How to deal with severe acute pancreatitis in the critically ill

Elisabeth De Waele[a,b], *Manu L.N.G. Malbrain*[a,c], *and Herbert D. Spapen*[a,c]

Purpose of review
To review recent literature on the management of patients with severe acute pancreatitis (SAP) admitted to an ICU.

Recent findings
SAP is a devastating disease associated with a high morbidity and mortality. Recent evidence advocates adequate risk assessment and severity prediction (including intra-abdominal pressure monitoring), tailored fluid administration favoring balanced crystalloids, withholding prophylactic antibiotic therapy, and early detection and treatment of extra-pancreatic and fungal infections. Urgent (within 24–48 h after diagnosis) endoscopic retrograde cholangiopancreatography is indicated when persistent biliary obstruction or cholangitis are present. Corticosteroid therapy (mainly dexamethasone) can reduce the need for surgical interventions, length of hospital stay, and mortality. Peritoneal lavage may significantly lower morbidity and mortality. Hemofiltration may offer substantial benefit but more studies are needed to prove its efficacy. Enteral feeding using a polymeric formula and provided early through a nasogastric tube is recommended but has no survival benefit compared with parenteral nutrition. Probiotics could be beneficial, however no clear recommendations can be made.

Summary
Management of SAP is multimodal with emphasis on monitoring, adequate fluid resuscitation, avoiding prophylactic use of antibiotics, cause-directed procedures or treatment, and organ support. There is a role for early enteral nutrition including probiotics.

Keywords
abdominal pressure, acute pancreatitis, fluid resuscitation, ICU, monitoring, nutrition

INTRODUCTION

Severe acute pancreatitis (SAP) is a common disease with many possible causes and complications. Mortality varies from 18 [1▪▪] to 82% in case of important necrosis [2]. In Europe, alcohol abuse remains the primary cause (43%), followed by biliary obstruction (33%) [1▪▪] which may affect more than half of nonalcohol consuming patients [2]. Infected pancreatic necrosis is associated with high mortality. Treatment of SAP necessitates a multimodal and multidisciplinary approach, involving gastroenterologists, abdominal surgeons, and intensivists [1▪▪]. This review will summarize recent advances.

PATHOPHYSIOLOGY

SAP arises from local enzymatic activation with subsequent inflammation escalating into an impetuous systemic inflammation which leads to tissue injury and organ failure [3]. Different mechanisms are involved in the occurrence of early or late organ failure during the course of SAP. Early organ failure (within 24–72 h) is mainly dominated by sterile systemic inflammation closely resembling severe sepsis and driven by the intestine (increased mucosal permeability with bacterial translocation) and adipose tissue (secretion of proinflammatory cytokines and mediators). Key determinants of this process are local and systemic hemodynamic disturbances, capillary leak with edema, coagulation disorders, and myocardial depression [4]. Late organ failure (beyond 2 weeks) is linked to septic and

[a]Department of Intensive Care Medicine, Universitair Ziekenhuis Brussel, Jette, [b]Clinical Nutrition Unit, Universitair Ziekenhuis Brussel and [c]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Brussels, Jette, Belgium

Correspondence to Elisabeth De Waele, MD, PhD, ICU Department, UZ Brussel, 101, Laarbeeklaan, 1090 Jette, Belgium. Tel: +32 2 477 51 78; fax: +32 2 477 52 53; e-mail: elisabeth.dewaele@uzbrussel.be

Curr Opin Crit Care 2019, 25:000–000
DOI:10.1097/MCC.0000000000000596

KEY POINTS

- Treatment of acute severe pancreatitis is supportive and based on fast resuscitation, including ample fluid administration with balanced crystalloids while avoiding fluid overload.
- Management of intra-abdominal pressure is mandatory.
- Specific forms of SAP require specific treatment (endoscopic retrograde cholangiopancreatography for biliary pancreatitis; fibrates, insulin/heparin and plasmapheresis for hypertriglyceridemia-induced pancreatitis).
- Prophylactic antibiotics are not advocated.
- Early enteral nutrition with standard polymeric formulas and probiotics are recommended.

infectious complications secondary to bacterial or fungal invasion of necrotic pancreatic tissue or peripancreatic fluid collections [5].

RISK ASSESSMENT SEVERITY PREDICTION

The list of risk assessment severity prediction tools is impressive. Recent findings suggest that the presence of underweight or overweight, development or persistence of organ failure, and assessment of biomarkers, such as cytokine levels might help to further improve identification of high-risk patients [6]. However, no single tool performs best and none has been proved to accurately distinguish moderately severe pancreatitis from SAP. Most tools poorly predict development of organ failure, infected necrosis, or outcome [7]. Red cell distribution, creatinine, and albumin serve as early indicators for mortality [8]. Patients with noninfectious extra-pancreatic complications, in particular those with acute renal failure requiring dialysis, have a significantly higher mortality rate [9].

THERAPY

Intravenous fluid administration

Intravascular hypovolemia and substantial second and third space fluid sequestration contribute to circulatory, particularly renal, failure but also compromise the pancreatic (micro)circulation which augments the risk to develop (peri)pancreatic necrosis [10]. Until today, large volume fluid resuscitation (i.e., $\geq$5000 ml within the first 24 h) is recommended [11,12]. However, too liberal fluid administration may be associated with risks that outweigh benefit [lung edema, intra-abdominal hypertension (IAH), and so on]. A recent international audit on fluid administration in patients with sepsis revealed that a higher cumulative fluid balance at day 3 but not in the first 24 h after ICU admission was independently associated with an increased mortality risk [13].

Little evidence sustains that goal-directed therapy, utilizing various parameters to 'target' fluid administration, or speed of volume resuscitation reduce morbidity or mortality [14▪]. Although there is controversy about the use of goal-directed therapy in sepsis in general, and SAP may not different [15].

The choice of fluid is primarily determined by recent data from studies in patients with sepsis and septic shock. Of notice is the shift from normal saline to 'balanced' crystalloids (Ringer's lactate or Plasmalyte) [16] and the abandoning of hydroxy ethyl starch solutions because of an increased risk of nephrotoxicity [17,18]. Ringer's lactate has been forwarded as the preferred resuscitation fluid because it may reduce pancreatic enzyme activity and acidosis. However, in patients with concomitant liver failure and impaired lactate clearance it may lead to increased lactate levels, especially at higher rates. Thereby lactate may lose its ability as a surrogate parameter for tissue hypoperfusion or oxygen delivery/oxygen consumption mismatch. As such other balanced solutions like PlasmLyte may be preferred. The recommended dose is 5–10 ml/kg/h. Up to 250–500 ml/h can be infused within the first 24 h, provided that the patient's volume status is timely and adequately evaluated [11].

Recently there is a paradigm shift in the way we look at fluids as drugs: Clinicians should be aware of the four phases of fluid therapy and the resuscitation, optimization, stabilization, evacuation concept. After the initial resuscitation some patients with SAP may need active deresuscitation to avoid the deleterious consequences of fluid overload on organ function (mainly kidneys) [19].

MONITORING

As previously stated goal-directed fluid resuscitation has been the preferred strategy for a long time. However, due to lack of evidence, clear-cut goals, and tools to guide resuscitation are often not given [20]. Assessment of filling status is important and diagnosis should not only be made based on clinical parameters (hypotension, mottled skin, increased capillary refill time) but also include biochemical (elevated hematocrit, protein, blood urea nitrogen, lactate), radiological using computed tomography or ultrasound (free abdominal fluid, bowel, and tissue edema, collections, abscess, hemorrhage, necrosis), hemodynamic (decreased mean arterial

pressure, increased central venous pressure or pulmonary capillary wedge pressure), advanced monitoring (decreased global end-diastolic volume, increased cardiac index, increased extravascular lung water, increased pulse pressure variation, stroke volume variation), and some new technologies (bio-electrical impedance analysis, electrical impedance tomography, total blood volume assessment with isotope techniques). The clinician should be aware that pressure-based preload parameters may be erroneously increased in patients with SAP and as such no longer reflect the true filling status. Therefore, volumetric preload parameters like global end-diastolic volume as trigger and extravascular lung water as safety parameter may be superior in patients with SAP [6,21,22].

Antibiotics

Pancreatic and extra-pancreatic infections frequently complicate SAP. Fluoroquinolones, carbapenems, metronidazole, and third-generation cephalosporins are antibiotics that sufficiently penetrate in areas of infected necrosis and thus are potentially useful to reduce the infection risk. Prophylactic antibiotic therapy, however, does not prevent infection in sterile necrosis [11] and failed to influence occurrence of (peri)pancreatic necrosis, single or multiple organ failure, hospital length of stay, and mortality [23]. Timing of antibiotic prophylaxis may be important. When only considering trials in which antibiotics were administered within 72 h after onset of symptoms or 48 h after admission, mortality rates and incidence of infected pancreatic necrosis were significantly lower in patients receiving antibiotics as compared with controls [24].

A third of the patients with SAP will develop extra-pancreatic infections, the commonest being bacteremia and pulmonary infections. Early detection and appropriate antibiotic treatment are imperative to ensure optimal recovery [25].

Fungal, predominantly Candida, infections are common in patients with infected pancreatic necrosis and pseudocysts. Protracted broad-spectrum antibiotic therapy and a prolonged ICU stay are associated with an increased fungal infection risk [26].

Endoscopic retrograde cholangiopancreatography

In general, treatment in SAP is mainly symptomatic rather than causative, with the only exception of endoscopic retrograde cholangiopancreatography (ERCP) in case of biliary pancreatitis [20]. Gallstones can get stuck in the ampulla of Vater. This impedes biliary drainage and causes increased intra-pancreatic duct pressure and enhanced activation of pancreatic digestive enzymes. ERCP-directed sphincterotomy with stone extraction resolves this detrimental injurious process. Urgent ERCP (within 24–48 h after diagnosis) is indicated in the presence of cholangitis or in case of persistent biliary obstruction without cholangitis [11,22,27,28]. Length of stay but not mortality are significantly lower after ERCP. Incidence of single or multiple organ failure, necrotizing pancreatitis, or infected (peri)pancreatic necrosis is not different between patients undergoing urgent ERCP versus conservative treatment [14▪].

Lowering triglyceride levels

Severe hypertriglyceridemia (HTG) is the third leading cause of SAP worldwide. Management of HTG-related SAP essentially relies on rapidly decreasing the high triglyceride levels. Fibrates remain the drug of choice for severe HTG (triglyceride levels >500 mg/dl) with niacin, statins, and omega three fatty acids as adjunctive treatment [29,30].

Apart from this pharmacological therapy, insulin/heparin and plasmapheresis have been proposed as potential therapeutic tools. Insulin lowers triglyceride levels by enhancing lipoprotein lipase activity and accelerating chylomicron breakdown. Heparin decreases triglyceride concentrations by facilitating release of lipoprotein lipase from endothelial cells. A combined insulin/heparin therapy lowers triglyceride levels by 50% within 1 day [31].

Plasmapheresis drastically removes triglycerides and chylomicrons from the circulation within hours after initiation. In addition, plasmapheresis downregulates the inflammatory cascade by eliminating proinflammatory cytokines and mediators [32].

A prospective study assessing plasmapheresis versus conservative treatment showed no difference in mortality, probably because initiating plasmapheresis was delayed. However, a large retrospective study found no mortality benefit in patients who received early (<36 h) plasmapheresis versus late plasmapheresis [33].

Pharmacological interventions

A meta-analysis of six randomized controlled and exclusively Chinese trials including 430 SAP patients showed that corticosteroid therapy (mainly dexamethasone) reduced the need for surgical interventions, length of hospital stay, and mortality [34]. A lot of debate has been going on since the publication of the 'Vitamin S' (Steroids) and Vitamin C trials for the Treatment of Severe Sepsis and Septic Shock [35]. The presence of critical illness-related corticosteroid insufficiency may indeed play a role

in patients with SAP, however, future trials of adequate size and duration should further explore the effects of steroids in SAP.

However, a recent Cochrane systematic review exploring adjuvant pharmacological therapy with antioxidants, aprotinin, atropine, calcitonin, cimetidine, EDTA, gabexate, glucagon, iniprol, lexipafant, nonsteroidal anti-inflammatory drugs, octreotide, oxyphenonium, probiotics, activated protein C, somatostatin, somatostatin and omeprazole, somatostatin and ulinastatin, thymosin, and ulinastatin concluded that none of those treatments offered any significant clinical or survival benefit [36]. Regional arterial infusion of protease inhibitors was also not efficacious in SAP [37].

Peritoneal lavage

Data are conflicting. A former meta-analysis comparing peritoneal lavage with conservative treatment in 469 patients with SAP showed no significant difference in risk of mortality and complications [38]. A more recent meta-analysis including 899 patients showed that peritoneal lavage significantly decreased morbidity and mortality [39]. Translumbar retroperitoneal endoscopy has also been described as a less invasive technique (compared with open abdomen approach) in infected pancreatic necrosis [40].

Extracorporeal techniques

Hemofiltration may beneficially influence the course of SAP by selective elimination of proinflammatory substances and more optimal control of fluid balance. Several small studies comparing continuous high-volume hemofiltration (HVHF) with conventional treatment in SAP patients demonstrated significant improvement of serum biological parameters, organ failure, and mortality [41,42]. Combined blood purification techniques (e.g., HVHF and hemoperfusion) [43] may provide an even more efficacious two-step approach but remain poorly studied. There may also be a role for cytosorb treatment (either as stand-alone or in combination with continuous renal replacement therapy) to attenuate the cytokine storm in the setting of SAP [44].

Nutritional interventions

Early enteral nutrition in patients with SAP is endorsed by the recent guidelines on clinical nutrition in ICU issued by the European Society for Clinical Nutrition and Metabolism [45▪]. Disease severity assessment must guide nutrition therapy. Within 24–48 h after ICU admission, enteral nutrition should be started at a low rate and increased to target infusion rate. This strategy will improve tolerance, minimizes the risk for ileus [46] and has proven benefit in acute pediatric pancreatitis [47].

Outcome of nutrition protocols vary among studies. Enteral nutrition does reduce infection but a recent meta-analysis [48] revealed no effect on mortality. Data on improved outcome by enteral nutrition are mostly derived from investigations that compare enteral with parenteral nutrition. Parenteral nutrition should be considered after 1 week from SAP onset [46] or, conform European ICU guidelines, earlier on an individual basis [45▪].

The American Society for Enteral and Parenteral Nutrition recommends the use of a naso/oro-enteric tube for accessing the gastrointestinal tract in SAP and a more distally placed infusion in case of intolerance to gastric feeding [46]. Sometimes, naso-jejunal rather than nasogastric tube positioning is preferred [2]. Ultrasound-guided placement of naso-jejunal tubes is a safe and quick procedure with success rates up to 93% [49]. Some authors allow a full caloric diet when bowel sounds are present [50].

The use of a standard polymeric formula is encouraged [46]. American guidelines recommend the administration of probiotics (Lactobacillus). Although a Dutch trial reported increased mortality, probiotics have been shown to reduce infection and hospital length of stay in a meta-analysis [46].

Correct implementation of a strict management protocol for SAP decreases mortality. A recent before-after study demonstrated a decrease in antibiotic use and an increased delivery of enteral nutrition [51].

Abdominal pressure monitoring and interventions

SAP is one of the main causes for IAH and abdominal compartment syndrome (ACS). Predisposing factors include the presence of capillary leak, massive fluid resuscitation, increased abdominal volume (pancreatic edema, hemorrhage, or necrosis) in combination with ileus [52▪]. Therefore, the Abdominal Compartment Society (www.wascs.org) advocates to perform serial intra-abdominal pressure (IAP) monitoring in patients with SAP [53].

Bladder pressure measurements are the gold standard and should be performed with the patient in the complete supine position at end-expiration with zero reference at the level where the mid-axillary line crosses the iliac crest. In case of IAH grade 2 and above (IAP > 15 mmHg) medical management strategies should be initiated to reduce IAP. These include optimization of abdominal wall compliance, evacuation of intraluminal contents, evacuation of free abdominal fluid, judicious fluid management and

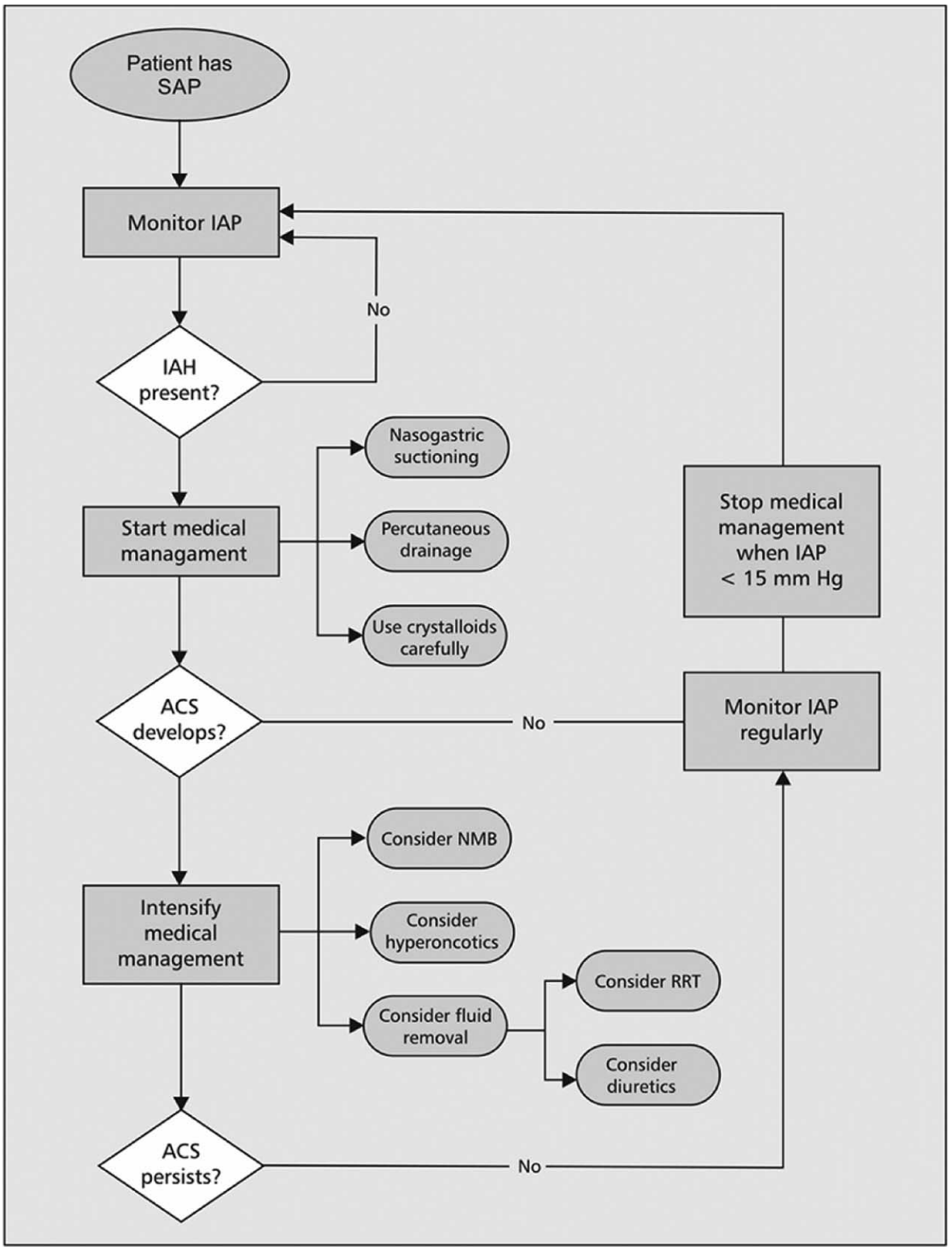

FIGURE 1. Medical management of intra-abdominal hypertension. Illustration of the approach of intra-abdominal hypertension by medical interventions. Reproduced with permission [21].

avoiding fluid overload, and optimization of end-organ perfusion (Fig. 1) [21]. The kidneys are considered the canary in the coalmine for IAH and usually the first organ failing when IAP gets above 15–20 mmHg. Surgical decompression should be avoided as long as possible in case of ACS (IAP > 20 mmHg with new onset failure) because of the risks of secondary infection and evolution to enterocutaneous fistulas and frozen abdomen [21].

CONCLUSION

SAP is characterized by fulminant inflammation causing local and remote tissue injury and finally organ failure. Mortality is declining but remains high. Large volume resuscitation has been traditionally advocated as initial treatment but should be outweighed to possible negative side-effects resulting from fluid overload. IAP monitoring (via the bladder) is mandatory. Advanced volumetric hemodynamic monitoring is preferred above traditional barometric preload indicators to guide fluid therapy. Prophylactic antibiotic treatment is discouraged but early detection and treatment of extra-pancreatic and fungal infections remains mandatory. Urgent ERCP should be performed in case of cholangitis or persistent biliary obstruction. Fibrates, insulin/heparin, and plasmapheresis are therapeutic tools in HTG-induced SAP. Steroids, hemofiltration, and peritoneal lavage are promising adjuvant treatments but need further investigation. Early enteral gastric feeding with standard polymeric formulas and probiotic use are recommended. The deleterious consequences of IAH on end-organ function should be avoided by medical management rather than surgical intreventions, as treatment is more symptomatic rather than causative.

Acknowledgements

Authors' contributions: E.D.W. and H.D.S. designed the article, M.L.N.G.M. participated in drafting the article. All authors have read and approved the final version.

Financial support and sponsorship

None.

Conflicts of interest

Dr Manu Malbrain is professor at the faculty of Medicine and Pharmacy at the Vrije Universiteit Brussels (VUB) and member of the Executive Committee of the Abdominal Compartment Society, formerly known as the World Society of Abdominal Compartment Syndrome (https://www.wsacs.org/). He is founding President of WSACS and current Treasurer. He is a member of the medical advisory Board of Pulsion Medical Systems (now fully integrated in Getinge, Solna, Sweden) and Serenno Medical (Tel Aviv, Israel), consults for Baxter, Maltron, ConvaTec, Acelity, Spiegelberg and Holtech Medical, and is co-founder of the International Fluid Academy (IFA). The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The content of the IFA website (http://www.fluidacademy.org) is based on the philosophy of FOAM (Free Open Access Medical education – #FOAMed). The site recently received the HONcode quality label for medical education (https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739). None of the remaining authors have any potential conflict of interest related to this article.

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