

Evidence Review Conducted for the Agency for Healthcare Research and Quality Safety Program for Improving Surgical Care and Recovery: Focus on Anesthesiology for Colorectal Surgery

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The Agency for Healthcare Research and Quality, in partnership with the American College of Surgeons and the Johns Hopkins Medicine Armstrong Institute for Patient Safety and Quality, has developed the Safety Program for Improving Surgical Care and Recovery (ISCR), which is a national effort to disseminate best practices in perioperative care to more than 750 hospitals across multiple procedures in the next 5 years. The program will integrate evidence-based processes central to enhanced recovery and prevention of surgical site infection, venous thromboembolic events, catheter-associated urinary tract infections with socioadaptive interventions to improve surgical outcomes, patient experience, and perioperative safety culture. The objectives of this review are to evaluate the evidence supporting anesthesiology components of colorectal (CR) pathways and to develop an evidence-based CR protocol for implementation. Anesthesiology protocol components were identified through review of existing CR enhanced recovery pathways from several professional associations/societies and expert feedback. These guidelines/recommendations were supplemented by evidence made further literature searches. Anesthesiology protocol components were identified spanning the immediate preoperative, intraoperative, and postoperative phases of care. Components included carbohydrate loading, reduced fasting, multimodal preanesthesia medication, antibiotic prophylaxis, blood transfusion, intraoperative fluid management/goal-directed fluid therapy, normothermia, a standardized intraoperative anesthesia pathway, and standard postoperative multimodal analgesic regimens. (Anesth Analg XXX;XXX:00–00)

Enthusiasm for enhanced recovery has grown in the perioperative medical and surgical communities primarily, in part, as it is an innovative approach to delivering standardized, evidence-based care that has been shown to improve patient care. Adoption of enhanced recovery pathways (ERPs) has been associated with reducing surgical complications, improving patient experience, and decreasing length of stay (LOS) and associated hospital costs without increasing readmission rates.^{1–4} Successful ERP implementation requires coordinating/collaborating

among the entire perioperative team, breaking down silos among preoperative, operating room, recovery room, and inpatient units, and creating multidisciplinary collaboration across perioperative disciplines (eg, surgery, anesthesiology, nursing, pharmacy, physical therapy, and others).

The Agency for Healthcare Research and Quality (AHRQ), in partnership with the American College of Surgeons and the Johns Hopkins Medicine Armstrong Institute for Patient Safety and Quality at Johns Hopkins, has developed the Safety Program for Improving Surgical Care and Recovery (ISCR), which is national effort to disseminate best practices in perioperative care to more than 750 hospitals across multiple procedure areas over the next 5 years. The program will integrate evidence-based processes central to enhanced recovery as well as surgical site infection (SSI), venous thromboembolic events, and catheter-associated urinary tract infections with socioadaptive interventions to meaningfully improve surgical outcomes, patient experience, and perioperative safety culture. Evidence-based clinical pathways will serve as the foundation for these efforts. To assist hospitals with transforming their perioperative care, the program will also include a registry for hospitals to track their progress in adhering to the clinical pathway and for benchmarking outcomes, patient engagement and education materials, change management and leadership training, as well as tools to facilitate local pathway adaptation, implementation, and program sustainability.

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The objective of this manuscript is to provide a comprehensive review of the evidence supporting the anesthesiology components of the AHRQ Safety Program for AHRQ Safety Program for ISCR in colorectal (CR) surgery. The surgical components were reviewed in parallel and are being reported separately. We conducted this evidence review with 2 aims: (1) to evaluate the evidence supporting anesthesiology components of CR pathways and (2) to develop an evidence-based CR protocol to help hospitals participating in the AHRQ Safety Program for ISCR program to implement evidence-based practices.

METHODS

A review protocol was developed with input from stakeholders (anesthesiologists and surgeons listed as the authors in this article; Figure). Two researchers (K.A.B., C.L.W.) reviewed current CR fast-track pathways from several major US health systems, extracted data on items included in major CR fast-track pathways, and present each item to the group (the above stakeholders as mentioned) for consideration. Meetings were conducted online or over telephone on a weekly basis. Items were included for consideration if majority consensus from the group (anesthesiologists and surgeons listed as the authors in this article) was reached. In addition, the group sought expert feedback to identify individual components for the AHRQ Safety Program for ISCR protocol in each perioperative phase of care (preoperative through postoperative; Table 1).

This evidence review should not be considered as a systematic review (SR) but an attempt to incorporate the latest evidence. The protocol was developed based on guidelines from several professional associations/societies (Table 2), and further literature searches were performed to confirm available evidence and to include recent evidence after the publication of the guidelines.⁵ The searches initially targeted CR surgery, and if no CR surgery literature was identified, the search was broadened to surgical procedures in general. Given the volume of literature in this field, a hierarchical method of inclusion was used based on study design. If we identified a well-designed SR or meta-analysis (MA), then we included it along with additional randomized controlled trials (RCTs) or observational studies published after the SR/MA, when possible. Results are described narratively.

RESULTS

Immediate Preoperative Carbohydrate Loading.

Rationale. The preoperative administration of oral carbohydrates (CHOs) may be associated with attenuation of the perioperative catabolic state, reduction in postoperative insulin resistance, and decrease in protein breakdown.

Evidence. We found several SRs assessing the effects of preoperative CHO loading in elective surgery.⁶⁻⁸ Overall, CHO loading was found to attenuate postoperative insulin resistance and decrease protein breakdown.⁷ One SR including studies in the CR surgery population concluded that CHO loading was associated with shorter LOS, faster return of bowel function, decreased loss of muscle mass,

and no increased risk of aspiration.⁹ Importantly, there are no reported adverse effects of CHO loading. There are limited data on the optimal preoperative CHO loading regimen for diabetic patients.

Summary. Routine CHO loading is recommended, although there is no consensus on the optimal solution or regimen. For diabetic patients, there are limited data; if CHO loading is done, adequate glucose management would be needed.

Reduced Fasting.

Rationale. Reduced fasting before surgery is hypothesized to be safe before induction of anesthesia.

Evidence. We identified 1 SR of 22 RCTs comparing different preoperative fasting regimens and postoperative outcomes after elective surgery.⁹ This review found that a shortened fluid fast was not associated with an increased risk of aspiration or related morbidity, and concluded that allowing patients to drink water preoperatively resulted in significantly lower gastric volumes.⁹

Summary. Evidence from RCTs supports reduced preoperative fasting (solids until 6 hours before induction and clear liquids until 2 hours before induction) because there is no evidence that this is associated with worse perioperative events (Table 2). Reduced preoperative fasting is also supported by several existing guidelines (Table 2).

Multimodal Preanesthesia Medication.

Rationale. The use of multimodal preanesthesia analgesia and antiemetic medication may improve patient outcomes such as pain control and nausea while also decreasing the use of opioid medication after surgery.

Evidence. Acetaminophen: We found 1 MA and 1 SR in elective surgery patients, which concluded the administration of preoperative acetaminophen (1 dose [orally, per os] or intravenous [IV]) was associated with reduced postoperative pain scores, reduced opioid consumption, and reduced incidence of postoperative vomiting.^{10,11}

Nonsteroidal anti-inflammatory agents: We identified several MAs evaluating the effects of preoperative nonsteroidal anti-inflammatory agent (NSAID) administration.^{12,13} These MAs concluded that preoperative COX-2 inhibitor administration was associated with reduced postoperative pain, opioid use, and postoperative nausea and vomiting (PONV) and that administration did not significantly increase the risk of bleeding or inhibit platelet function.^{12,13} There is a suggested association between NSAID use and anastomotic leak, but an SR failed to support this finding or felt data quality was insufficient to support this conclusion.¹⁴

Gabapentinoids: We identified several MAs evaluating the effects of preoperative gabapentinoid administration.¹⁵⁻¹⁸ Overall, it was found that preoperative administration of a single dose of gabapentin was associated with decreased postoperative pain and opioid consumption, but increased sedation, dizziness, and blurred vision.

Scopolamine: We found 2 MAs of preoperative placement of transdermal scopolamine and the effect on PONV.^{19,20} Both MAs found that scopolamine was associated with

Goal of our evidence review is to find the highest level evidence for each component of the clinical pathway.

General Overview

STEPS:

1. **PROTOCOL COMPONENTS.** Identify the critical components of the Optimal Surgical Recovery (OSR) protocol(s). These components will form the general foundation for the searches. Topics include – colorectal (CR) surgery, emergency general surgery, orthopedic (hip/knee), gynecology (hysterectomy), and bariatric.
2. **SEARCH.** For each component, perform a literature search that is procedure-specific. Search should be limited to English only. Keep track of the search terms. Initial searches can be for the specific component or for ERAS– this may vary by procedure so adjust as you see appropriate. We will also run our search terms by a librarian – as time permits. Also, you may need to search for broad surgical procedures. Examples of terms for ERAS: “fast track”, “enhanced recovery”, “clinical pathway”, “critical pathway”, “multimodal perioperative” and “perioperative protocol”. (Don’t limit searches by study design).
3. **INCLUSION/EXCLUSION terms and Screening.** Develop these terms for each protocol component – inclusion: specific procedure, perioperative period, component topic, reports outcomes, not case report, > ten sample size. Not necessary to track the reasons for exclusion at the title and abstract level.
 - For the full text article screen, track reasons for includes and excludes. Includes: 1. SR/MA, 2. RCTs, 3. Prospective/case controlled observational studies, 4. Retrospective observational studies. Excludes: 1. Not on the specific procedure, 2. Lack of postop outcome, 3. Not primary data, 4. Non SR, etc.

Hierarchy of the selecting includes:

- i. First identify well-done recent SR/Mas (within the past 5 years, if possible. If you have multiple SR/MAs then pick the most recent or the better quality ones. Well-done studies are:
 - Was a specific question(s) defined that the SR/MA set out to answer? Yes
 - Provided inclusion/exclusion terms and the search terms? Yes
 - Did the studies they included make clinical sense to do so? Yes (this is often a fail)
 - They did not pool RCT and observation data together unless state a strong justification. Yes
 - Was a quality assessment of the studies performed? (doesn’t really matter which tool). Yes
 - ii. Of note, if there is a well-done SR/MAs cross reference with search results looking for additional studies – ones performed after the SR/MA or ones that simply weren’t included. Include RCTs and observational studies performed after the SR/MA.
 - iii. If you use primarily observational studies (find none or just a few RCTs) then limit to the highest study design. For example, limit by sample size (n>100)/matched cohort/ multi-institutional, etc. Need to keep track of any specific decisions that change the inclusion/exclusions at this point.
4. **DATA ABSTRACTION**
 - **Evidence tables for RCTs.** This can be done later, but It will be helpful to develop these and include: **Article author name and year of publication, study design, multi- or single institution, sample size (f/u rate if relevant), surgical procedure(s), details of the component of interest, outcomes measured and findings (f/u time period for some outcomes).**
 - **Evidence tables for observational studies.** Include: **author name and year of publication, study design, multi or single institution, sample size (f/u rate if relevant), surgical procedure(s), details of the component of interest, outcomes measured and findings (f/u time period for some outcomes).**
 5. **REFERENCE MINING.** Check the references of the better studies for articles we may have missed. Then those identified from this step need to be screened.

Figure. Review protocol for colorectal surgery.

reduced PONV but also a higher prevalence of visual disturbances at 24–48 hours after surgery.^{21,22} The MAs reached mixed conclusions regarding side effects of scopolamine administration, with 1 MA supporting increased incidence of sedation, dry mouth, central cholinergic syndrome, and confusion with scopolamine administration²² and the other failing to identify these associations.²¹

Summary. MAs support the use of individual medications to reduce postoperative pain and nausea/vomiting (Table 2). A multimodal preoperative medication regimen is therefore recommended to optimize postoperative outcomes, and is also endorsed by guidelines (Table 2).

Alvimopan (μ Opioid Antagonists).

Rationale. Alvimopan administration before open surgery with opioid centric pain management regimens has been proposed to reduce postoperative ileus by blocking opioid binding at μ receptors in the bowel.

Evidence. We found several MAs evaluating the effect of μ opioid antagonists in gastrointestinal (GI) and abdominal surgery, which concluded that μ opioid antagonists were associated with accelerated GI recovery, reduced postoperative ileus-related morbidity, and shorter LOS.^{23,24} Two MAs demonstrated this benefit in the setting of fast-track surgery.^{23,24} MAs did not demonstrate a significant reduction in all-cause 30-day readmission rate with μ opioid antagonist use.

Summary. Data from MAs show that when used in open surgery with opioid centric pain management regimens, the administration of a μ opioid antagonist before and after CR surgery reduces postoperative ileus and LOS.

Intraoperative Antibiotic Prophylaxis.

Rationale. The administration of prophylactic IV antibiotics before surgical incision is believed to reduce the risk of SSI.

Evidence. We identified several SRs/society guidelines demonstrating the efficacy of IV prophylactic antibiotics before surgical incision as a means of reducing SSI risk.^{25,26} Furthermore, the administration of surgical antibiotic prophylaxis is supported by the Joint Commission and is among the Surgical Care Improvement Project (SCIP) Core Measure Set (SCIP Inf-1, prophylactic antibiotic received within 1 hour before surgical incision; SCIP Inf-2, prophylactic antibiotic selection for surgical patients).²⁶ Appropriate agents for CR procedures are summarized in clinical practice guidelines.²⁷

Summary. Data from RCTs summarized in SRs/society guidelines support the routine administration of prophylactic antibiotics to decrease SSI (Table 2). The choice of

Immediate preoperative
Reduced fasting
Carbohydrate loading
Multimodal preanesthesia medication
μ opioid antagonists
Intraoperative
Antibiotic prophylaxis
Blood transfusion
Fluids/goal-directed fluid therapy
Normothermia
Standard intraoperative anesthesia pathway
Postoperative
Standard postoperative multimodal analgesic regimen

Intervention	Outcome(s)	Studies	Population	Evidence	Guidelines
Immediate preoperative					
Carbohydrate loading	↓ insulin resistance, ↓ protein catabolism, ↓ LOS, faster return of bowel function	5 SRs	Elective surgery	+	√ ³¹
Reduced fasting	No adverse outcomes	1 SR	Elective surgery	+	√ ⁸⁹
Multimodal preanesthesia medication	↓ pain, ↓ PONV, ↓ opioid use	32 MAs, 4 SRs	Elective surgery	+	√ ²⁹
μ opioid antagonists ^a	↓ ileus, faster return of bowel function, ↓ LOS	6 MAs	GI/abdominal surgery	+	n/a
Intraoperative					
Antibiotic prophylaxis	↓ SSI	3 SRs/guidelines	All surgery	+	√ ^{23,24}
Blood transfusion	↑ SSI, ↑ infectious complications, ↑ anastomotic leak	5 observational studies	CR surgery	+	√ ^{24,28}
Fluids/goal-directed fluid therapy	↓ morbidity, ↓ LOS	9 MAs, 3 SRs	All surgery	+	√ ³¹
Normothermia	↓ SSI	1 RCT	CR surgery	+	√ ^{23,24,29}
Standard intraoperative anesthesia pathway	↓ pain, ↓ PONV, ↓ opioid use	37 MAs, 11 SRs	Abdominal surgery	+	√ ²⁹
Postoperative					
Standard postoperative multimodal analgesic regimen	↓ pain, ↓ PONV, ↓ opioid use	30 MAs, 15 SRs	All surgery	+	√ ²⁹

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CR, colorectal; GI, gastrointestinal; LOS, length of stay; MA, meta-analysis; n/a, a component not currently addressed in guidelines; PONV, postoperative nausea and vomiting; RCT, randomized controlled trial; SR, systematic review; SSI, surgical site infection.

^aIf opioids were used as major analgesic strategy.
 +A component where all evidence supported a given practice.
 √A component where all guidelines supported a given practice.

agent should follow American Society of Health-System Pharmacists (ASHP)/Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) guidelines, taking into account local patterns of resistance. Guidelines support weight-based dosing and redosing during prolonged surgery or if blood loss is >10 mL/kg to maintain adequate plasma levels according to the antibiotic used and its pharmacodynamics (Table 2).

Blood Transfusion.

Rationale. Blood transfusion during the perioperative period has been theorized to increase the risk of infectious complications and anastomotic leaks in CR surgery. There has also been concern that blood transfusions may negatively impact overall survival/recurrence after CR cancer surgery.

Evidence. We found no randomized, prospective studies of blood transfusion and the association with outcomes in the CR surgery population. We found several studies that looked at this association but used prospective or retrospective observational designs.^{28–30} These studies found that blood transfusion was associated with SSI, anastomotic leak, and additional infectious complications. Regarding cancer survival/recurrence, blood transfusion alone was not associated with poor prognosis, but blood transfusion in combination with an infectious complication was associated with disease recurrence and decreased overall survival.²⁹

Summary. There is evidence from observational studies that perioperative blood transfusion is associated with SSI, anastomotic leak, and overall infectious complications. There are limited data linking perioperative blood transfusion to oncologic outcomes including overall survival and time to recurrence. Current guidelines recommend judicious use of blood transfusion for patients with a hemoglobin between 6 and 10 g/dL during surgery based on clinical factors described previously.³⁰

Fluid Minimization/Goal-Directed Fluid Therapy.

Rationale. There is concern that excessive perioperative fluid administration causes increased demands on cardiac and renal function, fluid accumulation in the lungs, inhibition of GI function, and delayed recovery.

Evidence. We identified several MAs/SRs of intraoperative fluid management and goal-directed fluid therapy (GDFT) spanning a variety of surgical procedures, including CR.^{31,32} Most of these studies examined GDFT and, overall, concluded that compared to a liberal fluid therapy regimen, a GDFT regimen was associated with a reduction in complication rates including wound infection and cardiac complications, intensive care unit/hospital LOS, time to tolerate oral intake, abdominal complications, and postoperative hypotension, but no difference in mortality. The benefits of GDFT were most apparent in high-risk patients undergoing major surgery and patients not treated within an ERP. Whether GDFT therapy is superior to a restrictive fluid strategy remains uncertain.

Overall, guidelines recommend intraoperative fluid management to minimize fluid and maintain intravascular blood volume near baseline (euvolemia) or a “near-zero”

fluid balance.³³ Additionally, previous guidelines discourage replacement of perceived fluid losses from isosmotic bowel preparation.³³ An SR concluded that hydroxyethyl starches should not be used as these colloids are associated with increased mortality.³⁴

Summary. Intraoperative fluid management should aim to minimize fluid and maintain euvolemia. When available, GDFT is recommended and endorsed by guidelines for high-risk patients and when there is blood loss >10 mL/kg.

Temperature Control.

Rationale. Maintenance of normothermia has been suggested to help decrease risk of SSI.

Evidence. Several studies that evaluated the association between hypothermia and SSI in CR patients were identified. The RCT demonstrated that normothermia was associated with a reduction in SSI (6% vs 19%).³⁴ The other cohort studies failed to reproduce this result in adjusted analysis.³⁵

Summary. Evidence from 1 RCT supports the maintenance of normothermia during surgery to prevent SSI, a practice that is also supported by numerous guidelines (Table 2).

Standard Intraoperative Anesthesia Pathway.

Rationale. A standardized evidence-based perioperative anesthetic pathway has been proposed to attenuate the surgical stress response, improve postoperative pain scores, reduce opioid usage, and reduce PONV. Standardization has been a fundamental strategy to improve patient outcomes.³⁶ Although it is expected that hospitals of different sizes and resources capacities will be enrolled for the AHRQ Safety Program for ISCR, we will provide the evidence to allow each hospitals to tailor their pathway by choosing from the items that would be incorporated into their standardized pathway.

Evidence. Regional anesthesia/analgesia: We identified several MAs/SRs evaluating epidural use after abdominal surgery, including in the setting of CRERPs.^{19,37,38} Most studies used thoracic epidural analgesia (TEA) after open abdominal surgery, with epidural insertion before surgical incision. Compared to opioids, TEA provided superior postoperative analgesia, decreased some pulmonary/cardiac morbidity, and facilitated earlier return of GI function.^{19,37,38} One SR in CR surgery found that inclusion of local anesthetic in epidural infusion accelerated the return of GI motility and showed no difference in the incidence of anastomotic leak with epidural anesthesia use.³⁸ TEA with laparoscopic surgery does not appear to show improvement in LOS or significant benefit with regard to complications.²⁰ One MA of open CR surgery in the setting of ERPs showed that epidural use was associated with superior pain control but did not improve LOS or decrease morbidity compared to patient-controlled analgesia.³⁹

We found several MAs on the use of single-shot intrathecal (spinal) analgesia, which is typically administered before surgery when epidural analgesia will not be used.^{40,41} Spinal analgesia increased the duration of postoperative pain control by approximately 12 hours and decreased systemic opioid requirements intraoperatively and up to

48 hours postoperatively.^{40,41} Side effects of spinal opioid administration include increased PONV, urinary retention, pruritus, and respiratory depression (particularly with higher doses).⁴⁰

We found several MAs/SR on the effects of transversus abdominis plane (TAP) blocks, which are not used in combination with epidural or spinal analgesia and are often used for laparoscopic surgery.^{42,43} TAP blocks were associated with lower pain scores, decreased opioid consumption, and possibly with decreased opioid-related side effects.

Use of sedation (eg, midazolam) may improve patient satisfaction during regional anesthesia and increase the patient's acceptance of regional anesthetic techniques.⁴⁴ Although MA evaluating the effect of preoperative or intraoperative IV midazolam administration on PONV demonstrated a reduction in PONV with midazolam administration,⁴⁵ doses should be limited (eg, <2 mg) when possible to avoid potential residual sedative effects in the postoperative anesthesia care unit.

Intravenous lidocaine: We identified several MAs/SRs in CR and non-CR patients examining perioperative IV lidocaine infusion.^{46,47} Most of these studies found that IV lidocaine infusion was associated with decreased postoperative pain intensity, reduced opioid consumption, earlier return of GI function, and shortened length of hospital stay. There is a relative paucity of studies that have systematically assessed the incidence of adverse effects and the optimal dose and timing/duration of administration.⁴⁶

The optimal IV lidocaine regimen has not been determined. Some RCTs terminated infusion before the end of surgery, while others continued the infusion into the postoperative period on the surgical ward. One MA found that continuing IV lidocaine infusion beyond 60 minutes after surgery provided no added analgesic or GI benefit.⁴⁷

Ketamine: We identified 1 MA that included 12 RCTs on the use of intraoperative IV ketamine in abdominal and orthopedic surgery.⁴⁸ MA of these trials was not performed, but the authors concluded that overall, intraoperative ketamine use resulted in reduced postoperative pain scores and analgesic requirements.⁴⁸ Subanesthetic doses (sometimes started intraoperatively, sometimes started postoperatively) of IV ketamine improve postoperative analgesia, reduce opioid requirements, and may decrease PONV.^{49,50}

Adjuvant agents: Magnesium: We identified several MAs in non-CR patients that found that systemic magnesium (generally <4 g IV magnesium used) administered in the perioperative period was associated with lower postoperative pain scores and decreased opioid consumption.^{51,52} Although none of the included studies in 1 MA⁵¹ reported on clinical manifestations of magnesium toxicity related to high serum levels of magnesium, clinicians should be aware that there have been rare cases of prolonged neuromuscular block in cases of therapeutic hypermagnesemia.⁵³

Postoperative nausea/vomiting prophylaxis: We identified 1 evidence-based guideline for the management of PONV, which recommended a combination of the following pharmacologic classes of antiemetics: 5-hydroxytryptamine receptor antagonists (eg, ondansetron), corticosteroids (eg, dexamethasone), butyrophenones (eg, droperidol and haloperidol), antihistamines, anticholinergics (eg, transdermal

scopolamine), and neurokinin-1 receptor antagonists.⁵⁴ In addition, a 4–5 mg dose of IV dexamethasone in preventing PONV⁵⁵ appears to have similar efficacy in reducing PONV compared to a dose of 8–10 mg. Finally, the use of intraoperative propofol as part of total IV anesthesia was recommended to reduce baseline risk for PONV.⁵⁴

Ventilation and oxygenation: We found several MAs/SRs evaluating the effects of high inspired oxygen (F_{IO₂}) (typically 80%) during and immediately after surgery.^{56,57} Subgroup analyses of CR surgery patients suggest that in this population, high F_{IO₂} is associated with reduced SSI; however, a 2015 Cochrane Review⁵⁷ suggested that robust evidence was lacking for a beneficial effect of a fraction of inspired oxygen of 60% or higher on SSI, and that the evidence was insufficient to support the routine use of a high fraction of inspired oxygen during anesthesia and surgery. Concern has been raised previously that high F_{IO₂} during surgery might reduce long-term survival in cancer patients, but this hypothesis was not supported by a recent study.^{58,59}

Regarding tidal volume during intraoperative ventilation, we identified several MAs/SR that demonstrated that reduced tidal volumes (6–8 vs 10–12 mL/kg predicted body weight) result in decreased complications and reduced LOS.^{60,61}

Summary. The use of a standardized intraoperative anesthesia pathway is recommended (Table 2). With regard to anesthesia and analgesia, regional anesthesia should be used although the optimal dosing for each technique is uncertain. The use of intraoperative IV lidocaine or ketamine can be considered. IV magnesium is an additional optional analgesic agent.

In addition, the use of a comprehensive PONV reduction regimen is recommended. Depending on the risk profile of the patient, a variety of pharmacologic classes of antiemetics (5-hydroxytryptamine receptor antagonists [eg, ondansetron], corticosteroids [eg, dexamethasone], butyrophenones [eg, droperidol and haloperidol], antihistamines, anticholinergics [eg, transdermal scopolamine], and neurokinin-1 receptor antagonists) may be utilized for PONV prophylaxis.

Postoperative

Standard Postoperative Multimodal Analgesic Regimen.

Rationale. A multimodal opioid-sparing analgesic approach is proposed to improve pain control and minimize the use of and side effects from opioids.

Evidence. **Acetaminophen:** We identified several MAs/SRs of postoperative acetaminophen use, primarily in non-CR patients, which found that acetaminophen use lowered pain scores, decreased opioid use, and decreased PONV.^{10,62–64} In most trials, acetaminophen administration was scheduled. Administration can be orally, per os, or IV in patients who are nothing per os. Rectal administration is discouraged because absorption by this route is variable.⁶⁵ One SR demonstrated benefit to administration of acetaminophen in combination with NSAIDs over either agent alone.⁶⁶

Dextromethorphan: We found 1 SR and 1 MA of perioperative dextromethorphan use.^{67,68} The MA included 21 RCTs in non-CR patients and found that perioperative

dextromethorphan use reduced early postoperative opioid consumption and pain scores.⁶⁷ Though some findings were inconsistent with the MA, the SR concluded that dextromethorphan was a safe potential adjunct to opioid analgesia.⁶⁸

Gabapentinoids: We did not identify MAs or SRs specifically examining the efficacy of postoperative gabapentinoids on acute postsurgical pain, although several MAs/SRs support use of gabapentinoids in the overall perioperative period (including preoperative dosing) to reduce postoperative pain and PONV.^{15–18}

Lidocaine (transdermal): Several trials have evaluated the effect of lidocaine patches on acute postoperative pain.^{69,70} An MA found no difference in postoperative pain intensity, postoperative opioid consumption, or length of hospital stay with lidocaine patch use.⁶⁹ Conversely, a study in the laparoscopic surgery population has shown analgesic benefit to lidocaine patch use.⁷⁰

Local anesthetics (subcutaneous/intraperitoneal): Several MAs of continuous wound infusion for postoperative analgesia in primarily non-CR patients have produced mixed results.^{71,72}

One MA in laparoscopic surgery found that intraperitoneal local anesthetic may be associated with a reduction in postoperative abdominal pain, incidence of shoulder pain, and postoperative opioid consumption.⁷³

Tramadol: Several MAs of tramadol found weak-moderate postoperative analgesic benefit, which was significantly improved when combined with acetaminophen.^{74,75}

NSAIDs: Several MAs/SRs on NSAIDs after surgery demonstrated that perioperative NSAIDs (including COX-2 inhibitors) provided effective postoperative analgesia and decreased opioid utilization and PONV.^{12,76–79} Two MAs in non-CR surgery suggest that there is no increase in postoperative bleeding with NSAIDs.^{78,79} One MA suggested an association between NSAID use and anastomotic leak,¹³ but an SR failed to support this finding and felt data quality was insufficient to support this conclusion.¹⁴

Summary. Evidence supports the use of individual postoperative analgesic agents, including scheduled acetaminophen and NSAIDs, gabapentinoids, and tramadol. There are limited data to support continuous wound or intraperitoneal infusion at this time, and lidocaine patches have only limited support in laparoscopic surgical populations. Opioid medications should be judiciously used and the least amount should be used when possible (except in patients with preexisting chronic opioid-dependence). Overall, a multimodal postoperative analgesic regimen is recommended to achieve optimal pain control and to minimize opioid-related side effects.

DISCUSSION

The benefits of CR ERPs are well documented and include improved patient outcomes, reduced LOS, reduced morbidity, and no change in readmission rates.^{2,3} This review expands on guidelines endorsed by the Enhanced Recovery After Surgery Society and the American Society for Enhanced Recovery and includes additional best practices for preventable harms.^{1,33} Hospitals participating in the

AHRQ Safety Program for ISCR will be supported in expeditiously and sustainably translating this evidence base into practice over the next few years with the goal of moving the needle on surgical outcomes in the United States. Overall, we identified multiple components for the AHRQ Safety Program for ISCR CR protocol, including several anesthesiology components that are supported by the literature, existing guidelines, and/or expert consensus that should be delivered consistently for optimal perioperative care of the CR patient.

Based on these results, a comprehensive approach in the preoperative phase would involve oral CHO loading up to 2 hours before induction of anesthesia to adhere to updated fasting recommendations. Although the optimal CHO-containing solution (simple [eg, glucose] versus complex [eg, maltodextrin]) is unclear, some data suggest that preoperative oral intake of clear solutions containing certain CHOs may prevent perioperative protein catabolism and larger well-designed and appropriately powered RCTs are needed to better examine impact on meaningful clinical outcomes such as LOS or surgical complications.⁶⁷ In addition, a recently published network MA of RCTs comparing preoperative CHO administration with water, a placebo drink, or fasting⁸⁰ indicated that compared with fasting, preoperative low- and high-dose CHO administration decreased postoperative LOS by 0.4 (95% confidence interval, 0.03–0.7) and 0.2 (95% confidence interval, 0.04–0.4) days, respectively, although there was no significant decrease in LOS compared with water or placebo.

To simultaneously address considerations of perioperative analgesia and PONV, an oral medication bundle that includes acetaminophen, a COX-2 inhibitor, and a gabapentinoid is appropriate. These medications along with prophylactic antiemetic medications are also reasonable. That being said, it must be noted that there has been recent publications questioning the analgesic benefits of gabapentinoids as the quality of evidence for a clinically relevant benefit of gabapentin is low and the serious adverse events in available trials were poorly reported.^{81,82}

Clearly, certain institutional fasting guidelines may be modified to permit medications to be provided in the immediate preoperative period. Utilization of alvimopan in open surgeries with opioid centric pain management regimens may reduce incidence of associated postoperative ileus, although the benefit of alvimopan in present day enhanced programs and laparoscopic surgery is uncertain. While limited evidence is available to assess the impact of several medications provided in concert before surgery, medication profiles suggest this combination to be well tolerated by the majority of patients.

During the intraoperative phase, routine use of prophylactic IV antibiotics based on local bacterial resistance patterns is paramount to prevent SSI. Maintenance of normothermia through convective warmers or room temperature regulation is potentially effective for prevention of SSI as well. A concerted anesthesia protocol that employs strategies geared toward lung-protective ventilation, multimodal analgesia, and multimodal PONV prevention is also recommended. This includes low tidal volume ventilation (6–8 mL/kg predicted body weight), use of regional

analgesia in the form of TEA, spinal anesthesia/analgesia or TAP block where feasible based on local expertise and infrastructure, and administration of multiple PONV preventative agents guided by the risk profile of the patient. The benefits of using high F_{IO_2} in decreasing SSI is uncertain. Although some MAs indicate that the CR subset would benefit from high F_{IO_2} in decreasing SSI and the World Health Organization published recommendations for preventing SSIs and recommended administering oxygen at an inspired fraction of 80% intra- and postoperatively for up to 6 hours,⁸³ a recent trial⁸⁴ suggests that high intraoperative F_{IO_2} was associated in a dose-dependent manner with major respiratory complications and with 30-day mortality.

Although still controversial, available evidence supports judicious use of IV fluids based on a goal-directed protocol and a conservative blood transfusion strategy (ie, lower target hemoglobin transfusion triggers) in this setting. As recently noted, "... despite the significant evidence demonstrating the benefits of GDFT, there is no clear consensus about the most effective goals or the most appropriate monitoring device for guiding therapy ..."⁸⁵ It should be noted that current evidence suggests that GDFT is more effective outside an Enhanced Recovery After Surgery program, and a recent RCT showed that intraoperative GDFT compared to traditional fluid therapy management does not reduce primary postoperative ileus.⁸⁶ That being said, patients with significant comorbidities obviously may benefit from more intense hemodynamic monitoring.⁸⁵

In the postoperative phase, the primary emphasis is the application of a multimodal analgesic regimen. Selected regional analgesic techniques are naturally extended from the intraoperative phase. Selection of additional agents requires sensitivity to both route of administration (ie, nil per os status), potential patient-specific considerations (ie, relative contraindications based on existing comorbidities) and medication classification (ie, attempt to select agents that utilize alternative receptor binding locations). Although multimodal analgesia regimens have been highlighted for their ability to limit postoperative opioid requirements, thereby potentially hastening bowel recovery, there is as yet no consensus regarding the optimal combination of agents, dosing, or schedule of specific medications.

It should be emphasized that evidence regarding many of the elements of an ERP is in flux and new evidence continues to be published. It also should be noted that the recommendations provided on this document have been based on the best evidence available at the time of our literature searches. The development of recommendations is a dynamic process and protocols should be modified when new evidence is made available as some investigators have raised concern about the quality of assessment and reporting of adverse events in newer treatments of postoperative pain.⁸⁷

Ultimately, structural limitations at individual hospitals (eg, formulary, hospital policy, technical expertise, and other available resources) will necessitate local adaptation of these recommendations for successful implementation. With implementation of these pathways, there may be increased costs of acquiring equipment (eg, GDFT monitors) and drugs (eg, alvimopan); however, improved reduction in length of hospital stay and surgical outcomes has been shown to result in net financial savings in a US

hospital.⁸⁸ When developing the local pathway, priority should be made to developing consensus and identifying a standardized pathway for CR patients at the hospital. This is an essential first step toward reducing unnecessary variation in clinical care and optimizing perioperative outcomes. The CR AHRQ Safety Program for ISCR protocol components span all perioperative phases of care and will require transdisciplinary collaboration between surgeons, anesthesiology providers, nurses, hospital leadership, and patients. Importantly, as we unite to improve patient care for this program, these collaborations will extend to other areas, with anticipated improvement in clinical outcomes, patient experience, and workplace culture. ■■

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