cell damage and as a driver for the worsening of systemic damage resulting from hemorrhagic shock.

DIAGNOSIS AND MANAGEMENT OF COAGULOPATHY: A PENTAD CONCEPT-BASED APPROACH

Since coagulopathy is the result of a chain of events triggered by tissue ischemia during hemorrhagic shock, it is necessary to focus on reverting this primary triggering phenomenon. (8) The main goals shall be control of the source of bleeding and restoration of both amount and composition of the intravascular volume as soon as possible. (8,38-40). The assessment and adjustment of the minimum red cell mass to ensure the transport of nutrients and tissue extraction of organic waste is critical during the initial phases of the hemorrhagic shock.

Fluid replacement as a supplement to blood transfusion therapy must meet certain goals in terms of physical (hemodynamic parameters, infusion temperature, dilutional effects, etc.), and molecular aspects (reestablishment of electroneutrality, ionic contribution, osmolarity) aimed at achieving early a minimum vital organic perfusion able to progressively correct any metabolic imbalances. (8,41) Disproportionately high infused volumes of low pH fluid solutions worsens the acidosis resulting from hypoxia, further deteriorating the function of multiple systems, including hemostasis. This requires the fluid therapy to be based on dynamic goals such as the shock index, pulse pressure variability (or its byproducts) and ultrasound assessment to reduce the probability of over-resuscitation. If dynamic assessment of intravascular volume is not available, the recommendation is to consider a resuscitation fluids limited to ≤ 3 L during the first 6 hours of care (Table 1). (5,6,8)

Table 1. Diagnostic and management approach for the elements of the pentad and coagulopathy.

Element	Alteration	Treatment
Tissue oxygenation	<ul style="list-style-type: none"> - Hypoxemia - Elevated base deficit - Hyperlactatemia - Anemia 	<ul style="list-style-type: none"> · Avoid hypoxemia, with oxygen saturation goals $> 90\%$. · Lactate control and clearance over the first 24 hours. · Hemoglobin (RBC transfusion) in accordance with tissue perfusion indexes (SvO₂, DvaCO₂ or lactate).
Glucose metabolism	<ul style="list-style-type: none"> - Hyperglycemia 	Maintain blood sugar levels between 140-180 mg/dL
Calcium metabolism	<ul style="list-style-type: none"> - Hypocalcemia 	Maintain iCa > 1.15 mg/dL
Acid-base balance	<ul style="list-style-type: none"> - Metabolic acidosis - Elevated strong ion difference - Hyponatremia - Hyperkalemia - Elevated base deficit - Hyperlactatemia 	<ul style="list-style-type: none"> · Balanced saline-based resuscitation (Ringer's lactate, acetate, etc.). · Acid-base status control (base excess, lactate). · Reestablishment of volemia based on dynamic goals. · Early treatment of components affecting the acid-base balance.
Body temperature	<ul style="list-style-type: none"> - Hypothermia 	<ul style="list-style-type: none"> · Maintain active warming during the initial phases of resuscitation. · Try to maintain a core temperature $\geq 35.5 - 36.0$ °C.
Hemostasis	<ul style="list-style-type: none"> - Disturbed fibrinolysis - Hypofibrinogenemia - Altered thrombin generation - Platelet dysfunction - Thrombocytopenia 	<ul style="list-style-type: none"> · Early assessment of hemostasis (CCT-VET) - routine measurement of fibrinogen. · Early use of tranexamic acid (< 3 hours). · Early management with FFP if altered VET or need of $> 4-6$ U of PRBC (FFP:PRBC ratio of 1:1-2). · Limit repetitive FFP interventions using factor concentrates, cryoprecipitates, or plasma solvent/acellular detergent. · Assessment and fibrinogen replacement to achieve serum levels > 150 mg/dL. · CCT or VET dynamic assessment.

CCT: conventional coagulation test; DvaCO₂: Venous-to-arterial carbon dioxide difference; FFP: fresh frozen plasma; PRBC: packed red blood cells; RBC: Red blood cells; SvO₂: venous oxygen saturation; VET: viscoelastic tests.

Source: Authors.

The sequential assessment of the metabolic impact of hemorrhagic shock via monitoring of ionized calcium and blood glucose levels as an adjunct to the surveillance of other markers of tissue oxygen debt (base deficit, lactic acid, etc.) in regular practice, is critical for the stratification of systemic involvement and allows for the correction

of these two factors strongly associated with mortality. It is highly recommended to adjust ionized calcium levels ≤ 1.0 mmol/L and glucose ≥ 180 mg/dL as part of the comprehensive hemostatic resuscitation in these patients. When these measurements are not available, the recommendation is empirical calcium supplementation (20-

25 mg/kg as chloride and 40-50 mg/kg as gluconate) per every 4-6 units of any blood product. (31)

Active warming and assessment of core temperature over the course of all phases of major bleeding care, makes it mandatory to establish strong institutional policies for management of environments and active warming mechanisms. Ideally, the resuscitation and OR areas shall be pre-heated to provide room temperatures between 22-24°C. Active thermal protection systems (forced air or preheated gel/water mats per console) and fluid warming may be necessary to achieve temperatures $\geq 36^\circ\text{C}$ in most patients.

The proportion of plasma versus the rest of the blood products has been highly controversial. Most studies agree that a ratio of plasma:PRBC:platelets between 1:1-2:1 is associated with lower short-term mortality and early bleeding control. (42) However, during the past few years, the dogma on conventional use of plasma as a key strategy for the management of critical coagulopathy has changed towards other interventional measures such as the early use of antifibrinolytics, early fibrinogen replacement, factor concentrates (43) and acellular plasma in solvent/detergent. These strategies have been associated with lower therapeutic failures, decreased massive transfusion rates, and a smaller proportion of postoperative renal replacement therapy. Although these results are promising, further studies are needed to clarify about the appropriate use of these interventional therapies in patients with acute bleeding.

The management of hemostasis during critical bleeding is affected by the time to obtain specific information. Viscoelastic testing (thromboelastography: TEG®, rotational thromboelastometry: ROTEM®) contribute with more specific and rapid information than conventional laboratory tests, with time savings between 30 and 60 minutes. Viscoelastic testing may also be helpful to dynamically detect hemostatic disorders with early identification of coagulopathy patterns associated

with abnormal thrombin generation, altered fibrinogen kinetics and platelet dysfunction. (44) Overall, viscoelastic tests provide a rapid assessment of hemostasis for clinical decision-making and optimization of the use of blood products during hemostatic resuscitation. (45)

In conclusion, the proposed pentad model describes coagulopathy as an outcome that accounts for mortality within a sequence of events initiating with tissue hypoxia resulting from severe microcirculatory disruptions during critical bleeding. Hypocalcemia, hyperglycemia, acidosis and hypothermia are added to this sequence of events based on their dual role as surrogates and early drivers of systemic impairment.

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Statements

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Conflict of interests

All the authors declare that they have no conflict of interests to disclose.

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