

Enhanced recovery pathways in colorectal surgery: a consensus paper by the Associazione Chirurghi Ospedalieri Italiani (ACOI) and the PeriOperative Italian Society (POIS)

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SUMMARY: Enhanced recovery pathways in colorectal surgery: a consensus paper by the Associazione Chirurghi Ospedalieri Italiani (ACOI) and the PeriOperative Italian Society (POIS).

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Enhanced Recovery After Surgery (ERAS) pathway is a multi-di-

disciplinary, patient-centered protocol relying on the implementation of the best evidence-based perioperative practice. In the field of colorectal surgery, the application of ERAS programs is associated with up to 50% reduction of morbidity rates and up to 2.5 days reduction of postoperative hospital stay.

However, widespread adoption of ERAS pathways is still yet to come, mainly because of the lack of proper information and communication. Purpose of this paper is to support the diffusion of ERAS pathways through a critical review of the existing evidence by members of the two national societies dealing with ERAS pathways in Italy, the PeriOperative Italian Society (POIS) and the Associazione Italiana Chirurghi Ospedalieri (ACOI), showing the results of a consensus development conference held at Matera, Italy, during the national ACOI Congress on June 10, 2019.

KEY WORDS: Colorectal surgery - ERAS.

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1. Introduction and definition of minimal multidisciplinary requirements of an ERAS core team

Enhanced Recovery After Surgery (ERAS) pathway is a multi-disciplinary, patient-centered protocol consisting of an implementation of peri-operative management; it is aimed at reducing trauma and surgical complications, at a better recovery of physiological functions and at an early hospital discharge. In the field of colorectal surgery, randomized clinical trials have documented how the application of ERAS programs is associated with a reduction of up to 52% in 30-day morbidity (95% CI 0.36-0.73) and hospital stay up to 2.5 days (95% CI 3.9-1.1) (1). For the success of the pathway, the ERAS team is a critical core and leading figures within each discipline are important for adherence to the program.

It is generally believed that the surgeon is at the core of the ERAS multidisciplinary team (MDT); however, it is extremely important to include in the team a case manager (usually a nurse) who will facilitate the adherence to protocols, ensure optimal ERAS implementation and management of resources.

A “facilitator” has also been proposed; he or she should be a non-clinical member of managerial or administrative staff of the hospital, with specific skills and abilities, and must be enthusiastic about the program. The facilitator must have responsibilities, clear roles and has to organize the pathway together with the MDT: feedback processes, scheduled meetings, and audit during the implementation of the program and over a period of time thereafter. Continuous staff education is essential for the successful implementation of an ERAS program. Furthermore, the leaders must be passionate about ERAS, respected in the department and be able to convince work colleagues and management.

Therefore, a strong leadership, a dedicated “case manager”, a “facilitator” as well as an effective ERAS MDT are the strengths for a successful implementation of the program. If the core team is composed of a “trinomial leader” (surgeon, anesthesiologist, nurse) other specialists are also essential: residents, operating room and stoma nurses, dietitian or nutritionist, physiotherapist, auxiliary nurse, and research data coordinators and statisticians. Moreover, the role and contributions of a clinical pharmacist in peri-procedural areas, also to ensure patients to receive optimal

nutrition support with specialized products as immunonutrition, has been recognized.

Finally, the patient is the active, central actor of the “core” ERAS team: his education in an ERAS pathway is an essential part of the care. Along with verbal instruction, the patient must be provided of written material, in the form of a booklet (care-plans of the preoperative, intraoperative and postoperative period). Both the family and the patient must read well the booklet.

Despite the aforementioned benefits, the ERAS protocol still has a scarce diffusion and, where it is adopted, it often suffers from a partial adherence, since some items are considered difficult to apply or too much in contrast with the traditional management of the surgical patient. In particular, if the highest adherence concerns the pre- and intra-operative items overall, the lowest is found in the post-operative items (2, 3), although there is evidence about the greater impact of the latter on postoperative recovery (4). This data was also confirmed by a recent literature review which documented the existence of at least 19 different types of perioperative management protocols (5).

The guidelines of the ERAS Society® for colorectal surgery have recently been updated; they now include 25 perioperative items. It is interesting to note that a complete concordance between high quality of evidence and strong degree of recommendation is found only 7 items, while in the remaining 18 the degree of recommendation is often supported by a medium to low level of evidence (6). It is reasonable to assume that these discrepancies could contribute to an unfavorable diffusion of ERAS protocol in clinical practice.

The purpose of this paper is to support the proper application of the items analyzed below - including the most debated or with lower adherence - through a critical review of the existing evidence by members of the two national societies dealing with the diffusion of ERAS pathways in Italy, the PeriOperative Italian Society (POIS) and the Associazione Italiana Chirurghi Ospedalieri (ACOI), showing the results of a consensus development conference held at Matera, Italy, during the national ACOI Congress on June 10, 2019. All the results concerning the level of evidence, the grade of recommendation and the consensus rate for every single item are summarized in Tables 1, 2 and 3.

TABLE 1 - PREOPERATIVE ITEMS; GOR: GRADE OF RECOMMENDATION.

KEY POINTS	Level of Evidence	GOR	Consensus
All surgical patients should ideally receive tailored preoperative counseling from a dedicated ERAS multidisciplinary team	2b	A	98%
Preoperative risk assessment is important, but due to lack of RCT the evidence about its accuracy remains low	3b	A	98%
In frail patients, a geriatrician should be ideally involved in the multidisciplinary team	2a	B	90%
Smoking cessation and preoperative breathing exercise programs are recommended for patients having major surgery	1a	A	98%
Alcohol cessation may help reducing postoperative complications	3a	A	98%
Prehabilitation allows earlier recovery if compared to rehabilitation	2c	B	100%
A personalized physical prehabilitation program in high risk patients can decrease postoperative medical morbidity rates	2c	B	98%
Preoperative nutritional screening should be performed in all patients undergoing major gastrointestinal surgery	1b	A	88%
Malnourished patients should be treated with 7-10 days of preoperative oral nutritional supplementation (or parenteral nutrition when indicated)	1b	A	100%
Perioperative immunonutrition is recommended in malnourished patients undergoing major gastrointestinal surgery for cancer	2b	A	93%
Correction of anemia should be done before surgery. Recent intravenous iron preparations have a low risk of adverse reactions and are more effective than oral iron in restoring hemoglobin concentrations in both iron deficiency anemia and chronic disease anemia. Blood transfusion has long-term effects and should be performed in strictly necessary cases	1a	A	98%
A multimodal approach to PONV prophylaxis should be considered in all patients treated with ERAS protocols	1a	A	98%
When possible, non-pharmacological approaches focused on education and counseling addressed during the preoperative assessment should be preferred to medication strategies for pre-anesthetic preparation	1a	A	98%
Use of chlorhexidine-alcohol-based preparations for skin disinfection to reduce surgical site infections	1a	A	98%
Mechanical bowel preparation should not be used routinely in elective colonic surgery; it can be used in elective rectal surgery instead, if the creation of a diverting stoma is planned, to avoid stools remaining in the diverted bowel tract	1a	A	95%
In patients undergoing colorectal surgery clear fluids including CHO up to 2 hours and a light meal up to 6 hours before elective procedure should be taken. Patients with delayed gastric emptying and emergency patients should remain fasted overnight or 6 h before surgery. No recommendation can be given for the use of CHO in obese and diabetic patients	1a	A	98%

2. Preoperative counseling

Within a multimodal Enhanced Recovery Pathway, preoperative counseling plays a fundamental role. Since it has been established that the number and

severity of complications are closely related to preoperative functional capacity and psychological well-being, there has been increasing interest in targeting these issues with a multimodal intervention program (7). The preoperative period may be a golden time to

TABLE 2 - INTRAOPERATIVE ITEMS; GOR: GRADE OF RECOMMENDATION.

KEY POINTS	Level of Evidence	GOR	Consensus
Use of short-acting anesthetics	1a	A	100%
Cerebral monitoring to improve recovery and reduce the risk for postoperative delirium	1b	A	95%
Monitoring of the level and complete reversal of neuromuscular block	1a	A	92%
Perioperative near-zero fluid balance	1a	A	100%
Goal-directed fluid therapy in high-risk and in case of large intravascular fluid loss	1a	A	100%
Patients' temperature should be monitored for all interventions lasting more than 30 minutes and a core temperature > 36.5°C must always be obtained by using warming blankets and/or fluid warmers	1a	A	100%
A multimodal intra-operative opiate-sparing and a post-operative opioid-free strategy should be applied in ERAS programs whenever possible	1a	A	98%
Multimodal analgesia in combination with spinal/epidural analgesia or TAP blocks when indicated should apply	2a	A	90%
In elective colorectal surgery, the minimally invasive surgical approach should be employed, if the expertise is available	1a	A	98%
In elective colorectal surgery, if laparoscopy can't be used, patient should be included anyway into ERAS pathway	1a	A	100%
Routine use of prophylactic drainage in colorectal surgery shows no benefit in reducing postoperative complications in intra-peritoneal anastomosis	1a	A	98%
The routine use of nasogastric decompression following elective colorectal surgeries may be safely eliminated	1a	A	98%
Consider nasogastric tube insertion in selected patients with postoperative ileus, refractory to conservative management, to relieve gastric symptoms	1a	A	95%
Use of mechanical thromboprophylaxis until discharge and pharmacological prophylaxis for 28 days after surgery	1a	A	100%

minimize the physiological and psychological impact of surgery on patients and to mitigate some of the emotional distress associated with the anticipation of surgery and the recovery process (8, 9). Data reported in a Cochrane analysis confirm that psychological preparation and detailed information may be beneficial for the outcomes but, at present, the strength of evidence is insufficient to reach firm conclusions on the role of psychological preparation for surgery (10). A recent systematic review of pre-operative information format reported that multimedia formats increased knowledge more than booklets, which in turn increased knowledge more than verbal formats. The timing of information did not affect pre-operative anxiety, postoperative pain or length of stay (11). In a recent paper several variables have been found related

to unexpected prolonged lengths of stay, and anxiety was found as an independent factor associated with delayed discharge in colorectal surgery (12). Patients with relatives or carers should meet with a multidisciplinary ERAS team comprising a nurse, an anesthesiologist and a surgeon, all whom have a key role in providing detailed and procedure-specific information before admission to the hospital (10, 13).

KEY POINTS

All surgical patients should ideally receive tailored pre-operative counseling from a dedicated ERAS multidisciplinary team

- **level of evidence: 2B**
- **recommendation grade: A**
- **consensus 98%**

TABLE 3 - POSTOPERATIVE ITEMS; GOR: GRADE OF RECOMMENDATION.

KEY POINTS	Level of Evidence	GOR	Consensus
Perioperative fluid and electrolyte administration should aim to a net “near-zero” balance. For replacement of losses, saline 0.9% and saline-based solutions should be avoided, with balanced solutions being preferred. In patients receiving epidural analgesia, arterial hypotension should be treated with vasopressors after ensuring the patient is normovolemic	2a	A	98%
Elective colorectal surgery suggests urinary catheter removal in pod 1 for intraperitoneal resections and between pod 2 and 6 for medium and low rectum surgery based on urinary retention risk factors (male sex and epidural analgesia)	1a	A	98%
A multimodal prevention of post-operative ileus should be considered in all patients treated with ERAS protocol. This multimodal approach includes limited opioid administration, use minimally invasive surgery, not routine placement of nasogastric tubes and goal-directed fluid therapy	1a	A	100%
Hyperglycemia is a risk factor for complications and should be avoided and minimized using the stress-reducing elements of ERAS protocol including oral preoperative carbohydrate treatment, laparoscopic surgery and thoracic epidural analgesia	2b	A	97%
Early mobilization is recommended (postoperative days 0-3)	1b	A	100%
Early oral feeding is safe and beneficial in enhancing recovery. Most patients should be offered a regular diet within the first 24h of elective colorectal surgery according to their tolerance	1b	A	100%
In addition to a regular diet, high-protein oral nutritional supplements (ONS) are useful to reach adequate intake of protein and energy in the early postoperative course	2b	A	100%
Perioperative immunonutrition (administration of specific formula enriched with arginine, omega-3 fatty acids, ribonucleotides) is beneficial in reducing infectious complications	1b	A	97%
Immunonutrition should be considered in malnourished patients undergoing colorectal cancer surgery	2b	A	100%

3. Preoperative optimization of comorbidities

3.1 Risk assessment

Patients undergoing abdominal surgery show high postoperative mortality rates, ranging between 0.4% and 4%. This is especially true for high-risk/elderly patients. A specific preoperative assessment could be useful to identify these patients and stratify them to individualize a tailored perioperative care reducing perioperative morbidity and mortality (14). Different kinds of preoperative risk assessment scores have been proposed, but their use is limited due to the low level of evidence (15, 16). A recent paper analyzes the impact of ACS calculator on patients and consequently their

motivations to help the physician to decrease their own personal risk of postoperative morbidity. Nearly 90% of patients would like to review their ACS calculator score before surgical consent. After reviewing their risks, 70% wanted to take part in a prehabilitation program to decrease perioperative risk and 71% decreased anxiety. High-risk patients underestimated three times more than low-risk ones any complication and length of stay (17, 18).

KEY POINTS

Preoperative risk assessment is important, but due to lack of RCT the evidence about its accuracy remains low.

- **level of evidence: 3B**

- **recommendation grade: A**
- **consensus 98%**

3.2 Pre-operative frailty assessment

Frailty can be defined as a state of increased vulnerability resulting from age-associated decline in physiological reserves, a lack of physiological reserve seen across multiple organ systems; it results in an independent predictor of mortality, morbidity and institutionalization after surgery (19). Several studies have shown a strong association between frailty and adverse perioperative outcomes (20-22). According to EURECCA recommendation on rectal cancer, frailty and not chronological age should be used in preoperative risk stratification (23).

A recent systematic review and meta-analysis on 16 RCT with 444,885 patients from multiple surgical specialties demonstrated that the mFI strongly correlates with the risk of post-surgical morbidity and mortality after any kind of surgery (24). If frail, a geriatrician should be ideally involved in the multidisciplinary team. Mandatory frailty screenings are G8, mini-Cog, Timed Up and Go and history of falls.

- **level of evidence: 2A**
- **recommendation grade: B**
- **consensus 90%**

3.3 Smoking cessation

Smoking and respiratory diseases are associated with an increased risk of developing intra and post-operative pulmonary complications. These morbidities are common after major abdominal surgery and can increase mortality rates, hospital stay and costs (25). Several studies demonstrated that preoperative smoking cessation reduces such complications, with no agreement on duration at which the benefits become significant (26). The optimal preoperative intervention intensity remains unknown, but programs starting four to eight weeks before surgery appear mandatory to cut down respiratory and wound-healing complications (27, 28). The perioperative period may be a “golden moment” for smoking cessation, and all the physicians are well-positioned to get patients to quit smoking. Counseling, telephone quit lines and nicotine replacement therapy are effective and safe alternatives that require minimal effort from physicians (25, 29). A recent study has underlined interventions specifical-

ly aimed at improving respiratory functions: incentive spirometer, deep breathing exercises, physiotherapy and inspiratory muscle training (26). A recent review of 12 trials found evidence that preoperative inspiratory muscle training was associated with a reduction of postoperative atelectasis, pneumonia and duration of the hospital stay in patients undergoing cardiac and major abdominal surgery (30). Breathing exercises and preoperative physiotherapy session educates patients on the reason and necessity to do breathing exercises immediately after surgery and halves the incidence of postoperative respiratory complications (31).

KEY POINTS

Smoking cessation and preoperative breathing exercise programs are recommended for patients having major surgery, especially in those where pre-operative assessment has shown low levels of cardiorespiratory reserve

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

3.4 Avoiding Alcohol Abuse

Intensive drinking is associated with increased risk of postoperative complications such as infections, cardiopulmonary complications and bleeding episodes, but reducing consumption of alcohol can normalize these organ systems to some degree and may contribute to reduce the rate of complications after surgery (32).

Several no randomized studies have suggested an association between alcohol abuse and post-operative non-surgical site infections, morbidity and mortality. A systematic review and meta-analysis of 13 observational studies and 5 RCTs showed that consumption of more than two units (equal to a total of 50 ml spirits 40%, 150 ml wine 13%, and 500 ml 4% beer) per day increases the rate of postoperative infections, but not mortality. At least 4 weeks of alcohol abstinence is recommended (33).

Alcohol cessation interventions offered from four to eight weeks to participants may reduce the number of postoperative complications. Moreover, intensive preoperative alcohol cessation interventions, including pharmacological strategies for prophylaxis of relapse and withdrawal symptoms, may reduce postoperative complication rates significantly (34).

KEY POINTS

Several meta-analyses show the negative impact of alcohol abuse on postoperative outcomes and demonstrate that alcohol cessation may help reducing postoperative complications.

- **level of evidence: 3A**
- **recommendation grade: A**
- **consensus 98%**

4. Prehabilitation

Poor physical performance has been associated with an increase in postoperative morbidity and mortality rates (35-37). The concept of prehabilitation is analogous to marathon training: it is based on the principle that structured and sustained exercise over a period of weeks leads to improved cardiovascular, respiratory, and muscular conditioning (38). Prehabilitation is defined (39) as “A process in the continuum of care that occurs between the time of diagnosis and the beginning of acute treatment (surgery, chemotherapy, radiotherapy) and includes physical, nutritional and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments”.

For this reason early recovery protocols recently have focused their attention on preoperative physical training programs in order to deliver a physiologic stress that causes an adaptive response in all organs and tissue, thus improving the ability to withstand the incoming stress of surgery. In the last ERAS Society guidelines (6) the prehabilitation item received low recommendation due to great heterogeneity of studies.

In a randomized controlled trial (RCT) (40) the authors compared physical, nutritional and psychological prehabilitation to rehabilitation, measuring functional capacity by administering the 6-minute walking test (6MWT) upon recruitment and 4 and 8 weeks after surgery. The results showed that the prehabilitation group returned to baseline functional capacity earlier than the control group. In another RCT (41) physical prehabilitation by vigorous activity was compared to a regimen of walking and breathing exercises. The breathing-walking group had a faster recovery and a better outcome in the 6MWT. Even in a high-risk population (ASA III-IV and age>70y) a personalized physical pre-

habilitation program (42) can lead to a significant decrease in medical morbidity rates (31 vs. 62%).

However, prehabilitation programs are far away from being standardized, as well as from clear selection criteria. Current evidence, to date, demonstrates that, at worst, prehabilitation does no harm, and it can be a transformative clinical pathway to facilitate a better life for some patients. Further clinical research and population-based studies are awaited on this promising topic.

KEY POINTS

Prehabilitation allows earlier recovery if compared to rehabilitation

- **level of evidence: 2C**
- **recommendation grade: B**
- **consensus 100%**

A personalized physical prehabilitation program in high risk patients can decrease postoperative medical morbidity rates

- **level of evidence: 2C**
- **recommendation grade: B**
- **consensus 98%**

5. Preoperative nutritional care

Malnutrition may be present in 15 to 60% of hospitalized patients, and increases up to 70% in cancer patients. It has been classically characterized by weight loss (defined as unintentional weight loss of 5-10% or more), BMI<18.5 and loss of muscle mass, associated with decreased serum levels of albumin and pre-albumin. Malnutrition has been considered as the result of decreased oral food intake, increased catabolism, and systemic low-grade inflammation syndrome induced by malignancy and surgery. In patients with gastrointestinal cancer undergoing major abdominal surgery malnutrition has been significantly associated with increased overall and infective postoperative morbidity, increased mortality, increased length of hospital stay, as well as poorer oncologic outcomes and enhanced healthcare costs (43-47).

5.1 Preoperative nutritional screening and assessment

Preoperative nutritional assessment seems to be crucial to detect malnourished patients in need of nutritional interventions and to improve nutritional sta-

tus correcting specific deficits (48). There is no univocal consensus on how to accurately assess preoperative nutritional status (49). Moreover, the variable definition of malnutrition reported in literature may lead to inaccurate assessment and comparison of the nutritional screening tools. Although weight loss and BMI are easy-to-measure parameters that can be used at the time of diagnosis and admission, they don't provide reliable and complete information on the nutritional status of the patients. Several nutritional screening scores have been developed and validated to determine malnutrition and the risk of postoperative complications. To be efficient, screening should be brief, inexpensive, highly sensitive and have good specificity. Frequently used nutrition screening tools are the Nutritional Risk Screening (NRS) 2002 (50), the Malnutrition Universal Screening Tool (MUST) (51) and the Mini Nutritional Assessment-Short Form (MNA-SF) (52).

ESPEN (47) recently defined diagnostic criteria for malnutrition according to two options: 1) BMI <18.5 kg/m²; 2) combined: weight loss >10% or >5% over 3 months and reduced BMI or a low fat free mass index (FFMI). Reduced BMI is <20 or <22 kg/m² in patients younger and older than 70 years, respectively. Low FFMI is <15 and <17 kg/m² in females and males, respectively.

5.2 Preoperative nutrition support

Literature data indicate that malnutrition is a modifiable risk factor for surgery. In fact, randomized controlled trials showed that preoperative nutritional treatment improves clinical outcomes in malnourished patients (53, 54) and in patients at high risk of malnutrition (55) undergoing major gastrointestinal surgery, with higher benefits in patients with higher nutritional risk (56). For malnourished patients, oral nutritional supplementation (or additional parenteral nutrition when indicated) has the best effect if started 7-10 days preoperatively and is associated with a reduction in the prevalence of overall and infectious complications and anastomotic leaks (48). According to ESPEN guidelines (47), patients with severe nutritional risk should receive nutritional therapy prior to major surgery, even if operations including those for cancer have to be delayed. A period of 7 to 14 days may be appropriate, preferring the oral route whenever possible. No statement can be made concerning preoperative nutritional support in non-malnourished patients.

5.3 Immunonutrition

In recent years, the immune-enhancing nutrition (so far defined "immunonutrition") has been proposed to reduce postoperative complications and mortality in gastrointestinal cancer patients, even in patients without clear malnutrition. Immunonutrition, first described in 1992 (57), consists in preoperative oral nutritional formulas enriched by the addition of amino acids (glutamine and/or arginine), polyunsaturated fatty acids (omega-3 fatty acids), and a mix of nucleotides or RNA, which may increase immune responses by modulating inflammatory responses or enhancing protein synthesis.

Several meta-analyses of more than 80 randomized controlled studies have shown that patients undergoing major surgery may have reduced complication rates and reduced length of postoperative stay when given an immune-enhancing feed rather than a standard isocaloric, isonitrogenous feed (58): the first one identified significant reduction of infectious complications and length of stay (59), the others (60-62) confirmed that immunonutrition has significant benefits compared to control for non-infectious and infectious complications in non-malnourished surgical patients and in the absence of serious co-morbidities, although several bias (reporting, publication, industry support) were identified, limiting the generalizability of these results to all GI surgical candidates (58).

Notwithstanding this large amount of studies, currently available guidelines still show controversial recommendations: preoperative immunonutrition is recommended even in non-malnourished surgical patients by French guidelines (63) and in cancer patients by ASPEN guidelines (64), whereas ESPEN recommends it only in malnourished patients undergoing major cancer surgery (47) (refer also to chapter 25).

KEY POINTS

Preoperative nutritional screening should be performed in all patients undergoing major gastrointestinal surgery.

- **level of evidence: 1B**
- **recommendation grade: A**
- **consensus 88%**

Malnourished patients should be treated with 7-10 days of preoperative oral nutritional supplementation (or parenteral nutrition when indicated)

- **level of evidence: 1B**
- **recommendation grade: A**

- **consensus 100%**

Perioperative immunonutrition is recommended in malnourished patients undergoing major gastrointestinal surgery for cancer

- **level of evidence: 2B**
- **recommendation grade: A**
- **consensus 93%**

6. Management of anemia

Preoperative anemia is common in colorectal cancer patients (65). Although there is a strong indication for the correction of anemia in patients undergoing surgery (66), the manner and timing of treatment are often left to the discretion of individual clinical figures. Anemia is defined by the WHO as an Hb concentration < 130 g/L for men and <120 g/L for non-pregnant woman but recently it has been proposed that women should be considered anemic if Hb is between 120 and 130 g/L when an iron deficiency is present (67). Postoperative outcomes depend on the preoperative finding of anemia (68, 69). Patients with preoperative anemia are more subject to perioperative blood transfusions, and transfusions are moreover associated with increased perioperative morbidity (68-70). Hemoglobin and iron status should be evaluated before any major surgical procedure (66) because timely diagnosis and treatment of anemia are the only effective strategy to avoid perioperative anemia and transfusion needs (71). The most useful tests to diagnose the iron status are Serum ferritin and transferrin saturation (TSAT). Serum ferritin level evaluates iron stores, while TSAT reflects iron availability for erythropoiesis. When it is possible, oral iron supplementation can be attempted (66), but an intravenous iron course is suggested when a quicker response is needed (72). Regarding oral iron treatment, when the interval before surgery is at least 6-8 weeks and no contra-indications occur, daily (40-60 mg) or on alternate days (80-100 mg) supplementation with oral iron may be appropriate (6). However, many patients will not respond to oral iron treatment, especially those patients who have functional iron deficiency and chronic illness (73). In the absence of an increased Hb or in case the patient is intolerant to oral iron treatment, i.v. iron therapy has a role of preference to play. If surgery is planned in less than 6 weeks, i.v. iron therapy may also be the most effective option. Intravenous iron therapy

efficiently restores iron stores and increases Hb in anemia due to iron deficiency and a very low rate of adverse reactions is described in literature (74). In clinical practice, a dose of 1000-1500 mg of i.v. iron (i.e. carboxymaltose) is sufficient to restore iron stores in most surgical patients and can usually be given in one or in two divided doses (75). In a RCT (76) the authors compared the efficacy of preoperative therapy with intravenous versus oral iron; i.v. iron did not reduce the blood transfusion requirement but was more effective than oral at treating preoperative anemia and iron deficiency in patients undergoing colorectal cancer surgery. Actually, increase in hemoglobin after treatment was higher with intravenous iron (median 1.55 vs. 0.5 g/dl- $P < 0.001$). In addition Hb levels were thus higher at surgery after treatment with i.v. than with oral iron (mean 11.9 vs. 11.0 g/dl, $P=0.002$) as were ferritin ($p < 0.001$) and TSAT ($p < 0.001$) levels.

KEY POINTS

Anemia is frequent in patients affected for colorectal cancer and increases all cause morbidity. Correction of anemia should be done before surgery. Recent intravenous iron preparations have a low risk of adverse reactions and are more effective than oral iron in restoring hemoglobin concentrations in both iron deficiency anemia and chronic disease anemia. Blood transfusion has long-term effects and should be performed in strictly necessary cases.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

7. Prevention of nausea and vomiting (PONV)

Post-operative (PONV) and post-discharge (PDNV) nausea and vomiting are still common and cause of postoperative morbidity, increased length of hospital stay and delay in postoperative recovery (77). The etiology of PONV is multifactorial and involves three factors: patient, anesthetic and surgical (78). Female patients, non-smokers and those with a history of motion sickness are particularly at risk (79). The use of volatile anesthetic agents, nitrous oxide and parenteral opioids increases the risk of PONV (80) as well as major abdominal surgery for colorectal disease (81). Re-

garding postoperative analgesia in minimally invasive abdominal surgery and in particular in colorectal surgery, a multimodal strategy using regional anesthesia techniques such as epidural and transversal abdominal block (TAP) has been shown to reduce or eliminate postoperative opioid use which influences the prevalence of PONV (82-84). Prevention of PONV is crucial for patients undergoing colorectal surgery, as it can cause dehydration, delay in the return of adequate food intake and may require the placement of a nasogastric tube, increasing the administration of intravenous fluids and consequently the length of the hospital stay. PONV affects 30% (vomiting) to 50% (nausea) of all surgical patients and up to 80% of patients who are at high risk for developing these complications (85). In the literature there are many guidelines that stratify patients based on risk and which require antiemetic prophylaxis based on perceived preoperative risk (86) with a significantly reduction of PONV up to 40% of cases (87). An alternative therapeutic strategy that is very widespread but not yet proven could be to administer anti-emetic prophylaxis (between one and three drugs) to all patients who are having inhalation anesthesia, opiates or major abdominal surgery. This approach seems to be very widespread given the low cost and low side effect of commonly used antiemetic drugs (88). There are a large number of classes of first-line anti-emetic drugs, including dopamine antagonists (D2) (e.g. droperidol), serotonin (5HT3) antagonists (e.g. ondansetron) and corticosteroids (e.g., dexamethasone). The multimodal administration of antiemetic drugs can considerably reduce the incidence of PONV in high-risk patients and is associated with a high patient satisfaction (89). When a PONV rescue dose treatment is required, a different class of antiemetic should be administered compared to that given for prophylaxis (85). Recent Dexamethasone Reduces Emesis After Major Gastrointestinal Surgery (DREAMS) trial demonstrated that the use of single 8 mg dose of dexamethasone at induction reduced PONV at 24 h and reduced the need for rescue antiemetics for up to 72 h and increased the speed of return to diet after surgery without an increase in adverse events (90). However, the immunosuppressive effects of dexamethasone on long-term oncological survival are still unknown. In addition, other second-line drugs such as antihistamines (e.g. Promethazine), anticholinergics (e.g., Scopolamine) and other D2 antagonists such as metoclo-

pramide can be administered, but their use may be limited by side effects (sedation, dry mouth, vision disorders, and dyskinesia). Furthermore, as indicated by Apfel et al. in a meta-analysis of 2364 patients, it is important to underline that the routine use of acetaminophen which, in addition to the well-established analgesic effect in the postoperative pain control, demonstrates the ability to prevent nausea and vomiting (if administered before the painful onset) (91).

KEY POINTS

A multimodal approach to PONV prophylaxis should be considered in all patients treated with ERAS protocols. Patients with 1 risk factor should ideally receive a two-drug combination prophylaxis using first-line antiemetics. Patients with > 2 risk factors undergoing colorectal surgery should receive 2-3 antiemetics. When a PONV rescue dose treatment is required, a multimodal approach using different class of antiemetic should be administered compared to that given for prophylaxis.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

8. Pre-anesthetic medication

Scientific evidence accumulated so far suggests that most of the widely-used pharmacological pre-anesthetic strategies must be completely revisited, especially in light of the ERAS pathway. Improper management of the premedication stage, indeed, can compromise the result of the whole process. Classically, the administration of one or more pre-anesthetic agents is aimed to prepare the patient for anesthesia and surgical manipulation. Although this use of drugs prior to general anesthesia is mainly aimed at reducing patient's anxiety and apprehension, other objectives are the limitation of potential anesthetics-induced adverse effects such as those due to vagal stimulation, the strengthening of anesthetics action by reducing their dose as well as the dampening of intraoperative noxious stimulus, an optimal anterograde amnesia for pre- and postoperative events, and prevention of postoperative nausea and vomiting (PONV).

For this purpose, certain drugs have been widely used due to their ability to act through multiple mechanisms of action. For instance, promethazine shows

sedative, antiemetic and anticholinergic action. The use of promethazine and similar drugs has been almost completely abandoned. More recently, due to their anxiolytic, hypnotic, and amnesic effects, agents included among the benzodiazepine (BDZ) drug class represent the main pre-anesthetic medications. These drugs differ mainly in their pharmacokinetic properties as some of those are only slowly eliminated (i.e., long-acting BDZs) while others are short acting. Nowadays, long-acting BDZs, such as diazepam, are poorly used in anesthesiology practice, and they must be avoided within 12 hours of surgery because of their deleterious effects on the immediate postoperative recovery due to impaired mobility and oral intake. On the other hand, although widely-used, short-acting BDZs (e.g., triazolam and midazolam) may induce a variable impairment in psychomotor function up to 4 hours postoperatively which, in turn, may affect the patient's ability to mobilize, eat and drink (92). Furthermore, midazolam-induced comfort improvement has been recently reconsidered because, probably, this BDZ does not reduce the level of pre-operative anxiety (93). Despite this latter finding, midazolam can be tailored administrated to facilitate epidural or spinal anesthesia (6), or prior to the insertion of intravascular lines.

Another concern about the use of BZDs regards their potential effect on anesthesia-induced memory consolidation and prevention of the anesthesia awareness phenomenon (94). Results from large size clinical studies indicated that the genesis of this complication is quite multifactorial and rather than the use of BDZs, or other pre-anesthetic drugs, more careful intraoperative strategies (e.g., during the induction) can be really effective for its prevention (95). Another underestimated issue concerning the use of BDZs is their impact on the cognitive functioning after surgery, in elderly (96). In this population (aged > 60), the use of BDZs must be avoided because of the onset of postoperative delirium (POD) which represents the most common postoperative complication in older adults and a medical emergency requiring immediate assessment and treatment during the early postoperative. Moreover, other less investigated clinical manifestations of cognitive impairment have been linked to the use of premedication drugs and to inadequate perioperative management. Among these, postoperative cognitive decline or dysfunction (POCD), which is termed as a decline in a variety of neuropsychological

domains (e.g., memory, executive functioning, and speed of processing) emerging week to months after anesthesia and surgery (97).

The same recommendations as for BDZs are valid for opioids, medications that, combined or not with BDZs, are widely used in pre-anesthesia. Incongruous use of these drugs may induce occurrence of POD and POCD. Furthermore, while preoperative pain is a well-known predictor for postoperative pain, the role of opioids for pre-emptive analgesia has been widely questioned (98). On the contrary, a multimodal strategy combining several interventions seems to be the optimal approach to obtaining good postoperative analgesia. In turn, opioids should be avoided as they may affect the functional recovery following surgery by impairing postoperative mobilization and direct participation.

KEY POINTS

When possible, non-pharmacological approaches focused on education and counseling addressed during the preoperative assessment should be preferred to medication strategies.

Long-acting BDZs must be avoided.

If necessary (e.g., to facilitate epidural or spinal anesthesia, or prior to the insertion of intravascular lines) midazolam can be administrated although by careful titration and in patients aged less than 60 years.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

The use of opioids should be avoided.

- **level of evidence: 1B**
- **recommendation grade: B**
- **consensus 95%**

9. Antimicrobial prophylaxis and skin preparation

The use of intravenous antibiotic prophylaxis before colorectal surgery is associated with a reduction of surgical site infections; current gold standard is a single administration of a cephalosporin and metronidazole 60 minutes before surgical incision (99). It has recently emerged that the prophylactic administration of intravenous antibiotic associated with oral antibiotic reduces the rate of surgical site infections when compared with the administration of intravenous antibiot-

ic alone; these studies, carried out on patients undergoing mechanical bowel preparation, have a weak recommendation grade (99, 100).

Randomized clinical trials are underway to investigate the independent role of systemic and oral antibiotics, alone and in combination with each other and with mechanical bowel preparation; to date, there is no evidence to support the use of oral antibiotic in patients not undergoing bowel preparation (101).

There is high quality of evidence to support the use of chlorhexidine-alcohol-based preparations for skin disinfection to reduce surgical site infections in colorectal surgery (102, 103). Currently there is not enough evidence to support the use of other forms of antiseptics, such as preoperative shower, routine trichotomy and use of adhesive drapes, in the prevention of surgical site infections (104, 105).

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

10. Bowel preparation

Bowel preparation in elective colorectal surgery still remains a much debated topic to date. A meta-analysis of 36 studies showed that mechanical bowel preparation is not associated, in colorectal surgery, with an improvement of outcome in terms of anastomotic leak rates, surgical site infection, intra-abdominal collection, mortality, reoperation rate and hospital length of stay when compared to non-preparation (106).

On the contrary, mechanical preparation can cause dehydration, electrolyte disturbance and discomfort for the patient. Therefore, mechanical bowel preparation should not be used routinely in elective colonic surgery (high evidence quality, strong recommendation grade); it can be used in elective rectal surgery instead, if the creation of a diverting stoma is planned, to avoid stools remaining in the diverted bowel tract.

Otherwise the latest ASCRS/SAGES guidelines (107), relying mainly on a meta-analysis conducted on 1769 patients (100), recommend the combination of mechanical bowel preparation and both oral and intravenous antibiotic prophylaxis in elective colorectal surgery. Moreover, a retrospective analysis (108) that included 32.359 patients recommends the routine use of mechanical bowel preparation and oral antibiotics

before elective colorectal surgery to prevent surgical site infection (low quality of evidence, weak recommendation grade). The discrepancy with the European guidelines is evident and seems to be related to the emerging role of the oral antibiotic prophylaxis (109).

A large observational study (110), based on the ACS NSQIP database, did not show any benefit of mechanical bowel preparation combined with oral antibiotic prophylaxis compared to the use of oral antibiotics alone. Several randomized clinical trials are ongoing and will clarify the role of oral antibiotic prophylaxis in elective colorectal surgery (101-112).

KEY POINTS

Mechanical bowel preparation should not be used routinely in elective colonic surgery; it can be used in elective rectal surgery instead, if the creation of a diverting stoma is planned, to avoid stools remaining in the diverted bowel tract.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 95%**

11. Preoperative fasting and carbohydrate loading

Fasting from midnight was the gold standard for a long time, because it was thought that this ensures an empty stomach and therefore reduces the risk of pulmonary aspiration in elective surgery. There has never been any scientific evidence for this dogma. A meta-analysis, including a Cochrane review of 22 RCTs, showed that fasting from midnight does not reduce gastric content nor raises the pH of gastric fluid compared with patients allowed free intake of clear fluids until 2 hours before anesthesia for surgery (113, 114). In the last decade many studies have demonstrated that clear fluids can be safely given up to 2 hours and a light meal up to 6 hours before elective procedures requiring general anesthesia or regional anesthesia in children and adults (114, 115). Preoperative administration of oral carbohydrates (complex CHO-maltodextrin, 12.5%, 285 mOsm/kg, 800 ml in the evening before surgery and 400 ml 2-3 h before induction of anesthesia) has been shown to reduce the catabolic response induced by overnight fasting and surgery (116) and postoperative insulin resistance (117), decrease protein breakdown and better maintain lean

body mass and muscle strength, as well as beneficial cardiac effects (118). This observation has been confirmed even in obese (119) and diabetic (120) patients. The faster surgical recovery and better postoperative wellbeing from CHO still remains controversial, while few data so far support an effect on postoperative morbidity or mortality from this treatment. In a recent Cochrane Review including 27 trials involving 1976 patients undergoing elective minor and major abdominal surgery, orthopedic surgery, cardiac surgery and thyroidectomy (121), the administration of preoperative carbohydrate was associated with a greater absolute decrease in LOS (MD - 1.66 days, 95% CI - 2.97 to - 0.34) only in patients undergoing major abdominal surgery compared with the placebo or fasting group of patients. There are many evidences in literature that oral fluids including CHOs may not be administered safely in patients with documented delayed gastric emptying or gastrointestinal motility disorders as well as in patients undergoing emergency surgery (6). The preoperative administration of oral carbohydrates in diabetic and obese patients remains under discussion, however, both obese and diabetic patients have been increasingly included in recent studies of CHO (122) and no issues with regard to safety have been reported.

KEY POINTS

In patients undergoing colorectal surgery clear fluids including CHO up to 2 hours and a light meal up to 6 hours before elective procedure should be taken. Patients with delayed gastric emptying and emergency patients should remain fasted overnight or 6 h before surgery. No recommendation can be given for the use of CHO in obese and diabetic patients.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

12. Standard Anesthetic Protocol

Anesthetic protocols, as part of ERAS programs, should minimize negative effects of anesthesia on systemic homeostasis by promoting hemodynamic stability, optimal tissue perfusion and oxygenation, limiting the occurrence of post-operative delirium, facilitating emergence from anesthesia, accelerating gastro-intestinal function, and improving post-operative outcomes.

Key aspects of anesthesia in ERAS can be summarized in few points:

- Long-acting drugs should be avoided for pre-medication (e.g. morphine and/or diazepam). Patients' anxiety can be reduced by administering low dose of short-acting benzodiazepines (e.g. midazolam 1-2 mg) before going into the theater (123).
- Processed electroencephalography (pEEG) based anesthesia is now strongly suggested by Scientific Societies in order to personalize the anesthetic approach and minimize the risk of awareness in case of total intra venous anesthesia (TIVA) and burst-suppression-associated delirium and cognitive decline, especially in elderly and highly sensitive patients (6, 95, 124-126). PEEG allows to overcome the problem of inter-individual variability. Hypnosis should be delivered according to the appropriate combination of EEG waveforms associated with a specific range of the processed raw trace (i.e. Masimo-Sedline 25-50; Entropy and BIS 40-60) (127). The need for personalization is valid for both TIVA and halogenates-based anesthesia and the use of pEEG has demonstrated to avoid both accidental awareness and over-deep anesthesia (95, 123-126). Awareness occurs once in every 20,000 anesthesia and identifiable causes can be usually found (e.g. obesity, anesthesia seniority, cardiac surgery, emergency surgery, obstetric surgery, previous awareness). Differently, excessively deep anesthesia is extremely frequent and associated with increased postoperative delirium, worsening neurocognitive dysfunction, and mortality (123).
- Short-acting anesthetics may help to obtain a complete clearance shortly after the end of anesthesia and accelerate gastro-intestinal function. In addition, an opioid-sparing/opioid-free anesthesia strategy is recommended (see the chapter dedicated to analgesia). As underlined, anesthetic depth guided by pEEG helps to reduce the doses of drugs administered (126).
- Mean arterial pressure never should drop below 65 mmHg as negative outcomes such as Acute Kidney Injury (AKI) and myocardial injury have been demonstrated to be associated with hypotension even if mild and for short periods of time (128).
- Train of Four (TOF) or similar systems for neuromuscular blocking monitoring must be applied

every time a neuromuscular blocking agent is administered. Prompt recovery from muscular block is mandatory and residual effects on muscle block must be avoided to decrease the risks of respiratory complications (129).

KEY POINTS

Use of short-acting anesthetics

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

Cerebral monitoring to improve recovery and reduce the risk for postoperative delirium

- **level of evidence: 1B**
- **recommendation grade: A**
- **consensus 95%**

Monitoring of the level and complete reversal of neuromuscular block

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 92%**

13. Intraoperative fluid and electrolyte therapy

Two different fluid therapy approaches, “liberal” or “restricted”, have divided the literature for many years. While a clear definition of them is still lacking (130), the “liberal” approach, aimed at maximizing cardiac preload and stroke volume, is more associated with negative outcomes (e.g., cardiovascular complications, delayed bowel recovery, anastomotic healing) compared with the “restrictive” regimen, mainly aimed at reducing tissue edema and circulatory overload (131-133). A recent study on more than 650,000 patients undergoing elective colorectal surgery (16%) or orthopedic surgery (84%) showed a classic “U-shaped” outcome curve related with the fluid regimen (134). Worse outcomes (e.g., prolonged length of stay (LoS) with increased costs, increased incidence of postoperative ileus) were identified in the extreme quartiles of fluid administration on the day of surgery. Similar results were found by a retrospective analysis of more than 90,000 non-cardiac adult surgical patients (135). The first and fifth quintiles of total intraoperative fluids were associated with longer LoS and elevated costs higher levels of 30-day mortality, as well as increased incidence of postoperative respiratory complications and acute kidney injury (AKI). On the

contrary, the second quintile (900-1100 ml) was associated with better outcomes in terms of complications and mortality. The recent ReLief study, a randomized controlled trial that compared “restrictive” vs. “liberal” perioperative fluid strategies in 3,000 patients at increased risk of complications, found substantially unexpected results (136). In fact, the disability-free survival at one year (primary outcome) did not differ between the two groups and the “restrictive” group showed a higher rate of AKI. However, it is important to consider that the fluid balance over 24 hours after surgery in the “liberal” group was slightly superior to the “restricted” one. In light of this result, the authors themselves declared that their findings “should not be used to support excessive administration of intravenous fluid”. Therefore, the observed outcomes should be considered in terms of “adequacy” of fluid therapy rather than “restrictive” versus “liberal”. Finally, in patients at high risk of postoperative complications, a goal-directed fluid therapy (GDFT) strategy, based on pressure and flow parameters, may be the most efficient strategy. It has been clearly demonstrated that Stroke Volume Variation (SVV) and Pulse Pressure Variation (PPV) are sensitive methods to detect fluid responsiveness and guide fluid therapy and that clinical outcomes, including decrease in gastrointestinal complications, length of mechanical ventilation, time in ICU, and hospital LoS in high-risk surgeries are better in high risk patients whose fluid therapies was guided by SVV and/or PPV (137, 138).

Intravenous fluids are administered in the intraoperative phase with the aim of maintaining the volume, cardiac output and tissue perfusion, avoiding hyposaline overload, aiming at a balance tending to zero (123). Measurement of SVV with minimally invasive methods and the consequent targeted administration of intravenous fluids do not involve significant risks but ensures an additional benefit, compared to that already guaranteed only by the application of the ERAS protocol, only in patients at high risk or subjected to high-risk procedures (139).

Some final important considerations should be highlighted: a) balanced crystalloid solutions should be preferred as a standard choice over normal saline (NaCl 0.9%), which has been shown to increase the risk of hyperchloremic acidosis and AKI; b) fluid administration should be maintained after surgery only when fasting is absolutely necessary. Restarting oral and food water intake as soon as possible after surgery

is safe and strongly recommended (140); c) to enhance the probability that patients may tolerate a fast fluid intake, the whole package of ERAS items should be applied.

KEY POINTS

Perioperative near-zero fluid balance

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

Goal-directed fluid therapy in high-risk and in case of large intravascular fluid loss

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

14. Preventing intraoperative hypothermia

Patients' temperature should be monitored for all interventions lasting more than 30 minutes and a core temperature > 36.5°C must always be obtained by using warming blankets and/or fluid warmers. Hypothermia may increase the incidence of wound infection, blood loss, transfusion, and cardiac morbidity (141-144). Thermoregulation control is impaired in both general and neuraxial anesthesia and un-warmed surgical patients eventually become hypothermic. Monitoring systems include intra-vascular catheters, nasopharyngeal probes, and zero-heat flux devices.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

15. Postoperative analgesia

Pain control is a crucial part of ERAS programs and multimodal-multidrug strategies are now strongly recommended. Insufficiently treated pain eventually results in adverse events that prolong hospital stays and delay recovery. Over 20 years ago, Kehlet wrote: "The rationale for this (multimodal-multidrug) strategy is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side effects, due to resulting lower doses of analgesics and differences in

side-effect profiles and to decrease opioid related adverse effects (e.g., nausea, vomiting, sedation, ileus, pruritus, and respiratory depression" (145).

Opioids have been used for years and are today key medications for pain treatment but, their administration entails a wide range of serious adverse effects, including nausea and vomiting, ileus, respiratory depression, hyperalgesia, delirium, urinary retention, sleep disturbance, sedation and delayed functional recovery (146, 147).

Moreover, opioid assumption is suspected to cause immune depression, which may negatively influence long-term cancer outcomes. It has been demonstrated that morphine suppresses natural killer (NK) cell activity and T cell differentiation, promotes lymphocyte apoptosis, and decreases toll-like receptor 4 expression on macrophages. In addition, opioids (and volatile anesthetics) suppress cellular mediated immunity surveillance and may promote cancer cell proliferation and angiogenesis (148). A multimodal intra-operative opiate-sparing strategy and a post-operative opioid-free should be applied in ERAS programs whenever possible (146, 147).

A number of analgesics are today available, including acetaminophen and nonsteroidal anti-inflammatory drugs, which are widely used, and analgesic adjuvants, which are less commonly used in clinical practice despite their opioid-sparing effects being well documented: gabapentinoids, intra-venous lidocaine, nonsteroidal anti-inflammatory drugs, dexmedetomidine (not allowed in intubated patients during surgery), ketamine, have all demonstrated to well act as analgesic adjuvant in ERAS programs (145-147).

Thoracic epidural analgesia (149) remains the gold standard for open surgery; the greater diffusion of laparoscopic techniques with less surgical impact raised interest towards less invasive techniques (150).

Recent advances in analgesia for open abdominal surgery are the regional blocks. In some cases, surgery may commence as minimally invasive (i.e., laparoscopic and robotic-assisted surgery), but it may be converted into an open procedure. In these patients, a thoracic epidural catheter, commonly used in open surgery, may have not been placed and alternative blocks could be necessary for post-operative pain management. Transversus abdominis plane (TAP) block has been shown to be efficient in decreasing postoperative opioid consumption, leading to a subsequent decrease in the incidence of nausea (resulting from a de-

crease in opioid usage). Likewise, TAP block helps to maintain hemodynamic stability and can be performed when neuraxial anesthesia is contraindicated due to, e.g., coagulation issues or infection at the epidural puncture site. However, it lacks coverage for visceral pain, and as such requires additional methods of postoperative pain control (138, 145-147). Moreover, wound infiltration with local anesthetics, including trocar access for laparoscopy and robotic techniques, is also recommended as an adjuvant multimodal analgesic strategy. In all cases, good perioperative pain management is crucial for improved recovery. Finally, the existence of a dedicated pain service may not only facilitate the development of a multimodal analgesic regimen for ERAS pathways but also assist in the post-discharge management of analgesics.

KEY POINTS

A multimodal intra-operative opiate-sparing and a post-operative opioid-free strategy should be applied in ERAS programs whenever possible.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

Multimodal analgesia in combination with spinal/epidural analgesia or TAP blocks when indicated should apply.

- **level of evidence: 2A**
- **recommendation grade: A**
- **consensus 90%**

16. Surgical access. The role of minimally invasive surgery

At the introduction of Fast Track program, the standard surgical approach was open and short surgical incision were recommended; the role of transverse laparotomy was not so clear (151). The principles of minimally invasive surgery, based on the reduction of stress and on early post-operative recovery of the digestive functions, are well suited to the pathophysiological bases of the ERAS pathway in colorectal surgery.

In randomized clinical trials the laparoscopic colectomy for cancer provides shorter length of hospital stay, less pain, and decreased postoperative morbidity but similar long-term oncologic results compared to open colectomy (107, 152, 153). Minimally invasive

surgery for colonic resection has become the standard of care in many countries. In Italy, the diffusion of minimally invasive surgery in colic resections is around 35%. The diffusion of minimally invasive surgery in rectal surgery is higher (43%) due to centralization (154). Randomized trials can't prove that pathologic outcomes of laparoscopic surgery are equivalent to open surgery, even when performed by surgeons with laparoscopic expertise. However, reported long-term data outcomes between laparoscopic and open anterior rectal resection are similar (155, 156). Promising results for improving oncologic margins in rectal surgery could be reached by robotic surgery but these will require careful study. The ROLLARR trial shows no difference in conversion to open surgery comparing laparoscopic and robotic rectal resection with similar short-term outcomes, suggesting potential advantages of robotic surgery in more complex cases (157). No data comparing the trans-anal with laparoscopic approach are still available from the COLOR III (158) study while a comparative analysis between trans-anal and robotic approach should be planned.

The synergic effect on the postoperative recovery of the ERAS program in combination with minimally invasive approach is debated. LAFA trial demonstrates that patients undergoing resective colon surgery are more likely to benefit from using the ERAS pathway when combined with minimally invasive technique (159). Meta-analysis evaluating the role of laparoscopy within an optimal ERAS pathway do not allow definitive conclusions to be drawn (160, 161). Both the analysis of enhanced recovery national and international registries confirms that patients undergoing minimally invasive surgery within ERAS pathway have a reduction in hospitalization and rates of postoperative complications (162, 163). Rectal surgery is associated with certainly longer postoperative stay and lower adherence rates compared to colonic surgery. Stoma creation is definitely a slowing factor in patient recovery.

The recent guidelines of the ERAS society recommend, with high levels of evidence, the use of minimally invasive surgery both in colon and rectum resections (6). Minimally invasive surgery allows the reduction in complications, the optimization of fluid therapy, and the reduction in the use of opioids. In the long-term laparoscopy shows the reduction in adhesions, incisional hernia and probably in costs. Even the

American guidelines of enhanced recovery recommend the use of minimally invasive surgery in both colon and rectum resections where a sufficient expertise is available (107).

No exclusion criteria are described for the laparoscopic approach in colorectal resection when the learning curve is completed. Laparoscopy is probably one of the most important items of ERAS pathway, even in rectal surgery, but when the laparotomic approach is needed it should also be within ERAS program (164).

KEY POINTS

In elective colorectal surgery, the minimally invasive surgical approach should be employed, if the expertise is available.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

In elective colorectal surgery, if laparoscopy can't be used, patient should be included anyway into ERAS pathway

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

17. Drainage of the peritoneal cavity and pelvis

It was 1887 when Robert Lawson Tait wrote the unrivalled sentence: "When in doubt, drain". Even Theodor Billroth supported the idea that routine drainage was very useful after intestinal surgery (165). After more than a century, many surgeons still routinely place a drain in the abdominal or pelvic cavity after colorectal surgery, especially if an anastomosis is performed.

Prophylactic drainage is supposed to (166-168): decrease the anastomotic leakage, preventing fluid or hematoma collection and eventually evacuate abscess; minimize the severity of complication-related symptoms; identify at an early postoperative stage an anastomotic leak or intraperitoneal bleeding.

17.1 Prophylactic drainage

The meta-analysis of Urbach et al. (169) examined 4 randomized controlled trials with pooled data of 223 drained and 188 non-drained patients. The drained

group had higher rates of clinical leak (OR 1.5), mortality (OR 1.4) and wound infection (OR 1.7).

In his meta-analysis, Petrowsky (170) examined the value of prophylactic drainage in gastrointestinal surgery; he found a trend for an increased leak rate in drained patients after colonic or rectal resection compared to non-drained (4.2% versus 2.4%) despite there was not a statistically significant evidence. He stated that drains do not reduce complications rate in patients with primary anastomosis discouraging the use of prophylactic drainage. The main issue about the results of these meta-analyses is the heterogeneity of anastomosis site since they include series with both intraperitoneal and extraperitoneal. Similar results were found in a Cochrane review in the same year (171).

A more recent meta-analysis (172) examined 11 randomized controlled trials with pooled data of 1803 patients. There was no statistically significant difference between the drain group and no drain group for the overall anastomotic leakage rate, clinical anastomotic leakage and radiologic anastomotic leakage, mortality, wound infection, and re-operation. Even stratifying by sites (intraperitoneal vs. extraperitoneal), they found no significant difference between the two groups. Finally, in the meta-analysis of Manahem (173) that analyzed 660 patients with extraperitoneal anastomosis after rectal resection, pelvic drainage had no effect on the incidence of anastomotic leakage and mortality.

The GRECCAR 5 randomized trial (174) suggests that the use of a pelvic drain after rectal resection for rectal cancer does not confer any benefit to the patient.

In contrast with these, the Dutch TME trial (175) revealed that the presence of pelvic drain was strongly associated with lower leak rate (9.6%) compared with those without drain (23.5%) and this significance resulted in the relative risk of 2.5 by multivariate analysis.

17.2 Drainage in early leakage diagnosis

Urbach et al. (169) reported a low sensitivity (5%) of drain in early detection of anastomotic leakage: in their series only one out of 20 drains contained pus or enteric content at the time of diagnosis of leakage. Instead, Tsujinaka et al. (176) concluded that pelvic drainage has good sensitivity in detecting anastomotic leakage. The authors studied 196 patients who underwent to low rectal resection and primary anastomosis.

Anastomotic leakage was observed in 21 patients (10.7%). Changes in drain contents suggesting anastomotic leakage was seen in 15 of 21 patients (71.4%).

17.3 Drainage as a treatment option for anastomotic leakage

The management of anastomotic leak depends on the clinical scenarios: surgical re-exploration is required if patient presents diffuse peritonitis or septic shock (177). Otherwise, conservative treatment including administration of broad-spectrum antibiotics, drainage of abscess and nutritional support could be considered in cases of limited systemic symptoms. Tsujinaka et al. (176) reported that anastomotic leaks (extra peritoneal anastomosis) were resolved by conservative treatment with the existing drain in 10 of 21 (47.6%) patients, thus decreasing the rates of reoperation. In these patients, the pelvic drain was kept in place for a median duration of 52 days (range 32-169 days).

17.4 Drainage-related complications

Several complications directly related to the use of a drain have been described; Tsujinaka et al. reported that 2.5% of patients developed an abscess at the site of the drain, in 1.0% herniation of the omentum through the drain site after removal with 0.5% of them having a bowel injury (176). Others drain-related morbidities include pain at the site of drain, skin ulceration and bleeding (178,179).

17.5 Type of drainage

Both active (with suction) and passive drain (without suction) subgroups showed no significant correlation with anastomotic leakage rate and other complications when compared with no drain group according to meta-analysis of Zhang et al. (172).

The prospective study by Yeh et al. (180) for pelvic and other risk factors of leakage after elective anterior resection in rectal cancer showed that irrigation-suction drain is an independent risk factor for anastomotic leak. However, these observations may have been biased because the indication and drainage type were left to surgeon use and the type of drainage was discretionary.

17.6 Conclusions

Routine use of prophylactic drainage in colorectal surgery is not related to a reduction of postoperative

complications in intra-peritoneal anastomosis. However, some risk factors justify the selective use of drains in case of increased risk of post-operative morbidity.

On the other hands, no evidence support the possibility to avoid the use of drain in rectal cancer surgery with extra-peritoneal anastomosis: intra-operative factors and surgeons' preference still determine the choice of draining until a clear evidence against it is produced.

More than other surgical aspects, drainage is a direct expression of surgeons' attitude. A careful review of the existing evidence, especially in colon cancer surgery, should help surgeons not to drain.

KEY POINTS

Routine use of prophylactic drainage in colorectal surgery shows no benefit in reducing postoperative complications in intra-peritoneal anastomosis

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

18. Nasogastric Intubation

Colorectal surgery, as other abdominal surgeries, involves some degree of paralytic ileus in the immediate postoperative period as a response to surgical and anesthetic trauma, and has been linked to a higher number of postoperative complications. All this justified the postoperative nasogastric tube (NGT) to prevent ileus, intestinal dilatation, nausea and vomiting, and wound complications (eviscerations and eventrations), and even to protect the anastomosis.

However, during the 1980s and 1990s, NGT routine use repeatedly challenged on the basis of various trials (181-184).

Since 1984, Bauer et al. concluded that regular use of NGT was unnecessary, after evaluating the postoperative course of 200 patients, mainly operated on for colorectal resections, as it caused discomfort to many subjects and because complications were not increased in those with no NGT. Moreover, only 6% of the tubeless group needed an NGT later on (185).

Cheatham et al., in a meta-analysis of 26 trials including 3,694 patients undergoing elective laparotomy for all types of surgery, found a higher number of respiratory complications (atelectasis, fever, pneumonia) in patients bearing an NGT versus a tubeless group and reported a significant decrease in the num-

ber of days to first oral intake in patients without a NGT compared with those treated with a NGT. The use of an NGT did not decrease dehiscence, wall hernias, or hospital stay. Although patients with no NGT showed more abdominal dilatation and vomiting, only 7% of them needed a NGT (184).

Colorectal surgical patients recovering without a NGT have a significantly decreased time to recovery of bowel function compared with those with a NGT (186-190). A meta-analysis published in 2005 based on 28 studies, 7 of which were related to colorectal pathology, showed a quicker intestinal function recovery in subjects without NGT. There were no significant differences regarding dehiscence or anastomotic leaks between both groups. Similarly, in the same meta-analysis updated to 2010 in a Cochrane Review of 37 prospective randomized trials (5,711 patients) reported earlier return of bowel function in patients without a NGT (191). Moreover, early oral feeding (EOF) after elective colorectal resection was beneficial and safe in enhancing recovery. EOF was associated with a lower incidence of postoperative complications and a reduction in length of hospital stay (143). Wen-Zhang Lei et al. (189) in a prospective randomized study on 368 patients submitted to colorectal resective surgery reported a statistically significant higher frequency of pharyngo-tonsillitis in patients carrying an NGT. A recent meta-analysis of 7 RCTs including 1416 patients (192) confirmed these data but showed vomiting was more common.

18.1 Conclusions

The routine use of nasogastric decompression following elective colorectal surgeries may be safely eliminated except for evacuating air that may have entered the stomach during ventilation by the facial mask prior to endotracheal intubation and is recommended in laparoscopic cases to prevent inadvertent gastric injury. If placed during surgery, nasogastric tubes should be removed before the reversal of anesthesia. Avoidance of routine nasogastric decompression increased comfort and mobility of patients. It is recommended to consider nasogastric tube insertion in selected patients with postoperative ileus, refractory to conservative management, to relieve gastric symptoms.

KEY POINTS

The routine use of nasogastric decompression following elective colorectal surgeries may be safely eliminated.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

Consider nasogastric tube insertion in selected patients with postoperative ileus, refractory to conservative management, to relieve gastric symptoms.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 95%**

19. Thromboprophylaxis

Patients suffering from neoplasia are at risk of developing a condition of venous thromboembolism (VTE) that represents a serious complication arising after abdominal surgery. The mechanisms underlying this risk include platelet hyperactivation by procoagulant neoplastic proteins, increased cytokines and also alterations induced by chemotherapeutic treatments. Furthermore, surgery increases this risk both for tissue damage and for the possible postoperative immobility of the patient.

A prophylaxis regimen must be defined based on the patient's individual risk factors. These include advanced age, previous major surgery, obesity, heart disease, oncologic disease stage, major IBD surgery and duration of the procedure, bleeding complications and blood transfusions, occurrence of septic complications, ambulation and length of stay and moreover the administration of chemotherapy (193). High-quality evidence supports the use of perioperative mechanical thromboprophylaxis, which includes compression stockings and/or intermittent pneumatic compression, as a measure to reduce the incidence of deep vein thrombosis in patients undergoing abdominal surgery (194-196).

High level of evidence also supports pharmacological prophylaxis with heparin, because its use in the postoperative period is associated with a reduced incidence of symptomatic venous thromboembolism and overall mortality with a very low risk of bleeding; administration of low molecular weight heparin once daily is recommended (197-199).

Concerning the duration of pharmacological thromboprophylaxis, a meta-analysis of 4 randomized clinical trials (198) and guidelines (200) recommend the use of heparin for 28 days after major abdominopelvic surgery for cancer.

Considering the low incidence of thromboembolic events reported in literature (201, 202), surgical stress reduction given by many elements of the ERAS protocol (such as minimally invasive surgery and modern anesthetic techniques) and early mobilization of patients, it is possible that some of these recommendations should be reviewed, and studies evaluating the use of shorter or even no prophylaxis are needed. However, given the lack of such studies, the frequency of high thromboembolic risk among patients undergoing colorectal cancer surgery and the severity of complications, a strong recommendation grade supports the use of mechanical thromboprophylaxis until discharge and pharmacological prophylaxis for 28 days after surgery.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

20. Postoperative fluid and electrolyte therapy

“Zero fluid balance”: this should be the target of the patient undergoing abdominal surgery according to the Enhanced Recovery After Surgery (ERAS) protocol. Scientific studies from 25 years ago (203) showed that early oral fluid intake immediately after surgery and, subsequently, solid food diet, was a safe and feasible program without an increased risk of anastomotic leakage in patients undergoing abdominal surgery; on the other hand, the “ancestral” fear of the surgeon that early re-feeding (even liquid diet) could determine higher anastomotic leakage risk has always made surgeons to prefer a conservative attitude towards a delayed feeding both for liquids and solid diet after abdominal surgery.

The cultural revolution of the ERAS protocol requires a shift from traditional management “zero (nil) by mouth” to “zero fluid balance” because resuming early oral diet showed reduced length of hospital stay, fewer postoperative complications, lower mortality rates, fewer adverse events and better quality of life (204, 205); findings about the incidence of septic complications are inconclusive (143, 206).

General ERAS rule is to have a complete perioperative fluid management optimization; this is critical to help improving pulmonary function, tissue oxygenation, gastrointestinal motility, and wound healing; im-

proving fluid management during this period leads to a sharp decrease of complications, decrease of length of stay, and enhanced patient outcomes. Therefore, patients undergoing colorectal surgery with ERAS protocol should stop intravenous fluid infusion as soon as possible and at least by POD 1; fluid therapy should be kept at a minimum, except particular clinical situations (207): in fact, with optimal control of PONV and pain, possibly after mobilization in the chair, the patient should be stimulated to drink clear liquids after 4 hours from the end of the operation: coffee, in particular decaffeinated, is well-tolerated and well-accepted, safe, without adverse events and expedites the time to bowel motility and the ability to tolerate food for the purpose to avoid even the onset of postoperative ileus (208-210).

Post-operative fluid therapy must be started only if necessary and must be suspended as soon as possible; this must be the bridge towards an early, truly physiological re-establishment, which is associated with significant reduction of morbidity and costs to health care providers (211, 212).

In case of vomiting, high loss of fluid from the stoma, surgical leakage of blood, or impossibility to take oral fluids, it is necessary to reintegrate the losses always in order to obtain a “zero fluid balance”. The classical saline solution (sodium chloride 0.9%) is called “physiological solution” but actually 0.9% saline is neither normal nor physiological because there is a strong and wide impact of saline infusion in the whole homeostasis of the organism, specifically on systemic acid-base balance and renal hemodynamics.

An indiscriminate use of saline-infusion, especially for acutely ill patients, may cause unnecessary complications and should be avoided, leading to sodium overload and hyperchloremic acidosis (213, 214); NaCl infusion (>2 liters) in healthy adults induces hyperchloremia which is associated with metabolic acidosis, hyperkalemia, and negative protein balance; emerging evidence suggests that administration of 0.9% saline could be harmful mainly through high chloride content and that the use of fluid with low chloride content may be preferable in major surgery and intensive care patients (215). Administration of 0.9% saline is the leading cause of metabolic hyperchloremic acidosis in critically ill patients; it has negative effects on coagulation, renal function and increases mortality by hyperchloremic acidosis; it can cause interstitial fluid overload, impairment of renal hemodynamics and a

reduction in urinary water and sodium excretion as a result of a reduction in renal blood flow and glomerular filtration rate (215). There is good evidence supporting the avoidance of unnecessary fasting and the value of an individualized perioperative IV fluid regimen, with transition to oral fluids as soon as possible, to help patients recover from major surgery (216). Recent scientific studies show hypotonic rather than isotonic crystalloids should be used, the latter containing higher concentrations of sodium and cations. In cases where an infusion of post-operative fluids is really necessary it is not clear whether there are advantages in the use of crystalloids versus buffered crystalloids versus colloids (216, 217).

Particular clinical conditions may require continuing the post-operative infusion therapy:

- hypotension in patients with epidural analgesia,
- post-operative oliguria
- vomiting, loss of fluid from the stoma, surgical leakage of blood

In case of hypotension in patients with epidural analgesia, it is advised to use vasopressors rather than intravenous fluids in order to maintain “zero fluid balance” (218).

In case of post-operative oliguria (urine output 0.5 ml/kg/h, or 500 ml in 24 h in an adult), before starting an infusion therapy it is advised to carry out a careful clinical examination of the patient and of his vital parameters, to make a hydro-electrolyte balance and to maintain a careful monitoring of diuresis.

It is necessary to differentiate true oliguria with systemic clinical signs (sweating, hypotension, and tachycardia) into a differential diagnosis with post-operative response of the organism to the surgical stress through renal vasoconstriction and water retention. In the absence of systemic clinical signs, it is still possible to safely restrict fluid infusion (219, 220); no reliable evidence from the available literature suggests that interventions during surgery can protect the kidneys from damage: recent methods of detecting renal damage such as the use of specific biomarkers and better-defined criteria to identify renal damage (221).

In case of high loss of fluids from the stoma or surgical leakage of blood it is necessary to perform a fluid balance and integrate the lost liquids; blood transfusion should be limited as much as possible because it is associated with adverse clinical outcomes, including increased mortality (222). In the event of vomiting, the lost fluids and electrolytes must be replenished and

appropriate infusional therapy must be provided concurrently with PONV control by intravenous administration of antiemetic drugs: serotonin antagonists (Ondansetron max 32 mg/day, Granisetron max 9 mg/day) (223-227) or pro-kinetics such as Metoclopramide, widely diffused, safe, tolerable, harmless, and inexpensive, but with less efficacy on nausea and on the prevention of paralytic ileus after surgery (228, 229). However, it is necessary to identify the patients at high risk of PONV. A multimodal approach with combination of pharmacological and non-pharmacological prophylaxis along with interventions that reduce baseline risk can be employed (230).

KEY POINTS

Net “near-zero” fluid and electrolyte balance should be maintained. Despite published guidelines, perioperative fluid and electrolyte administration are usually excessive and associated with postoperative morbidity (231). Immediately after surgery the patient must be stimulated to take an oral diet as soon as possible and the infusion therapy must be interrupted as soon as possible except in special cases. To cover pure maintenance needs, hypotonic crystalloids should be used (rather than isotonic crystalloids, which contain high concentrations of sodium and cations). For replacement of losses, saline 0.9% and saline-based solutions should be avoided, with balanced solutions being preferred. In patients receiving epidural analgesia, arterial hypotension should be treated with vasopressors after ensuring the patient is normovolemic (6).

- **level of evidence: 2A**
- **recommendation grade: A**
- **consensus 98%**

21. Urinary drainage

The use of urinary catheters after abdominal and pelvic operations is a common surgical practice. Urinary drainage during and after colorectal surgery is used traditionally for two main reasons: prevention of urinary retention and monitoring of urine output, but the duration of catheterization is directly related to the risk of urinary tract infection (UTI).

Medical and surgical literature demonstrates that longer duration of catheterization is associated to increased rates of postoperative catheter-associated UTI and other poor outcomes. Up to half of patients with

indwelling catheters for over 4 days will develop bacteriuria or candiduria (232-234). Among patients with bacteriuria, UTI symptoms develop in 24% and bacteremia from a urinary tract source develops in 3.6% of cases.

Urinary catheterization is associated with higher mortality rates during hospitalization and longer lengths of stay, and it has been implicated as a cause for other complications related to restricted mobility, including venous thromboembolism, nosocomial pneumonia and delirium (235).

Thus, early removal of the urinary catheter reduces the incidence of postoperative complications associated with UTI but the duration of catheterization in order to avoid post-operative urinary retention has not been standardized.

Urinary catheter removal after major abdominal and thoracic surgery on day 1 versus day 4 markedly reduced the risk of UTI (2 vs. 14%), with a low risk of urinary retention in both groups (8 vs. 2%) (236). A large observational study (n = 513) confirms low retention rates (14%) in patients undergoing colorectal surgery within an established ERAS protocol including early catheter removal (237). This study highlighted male gender and postoperative epidural analgesia as important independent predictors of retention. Thus, tailored removal of the bladder catheter can be guided by such risk factors.

According to the most recent ERAS Society Guidelines (6), routine transurethral catheterization is recommended for 1-3 days after colorectal surgery. The duration should be individualized based on known risk factors for retention: male gender, epidural analgesia and pelvic surgery. Patients at low risk should have routine removal of catheter on the first day after surgery, while patients with moderate or high risk may require up to 3 days.

Extended bladder catheterization may be required in selected cases undergoing complex pelvic reconstructive surgery. A recent meta-analysis has confirmed that when the duration of postoperative catheterization exceeds 5 days, a suprapubic tube or clean intermittent catheterization are safer alternatives to the standard transurethral catheter (238). These recommendations agree with guidelines from the Centers for Disease Control and Prevention (239) which suggest that for routine, intraperitoneal colorectal resection, the urinary catheter can be removed on postoperative day 1 while for mid to low rectal surgery, the

urinary catheter can be removed on postoperative day 3 to day 6, depending on the patient's risk for urinary retention.

Most guidelines recommend early removal of the bladder catheter, which is correlated with a reduction of UTI rates and a reduced length of postoperative hospital stay (240-242).

KEY POINTS

Early removal (pod 0-3) of urinary catheter reduces urinary tract infection risk.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

Elective colorectal surgery suggests urinary catheter removal in pod 1 for intraperitoneal resections and between pod 2 and 6 for medium and low rectum surgery based on urinary retention risk factors (male sex and epidural analgesia).

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 98%**

22. Prevention of postoperative ileus

Prolonged postoperative ileus is a major contributor to patient discomfort, delayed discharge and increased costs; hence, its prevention is a key objective of enhanced recovery protocols. Many of the core elements of ERAS protocols, such as (1) limiting opioid administration through application of multimodal analgesia techniques (including use of mid-thoracic epidurals and peripheral nerve blocks), (2) use of minimally invasive surgery, (3) eliminating routine nasogastric tube placement, and (4) maintaining fluid balance including goal-directed fluid therapy, can limit the duration of postoperative ileus (6). Additional interventions and pharmacological agents that specifically target ileus are available. Peripherally acting l-opioid receptor (PAM-OR) antagonists with limited ability to cross the blood-brain barrier (alvimopan, methylnaltrexone, naloxone and naloxegol) can ameliorate opioid-induced bowel dysfunction without reversing analgesia through central l-opioid receptor antagonism. Of these agents, alvimopan is the best studied in the context of limiting duration of postoperative ileus (6). This drug is currently approved by the US Food and Drug Administration (FDA) but not universally available, for

the indication of accelerating upper and lower gastrointestinal recovery following partial large or small bowel resection with primary anastomosis (6, 243). Conflicting data on their efficacy, costs and concerns over cardiovascular complications, limit recommendation for routine use of these agents, particularly in the context of increasingly wide-spread application of opioid-sparing anesthesia and analgesia techniques and of minimally invasive surgery.

Several RCTs have evaluated the efficacy of postoperative gum chewing in reducing duration of postoperative ileus. A Cochrane review of this topic concluded that, while gum chewing may be associated with mild reductions in ileus duration, the evidence on this topic is largely limited to small, poor quality studies (244). A well-designed, large-scale multicenter RCT evaluating the effects of postoperative gum chewing in patients undergoing abdominal surgery and on ERAS pathways was reported (245). Gum chewing had no impact on time to first postoperative flatus or bowel movement, on postoperative length of stay, or on incidence of postoperative complications. Currently available evidence does not support the efficacy of gum chewing in reducing duration of ileus in patients undergoing abdominal surgery on ERAS pathways. Accordingly, its routine inclusion as a component of ERAS care is not recommended. Various other agents that have been tested for efficacy in reducing duration of postoperative ileus, including laxatives and coffee. In prospective controlled trials, reductions in various indices of postoperative ileus have been observed to occur with oral bisacodyl administration in patients undergoing colorectal surgery (246), with oral magnesium oxide administration in patients undergoing hysterectomy (247), with oral daikenchuto (a traditional Japanese herbal medicine) administration in patients undergoing gastrectomy (248), and with oral coffee administration in patients undergoing colorectal surgery (249). These studies have methodological limitations, and confirmatory studies are needed before routine application is recommended.

KEY POINTS

A multimodal prevention of post-operative ileus should be considered in all patients treated with ERAS protocol. This multimodal approach includes limited opioid administration, use minimally invasive surgery, not routine placement of nasogastric tubes and goal-directed fluid therapy.

- **level of evidence: 1A**
- **recommendation grade: A**
- **consensus 100%**

23. Postoperative glycemic control

Insulin resistance is the cause of postoperative hyperglycemia. Increasing insulin resistance (250) and glucose levels (251) have been shown to be associated with complications and mortality after major abdominal surgery. This risk increases with higher insulin resistance and/or higher glucose levels. This leads to an osmotic shift of fluid into the vascular space and an increased availability of glucose for glucose-dependent tissues such as white blood cells and the brain.

Although hyperglycemia after surgery was reported in 1934, it was not until 2001 that negative consequences of perioperative hyperglycemia were fully recognized, with the publication of a large RCT comparing permissive hyperglycemia with strict glycemic control by intensive insulin therapy (252). Morbidity and mortality were decreased in the intervention group. In elective surgery, there are opportunities to prevent insulin resistance from developing in the first place (6).

Several interventions that blunt insulin resistance are part of the ERAS care pathway, including oral preoperative carbohydrate treatment, laparoscopic surgery and thoracic epidural analgesia. Several treatments in the ERAS protocol affect insulin action/resistance (253, 254) and hence glucose levels directly or indirectly (bowel preparation prolonging preoperative fasting; preoperative carbohydrate treatment instead of overnight fasting). The prophylaxis and treatment of PONV to support nutritional intake involves: avoiding fasting; maintenance of fluid balance to support bowel movements; epidural anesthesia to reduce the endocrine stress response from the adrenal glands; avoiding the use of opioids disturbing bowel movements; avoiding anti-inflammatory treatments to reduce stress; avoiding tubes and drains; and active mobilization (6). None of these treatments carry the risk of hypoglycemia. A recent large RCT showed that preoperative carbohydrates load limited postoperative glucose concentrations and reduced the need for insulin (117).

Two trials have shown that surgery within ERAS is associated with partial or complete attenuation of key stress responses. In the first, unchanged postoperative

nitrogen losses, neutral nitrogen balance, minimal insulin resistance and preserved normoglycemia during feeding were found after major open colorectal surgery (255). A recent four-way randomized study of laparoscopic versus open surgery and ERAS versus traditional care assessed the independent effects of laparoscopic surgery and ERAS (159). ERAS was associated with a blunted stress mediator response, measured by growth hormone concentration changes. The association to postoperative adverse outcomes appears to be the strongest in subjects without a diagnosis of diabetes (256).

KEY POINTS

Hyperglycemia is a risk factor for complications and should be avoided and minimized using the stress-reducing elements of ERAS protocol including oral preoperative carbohydrate treatment, laparoscopic surgery and thoracic epidural analgesia.

- **level of evidence: 2B**
- **recommendation grade: A**
- **consensus 97%**

24. Early Mobilization

In abdominal surgery, postoperative complications remain major clinical concern. Early mobilization after surgery has been the target of scientific studies since more than seventy years ago (257). Today, early mobilization represents one of the hinges to avoid postoperative complications (6).

Multiple benefits come from patient's mobilization: avoiding muscular and cardiovascular decay, better mood, lesser risk of developing pulmonary complications, low percentage of thromboembolic complications and insulin resistance (258).

A clear benefit of early mobilization was demonstrated even in intensive care units, where attempts to mobilize critically ill patients early after surgery could be easily disregarded (259).

Early mobilization is a fundamental item in abdominal surgery and, in particular, in Enhanced Recovery After Surgery (ERAS) program application; the active patient participation is pivotal in order to reduce overall hospital stay, decrease complication rates, and have a better tolerance of oral diet from the first hours after surgery (260, 261).

Patient mobilization still represents a critical component of the program, as age, comorbidities and surgical procedure risk to impair the whole performance. Basically, once realized the ground level of ERAS, as optimized pain and PONV control without narcotics and antiemetics drugs, it might be useful to find tools that encourage the patient to move. A recent randomized trial showed the use of a device, an activity tracker wristband, capable of giving feedback to the patient on steps taken, to enhance active postoperative mobilization (262).

Therefore, early mobilization is recommended (postoperative days 0-3); it is safe and effective to achieve an "aggressive" mobilization even a few hours after the end of surgery, stimulating the patient to carry out the initial mobilization exercise by staying in bed, then getting up and carrying out, when possible, small steps inside the room or the ward. Several degrees of failure of early mobilization may be due to pre-operative factors as (a) patient motivation-performance that should be enhanced by optimal prehabilitation and counseling (b) pre-existing comorbidities or post-operative factors as (c) inadequate control of pain, (d) continued intravenous intake of fluids, (e) prolonged indwelling urinary catheter; (f) inadequate PONV control (263).

On the other hand, a standard definition of an adequate early mobilization is still lacking, as objectives are different in local protocols, and there is no evidence to support the value of allocating additional resources to ensure early mobilization (264). Bed rest is harmful, but the allocation of additional resources to implement structured early mobilization beyond integration into multi-modal enhanced recovery protocols has not shown to be of benefit.

Summary and recommendation:

Early mobilization through patient education and encouragement is an important component of enhanced recovery after surgery programs; prolonged immobilization is associated with a variety of adverse effects and patients should therefore be mobilized.

KEY POINTS

Early mobilization is recommended (postoperative days 0-3).

- **level of evidence: 1B**
- **recommendation grade: A**
- **consensus 100%**

25. Postoperative nutritional care

Early oral feeding within 24h of colorectal surgery may lead to a shorter length of hospital stay and reduce the risk of postoperative complications, although further trials are needed to enhance the understanding of early feeding with regard to the latter outcome (140, 188, 205, 206). Notably, early return to oral feeding neither appears to have a detrimental effect on anastomotic healing process nor increases colorectal anastomosis leak rate (206, 265, 266).

It is accepted that minimal preoperative fasting, carbohydrate loading, early resumption of normal solid diet and forced mobilization have been consistently associated with decreased surgical stress response (267, 268), as well as decreased morbidity, length of stay and costs of hospitalization (204, 206, 269-271). After major colorectal surgery, in patients treated with preoperative carbohydrates and thoracic epidural anesthesia, complete enteral feeding initiated immediately after the operation normalizes glucose levels and is associated with abolition of the catabolic response to surgery such that there is no net loss of body nitrogen (protein) (255, 268). Surgery elicits a series of reactions including release of stress hormones and inflammatory mediators (i.e. cytokines). The cytokine response to infection and injury has a major impact on metabolism. It causes catabolism of glycogen, fat and protein with release of glucose, free fatty acids and amino acids into the circulation, so that substrates are diverted from their normal purpose of maintaining peripheral protein (especially muscle) mass, to the tasks of healing and immune response (272, 273). Nutritional therapy may provide the energy for optimal healing and recovery, but in the immediate postoperative phase may only minimally counteract muscle catabolism. To restore peripheral protein mass the body needs to deal with the surgical trauma and possible infection adequately. Nutritional support/intake and physical exercise are prerequisites to rebuild peripheral protein mass/body cell mass. Severely malnourished patients may exhibit an adynamic form of sepsis with hypothermia, leukopenia, somnolence, impaired wound healing and pus production, altogether leading to slow deterioration and mortality. In this situation, nutritional therapy will not maintain or build up muscle mass but may restore an adequate stress response, promoting the chances of recovery (47).

In several randomized controlled trials, most pa-

tients tolerate early resumption of oral intake after colorectal surgery despite incomplete gastrointestinal functional recovery (274, 275). The need to postpone oral feeding until after the resolution of colonic ileus is questioned by the evidence that small intestinal motility followed by gastric motility has been shown to return earlier than colonic motility. The majority of patients who are fed earlier tolerate the gradual dietary advancement (liquids followed by solids) before their first postoperative bowel movement (203). Despite a widespread practice, there is no clear evidence suggesting the clear liquid diet to be better tolerated as the initial diet of choice. Clear liquid diets are typically composed of foods that are transparent and liquid at body temperature. Juice, gelatin, tea, soda, and broth are typical of most clear liquid menus. Although easily tolerated, this diet is not palatable to all patients. Nutritionally, it is grossly inadequate to meet even the basal metabolic needs of a patient, much less the increased demands of the postsurgical period, as it provides a maximum of 1,100 calories and virtually no protein per day (276). Some report that low residue diet, rather than clear liquid diet, after colorectal surgery is associated with less nausea, faster return of bowel function, and a shorter hospital stay without increasing postoperative morbidity when administered in association with prevention of postoperative ileus (6). Soft or bland solids are often chosen by patients who are allowed to self-select their initial meals (277, 278). In a survey study, postoperative colorectal patients preferred foods not typical of the clear liquid diet in most cases. The idea of offering a diet that contains a variety of foods for patients to self-select based on how they feel may enhance intake and tolerance, as well as facilitate hospital discharge (278). No differences in the length of postoperative ileus or tolerance of diet are noted when laparoscopic and open colorectal procedures are compared (47, 203).

The importance of an early normal diet is emphasized by the association between decreased food intake and in-hospital mortality, and between increased morbidity and decreased food intake (279, 280), reporting further that more than half of patients does not eat the full meal provided by the hospital (280). While early oral feeding is the preferred mode of nutrition, avoidance of any additional nutritional therapy bears the risk of underfeeding during the postoperative course after major surgery, because it is necessary to reach energy and protein requirements. Surgical stress can

cause an acute depletion of arginine, which both impairs T cell function and wound healing (6).

25.1 Oral nutritional supplements

A large prospective series showed that spontaneous food intake after colorectal resection within an ERAS protocol rarely exceeds 1200 kcal/day and patients lose weight and muscle mass in the postoperative phase (281). There may, therefore, be a role for extended routine use of additional oral nutritional supplements (ONS) in ERAS protocols to supplement total food intake. A recent prospective cohort study conducted in colorectal surgery patients within an ERAS pathway demonstrated, in patients receiving high-protein ONS postoperatively, that consumption of >60% of protein needs over the first 3 postoperative days was associated with a 4.4-day reduction in LOS (282). Additional oral nutritional supplements (ONS) have been used to reach energy and protein requirements following colorectal surgery. Some randomized controlled trials (283-287) evaluated the effects of postoperative ONS on nutritional and functional parameters as well as on clinical outcomes and healthcare costs. There is some evidence to suggest that ONS improve weight reduction and nutritional intake, although the benefits on clinical and patient-related outcomes are unclear. ONS may be useful in the immediate postoperative stage (288). In an RCT on 55 patients, low-volume oral supplements were found to increase daily intake and reduce hospital stay following elective colorectal surgery (283). Another RCT (284) on 179 patients showed that perioperative ONS was associated with reduced weight loss and lower incidence of minor complications. The latter effect was evident also with postoperative supplements only, and the benefit of postoperative ONS on clinical outcomes occurred independently of nutritional status. Use of ONS led to cost savings per patient, irrespective of when supplements were administered, although the differences were not statistically significant. Keele et al. (285) evaluated the short- and long-term benefits of ONS following open elective gastrointestinal surgery, mostly performed for either benign or malignant colorectal disease. ONS significantly improved nutritional intake and weight loss, functional outcomes and minor complications in the inpatient phase only. Another study did not prove any benefit of post-discharge ONS in terms of postoperative function, fatigue or well-being, despite enhanced protein intake and gain

in weight and lean body mass (286). MacFie et al. (287) found that patients randomized to receive supplements achieved increases in protein and energy intake compared to non-supplemented group. However, this increase was not associated with any beneficial effect on surgical outcomes as well as functional and nutritional status.

25.2 Immunonutrition

Surgical stress impairs both immune function and increases the risk for postoperative infectious complications (289, 290). Other factors including malnutrition and cancer that are common in surgical patients may contribute (59). Immunonutrition has been developed to enhance perioperative immune-metabolic and inflammatory response. It involves the administration of biologically active nutrients with immunomodulation and anti-inflammatory properties usually administered via oral or enteral routes. Immunonutrient mixtures, which contain omega-3 fatty acids (n-3 FA), arginine and ribonucleotides, seem to have the best evidence level to support their use in surgical patients (291, 292).

Several meta-analyses of RCTs provide evidence that perioperative immunonutrition results in reduced postoperative infectious complications as well as shorter length of stay and hospital costs in patients undergoing gastrointestinal surgery for malignancy (59, 61, 292-298). However, the included studies show a great heterogeneity with regard to study populations, performed surgical procedures, immunonutrient mixtures and their application protocols, thus impairing data comparison and interpretation. Furthermore, evidence for the appropriate risk groups and the timing of intervention is not definitely clear (47).

Some guidelines have provided indications about the use of immunonutrition in surgical patients. Based on an extensive review of multiple RCTs and meta-analyses, the ESPEN guidelines on perioperative nutrition recommended that peri- or at least postoperative administration of immunonutrients (arginine, n-3 FA and ribonucleotides) should be given in malnourished patients undergoing major cancer surgery (47). The recent 2018 ERAS Society Recommendations suggest that perioperative immunonutrition in malnourished patients is beneficial in colorectal cancer surgery (6). Accordingly, the 2012 French clinical guidelines on perioperative nutrition recommend that malnourished patients undergoing elective digestive

cancer surgery receive pre- and postoperative enteral feeding with pharmaconutrients (63).

A limited number of randomized controlled trials (299-305) and a meta-analysis (291) about post- or perioperative immunonutrition specifically focus on colorectal surgery.

Braga et al. (299) conducted a study on 200 patients who were randomized into four groups. The authors found that preoperative (5 days before surgery) or perioperative (preoperative treatment prolonged after surgery by jejunal infusion) supplementation with arginine and n-3 fatty acids was associated with a significantly better immune response, gut oxygenation, and microperfusion compared to both standard isoenenergetic and isonitrogenous diet and no supplementation. The rate of infections in the groups receiving immunonutrients was significantly lower than in the groups who did not ($P < 0.04$ pre-op and peri-op vs. control and conventional), while the incidence of non-infectious complications was similar in both groups. The difference in the rate of anastomotic leak was not statistically significant, although better microperfusion and oxygenation of the bowel may be associated with the trend to a lower anastomotic leakage rate in the groups receiving immunonutrition (6% in peri-op and pre-op groups compared with 11% in the control and conventional groups).

Another RCT (300) compared perioperative (7 days before and 7 days after surgery) administration of an n-3 FA-enriched ONS to standard isocaloric and isonitrogenous ONS in 148 patients undergoing elective colorectal cancer surgery. Immunonutrition was found to significantly alter the FA content of granulocyte membranes (higher level of n-3 FA and lower level of arachidonic acid in compared to the standard ONS group). However, this was not associated with improved postoperative outcomes. Factors that may have affected these results include: rather low compliance to postoperative supplementation due to nausea, vomiting, lack of appetite, presence of gastric tubes and postoperative ileus; insufficient study power; high proportion of well-nourished patients; inclusion of n-3 only in the immunonutritional formula.

In a smaller prospective randomized study (301) on 28 normally nourished patients undergoing elective laparoscopic colorectal surgery for benign and malignant disease, perioperative (6 days before and 3 days after surgery) immunonutrition with arginine, omega-3 FA and ribonucleic acid proved to be safe and useful in in-

creasing the immunologic cell response. A significant increase in the values of CD4 lymph cells by the time of surgery with a positive trend throughout the postoperative period was observed in the immunonutrition group compared to the traditionally nourished group. There were no differences with regard to postoperative clinical and functional outcomes as well as complications. Although immunonutrition was combined with fast-track principles, the sample size was small.

Two studies (302, 303) evaluated benefits of immunonutrition on colorectal cancer patients within an ERAS protocol. A recent multicenter RCT (302) analyzed 244 normo-nourished patients receiving either hypercaloric hypernitrogenous supplement or immune-enhancing feed for 7 days before colorectal resection and 5 days postoperatively. Compliance to ERAS protocol was higher than 80%. Immune-enhancing fed patients had higher levels of lymphocytes on the third post-operative day. A decrease in the total number of complications was observed in the immunonutrition group, primarily due to a significant decrease in infectious complications (23.8% vs. 10.7%). Among the infectious complications, surgical site infection was significantly different between groups (17.2% vs. 5.7%), with similar anastomotic leakage rate. Although not significant, other infectious complications were lower in the immunonutrition group that also experienced a significant lower incidence of minor complications (25.4% vs. 13.1%).

In a series of 128 laparoscopic colorectal cancer resections from the same group, patients receiving immunonutrients pre- and postoperatively had fewer wound infections than those who received dietary advice (0% vs. 11.5%). No other differences between the groups were identified (303).

A recent meta-analysis (291) including nine studies with 1004 participants evaluated the effects of enteral or parenteral immunonutrition in colorectal cancer patients. Nutrient dose ranged from 3 to 15.8 g/d in enteral formula and from 0.2 to 0.4 g/kg/d in parenteral formula. Overall, the pooled results supported that enteral immunonutrition improves length of hospital stay (pooled MD, 2.53; 95% CI, 1.29-3.41) and infectious complications, including surgical site infections (pooled OR, 0.25; 95% CI, 0.22-0.58) and superficial/deep incisional infections (pooled OR, 0.27; 95% CI, 0.12-0.64). Two RCTs (304, 305) evaluating the role of postoperative parenteral immunonutrition were included in the analysis. Parenteral feeding

was associated with lowered magnitude of inflammatory responses and improved immune-function as well as reduced hospital stay. The authors speculate that immunonutrition should be encouraged in the clinical practice, and it may be more effective within ERAS protocols. Whether immunonutrition has a long-time effect of patients also needs to be clarified in future studies (291).

Immunonutrition might also improve post-discharge outcomes. A database analysis of 722 elective colorectal resections demonstrated significantly fewer readmissions and hospital days during the 180 days after index hospitalization in patients receiving arginine-based immune-enhancing feed. Clinical benefits included decreased risk for infections and venous thromboembolism. Mean total costs per patient were less by \$2500 at index hospitalization, \$3500 less through 30 days of follow-up, and \$5300 less over 180 days compared with the control group, although the differences were not statistically significant (306).

25.3 Artificial nutritional support

Since in modern practice it is advisable to manage surgical patients according to ERAS principles (early oral feeding within 24 h after surgery), indications to postoperative artificial nutrition should change (266).

According to the ESPEN 2017 guidelines (47) artificial nutritional support should be implemented early postoperatively in malnourished patients or those patients at high risk of developing malnutrition, in those who develop severe postoperative complications early after operation, and in well-nourished patients who do not tolerate at least 50% of their caloric and protein requirement by POD7 for any reason.

The oral or enteral route is preferred for perioperative nutritional support (47).

KEY POINTS

Early oral feeding is safe and beneficial in enhancing recovery. Most patients should be offered a regular diet within the first 24h of elective colorectal surgery according to their tolerance

- **level of evidence: 1B**
- **recommendation grade: A**
- **consensus 100%**

In addition to a regular diet, high-protein oral nutritional supplements (ONS) are useful to reach adequate intake of protein and energy in the early postoperative course

- **level of evidence: 2B**
- **recommendation grade: A**
- **consensus 100%**

Perioperative immunonutrition (administration of specific formula enriched with arginine, omega-3 fatty acids, ribonucleotides) is beneficial in reducing infectious complications

- **level of evidence: 1B**
- **recommendation grade: A**
- **consensus 97%**

Immunonutrition should be considered in malnourished patients undergoing colorectal cancer surgery

- **level of evidence: 2B**
- **recommendation grade: A**
- **consensus 100%**

26. Audit and implementation

Despite the well-established benefits of an ERAS program, such as reduced complication rates, reduced hospital costs, and increased patient satisfaction, effective penetration of these programs can be slow and random (3, 307, 308). When the implementation of an improvement program is slow, it may be important to identify and redirect local barriers and enablers (309-311). The process of understanding barriers and enabling factors is considered important because it can be an effective predictor of health professionals' intentions to change their clinical behavior (312), allowing to develop customized strategies that address these problems and support a successful implementation at any level: the patient, the healthcare team, the organization or the community (313).

Professionals can perceive different factors as obstacles. For doctors, the commonly declared barriers include organizational constraints, prevailing social practices and opinions (i.e., current practice standards, key opinion leaders disagreeing with the proposed change) and personal barriers such as not knowing or not believing in the evidence of the program, or simply not wanting to change their clinical practice (314, 315). For nurses, barriers mainly involve the lack of time, resources and access to literature, better if translated and adapted for use in clinical practice. Other constraints include the lack of support from the administration and other health professionals. Unfortunately, the information available on implementation barriers as a multidisciplinary team is much more limited.

The most commonly cited obstacles in the adoption of an ERAS program relate to time and personnel restrictions required to develop the guidelines locally, limited hospital resources (financial, personnel, space restrictions and education), resistance from other members of the perioperative team, need for commitment of the entire multidisciplinary team, lack of knowledge on the benefits of specific scheduled interventions, perceptions on patients' social and cultural values and institutional barriers (lack of nursing staff and lack of financial resources from the hospital). At the individual level, the main barrier is identified in the resistance to change of various team members, and secondly, poor communication and lack of collaboration among team members.

Enabling factors are commonly reported: a standardized guideline based on clear evidence, a series of standardized pre- and post-operative orders, education and training for the entire multidisciplinary perioperative team, patients and families, and a local ERAS "promoter". Generally, surgeons and anesthesiologists emphasize the need for high quality evidence, while nurses express more concern about patient education and satisfaction. All the different professional figures have suggested how greater communication between team members would be needed. Overall, there are many obstacles to the implementation of an ERAS program; however, the most common barrier is fundamentally linked to the multidisciplinary nature of the program.

The implementation strategy most commonly used is "bottom-up", i.e. taking shape from the starting point (bottom) or from the initial situation; it considers the final objective, induces to construct a sequential path organized in successive passages in which the anchorage between intermediate goals and final goal is generally sought in an intuitive way (heuristic).

This strategy includes identifying local facilitators, developing standardized materials, developing education and training, auditing and feedback, supporting hospital administration and communication strategies and, finally, developing a structured and periodic clinical audit.

It is important, as previously stated in the introduction, to identify a facilitator in each discipline, nurse, anesthesiologist and surgeon. The identification of an administrative facilitator can be useful for obtaining and protecting the resources for the program. The main role of the facilitators is to guide the imple-

mentation. They should meet regularly with members of the perioperative team and facilitate education and communication by presenting multidisciplinary educational cycles and teaching sessions to raise awareness and acceptance of guideline recommendations. Having a facilitator of each discipline allows open communication between these leaders who represent the main stakeholders. Secondly, they are fundamental to face problems and concerns of the specific discipline. For example, nurses might be worried about the time needed to mobilize the patient starting on the day of surgery. The facilitator nurse can work with the team to discuss these problems in particular and find a plan of action that is acceptable to the rest of the team. The facilitator also acts as a link between the other disciplines. For example, ward nurses might be better able to identify problems with adherence to specific guidelines for an individual surgeon. The nurse facilitator can communicate this to the surgeon facilitator who can then interact with these surgeons to understand and address their concerns.

Creating standardized materials, such as pre-printed orders, is essential to increase compliance. These order sets function as a constant reminder to staff about the prescription of antibiotics, thromboprophylaxis, early feeding and early removal of drainages and catheters. Each center will have its own order registration system; it is important for the organization to be willing to change these orders to reflect the program's recommendations. In addition to the order sets, clinical pathways are also an important element that could be of help to all healthcare professionals. Clinical pathways must detail all the recommendations of the guidelines on the entire journey of the patient related to surgery (for example, a clinical pathway should outline recommendations such as preoperative patient education, fluid management and postoperative mobilization). Clinical pathways outline daily goals and explicitly specify the roles and responsibilities of healthcare professionals for each of them. These paths allow perioperative team members to understand all phases of the patient's journey and provide the same information to all patients and families.

Providing education to the perioperative team and to patients (and their families) is a very important element for a correct ERAS implementation. Educational tools such as posters, reminders and flow-charts help local facilitators provide a coherent educational message. Clinical pathways and care maps that provide a

visual representation of the pathway help to reduce variability among professionals and guide the management of the most common postoperative complications. Examples of clinical pathways in ERAS are the management of urinary retention, checklists to guide the intraoperative management of fluid therapy and the creation of daily flow diagrams.

Educational resources for patients should provide information on what is expected of them as active participants in their recovery and in the proposed “milestones”. As part of the ERAS program, patients are asked to complete a daily “Patient Activity Log” included in their instruction booklet, where information about their activity, oral intake, and pain control is recorded. This registry has been strongly embraced by patients and nurses as it provides information to healthcare professionals while also strengthening patients’ expectations.

While many units employ parts of the ERAS protocols, and believe they are actually performing ERAS in their practice, it is impossible to know the details of ERAS protocol usage without an ongoing, in-depth continuous audit that includes process measures. The “magic” of ERAS is to have the best practices used in as many patients as possible. That being said, compliance with each element in an ERAS protocol is not 100% necessary for results. There will be exceptions to the use of some of the elements for some patients: at the beginning of the implementation, the use of ERAS is generally in compliance with only about 50% of the items, and an increase in overall compliance over 70% is associated with better results (faster recovery and less complications) (316). POIS investigators tried to identify several “core” items that need to be absolutely fulfilled at the beginning of the implementation process (242). On the other hand, the ERAS Compliance Group published outcomes on over 2300 patients undergoing elective colorectal cancer surgery, demonstrating that outcomes such as complication rates and length of postoperative hospital stay are inversely related to the items compliance rates (162).

Finally, an effective implementation program must provide for the local establishment of 4 to 5 training

courses for personnel involved over a period of 8 to 10 months. Each time interval between the various courses must be used for a coaching process aimed at solving any practical implementation problem. These courses must be organized and carried out by the facilitators of each clinical discipline related to the program (surgeons, nurses, anesthesiologists, dieticians, physiotherapists, etc.). These courses are of fundamental importance to strengthen the clinical basis of the program and to adapt the evidence contained in the ERAS guidelines to the local clinical reality. From a practical point of view, in fact, the evidence-based ERAS guidelines must be translated into the clinical routine of the respective hospitals; with this process it is possible to obtain a remarkable change from traditional practice, institutional protocols and integrated clinical care pathways. Moreover, external education by means of triplets of professionals (e.g. nurse, surgeon, anesthesiologist) visiting centers with fully implemented ERAS programs may strongly help to reinforce clinical change.

During the implementation process, a certain degree of opposition both open and (even more) silent should be expected. The right amount of time is strongly needed for discussions and to study the data behind the changes. It is very important that this aspect is treated with the proper respect and understanding, bearing in mind that people need time to make a change and that most people really do not like to change at all. Using feed-back of real data is very powerful, even showing everyone what is really happening and not allowing the easy onset of unfounded beliefs.

Therefore, it is to be expected that change will take time. It is important that the team that manages the ERAS project is fully “on board”, united, and at ease with the execution of the protocol. The ERAS team must gain first-hand experience in order to help other colleagues to follow the most universally used paths. Finally, top-down initiatives such as explicit resolutions on ERAS programs and allocation of financial resources coming from hospital management are eagerly awaited in order to help breaking any residual resistance to changement.

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