Enhanced recovery after surgery: Current status and future progress

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Keywords:
enhanced recovery after surgery; perioperative care; hospital length of stay

Abstract

Enhanced Recovery After Surgery (ERAS) pathways were first introduced almost a quarter of a century ago and represent a paradigm shift in perioperative care that reduced postoperative complications and hospital length of stay, improved postoperative quality of life, and reduced overall healthcare costs. Gradual recognition of the generalizability of the interventions and transferable improvements in postoperative outcomes, led them to become standard of care for several surgical procedures. In this article, we critically review the current status of ERAS pathways, address related controversies, and propose measures for future progress.

Introduction

It is now almost a quarter of a century since Henrik Kehlet and colleagues from Copenhagen, Denmark proposed a paradigm shift in perioperative care that reduced hospital length of stay (LOS) after laparoscopic colectomy [1]. Their original bundle of interventions, with further elements, has become known as fast-track or enhanced recovery after surgery (ERAS) pathways. Benefits associated with enhanced recovery pathways include reduced postoperative complications, reduced hospital LOS, and improved postoperative quality of life, as well as reduced overall healthcare costs [2,3]. Gradual recognition of the generalizability of the interventions and transferable improvements in postoperative outcomes, led them to become the standard of care for several surgical procedures [2,4,5]. There is also evidence of the potential benefits in high-risk patients, such as older adult patients, those with low functional reserve, or those undergoing emergency surgery [6,7].

In this article, we critically review the current status of ERAS pathways, address related controversies, and propose changes for future progress. Detailed discussions on several components (e.g., preoperative risk assessment and risk stratification, prehabilitation, carbohydrate loading, immunonutrition, optimal general anesthesia techniques, goal-directed hemodynamic management, procedure-specific pain management, patient-related outcomes, and outcomes such as failure to rescue, and days alive and out of hospital are presented separately in this issue of the journal.

Components of ERAS pathways and impact of compliance on outcomes

An ERAS pathway typically includes approximately 20 interventions (elements or components) divided into three distinct phases e the preoperative, intraoperative, and postoperative periods. The relative

contribution of individual interventions is not clear, but it is accepted that not all components are equally weighted with respect to their influence on postoperative recovery. Nevertheless, a positive link between increasing levels of compliance to ERAS elements and improved clinical outcomes and reduced hospital LOS has been well documented [8-12]. However, the current clinical application of the findings from these studies remains questionable because of rapidly changing evidence and practices. For example, initially recommended components lack definitive evidence and, thus, need to be revisited (e.g., avoidance of preoperative mechanical bowel preparation [MBP], preoperative com-plex carbohydrate, the use of epidural analgesia in minimally invasive procedures and the routine use of goal-directed fluid therapy [GDFT]), and some procedure-specific components are inappropriately applied to all surgical disciplines [5]. Other confounders include the "Hawthorne effect" (i.e., the tendency for research participants to modify their behavior because they know they are being observed) and some interventions (e.g., the preoperative optimization of comorbid conditions, avoidance of prolonged preoperative fasting and adequate hydration during the fasting period, maintenance of normothermia, intraoperative antibiotic prophylaxis, nausea and vomiting prophylaxis, and venous thromboembolism [VTE] prophylaxis) have become the standard of care and are being used in the control groups.

One of the core elements for the success of an ERAS program includes the use of a minimally invasive surgical approach, which is associated with improved short-term outcomes, including post-operative pain level and morbidity, as well as a reduced hospital LOS [13]. In addition, compliance with postoperative components is most strongly associated with improved recovery, although they are most difficult to achieve [14]. Of note, the lack of compliance with ERAS pathways may be due to inadequate knowledge, inability or wish to change, controversial recommendations, too many components, and the lack of clinical leadership [5].

Preoperative considerations

Preoperative optimization of comorbid conditions

Because preexisting comorbidity can influence postoperative outcomes and the quality of recovery, preoperative identification and the optimization of comorbid conditions has become a standard of care [15]. Also, risk stratification can be used to identify patients at high risk of developing postoperative complications, and implement specific preoperative interventions as well as modify perioperative care. In addition, the assessment and treatment of preoperative anemia [16,17], malnutrition [18,19], and frailty [20] have been shown to influence postoperative outcomes, particularly in the older adult patients. Preoperative nutritional support has been shown to improve postoperative outcomes and shorten hospital LOS [18,19]. Modern preoperative clinics constitute interdisciplinary collaborations, including preoperative anesthesia and surgical assessment and global optimization as well as patient engagement to achieve shared decision-making [21,22]. Shared decision-making tools may be used to aid patient decision-making [21,23] and improve patient-centered outcomes [24].

Venous thromboembolism prophylaxis

Postoperative VTE, which includes deep venous thrombosis and pulmonary embolism, is one of the common causes of morbidity and mortality. Therefore, VTE prophylaxis has been emphasized. The risks of VTE in the surgical population includes intrinsic patient factors, type, site and the duration of surgery, and postoperative immobilization. Several scoring systems that calculate individual risk of postoperative VTE (e.g., Caprini score [25]) have been validated in some surgical procedures. Several professional societies have published guidelines for the management of postoperative VTE [26,27]. However, the limitation of these guidelines is that they are developed based on evidence from outside ERAS pathways. Early mobilization within ERAS pathways

should reduce the risk of VTE. Furthermore, with shortened hospital LOS, VTE may occur in days to weeks after discharge home. Unfortunately, the type and duration of VTE prophylaxis within ERAS pathways is not well studied. Nevertheless, the most recent guidelines from the American Society of Hematology recommend VTE prophylaxis with either mechanical prophylaxis using intermittent compression devices (rather than graduated compression stockings) alone or in combination with pharmacological prophylaxis depending upon the patients' intrinsic risk of VTE, the type of surgical procedure, and the risk of perioperative bleeding [26]. Thus, mechanical prophylaxis alone would be used in patients with high bleeding risk, while a combination of mechanical and pharmacological prophylaxis is preferable in patients with high VTE risk [26]. Of note, the prophylactic placement of inferior vena cava filters is not recommended even in patients undergoing major surgery [26]. However, for patients undergoing a major surgical procedure, extended (i.e., more than 3 weeks after surgery) prophylaxis is recommended [26].

Prehabilitation

Prehabilitation, which includes cardiopulmonary conditioning and muscle strengthening, has been shown to influence postoperative recovery by improving functional status and reducing frailty [28]. A systematic review of 9 studies showed that nutritional prehabilitation on its own or when combined with an exercise program in patients undergoing colorectal surgery significantly shortened the length of hospital stay by two days, and accelerated the return to preoperative functional capacity [29]. However, optimal patient- and procedure-specific approaches are lacking. Furthermore, its practical application remains challenging because this may delay surgery by approximately 4-6 weeks. Future studies are necessary to define the role of prehabilitation, including indications and specific interventions.

Patient and family education and counselling

Patient and family education and counselling are arguably among the most important elements, despite the fact that they are not supported by strong evidence [5]. The importance of involving patients and their carers in the process of preparing for, undergoing and recovering from surgery cannot be underestimated [21]. Clear instructions on what the patient can expect and what is expected from them help engender a sense of responsibility and feeling of partnership among patients and carers. Details of the goals to be achieved during the perioperative period and factors which need to be met to achieve hospital discharge help improve clarity. A systematic review of 45 studies found than an improved understanding, and the expectation of patient recovery resulted in improved healthcare outcomes [30]. Increased cooperation on the part of the patient can only help accelerate the recovery process as there is some evidence that the provision of this counselling reduces patient anxiety, im-proves early postoperative mobilization [31], postoperative pain levels, and hospital LOS. This has been further reinforced by a recent Cochrane review [32], which supported the role of psychological preparation in optimizing patients' behavioral recovery, negative affect, and postoperative pain levels.

Avoidance of prolonged fasting

Prolonged preoperative fasting is frequently associated with electrolyte imbalance, hypoglycemia, and hypovolemia [33]. In addition, there is evidence that prolonged preoperative starvation results in a metabolic response, which leads to increased insulin resistance and an acute-phase response [33]. In a large cohort of children, prolonged preoperative fluid fasting was associated with an increased risk of postanesthetic hypotension [34]. Therefore, it is critical to avoid prolonged preoperative fasting and place emphasis on adequate hydration during the fasting period. Contemporary guidelines

produced by a range of Anesthesia Societies have recommended a fasting period of two hours for clear liquids and six hours for solid foods [35]. However, recent evidence suggests that patients should be allowed to drink water if they are thirsty in the preoperative period [36-38]. Despite guidance, there is evidence that these fasting times are often poorly adhered to [39,40].

Carbohydrate loading

The use of preoperative carbohydrate loading remains controversial [41-44], despite extensive basic scientific evidence that this intervention reduces postoperative insulin resistance, which results in hyperglycemia, poor glucose uptake, and resultant glycogen storage, which can lead to muscle degradation [45]. A Cochrane review of 27 randomized controlled trials (RCTs) of elective surgical procedures, including abdominal, orthopedic, cardiac, and thyroidectomy found that carbohydrate loading (defined as at least 45 g of carbohydrates) was associated with a small reduction in hospital LOS, although this was based upon low-quality evidence [42]. However, there was no difference in postoperative complication rates when compared with either water or fasting. A network meta- analysis of 43 RCTs undergoing elective surgical procedures compared preoperative low (10-44 g) or high (45 g or more) dose carbohydrate with water or placebo [41]. This analysis demonstrated no benefit from preoperative carbohydrate loading at either dose when compared with water or placebo in terms of hospital LOS or surgical complication rate, although carbohydrate loading was associated with a small but significant reduction in hospital LOS versus fasting alone. However, a recent RCT showed that there was no difference in postoperative infective complications between patients given preoperative carbohydrate drinks and controls although those who received carbohydrate drinks required lower doses of insulin to control postoperative blood glucose concentrations [46]. Thus, preoperative complex carbohydrate use adds to unnecessary costs.

However, the administration of simple cheaper sports drinks may improve patient satisfaction by reducing preoperative thirst and hunger. Nevertheless, evidence for the efficacy of the latter are currently lacking.

Bowel preparation

MBP reduces fecal bulk and bacterial colonization, thereby reducing surgical site infection (SSI) and anastomotic leak rates. However, concerns have been raised that by liquefying the feces, there is an increased risk of spillage and evidence suggests that bowel preparation does not result in a gross reduction in gut microbial flora counts. Several meta-analyses of RCTs and observational trials in elective colorectal surgery found that, compared with no preparation, MBP alone does not influence postoperative complications (e.g., anastomotic leak, SSI, intra-abdominal collection, mortality, reoperation, and hospital LOS) [47,48]. Another meta-analysis of 28 RCTs and 12 cohort studies found that oral antibiotic preparation (OAB), either in combination with MBP or alone, reduced postoperative complications in elective colorectal surgery [49]. The authors noted that the positive benefits from retrospective cohort and database studies were tempered when evidence from RCTs alone were considered [49]. Furthermore, there was a need to differentiate between the benefits of combined MBP and OAB, and OAB alone [49,50]. Overall, the ERAS guidelines currently recommend against the use of routine preoperative bowel preparation in colonic surgery [51]. However, MBP is recommended in patients undergoing an anterior resection with diverting stoma [52], albeit based upon very little evidence.

Shortening the duration of ileus

Frequently, ERAS recommendations include alvimopan, a peripheral opioid antagonist, as it has been reported to accelerate gastrointestinal recovery,

reduce postoperative ileus, and shorten hospital LOS [53-55]. However, significant bias exists in the studies showing benefits including variation in the types of abdominal surgical procedures (e.g., bowel resection, simple and radical hysterectomy, and radical cystectomy) as well as approach to the surgical procedure (i.e., open versus laparoscopic) [56]. More importantly, all the studies showing benefits used very high opioid doses in the perioperative period, and thus the role of alvimopan in modern practice, which involves an opioid-sparing approach remains controversial. In addition, as alvimopan is not readily available outside the United States, its use is limited.

Intraoperative interventions

Intraoperative interventions that are the standard of care include antibiotic prophylaxis [57], lung protective mechanical ventilation (i.e., tidal volumes 6-8 mL/kg, ideal body weight with positive end expiratory pressure 5-10 cm H_2O) [58], the maintenance of normothermia, and glycemic control.

Fast-track anesthetic technique

Although anesthesia-related mortality is extremely low (<1:100,000 anesthetic procedures), despite an increase in the patient comorbidity and surgical complexity [59], it is well recognized that anesthetic techniques can influence short-term and long-term morbidity, which may delay recovery. The use of regional anesthesia has been recommended as it is associated with reduced incidence of postoperative mortality, pulmonary complications, acute kidney injury, deep venous thrombosis, infections, and blood transfusion [60]. However, recommendations for regional anesthesia are based on low level of evidence. In addition, the general anesthetic technique used does not reflect current practice. Furthermore, perioperative care, including surgical techniques have evolved significantly over time.

Nevertheless, most major surgical procedures require the administration of general anesthesia. The residual effects of hypnotic sedatives, opioids, and muscle relaxants have been shown to in- fluence not only short-term but also long-term outcomes (30-day readmission rates and cognitive function). High intraoperative opioid and muscle relaxant doses have been shown to increase 30-day readmission rates. Similarly, deep anesthesia can have detrimental consequences in high-risk populations. Because the drugs used during general anesthesia have additive or synergistic effects, a minimum number of drug combinations should be used. Also, when possible, drugs should be short-acting and should be administered at the lowest possible doses. Thus, the routine use of midazolam as premedication is inappropriate because of high risk-benefit ratio. The superiority of choice of inhalation anesthesia versus totally intravenous anesthesia, even in high-risk populations, including patients with cancer, is unclear. Similarly, the role of opioid-free anesthesia remains controversial. In fact, there is a concern that the analgesic adjuncts (e.g., ketamine, dexmedetomidine, lidocaine, and magnesium infusions) used in opioid-free anesthesia technique may be detrimental to recovery.

Goal-directed hemodynamic management

In recent years, goal-directed hemodynamic management, which includes fluid and blood management has been emphasized [61,62]. The aim of goal-directed hemodynamic management is to maintain adequate perfusion pressure and oxygen delivery. This is achieved by optimizing intravascular volume and the rational use of vasoactive drugs such as vasopressors and inotropes [63]. Of note, this approach uses both static (e.g., mean arterial pressure) and dynamic (e.g., stroke volume variation and pulse pressure variation) hemodynamic variables. Although the target mean arterial pressure remains controversial, most accept a value of 65 mmHg.

Initially, GDFT was considered a critical component of ERAS for all surgical patients. However, recent evidence has demonstrated that GDFT does not confer any benefits in the setting of an ERAS pathway (versus traditional care) [64-66]. The implementation of ERAS pathways, which emphasizes good hydration during the fasting period, minimal invasive surgical approach, which reduces intraoperative blood loss, and the early resumption of oral intake, maintains perioperative intravascular volume. Thus, the routine use of GDFT is unnecessary and can lead to unintended consequences, and increased costs. Thus, the use of a "zero fluid balance" approach, which includes the administration of low intra- operative fluid (~3 ml/kg/h balanced crystalloid solution) and the replacement of blood loss with crystalloids in a 1:1 or 1:1.5 ratio, is adequate [67]. A large international, multicenter study in high-risk patients undergoing major abdominal surgery concluded that although restrictive fluid regimen did not influence postoperative disability-free survival, it was associated with higher incidence of acute kidney injury [68]. However, this study is limited due to its pragmatic design and associated variability in perioperative care, including variability in anesthetic techniques (e.g., hemodynamic management, the use of regional anesthesia, and opioid dose), surgical care, elective and emergency surgery, and postoperative nursing care and physical therapy [69]. Overall, the use of GDFT is appropriate in high-risk patients undergoing major invasive (open) surgical procedures. The areas that remain deficient include the implementation of optimal perioperative anemia and blood transfusion management.

Nausea and vomiting prophylaxis

It is well documented that postoperative nausea and vomiting (PONV) adversely impacts upon postoperative outcomes, including reduced ability of the patient to comply with the postoperative goals of an ERAS program such as early oral intake and ambulation [70]. However, PONV continues to be a major challenge most likely because guidelines based on risk prediction

models are poorly implemented. Strategies to prevent and treat PONV include pharmacological and nonpharmacological measures. For routine multimodal antiemetic prophylaxis patients should receive two to three anti-emetics from different classes either preoperatively or intraoperatively [71]. Patients at very high-risk(e.g., the history of motion sickness, history of previous PONV, and high opioid requirements after surgery) should receive three to four antiemetics. In addition, baseline risk may be reduced with theuse of total intravenous anesthesia and adequate hydration [72].

Preoperative PONV prophylaxis would include scopolamine transdermal patch (1-3 h prior to surgery) or aprepitant 40 mg orally (1-3 h prior to surgery), while intraoperative options include dexamethasone 8-10 mg IV at the induction of anesthesia, dopamine D_2 antagonist (droperidol 0.625-1.25 mg IV) at the end of surgery, and serotonin 5-HT_3 antagonist (ondansetron 4 mg IV or palonosetron 0.75 mg IV) at the end of surgery. In addition to antiemetic effects, dexamethasone hasanalgesic and anti-inflammatory effects that can facilitate recovery, and thus has been increasingly included in ERAS pathways. Of note, a single intravenous dose of dexamethasone (8-10 mg) does not seem to influence wound infection and healing [73-75].

Rescue PONV in the recovery room could include an antiemetic of a class not administered pre- operatively or intraoperatively or promethazine 6.25 mg IV. On the wards, ondansetron (4 mg IV or8 mg orally disintegrating tablet [ODT]), promethazine 6.25-12.5 mg IV, prochlorperazine 2.5-5 mg IV,or dimenhydrinate 25-50 mg IV could be administered. There is no benefit of repeating the same antiemetic administered intraoperatively. Post-discharge nausea and vomiting may be treated with ondansetron 8 mg ODT or over the counter antiemetics such as meclizine and dimenhydrinate. Of note,the cost-effectiveness of second generation antiemetics such as 5-HT_3 antagonists, NK1 antagonists, and dopamine antagonists (e.g., amisulpride) need further study.

Procedure-specific pain management

Patient- and procedure-specific pain management is a critical component of an ERAS pathway. The preoperative identification of patients at high risk of postoperative pain is important [76,77]. Opioid-sparing multimodal analgesia improves outcomes by reducing the risks of opioid-related adverse events such as nausea, ileus, respiratory depression, sedation, and delirium [78]. Also, the choice of an analgesic technique would depend upon the balance between the invasiveness of the analgesic technique and consequences of pain as well as adverse event profile of the intervention [79]. Importantly, the primary aim should be to facilitate ambulation, rather than achieve a certain pain score.

Unless there are contraindications, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 specific inhibitors should be administered preoperatively or intraoperatively, and continued into the postoperative period. In addition, a single intraoperative dose of dexamethasone 8e10 mg IV is recommended. Furthermore, regional/local anesthetic techniques should be used when possible. However, the role of neuraxial blocks in the ERAS setting is decreasing because of concerns of adverse events that might delay ambulation and availability of alternative analgesic techniques that can provide similar pain relief as well as similar recovery outcomes. Peripheral regional analgesic techniques such as interfascial plane blocks and surgical site infiltration techniques are recommended due to their high success rate and minimal adverse effects [80-82].

A recent meta-analysis concluded that intravenous lidocaine infusions reduce pain and opioid requirements as well as hasten gastrointestinal recovery [83]. Thus, intravenous lidocaine infusion is recommended in patients undergoing abdominal surgery with contraindications to commonly used analgesics (e.g., paracetamol and NSAIDs). However, the role of single dose of ketamine (25-100 mg) remains controversial because its

benefits over basic analgesics (i.e., paracetamol and NSAIDs) are un-clear, and there are concerns of adverse effects such as nightmares and sleep disturbances. Similarly, the role of gabapentinoids (i.e., gabapentin and pregabalin) is controversial due to limited benefits [84] and potential for adverse effects such as sedation, dizziness, visual disturbances, and orthostatic hypotension [85,86]. Nevertheless, when gabapentinoids are used (e.g., surgical procedures with a high propensity of persistent postoperative pain), they should be used with great caution and at the lowest possible dose. After discharge home, acetaminophen (paracetamol) and NSAIDs or cyclooxygenase-2 selective inhibitors should be used on a regular "round-the-clock" or "scheduled" basis. Opioids may be used as "rescue" analgesics on an "as needed" basis rather than on a scheduled basis. Patients should also be educated about nonpharmacological ways of alleviating postoperative pain, such as the application of ice, elevation of the operated extremity, music, and cognitive behavioral modalities.

Postoperative interventions

Early oral nutrition and avoidance of salt and water overload

Early postoperative oral nutrition is important for enhanced recovery, and it is safe and well tolerated with the exception in those patients with delayed gastric emptying [87]. It is also critical to avoid postoperative fluid overload. In addition, the choice of crystalloid (0.9% saline vs. balanced electrolyte solutions) also influence postoperative outcome. Salt and water overload of more than 2.5 L and excess 0.9% saline, resulting in a hyperchloremic metabolic acidosis, detrimentally impact post-operative outcomes [88-95].

Early mobilization

Early mobilization as an individual factor has not been extensively investigated; however, it has long been recognized to improve pulmonary function, improved gastrointestinal function, reduced VTE, and the loss of muscle mass and function. The inability to mobilize after elective surgery may be a reflection of poor postoperative pain control, PONV, orthostatic intolerance, postoperative morbidity, continuous dependence on intravenous fluids or a lack of patient motivation. This raises the issue whether the superior clinical outcomes associated with early mobilization may be due to the effects of the interventions.

Summary

ERAS pathways are increasingly being embraced as they allow the standardization of perioperative care and improves perioperative outcomes. A multidisciplinary approach (e.g., collaboration between anesthetists, surgeons, perioperative nurses in the hospital, and community nurses after discharge) is necessary to ensure high compliance rates and achieve maximum benefits [96]. Conflicting recommendations may be a major factor for the lack of implementation or patchy implementation of ERAS pathways. Although evidence for components of ERAS pathways continue to evolve, some are accepted as dogma without adequate evidence of their efficacy, and in some cases evidence suggests that they are not beneficial at all or even deleterious to outcomes. However, in a day-to-day practice level this is likely lost, and all components are regarded as compulsory, irrespective of the evidence for their use. Of note, ERAS by its very definition is complex pathway requiring multidisciplinary, multimodal interventions, and as such it would be difficult, if not impossible, to investigate each individual intervention, even with a cluster trial. This has led to the question of identification of the most important interventions necessary for improved outcomes and whether

"partial ERAS," where institutions could choose interventions that suit them and are easy to implement, when compared with the more complex interventions, is valid. However, small gains over a select number of clinical factors may result in a significant improvement in clinical outcome for the patient. This is described in the concept of "the aggregation of marginal gains," which suggests that even small (1%) improvements in performance in each of a multitude of different areas would add up to a marked overall improvement [97].

Although the ultimate goal is to minimize postoperative organ dysfunction and enhance recovery, it is necessary to address the early identification and management of complications in the hospital (i.e., failure to rescue) as well as after discharge from the hospital (i.e., days alive and out of hospital). Finally, measuring compliance with ERAS elements through an audit program is essential to evaluate success and in form the need for protocol modification. Although hospital LOS and readmission rates are commonly used to define success of an ERAS pathway, they do not reflect the true recovery of a patient, and thus, there needs to be emphasis on patient-reported outcome measures [98].

Practice Points

- ERAS principles are appropriate for all surgical patients.
- Interdisciplinary collaboration between healthcare professionals, including anesthetists, surgeons, hospital managers, and perioperative and community nurses, is needed for the successful implementation of ERAS.
- Several interventions have become standard of care e minimally invasive surgical approach and avoidance of drains, nasogastric tubes and urinary catheters, preoperative identification and the optimization of comorbid conditions, avoidance of prolonged preoperative fastingand adequate hydrat on dur ng the fasting period.

Research Agenda

- Guidelines are contradictory e standardization for guideline development is necessary.
- Identify which combinations of elements are most important to produce positive outcomes.
- ERAS programs should be evaluated in real-world practice.
- Impact of ERAS on patient-reported outcomes should be studied.
- Prevention and management of postoperative fatigue, delirium, and cognitive dysfunction.
- Pharmacological approaches to attenuate surgical inflammatory responses (e.g., high-dose steroid administration).

Funding

No external funding was received for this article.

Declaration of competing interest

KER has no conflicts of interest to declare. DNL has received unrestricted research funding from B. Braun and speaker's honoraria from Fresenius Kabi, B. Braun, Shire, and Baxter Healthcare for unrelated work. He is also the Chair of the Scientific Committee of the ERAS® Society. GPJ has received honoraria from Baxter Pharmaceuticals and Pacira Pharmaceuticals.

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